Epidemiology for the Uninitiated

Aetiology—comparison between communities

GEOFFREY ROSE, D J P BARKER

British Medical Journal, 1978, 2, 1483-1484

Occasionally descriptive epidemiology gives an immediate indication of the aetiology of a disease. The discovery of the relation between childhood lymphoma in Africa and malaria is one example of this. But, more usually, aetiological hypotheses arise from other sources, and their critical investigation requires special kinds of epidemiological data.

Clearly, only certain kinds of causative influence are accessible to epidemiological investigations, and no disease is the result of one influence alone. The concern of epidemiology is not to unravel the many interactions that result in illness, but to identify those determinants that are susceptible to manipulation, and, thereby, prevent disease. Epidemiological evidence about causation is often circumstantial and incomplete, but it is a guide to action.

A well-known recent hypothesis suggests that lack of dietary fibre is a cause of a group of diseases, the so-called "diseases of civilisation," which include appendicitis, gallstones, diverticulosis, ischaemic heart disease, carcinoma of the large bowel, hiatus hernia, and varicose veins. Epidemiological evidence to support such a hypothesis can be of three kinds: (i) comparison of communities with different amounts of dietary fibre intake to show that there are corresponding variations in the incidence or prevalence of the diseases; (ii) comparison of individuals to show that dietary fibre intake correlates with the presence or absence of disease; (iii) so-called intervention studies, in which the dietary fibre intake of a population is increased, and the incidence of disease is seen to decline in relation to comparison populations whose dietary fibre intake remains unchanged. The first of these three kinds of evidence will be considered in this article.

Geographical variations

Central to the dietary fibre hypothesis is the rarity with which the "diseases of civilisation" are encountered in clinical practice in Africa and elsewhere in the non-industrial world. Nevertheless, the frequency with which diseases present to doctors may be a poor guide to their true frequency in the community; and in interpreting geographical data of any kind it is necessary to take account of three influences which may give a misleading impression of variations in incidence and prevalence.

Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT

GEOFFREY ROSE, DM, FRCP, professor of epidemiology

Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton SO9 4XY

D J P BARKER, PHD, MRCP, reader in clinical epidemiology

The number of cases of a disease recorded by hospitals, clinics, or in special surveys is partly determined by peoples' willingness and ability to seek medical attention. Varicose veins are seen not infrequently during village surveys in Africa, but people with this disorder are less likely to seek treatment than in Western cities. Patients with acute surgical emergencies, such as appendicitis, are more likely to die before they reach hospital. Differences between industrial and non-industrial countries in the levels of ascertainment of disease are, of course, considerable. Such differences persist on a smaller scale within industrial countries, where patients' attitudes and access to medical care differ between rural and urban areas and from one region to another. In Britain, where almost all cases of perforated appendix or fractured humerus receive medical attention, the ascertainment of disorders such as depression or hypertension may vary greatly between the Highlands of Scotland and the suburbs of London.

In studies of international variations in disease frequency there is usually no standardisation of the diagnostic criteria for a disease. This may be of little consequence for disorders such as gall stones—which are readily recognisable—but for ulcerative colitis (which is sometimes included with the "diseases of civilisation") there must be definite variation in diagnostic practice between countries where bacillary and amoebic dysentery is common and those where it is not.

Non-industrial countries have a greater proportion of children than industrialised countries—where survival into adult life is more usual. In Egypt, for example, half the population is under 20. This must be taken into account when reviewing data on diseases of the elderly, such as diverticulosis. The difficulties posed by variations in population structure may be accommodated by age/sex standardisation (see 30 September, p 941). Unfortunately this is often neglected. Knowledge of the world distribution of gall stones comes mainly from numerous necropsy series which have been documented over the past century. In only a minority of the published reports are ages recorded, and quantitative comparison from one country to another is therefore impossible.

Time trends

The dietary fibre hypothesis is not based solely on interpreting geographical variations, but on changes in disease distribution over time. In Western countries in the past century there has been an apparent steep rise in the frequency of the "diseases of civilisation." Interpretation of such so-called secular trends in disease is liable to the same difficulties as geographical variations. As health services have improved, so too has the ascertainment of disease; diagnostic criteria and techniques have changed; and the proportion of elderly people in the population has risen. Whereas with geographical variations differences in ascertainment, diagnosis, and population structure are accessible to current inquiry, documentation of secular changes is more difficult, dependent as it is on observations made and often

scantly recorded many years ago. Nevertheless, the reality—if not the true size—of secular trends may sometimes be established with reasonable certainty. Discussion of the rise of lung cancer incidence during this century has been an instructive example of this.

Migrants

Further support for a hypothesis based on apparent differences in disease frequency among communities may be drawn from studies of migrants. Japanese migrants to Hawaii have seven times more carcinoma of the colon than Japanese in Japan, which suggests a close dependence of the disease on environment and points to the need for dietary comparisons between the two groups. Interpretation of observations on migrants, however, presents certain difficulties, for the migrants may be unrepresentative of the population they leave. Norwegian immigrants into the United States of America, for example, have a

higher incidence of psychosis than people in Norway. Although this may indicate environmental influences in the USA which lead to psychotic illness, it may also be a result of selective emigration from Norway of people more susceptible to mental illness, or of the unusual stresses imposed on immigrants during their adjustment to a foreign culture.

If the reality of geographical and time trends of the "diseases of civilisation" is accepted—notwithstanding the difficulties inherent in the data—they can be correlated with variations in dietary fibre intake. Nevertheless, such a comparison will provide only circumstantial and inconclusive evidence of a causative link. In general, epidemiological evidence on disease causation is not rigorous; but it may be strengthened by using more than one method of study. Our next article considers methods that depend on comparisons between subgroups within a population rather than between different populations.

