PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Epidemiology for Geochemists [and Discussion]

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Epidemiology for geochemists

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Epidemiologists study the distribution and the determinants of disease in human populations. Geochemists may be more concerned to find diseases to fit the observed patterns of geochemistry. This paper is concerned with the application of epidemiological techniques to the interrelations between health, disease and geochemistry, with particular reference to the hazards of man-made chemicals in the environment. Descriptive studies of disease in terms of person, place and time allow for crude comparison with the results of geochemical mapping and for the development of hypotheses. Analytical studies allow for the exploration of these hypotheses but demand careful sampling techniques and vigorous quality control. The epidemiological approach should be directed towards the identification of national/regional problems and of high-risk groups, the definition of priorities and the opportunities for preventative measures. The problems and possibilities for epidemiological research are illustrated from recent and current studies.

Introduction

This presentation is an attempt by an epidemiologist to examine the relations between environmental geochemistry and health, and in particular to look critically at the methods used in our joint endeavours. By environmental geochemistry, I understand the study of the distribution and concentration of chemical elements in the environment, whether their presence (or absence) arises from natural phenomena or as a result of man's involvement with the soil, water or atmosphere.

In the past, the geochemist has been primarily concerned with the elements themselves; only secondarily has he become concerned with their effects on plants and animals and only very recently has he become deeply concerned with their effects on health and disease in man. Our knowledge concerning the ill effects associated with gross contamination of the environment has increased considerably in the last two decades, and the dramatic nature of many of these 'severe environmental assaults' has brought with it an awareness that there may be ill effects from 'lower, more prolonged and sometimes insidious exposures' (Higgins 1975). And so the geochemist has, metaphorically speaking, picked up a stethoscope and gone looking for diseases to fit the geochemical information.

The epidemiologist, on the other hand, is concerned with the distribution and the determinants of diseases (and injuries and biological variables) in human populations. He is faced with widespread chronic diseases, cancer and cardiovascular disease in particular, for which he has established few firm relations. He has a growing suspicion that some of those elements that concern the geochemist might also concern him. His concern is to establish quantitative relations between the extent and the types of illness and the factors which influence their distribution, some of which may be causally related to the disease. The implication of this approach is that disease is not randomly distributed throughout a population, but that subgroups differ in the frequency of different diseases. Information about this uneven distribution can be used in the search for causes and can show the way towards methods of control and prevention.

Our present concern is not with the dramatic events involving exposure to high concentrations of toxic chemicals, e.g. methyl mercury in Japan (Minamata disease) and Iraq, events which are solved relatively easily and relatively speedily, but with the possible effects on health of much lower doses of chemicals, often over long periods of time and usually delivered and received in a subtle and insidious manner. This is where epidemiologist and geochemist meet and where each must be concerned to know something about the information and skills of the other.

The coming together of geochemists and epidemiologists seems so reasonable that one might well ask why it has taken such a long time to get started. Almost certainly the answer lies in technological development. We now have the techniques that enable us to measure incredibly small amounts of elements in soil, water or air or in animal or human subjects – in blood, urine, faeces, hair, fingernails and in tissue from various organs. This new ability brings with it considerable pressures to prove the usefulness and the cost-effectiveness of our technological achievements. It is for this reason that we are now confronted not only with diseases in search of aetiological factors but with potential factors in search of appropriate diseases.

Making maps

A straightforward view of the function of the epidemiologist in relation to the new demands of geochemistry is that he should provide maps of morbidity or mortality that would be compatible with the compilation of geochemical maps. Epidemiology does include the preparation of maps showing the spatial distribution of various diseases and in skilled hands this can illuminate the disease problem in terms of possible associated factors. Thought-provoking patterns may emerge from what started out as a seemingly haphazard array of data.

The classic study of cancer frequency in relation to different sources of water supply in west Devon (Allen-Price 1960) involves consideration of geological structure, thus making it a small forerunner in environmental geochemistry studies. Cancer and other deaths over a 20 year period were plotted on a large-scale map and an extraordinary distribution of cancer became apparent. In one hamlet the ratio of cancer to other deaths was 1 : 12, while in an adjoining hamlet it was 1 : 3. The parishes with the highest cancer frequencies derived their water supplies from underground sources (wells or springs) and were mainly on the highly mineralized Devonian or granite strata. The conclusions drawn from this study were that 'some cancer provoking agent is more active in one area than in the other . . . and this agent is a trace element, occurring in sufficient concentration on the Devonian strata to be capable of detection'. Simple mapping of this kind can be remarkably effective – and it can also be remarkably misleading.

