described but mistaken fears about quality of care and patient satisfaction that prevents team care progressing.

Let there be no mistake, I believe in the National Health Service, I love working in it, I am happy to have entered medicine in the year that it was born. I have proclaimed, I think convincingly, its virtues in several parts of the world. Nevertheless we must be ever watchful that it does not become wasteful.

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The role of skeletal scanning in clinical oncology

SIR,—The review by Drs James H McKillop and I Ross McDougall (9 August, p 407) on the value of bone scanning in clinical oncology included the observation that scanning is less effective than skeletal radiology for detecting bone lesions in multiple myeloma. We have recently studied the skeletal radiology and isotope scan images of a series of patients with multiple myeloma and made the following observations.

(1) Of 18 patients so far studied, there has been no instance where there has been a normal bone scan and an abnormal skeletal radiograph. (2) While lesions (particularly lytic lesions) are more frequently seen in the limbs and skull on *x*-ray examination than on isotope scan, radiology is inferior to bone scanning in detecting rib lesions. (3) The majority of isotope scan abnormalities are areas of increased activity due to repair consequent on fracture. However, in one case a "cold area" was detected on scanning and this corresponded to a large lytic area on the *x*-ray film. We concluded that small lytic lesions not at present detected by bone scanning are not seen merely because of resolution problems.

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Breast cancer trials—a new initiative

SIR,—There is obviously no shortage of patients with carcinoma of the breast for entering into clinical trials, as clearly outlined in a recent paper in the *Lancet*.[1] It would appear that only approximately 8% of eligible patients with breast cancer are entering such studies. Yet, to quote the leading article that accompanied this paper, "the structure of the National Health Service offers scope for clinical trials on a scale which most countries could not hope to undertake."[2] Failure to recruit patients into current trials suggests that the questions posed by the individual studies are not those which are of immediate interest to the majority of clinicians in this country or that in addition there may be a natural reluctance on the part of many surgeons and radiotherapists to take part in studies which involve additional, unrewarded effort. Therefore before launching a new study it is important that the question posed should be uppermost in people's minds and that it can be answered with minimal effort on the part of busy clinicians working in a Health Service which is in the process of being starved of resources.

There are two major questions to which we need address ourselves in the next 10 years concerning the management of early breast cancer: (1) Will some form of adjuvant systemic therapy salvage more lives following conventional local treatment? (2) Is breast conservation a realistic alternative to mastectomy with an acceptable risk? It is the purpose of this new initiative to pose the first question in a way that is both statistically efficient and minimal in the demand it makes on the contributing clinicians, and on the patients themselves.

The Cancer Research Campaign trial concerning the local management of early breast cancer in a recent publication gave added support to the view that the outcome following local therapy is predetermined by the extent of dissemination at the time of diagnosis.[3] Unfortunately, at the present time it is impossible to quantify accurately the residual tumour burden in patients following mastectomy for apparently localised disease. Neither is there any real way of monitoring the behaviour of such micrometastases in response to adjuvant systemic therapy. It is therefore largely guesswork based on extrapolation from the behaviour of the advanced disease whether an increased cure rate might follow the administration of aggressive long-term combination chemotherapy, a short course of single-agent chemotherapy, or for that matter some form of endocrine manipulation. There are at present many groups in the world investigating aggressive systemic chemotherapy, expecting large returns at the expense of increased morbidity. If such an approach does in fact produce an increase of say 30-40% in 10-year survival, then of course it would be necessary to reorganise the oncology services in this country so that complex treatment would be available for all patients. In the meantime there is a need for other groups to investigate the so-called "soft option," such as endocrine therapy or short courses of single-agent cytotoxic therapy. Such an approach might indeed benefit a smaller proportion of cases but because of the ease of administration the results would be immediately acceptable to the generality of clinicians and available to all patients within the current structure of the National Health Service.

At present there are a handful of trials of adjuvant systemic therapy in early breast cancer which have demonstrated encouraging results either in the delay of recurrence or in an improvement in survival.[4–7] However, it is worth noting that the studies with the longest follow-up—namely, those originating from Oslo[4] and Toronto[5]—have demonstrated an unequivocal, albeit modest, improvement in survival as a result of the application of the "soft options." It is with these thoughts in mind that a new initiative has been taken in launching a randomised prospective trial to investigate the benefits of a short course of cyclophosphamide in the immediate postoperative period (similar to the Oslo trial), a long course of adjuvant antioestrogen therapy (similar in intent to the Toronto trial), and a combination of the two regimens, using a 2×2 factorial design. The administration of such simple systemic therapies should be within the skills of any surgeon or radiotherapist, the treatment should be very acceptable to the patient, and one might anticipate modest benefits in survival at ten years of the order of 10-20%. When it is considered how many women die each year of carcinoma of the breast, it could be anticipated that such an approach might lead to the salvage of over 1000 women's lives each year at very small cost. Unfortunately, in attempting to demonstrate these modest improvements one is immediately faced with statistical difficulties. In order to detect such a difference (should it in fact exist) at an acceptable level of significance, in excess of 1000 patients need to be recruited within a relatively short time.[8] This is not an unreasonably ambitious target as the Cancer Research Campaign trial was able to recruit in excess of 2500 patients. The headquarters staff who co-ordinated the original study are responsible for launching this new initiatiye, and in addition the Cancer Research Campaign has awarded a further generous grant so that the new trial can be run with business-like efficiency.