Eventually this series will be collected into a book and hence no reprints will be available from the authors.

How should paracetamol poisoning in pregnancy be treated? Would oral methionine be contraindicated?

Methionine is an amino-acid and is a constituent of the normal diet. There appears to be no evidence that it is teratogenic in man, but it should not normally be administered in large amounts to pregnant women. On the wider implications of paracetamol, sulphhydryl donors, and pregnancy there is also no conclusive information. The logic of using sulphhydryl donors (such as cysteamine, methionine, and acetylcysteine) as treatment for paracetamol overdose is based on the hypothesis that paracetamol hepatotoxicity is caused by a reactive metabolite that depletes liver glutathione stores (the normal detoxification step) and then causes macromolecular damage. It should be emphasised, however, that guidelines have been defined for using this type of treatment.¹ In paracetamol overdose during pregnancy the risk of damage to the fetus is uncertain but may be presumed to be related to the maternal plasma paracetamol concentration. It would therefore be unwise to administer methionine without a prior paracetamol determination. Although paracetamol overdose in pregnancy has occurred, the numbers of patients affected are small, and it has not been determined if the effect on the fetal liver is equivalent to that on the mother. Recent animal work suggests it might not be. The liver of the fetal and baby mouse develops glutathione synthesising enzymes before mono-oxygenases (the enzymes that metabolise paracetamol), thus producing an inbuilt defence against paracetamol toxicity. The concentrations of glutathione in the fetal mouse are lower than those in the adult.² Extrapolation to man is difficult because human hepatic glutathione concentrations are lower than those of animals. The human fetal liver can metabolise paracetamol to the reactive intermediate, though its ability to do this may be less than that of adult liver as judged by apparent K_m and V_{max} values.³

¹ Prescott, L F, *et al*, *Lancet*, 1974, **1**, 588.

² Lambert, G H, and Thorgeirsson, S S, *Biochemical Pharmacology*, 1977, **25**, 1777.

³ Rollins, D, *et al*, Abstract 756, 7th International Congress of Pharmacology, Paris, July 1978.

Recently there has been rather pejorative comment about the value of physical fitness, in particular jogging. Is there any objective evidence that an improvement in physical fitness improves higher mental function?

There appear to be some long-term psychological benefits as a result of regular exercise.¹⁻³ In controlled studies various authors have observed increases in extraversion, self-confidence, self-awareness,² and improvements in recall in the elderly.⁴ It has been claimed that the quality of learning, mental concentration, and intellectual performance achieved by students and others improves with physical fitness, but this is not supported by well-controlled observations. On the other hand, there is strong evidence for physiological improvement when people with a sedentary lifestyle take up regular exercise; they report that they feel better within only a week or two. They report this sense of improved wellbeing because they notice an improvement in their physical work capacity and a reduced sense of

effort for any given task.⁵ They can work harder, longer, and with less fatigue than when they were inactive, and the range of physical activities in which they can comfortably participate has been extended. The rapidity with which physiological improvements in muscular and cardiovascular function occur with regular exercise, and their magnitude, are sufficient to explain their reported improvement in the quality of life. Mood and morale will improve secondary to these general physiological changes.

¹ Collingwood, J P, *et al*, *Scandinavian Journal of Clinical and Laboratory Investigation*, 1970, **26**, 295.

² Myrtek, M, and Villinger, U, *Medizinische Klinik*, 1976, **71**, 1623.

³ Schofield, L J, and Abbuhl, S, *Journal of Clinical Psychology*, 1975, **31**, 745.

⁴ Stamford, B A, *et al*, *Research Quarterly of the American Association for Health, Physical Education and Recreation*, 1974, **45**, 34.

⁵ Åstrand, P O, and Rodahl, K, *Textbook of Work Physiology*. New York, McGraw-Hill, 1977.

Why is a relative, or absolute, neutropenia and a relative, or absolute, lymphocytosis often found in intracellular infections (including viral infections, TB, and brucellosis)?

Neutropenia is common in viral and rickettsial infections. In glandular fever and infectious hepatitis the fall in the number of neutrophils appears in the first one or two days of the illness, possibly corresponding to a phase of viraemia. The count may rise in the second week becoming normal at the end of that week. Occasionally severe agranulocytosis may be present. Similar changes occur in brucella, typhoid, and malarial infections. The explanation for these changes is not well understood. A shift of neutrophils from a circulating to a marginal pool in the circulation has been proposed in acute malarial infection¹ but increased granulocyte destruction or use corresponding to a period when the infective agent is in the blood has also been suggested. An absolute increase in lymphocytes that occurs in children rather than in adults is part of the immunological response to the infective agent, a phenomenon best exemplified in glandular fever.

¹ Dale, D C, and Wolff, S M, *Blood*, 1973, **41**, 197.

A 10-year-old boy, attending an ESN (M) school, was born from a father-daughter incestuous relationship. He is in the care of the social services department, which is trying to find him a foster home. Should he be told the circumstances of his conception, and if so, when?

As this boy is clearly educationally subnormal, this obviously alters his understanding of any day-to-day situation. The fact that he was born from a father-daughter incestuous relationship should on no account be conveyed to him as this would in no way contribute to any future constructive management of his problem. This is especially so since his family have clearly rejected him. As a rider I would hope, in view of the degree of consanguinity of his parentage, that well-recognised causes of mental subnormality, such as hypothyroidism, have been excluded.