this gives a clue about why some serotypes are more pathogenic than others.

The sporadic outbreaks of disease are described in the article as something of a mystery. However, there are three possible sources. Firstly, air travel allows the rapid transport of the natives of an endemic area, who may bring with them a mild eye or pharyngeal infection, and of Westerners who become infected in an endemic area and return before the onset of symptoms (incubation lasts up to 14 days). Secondly, infection may persist as chronic conjunctivitis.[6] Thirdly, an extra-ocular site could be the source of virus causing eye disease. Group II adenoviruses have been isolated from the genital tract of asymptomatic women.[1 7] These adenoviruses could join the TRIC (trachoma inclusion conjunctivitis) agent as a cause of an oculogenital syndrome. In the case of the TRIC agent very occasional eye infection appears to be the result of a common genitourinary infection,[8] whereas occasional infection of the genitourinary tract by adenovirus could be the source of outbreaks of eye disease.

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Squash ball to eye ball: the likelihood of squash players incurring an eye injury

SIR,—The article on squash eye ball injuries (3 October, p 893) emphasised the dangers to the eye in this sport. At our college two students have sustained intraocular haemorrhage as a result of squash ball injury but fortunately both recovered full eyesight.

With the aid of a skull it is easily seen how neatly the British squash ball fits into the eye orbit. I understand that the American squash ball has a greater diameter and the adoption of this ball in Britain would minimise eye injuries. Some years ago I wrote to the medical adviser to the Squash Rackets Association on this subject and he promised to pursue the matter. In view of the evidence now presented this proposal deserves further consideration.

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Breast transillumination using the sinus diaphanograph

SIR,—I was most interested to read of the Nottingham experience of the use of diaphanoscopy in the diagnosis of breast disease (8 August, p 411) and Dr A J Hedley's subsequent comments (29 August, p 618). There appears to be some confusion surrounding the circumstances of the women to whom the data relate. Mr H W Holliday and Professor R W Blamey clearly state that the women were patients aged 16-80 years. They have presumably presented for breast assessment and further investigation of symptoms or suspected clinical abnormalities or both, either via their practitioners or as a result of the extensive health education programme being undertaken in Nottingham as part of the British trials for the early detection of breast cancer. The data do not refer to the use of the technique in the screening context as Dr Hedley assumes.

Final outcome in 32 women submitted to diaphanoscopy

Result of diaphanoscopy	Cancer	Benign biopsy specimen	Cyst	No biopsy	Total
Cancer	2	2	3		7
Cyst	—	—	4		4
No lesion	8	3	2	8	21
Total	10		22		32

Evaluation of a potential screening technique must take into account not only its ability to demonstrate an abnormality when symptoms or signs are clearly present but also its efficiency in detecting an abnormality in symptomless women. A very low false-negative rate is mandatory; a low false-positive rate, though desirable, is less essential provided that further investigation can be carried out quickly. Any potential screening technique must be capable of detecting the majority of breast cancers when they are not larger than 2 cm in diameter, at which stage the majority will be node free, without metastases, and of excellent prognosis. No indication of the staging of the cancers demonstrated by diaphanography is given, but a technique which shows the clinically obvious lesion does not necessarily demonstrate the occult lesion.

The South-west Surrey Health District is one of the screening populations for the British trials, all women in the district aged 45-64 having been invited to be screened by clinical examination and single-view mammography, with an attendance rate of 69%, and a detection rate of 5·5 cancers per 1000 women screened (16 775 screened), of which 39% were 1 cm or less and 67% 2 cm or less. Prior to a consideration of the place of diaphanoscopy at the screening clinic a feasibility study was undertaken at the review clinic to which screened women with suspected abnormalities are recalled for further investigation or assessment. Diaphanoscopy using the sinus diaphanograph has been carried out on 32 such women; photography, while providing a record, did not add to the information from diaphanoscopy. No attempt was made to differentiate between fibroadenomas and cancers; all dark shadows were considered to be possible malignancies.

One of the diaphanoscopy-positive cancers was an inflammatory lesion of over 5 cm in a woman who referred herself to the screening clinic; the remainder were symptomless women attending for routine screening. The standard indices of efficiency were: true positive 20% (2/10), true negative 77% (17/22), cysts containing dark fluid being the commonest cause of a positive diaphanoscopic result. The predictive powers of the test were: positive = 30% (2/7) and negative = 60% (17/25). All cancers were detected by mammography which, when combined with clinical examination, in this project has an efficiency at one year of 91%.[1] The clinical findings and pathological size of the cancers are of interest. Of the nine screening cancers, four gave a palpable abnormality, a mass under 2 cm in three and a 4-cm area of thickening in another; two had no palpable abnormality but a small skin dimple was detected on contraction of the pectoral muscles; and in the other three no clinical abnormality was found. One woman had a purely intraduct carcinoma (clinical skin dimple plus microcalcification on her mammogram); the other eight had invasive lesions 2 cm or less in diameter, five of them being 1 cm or less.