To conclude, therefore, it is not unrealistic to launch another major study in the United Kingdom, where there are "untapped resources" of nearly 20 000 new cases of breast cancer a year, and where there exists organisational expertise to handle the large volume of data that will be generated. If any surgeons or radiotherapists reading this letter are interested to learn more about the study or are willing to participate, protocols are available on application to the trials centre, or alternatively a visit by one of the trials co-ordinators can be arranged. An open meeting to launch the study formally will take place at the Cancer Research Campaign headquarters at 2 Carlton House Terrace, London SW1, on Tuesday, 28 October, at 2.30 pm.

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Geographical analysis of cardiovascular mortality: a cautionary note

SIR,—An article by Dr S J Pocock and others (24 May, p 1243) concerned with the study of regional variations in cardiovascular mortality demonstrates many of the problems that are commonly encountered in the geographical analysis of medical data. The following comments have an important bearing on any considered interpretation of the results.

(1) The choice of "towns" as observational units largely predetermines the relationships that are identified.[1 2] In what way are "towns," which are arbitrary definitions for administrative purposes and possessed of vastly different degrees of internal hetereogeneity in terms of the variables studied, meaningful entities for a study of cardiovascular mortality? For purposes of geographical analysis it is not sensible to use any set of areal units merely because data exist for them and be totally oblivious of the effects that this choice has on the results.

(2) It should be clearly understood that statistical analysis can never *explain* geographical variations; it can at best only *describe* some of the observed spatial data patterns, patterns which depend on the areal units used in the analysis. Causal inferences

are exceptionally difficult to make from geographical data.[3]

(3) Furthermore, the analysis of data for towns need not provide any useful guide to the results obtained by analysing the same data at the individual level. The aggregation of data for individuals into towns creates all manner of spurious geographical associations, which statistical techniques are very adept at identifying.

(4) Statistical analysis of geographical data suffers from a number of problems that have been completely ignored. In this respect the study repeats many of the mistakes that characterised geographical studies in the 1960s.

(5) Excessive emphasis is placed on testing the parameters of linear regression models for significance. Unless the data were collected by simple random sampling, which they were not, significance tests are meaningless. Statements such as "... a highly significant regression coefficient ($p<0{\cdot}001$)" are totally misleading.

(6) To make matters worse, it is recognised that the residuals are spatially autocorrelated: "Some towns ... had a higher cardiovascular mortality than the model predicted ... such towns tended to occur in geographic clusters." Yet the serious consequence this has for regression models is overlooked.[4]

(7) Many other aspects of the statistical analysis are unsatisfactory. For example, no indication of the form of the data frequency distributions is given; it is admitted that the relationship is really non-linear, so there is specification error; the choice of variables appears indiscriminate, as is also the global logarithmic transformation; and there may well be multicollinearity problems owing to the use of highly intercorrelated variables in regression models.

(8) No attempt is made to account for the surprisingly high correlations between cardiovascular disease and both latitude and longitude ($r=+0{\cdot}74$, $+0{\cdot}68$). If correlations of this magnitude occur for what appear to be nonsense relationships, what hope is there for finding a real water quality effect ($r=-0{\cdot}67$)?

(9) Finally, the models used are poor from a theoretical point of view. They assume that people who died in 1969-73 have experienced all their lives a uniform water quality of the type that occurred in the town where they happened to be living when death occurred.

Few would deny that geographical mapping of medical data can reveal all kinds of interesting distributional patterns. However, it is essential that the analyses of these patterns are carried out with an appropriate degree of rigour. Regrettably it appears that medical researchers often lack sufficient experience of, or have no expertise in, geographical analysis. The availability of geographical data and statistical packages seems to have encouraged all manner of madness.

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**We sent this letter to the authors, and Dr Pocock and Professor Shaper reply below. —ED, *BMJ*.

SIR,—Thank you for the opportunity of replying to the comments on our British regional heart study made by the Newcastle geographers.