In the west Devon study the largest parish (6000 people) experienced 12 cancer deaths in 20 years and the parish with the highest frequency of cancer deaths (total population 120) had 1 cancer death in 20 years. We are obviously confronted with a problem of very small numbers and no concept of rates. But even more important is the use of crude proportional mortality, i.e. the proportion of cancers in relation to deaths from other causes, without reference to age or sex or to any suitable baseline figures which might indicate the expected proportional mortality (Alderson 1976). Without knowledge of the age and sex structure of the communities and with little information on the nature of the cancers involved, the value of this small classic in

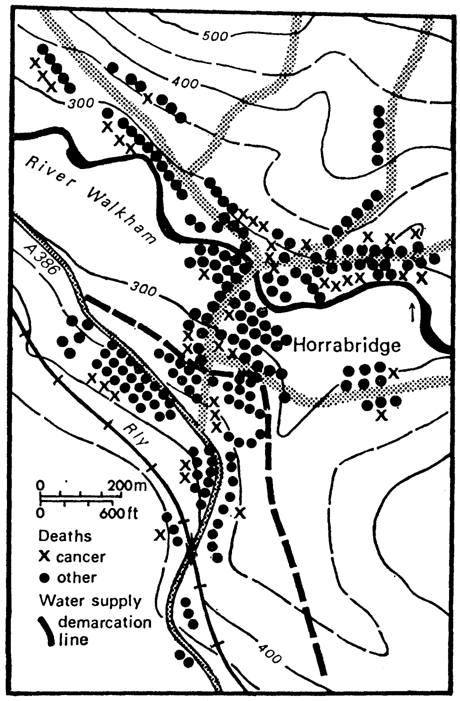

Figure 1. Cancer deaths and deaths from other causes mapped in relation to three sources of water (i) north of River Walkham. (ii) between the Walkham and the demarcation line and (iii) south and west of the demarcation line (Learmonth 1972, after Allen-Price 1960). Contours marked in feet.

environmental geochemistry is difficult to determine. Its importance is that it illustrates at an intimate level many of the problems encountered in the mapmaking approach to epidemiology and geochemistry.

Demographic maps

One of the problems of mapmaking is that we feel constrained to use the normal geographical maps showing the relevant administrative areas (choropleth maps) because they are the usual ones available. However, we also need information about the size of the population at risk in the areas concerned. In the usual map, weighting cannot be given readily to large urban populations which occupy small areas, while small rural populations sparsely distributed over large areas may appear to be overrepresented. This has led to the development of the demographic map in which the area of each administrative unit is made proportional to its population, while contiguity of geographical boundaries and the relative geographic positions are maintained as far as possible. These figures show average mortality rates for Scotland on a conventional map and on a demographic cartogram (Forster 1966). The principal value of the cartogram is that it enables the essential features of a distribution pattern to be quickly appreciated. Thus, Glasgow is the most prominent area of unfavourable mortality experience in west central Scotland and within this area the large burghs of Greenock and Coatbridge stand out in marked contrast by virtue of their low mortality rates. Development of these demographic maps offers possibilities for relating disease rates both to local populations at risk and to geographical position. They may well have an advantage over the geographic base maps for the presentation of areal data in epidemiology and geochemistry.