Our results fully support Mr Holliday and Professor Blamey in their view that diaphanoscopy has no routine place to play in the investigation of women with breast abnormalities, being less reliable than palpation as an indication for biopsy. Since the technique gave no indication of abnormality in eight of the nine symptomless women with early breast cancer, it would seem to have no place in screening for the disease in the age group 45 years and over, being less efficient than a detailed clinical examination. It is particularly unfortunate that the frequently false-negative result in early cancers is combined with the high degree of reassurance that the carrying out of the test gives to the woman, who can look down and see her breast clearly transilluminated.

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[1] Thomas BA, Price JL, Boulter PS. *Clinical Oncology* (in press).

Cardiovascular risk factors in middle-aged men in 24 towns

SIR,—A recent paper by Professor A G Shaper and others (18 July, p 179) contains a number of fundamental methodological weaknesses that render the results virtually useless.

We criticised an earlier paper on cardiovascular mortality by these authors for its geographical indiscretions (13 September 1980, p 742). The present research is geographically naive. It is frankly doubtful whether much can be discovered about geographical variations in cardiovascular disease by studying a small non-random sample of non-comparable entities ("towns"). We think it unlikely that towns can be found that are representative of standard regions and we are concerned that the mixture of data for different units and different dates will result in all manner of spurious relationships. The authors assume that medical data for a random sample of males belonging to a non-randomly selected practice in a town can be mixed with other data for that town, and further that survey data relating to a possibly non-representative sample of males aged 40-59 (in 1978) can be meaningfully related to standardised mortality ratios for all males aged 35-64 (in 1969-73) and census data for some males (in 1971).

The gross misuse of statistical methods is disturbing—for example, significance tests without a null hypothesis and multiple regression models with mixed measurement scales. There are plainly insufficient data to do the geographical analysis properly, while the value of the medical survey data has been reduced by the application of non-representative sampling procedures and inappropriate methods of analysis. It is possible that something useful could still be squeezed out of the data by categorical data analysis or AID,[1] but the problems associated with the sampling design are insoluble.

We do not deny that exploratory statistical and geographical analysis techniques can be usefully applied to medical data. However, it is essential that the research has realistic objectives and that its weaknesses and limita-

tions are both understood by the researchers and communicated to others. In our view the present paper fails to meet these criteria.

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[1] Sonquist JA, Baker EC, Morgan JA. *Searching for structure*. University of Michigan. ISR, 1974.

SIR,—The interesting research of Professor A G Shaper and others (18 July, p 179) assessing cardiovascular risk factors in middle-aged men attempted to define the contribution of alcohol intake on the basis of the answers to three questions. They indicate that measurements on the population sampled included a full haematological study. It would be interesting to know what the correlation was between mean cell volumes and defined heavy drinking. Any such correlation would be further evidence for the usefulness of estimations of mean cell volumes,[1] and could point to their use as population screening instruments.

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

SIR,—While we acknowledge the sincerity of the above comments by Dr Openshaw and Mr Charlton we would question their practicality. Naturally, we appreciate the desirability of random sampling but in the real world we must make sensible and cautious inferences based on the most reliable data we can assemble. We see no basis for their statements concerning the inappropriateness of the statistical methods.

In reply to their comments on our earlier paper we explained why we used certain towns as units rather than attempting to select towns randomly or select subjects randomly without reference to towns (13 September 1980, p 743). The caution expressed in our recent paper regarding the town-based data is carefully stated and we specifically asked that "the approach must therefore be regarded as useful but preliminary." The Regional Heart Study has very realistic objectives and its limitations are clearly understood by us and have been communicated in our publications.

With regard to Squadron Leader Fowlie's question, we have examined the relationship between alcohol consumption, biochemistry, and haematology in the British Regional Heart Study; and, as he suggests, it adds considerably to the weight of evidence regarding indications of heavy drinking. We are continuing to explore these data and will in due course draw attention to several variables other than the mean cell volume which are of considerable importance.

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Mistletoe hepatitis

SIR,—A recent case history was documented in this journal by Drs John Harvey and D G Colin-Jones (17 January, p 186) in which a herbal preparation containing motherwort, kelp, wild lettuce, skullcap, and mistletoe was ingested by a 49-year old woman who presented with symptoms of hepatitis. That the *preparation* was indeed the aetiological agent could be demonstrated by a "challenge test."