We studied towns because they are eminently sensible units for studying geographical variations in cardiovascular mortality. Larger units such as the English regions are few in number and too heterogeneous, while smaller units such as wards have populations too small to provide accurate estimation of mortality rates. Towns tend to be fairly homogenous in climate and water quality but less so in socioeconomic conditions. However, our field work experience in 25 towns in England, Wales, and Scotland leaves us convinced that quantifying socioeconomic conditions on a town basis is a valuable contribution to our study. Towns may not be theoretically perfect units but it seems reasonable to deal with real problems in a practical framework. We were most concerned about the problem of internal heterogeneity of towns from the point of view of their water supplies and this was carefully investigated. The conclusions of the study are robust to the exclusion of those towns whose water supplies are more variable. Migration between towns is not on a large enough scale to bias the study, and water quality in most towns has been stable over many decades. We have no information from which to draw conclusions regarding the duration of exposure required to produce a cardiovascular effect.

We *describe* geographical associations in order to attempt to *explain* which socioeconomic and environmental factors are related to cardiovascular mortality. Of course we realise that causal inferences are not readily sustained by this type of data, which is precisely why we have taken so much care to determine whether the observed relationship between water hardness and cardiovascular mortality could be attributed to other factors.

We are conscious of the differences between group-based and individual-based data. However, disagreement between these two types of data does not necessarily invalidate the findings within either type of data. But agreement may occur and our study shows an association between socioeconomic factors and cardiovascular mortality which is also seen in many individual-based studies. Phases 2 and 3 of the regional heart study are evidence of our concern to produce more specific cross-sectional and prospective data on cardiovascular risk factors by using individuals rather than towns.

Statistical tests of significance *are* useful in assessing whether the relationship between two variables can be attributed to chance. Observational studies like ours, which by their nature preclude random sampling, obviously require caution in their interpretation. Statements such as "... highly significant regression coefficient ($p<0{\cdot}001$)" should not be misleading to those who understand the statistical method and its function as an objective guideline to rational thought.

We have spent considerable time investigating the impact of spatial autocorrelation on our regression models. This required the development of new statistical theory as models previously used in this area appeared implausible. We have now completed analysis using these new models and, as anticipated, the results and conclusions in our paper are not altered to any important degree. These new methods and results will be submitted to a more technical journal in the near future.

We have shown that geographical variations in cardiovascular mortality (including correlations with latitude and longitude) can be related to water hardness, climate, and socioeconomic factors. No single observational study can establish causal relationships but the association between water hardness and cardiovascular mortality has been reported in many different countries. On the available evidence, we consider it reasonable to conclude that some factor in drinking water closely related to hardness is directly affecting cardiovascular mortality.

Dr Openshaw and Mr Charlton are clearly disturbed by our report on the regional heart study, as evidenced by their somewhat intemperate comments. We have spent considerable time in discussion over many years with geographers, geologists, geochemists, and others concerned with environmental studies and we will continue to do so. We welcome comment on the regional heart study but would suggest that in future it be phrased in the usual scientific language of rational discussion.

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Cholesterol and mortality rates

SIR,—Mr A R P Walker (31 May, p 1320) correctly warns that only total mortality can be used as an end point to test the value of community-based intervention. However, both he and Dr Robert Beaglehole and others (2 February, p 285) fail to see the significance in the observed "inverse relation between serum cholesterol level and overall mortality" in the New Zealand Maoris. The relation between serum cholesterol and mortality is a U-shaped curve when a human population has a life style which allows a wider range of cholesterol levels. One prospective study of United States adults published over a decade ago showed the lowest overall mortality at a cholesterol level of 5·83-6·45 mmol/l (225-249 mg/100 ml), with higher mortality above and below.[1] It appears that the Maoris represent only the lower limb of this U-shaped curve. Obviously, a change in their habits which would allow a wider range of values would show a similar U-shaped curve. A similar U-shaped mortality curve can be seen with a wide range of body weights.[2] Extremes of leanness and obesity are more hazardous than an average weight.

We have observed that cardiac patients in marathon training can easily move their body weights and cholesterol levels down to extremely low values in a short time, and we have expressed concern over the higher risk these low values may represent.[3] The necropsy findings differ at these extremes of body weight and cholesterol. Complicated atherosclerosis is more common at the upper end of the scale of obesity and elevated serum lipids; however, rhythm deaths are more common at the lower extremes of underweight and low lipids. Since dietary restrictions were common among the cases of rhythm death we have seen, we have been using the term "nutritional arrhythmias" for these cases. We caution that intervention efforts directed against one disease process should not increase overall mortality by introducing a new risk.

Necropsy studies offer a more precise method of classifying deaths. In the future we should try to separate the complicated atherosclerotic deaths (thrombosis, infarction, etc) from the rhythm deaths, which show no acute lesions.

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Heart disease in different ethnic groups

SIR,—In your leading article about heart disease in different ethnic groups (16 August, p 469) you raise the question "What do the ethnic differences mean?" In reply you refer to "a large genetic component" but add that