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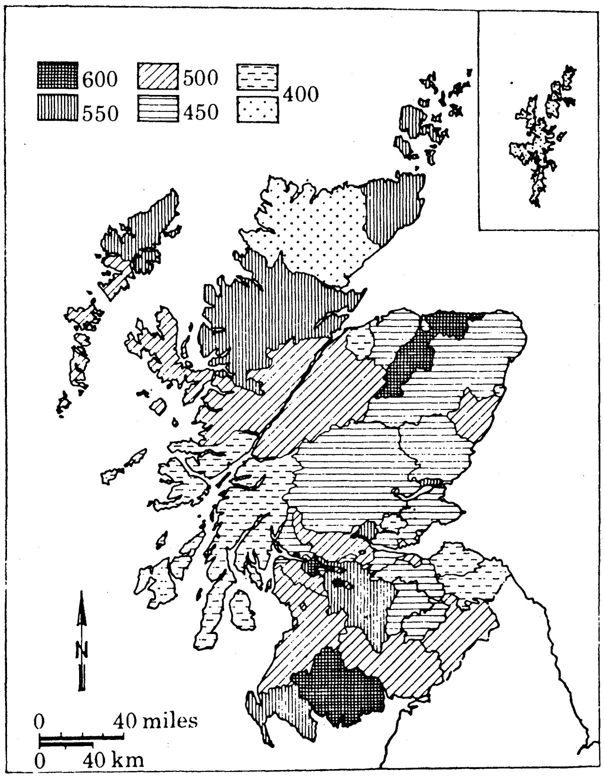
One cannot discuss medical mapping without reference to the National Atlas of Disease Mortality in the United Kingdom produced by Melvyn Howe (1970) on behalf of the Royal Geographical Society. His maps show the spatial patterns of variations in disease mortality in the United Kingdom by using data for 1954–8 and 1959–63. Aware of the considerable variation in age and sex structure of the population in different parts of the country, Howe has used the Standardized Mortality Ratio (S.M.R.), a summary index which compares the number of deaths actually occurring in an area with that which would be expected if the national mortality



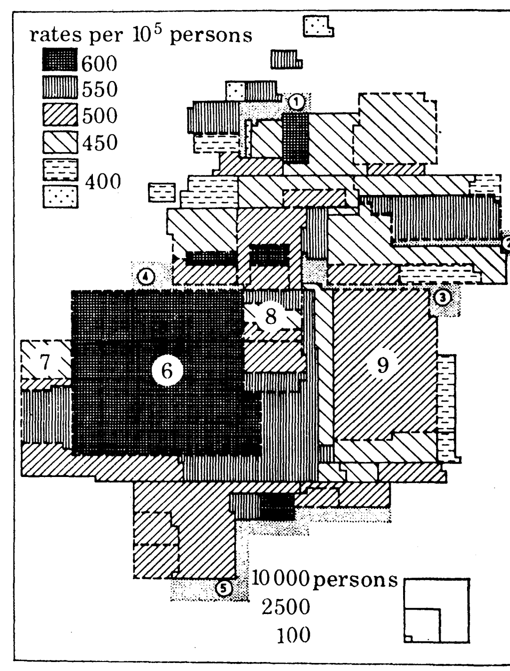


Figure 2 Figure 3

Figure 2. Conventional map of Scotland, showing average mortality rates per 10^5 persons for 1959–63, all causes of death, females 45–54 years (Forster 1966).

Figure 3. Cartogram of Scotland showing average mortality rates 1959–63, all causes of death, females 45–54 years (Forster 1966). 1, Moray Firth; 2, Firth of Tay; 3, Firth of Forth; 4, Firth of Clyde; 5, Solway Firth; 6, Glasgow; 7, Greenock; 8, Coatbridge; 9, Edinburgh.

rates by age and sex were applied to the population of that area. Unfortunately, these geographically based maps covering the 1954–8 period give undue prominence to the S.M.Rs of the extensive but sparsely and unevenly populated areas of the U.K. and provide insufficient weighting in local areas of dense population. An incorrect visual impression of regional intensities of mortality incidence is thus created.

For the 1959–63 period, Howe has introduced a demographic base map for the presentation of the areal data, having computed S.M.Rs for each of the 320 separate administrative units in the U.K. for each selected cause of death and for each sex separately. On the new maps, the size of the symbols is proportional to the populations at risk. Large counties with small

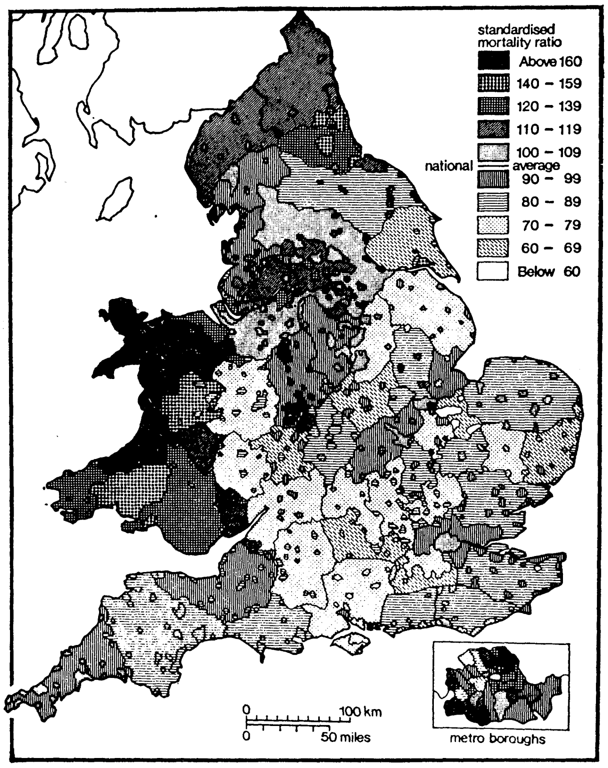


Figure 4

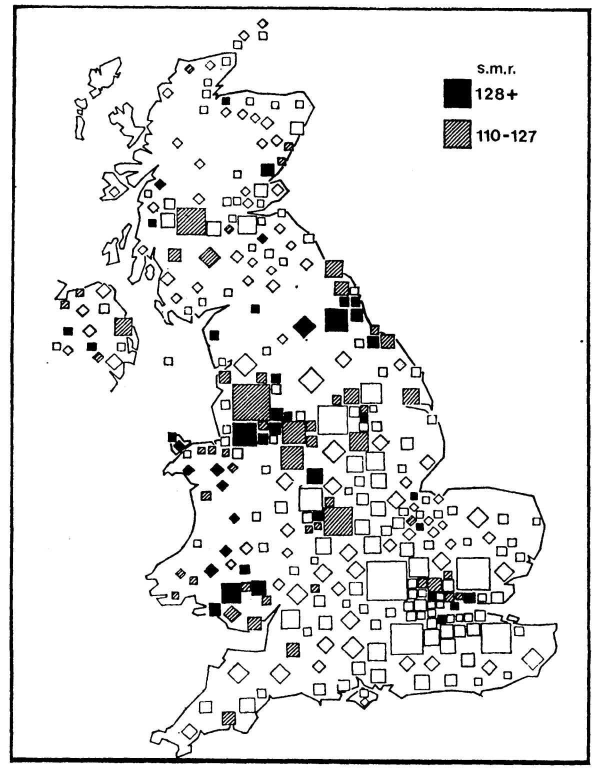


Figure 5

Figure 4. Choropleth map. Cancer of stomach (males) 1954–8 in England and Wales (Howe 1970).

Figure 5. Demographic map. Cancer of stomach (males) 1959–63 in England, Wales and Scotland (Howe 1970).

populations are thus relatively reduced in area and the main centres of population assume increased proportions. It is visually more acceptable than the demographic cartograms previously presented for Scotland but may lack the usefulness provided by the more schematic and less representational forms.

Probability maps

A statistically sophisticated technique is that of probability mapping and such maps have been made for the occurrence of deaths from brain tumour in southern Poland, stomach cancer in South Africa and leukaemia in England and Wales (White 1972). Probability maps are concerned not only with the mapping of morbidity and mortality but with displaying the statistical significance of the data. The probability maps appear as filtered data through which only the non-random recordings appear. In this way, attention is drawn to a limited number of counties on each map.

Aggregates of years can be used to provide aggregates of probability, or a map summarizing experience over a much longer period can be presented. The long-term probability data for leukaemia in England and Wales show a higher than expected value for several counties in the southeast and along the south coast. Areas of low incidence include Glamorgan and some of the industrial counties of the Midlands and northern England. As an aid to the formulation of

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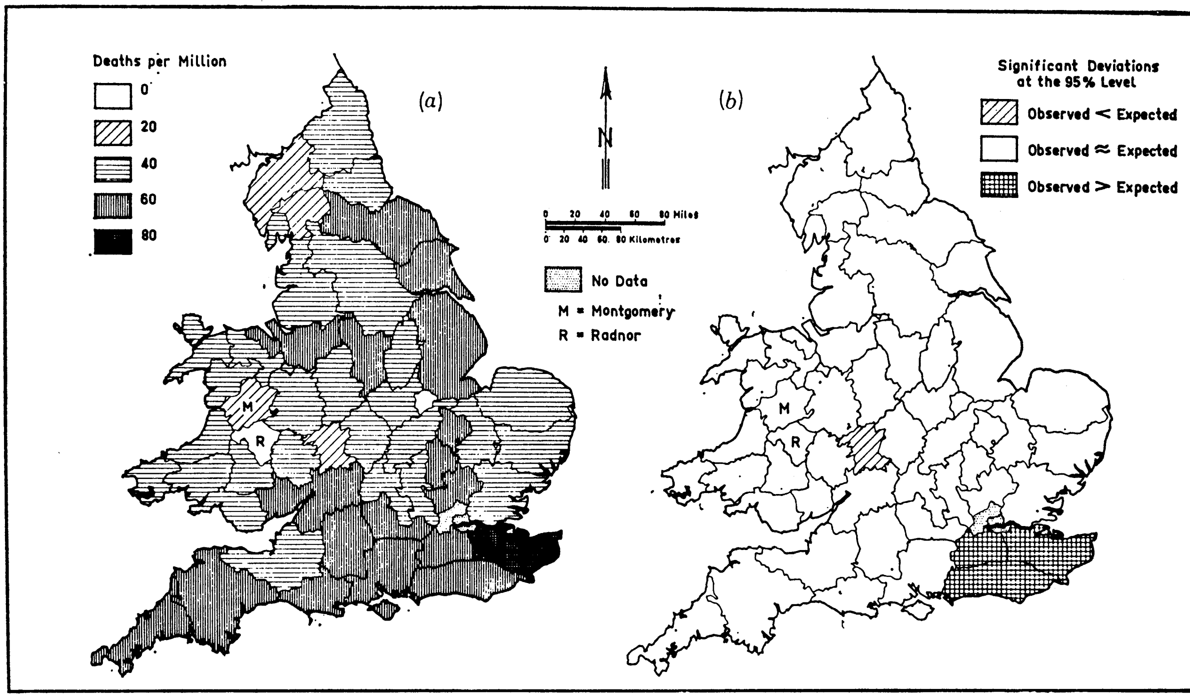

FIGURE 6. (*a*) Incidence of leukaemia mortalities in England and Wales 1963 and (*b*) probability of leukaemia mortalities (White 1972).

hypotheses, it can be seen that such a distribution is incompatible with any suggestion that leukaemia may be positively correlated with air pollution.

BEYOND THE MAPS AND AMONG THE PEOPLE

If mapping does anything for the epidemiologist and the geochemist, it provides the basis for aetiological hypotheses which can then be tested. There are a wide variety of strategies available to test hypotheses regarding the association between disease and a suspected factor or between a suspected factor and disease. The method one chooses depends on the hypothesis, the precise aim of the study, on the time and resources available to carry out the work and on the precision needed in the study. It is my belief that far more important contributions to the elucidation of disease aetiology will arise from geochemistry's involvement in these analytical studies than is likely to accrue from further detailed mapping. This is not to decry the usefulness of mapping but to emphasize the need to go beyond the maps and among the people.

1. *Case–control studies*

These studies start with persons already diseased and a comparison is made of the frequency of the suspected causal factor in these cases with its frequency in a control group. Relatively quick and cheap, this is an essentially retrospective method in that it looks backward in time to possible initiating factors in people who are already diseased. Such a method can be used to see whether individuals have been exposed to environmental geochemical influences in the past, but only if markers of such exposure are still present. As many trace metals are not readily excreted and accumulate in human tissues, their presence can often be determined in life or death in blood, hair, nails or the tissues of various organs. Case–control studies have serious disadvantages and, in particular, bias (systematic error) arises in the selection of both cases and controls. Furthermore, if an association is demonstrated with a particular marker, it may be impossible to tell whether this is a result of the disease, a result of treatment or a true indication of a causal association.

2. *Cross sectional surveys*

A defined population is chosen and the status of each person is determined in terms of disease and exposure to the suspected factors. A comparison is then made between the frequency of the factor in the cases and the non-cases (healthy). Clearly, findings in a study of this kind are more reliable and less biased than in a case–control study, but where the prevalence of a disease is not high, very large numbers may need to be studied. In terms of environmental geochemistry, unless there is a fairly wide range of exposure gradient to the suspected factor, the results of such a cross sectional survey may be of little value.

3. *Longitudinal* (*cohort*) *studies*

Such studies are prospective in design and compare the incidence rate of disease in two or more groups, exposed to the suspected causal factor in different degree. Longitudinal studies tend to be time-consuming and costly and are beset by all the administrative and quality control problems of large-scale research programmes. Nevertheless they are the only way in which incidence rates can be determined and thus accurate estimates obtained of relative and attributable risk.

4. *Natural experiments*

In societies with good routine recording systems for morbidity and mortality, it occasionally happens that changes occurring in environmental situations are accompanied by discernible changes in morbidity or mortality. The smog of 1952 and the associated increase in deaths from bronchitis and heart disease is a classic example. In the field of geochemistry, such natural experiments occur frequently on a short-term accidental basis but rarely on a long-term basis. Where they do so occur, the opportunities are rarely exploited.

5. *Intervention studies* (*controlled trials*)

Hypotheses for a causal relation can be examined by removing the suspected factor and demonstrating a reversal of risk. In theory and in practice this has limitations in relation to environmental geochemistry, for very long latent periods and very low degrees of exposure to a factor may be involved, as well as irreversibility in the pathological processes concerned, e.g. cancer and cardiovascular disease.

The 'water story'

The 'water story' in the United Kingdom provides a good example of the coming together of epidemiology and environmental geochemistry. It exemplifies the use of mortality data in conjunction with other sets of routinely available information and it serves as a model for ways in which one may move from mortality data to the study of morbidity and from morbidity to the physiological variables associated with health and disease.

The 'water story' started in Japan, where an agricultural chemist, Kobayashi, demonstrated a spatial relation between death rates from apoplexy (stroke or cerebrovascular disease) and the acidity of river water used for drinking purposes. In the United States, Schroeder re-examined these data and American data in terms of water hardness and demonstrated a strong association between death rates from cardiovascular disease and the hardness of drinking water. The softer the water, the higher the c.v.d. mortality rate; the harder the water, the lower the death rate. In the U.K., studies by the M.R.C. Social Medicine Unit have confirmed the relation for this country and have also examined the natural experiment resulting from changes in water supply to certain areas (Crawford 1972).

Fairly sophisticated statistical techniques are required in these studies to cope with the problem of multiple variables, both environmental and socioeconomic. The work of Gardner (1973, 1976) in particular must be cited as a guide to the methods needed to attempt explanations of mortality in terms of environmental factors. Multiple regression analysis enabled the contribution of each of the various factors to different causes of death to be assessed and the size of their effect quantified. By using the same technique, data on the factors for other towns were used to predict mortality rates and these were compared with actual results obtained. One can thus not only predict mortality rates in terms of known environmental factors but one can also begin to see which towns do not fit the expected patterns of mortality, and the further study of these 'outliers' becomes of special interest (Clayton 1976).

Mortality studies can only provide a preliminary examination of an hypothesis and have to be followed by more detailed studies with the use of other approaches. Examples of these other approaches in the 'water story' include pathological and biochemical studies on autopsy material (Crawford & Crawford 1967) and clinical and biochemical studies of men living in areas supplied with hard or soft water (Stitt *et al.* 1973; Shaper *et al.* 1975). These studies provide obvious opportunities for the participation of those concerned with the geochemical approach but such opportunities have only occasionally been exploited (Crawford & Clayton 1973).

Regional heart study

The 'water story' remains unsolved and there are several aspects of it that demand that it should not be left as an interesting but unimportant oddity. First, it has drawn attention to the striking regional variations in cardiovascular disease within the United Kingdom and the explanation of this phenomenon is in itself of obvious importance. Secondly, it has suggested that there may be an environmental factor, water quality, which is associated with variability in death rates from cardiovascular disease. If this relation is causal and if the factor in the water can be determined and altered in a beneficial direction, then we are faced with a preventive health possibility of considerable magnitude.

The current approach to the 'water story' once again starts with mortality data and environmental variables. This time it is focused on the 5 years around the 1971 Census and on all towns in England, Wales and Scotland with populations in 1971 over 50000. By using aggregates of some rural areas, we now have some 240 towns giving a wide geographic cover of Great Britain and filling in many areas not covered by the previous studies. A team from the Water Research Centre has visited each town and completed a detailed documentation of water supply, water treatment and water chemistry. These water data, together with the mortality data, are being analysed in conjunction with a wide range of other variables including temperature, rainfall, latitude, and a variety of socioeconomic indices.

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From these 240 towns we have selected 22 in England, Wales and Scotland, covering all geographic areas and representative of the wide range of cardiovascular mortality and water hardness. In each town, a representative general practice is invited to collaborate and from its age and sex register, a random selection of men aged 40–59 years are invited to participate. Full physical examination, electrocardiographic and lung function studies, detailed blood chemistry, including lead and cadmium studies, are carried out and a questionnaire administered which deals with a wide range of variables including residence changes, occupation and smoking. At the same time a team from the Water Research Centre carries out a study of tap water usage and quality in a 10% sample of the men. The men are then followed for morbidity and mortality and it is expected that some 7500 men will ultimately be included in the study. The aim is to determine the role played by the conventional risk factors (e.g. smoking, hypertension, blood lipids) in the marked regional variations in the incidence of cardiovascular disease and stroke and to assess the possible role of water factors in this regional variation. It requires little imagination to conceive the possibilities within the structure of such a national study for a close association between epidemiologist and geochemist. It would be pleasant to end on a note suggesting that such possibilities had not only been considered but were being exploited to the full. It will be clearly understood if I say that something is being done, but that the major potential of such a framework remains to be developed.

Conclusion

I have dealt in a somewhat summary way with the obvious possibilities for closer association between epidemiologists and geochemists. The making of maps is a beginning but can only provide the crude material for the development of disease hypotheses. If the geochemist is to make a major contribution to the understanding of health and disease, he must be involved in the analytic studies of epidemiology and must play a role in their design and execution. The epidemologist will welcome such interest and expertise and perhaps together they may solve some of the major mysteries surrounding cardiovascular disease and cancer.

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Discussion

M. L. STRAF (*Department of Statistics, London School of Economics and Political Science, Houghton Street, London W.C.2, U.K.*). Drinking water is only one of the pathways through which pollutants and other substances reach man. Other pathways, such as inhalation of ambient and indoor air and ingestion of food in one's diet, are important sources. If an epidemiological study is to have more meaningful results, it should take into account as many as possible of the important factors that may affect the response being measured. A National Academy of Sciences–National Research Council committee studying environmental monitoring in the United States recommend to federal government agencies that they conduct a long-term multi-city study of the effects of air pollution on human health. One important aspect of this recommendation is that variables of drinking water quality also be included where they are relevant in the aetiology of diseases studied. (Study Group on Environmental Monitoring 1977 *Environmental monitoring*, Washington, D.C.: National Academy of Sciences). Moreover, the Committee suggested that the water be measured at the tap, not merely at mains or treatment plants, which, as Mr Wilson has told us, can be important. Conversely, we can learn more if epidemiological studies of the effects on human health of known or potential pollutants or other substances in drinking water took into account the many pathways to man; the effects of other substances; and, where relevant, the effects of one's social and physical environment. Are there such studies?

R. M. S. PERRIN (*Department of Applied Biology, University of Cambridge, U.K.*). Professor Shaper mentions that in the investigation of drinking water consumed by study groups, water will be analysed 'at the tap' to allow for metal contamination in distribution. It would appear that some further refinement might be needed to allow for the fact that many people do not actually drink large amounts of tap-water but rather tea or coffee from which much of the hardness, and coprecipitated minor elements, may have been removed by boiling, while men in particular may consume beer brewed in geochemically distinct areas. On the other hand, Ca and Mg may be precipitated in cooked vegetables. It seems, therefore, that particularly close investigation of life styles will be needed for results to be meaningful.