We are in agreement with statements in that paper that the voluminous literature available on the ingredients of the preparation lack data suggesting that they would produce hepatotoxic effects in animals or humans. Further, it can be stated that even though some of these herbs contain substances that show marked biological effects when measured in specific bioassay procedures—such as β-phenethylamines in "mistletoe"—none of these compounds have been reported to induce adverse effects on the liver. Indeed, most are inactive when given orally.

What is suggested by the report is that the preparation taken by the 49-year-old woman contained something other than the stated ingredients, and that one or more of these may have been responsible for the toxic symptoms seen in the subject. This would not be an uncommon finding. A number of recent cases of toxicity following the ingestion of Chinese herbal preparations intended for the alleviation of arthritic symptoms have been found to contain phenylbutazone, indomethacin, and other ingredients, not stated on the label, which were the toxic ingredients.

Thus the article by Drs Harvey and Colin-Jones documents for the scientific literature a presumption that "mistletoe" is hepatotoxic. Since no data were presented in support of this, we feel that a clarification of the paper is warranted. The most important implication of the report is that drug and food regulatory agencies should be alerted to the fact that the consumer currently has little protection with regard to being assured that the label of a herbal product reflects the contents of the package.

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Hepatitis and ketoconazole therapy

SIR,—Drs J S Heiberg and Else Svejgaard have described a case of signs and symptoms of hepatitis during ketoconazole therapy (26 September, p 825). A multicentre study of 2500 patients with various fungal infections has shown ketoconazole to be both effective and without significant adverse effects.[1] The most frequently reported side effect was nausea, seen in about 3% of patients. In addition, biochemical and haematological monitoring revealed no laboratory abnormalities attributable to the drug.[1] We now have on file the results of liver function tests in 988 patients treated with ketoconazole (200-400 mg daily) for periods of up to 18 months. Eleven per cent of patients have shown transient abnormalities in liver function test results—1·2% before treatment only, 0·8% during treatment only, and 9% both before and during treatment. None was accompanied by any clinical evidence of hepatitis.

As an example, a 5-year-old girl with chronic mucocutaneous candidiasis had a history of hepatitis in infancy of unknown aetiology. This patient also had elevated serum transaminase levels prior to ketoconazole therapy and during two separate courses of treatment she showed further rises in her serum transaminase levels without other stigmata of liver disease. During a subsequent course of treatment with ketoconazole (which is continuing) her liver enzymes have remained within normal limits.

Apart from the case described by Drs Heiberg and Svejgaard the only other published account of symptomatic liver dysfunction possibly caused by ketoconazole is that of Petersen *et al*,[2] who also reported on four patients with transiently elevated serum transaminase levels. We are aware of three other patients to date who exhibited abnormal serum transaminase levels accompanied by signs and symptoms of hepatitis during ketoconazole therapy. In each case the patient's condition improved and liver function tests returned to normal on withdrawal of the drug. Of these patients, one had a past history of idiosyncratic reactions to other drugs, including griseofulvin, co-trimoxazole, and tetracyclines; and another had been admitted to hospital previously with infectious hepatitis. Other potential causes of the disorders observed were excluded so far as possible. Nevertheless, the possibility that some of these cases were due to undiagnosed non-A, non-B viral hepatitis[3] cannot be excluded. A detailed analysis of liver function test results in patients treated with ketoconazole is being prepared for publication. The data are available on request.

Ketoconazole is now available in a number of countries, including the United States and the United Kingdom; and we estimate that it has been given to 50 000 patients. If the cases of hepatitis reported by Drs Heiberg and Svejgaard and ourselves are drug related, and some of them may be, the incidence must be very low. There is, however, no evidence at present that transient changes in liver enzymes without jaundice or hepatitis necessarily signal the need for permanent withdrawal of ketoconazole therapy.

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SIR,—I read with interest the article about toxic hepatitis during ketoconazole treatment (26 September, p 825).

A 62-year-old patient of mine started treatment with ketoconazole in May 1981. Two months later he complained of malaise, myalgia, and pruritis and said that he had pale stools and dark urine; he had not noticed that he had been jaundiced. Physical examination was unremarkable but investigations revealed that his bilirubin was 48 μmol/l (2·8 mg/100 ml), alkaline phosphatase 396 IU/l, aspartate transaminase 228 IU/l, alanine transaminase 697 IU/l; the urine contained no bilirubin or excess urobilinogen. He continued to take ketoconazole and a week later his bilirubin had fallen to normal while his alanine transaminase had risen to 890 IU/l and aspartate transaminase to 411 IU/l. His symptoms all improved and his biochemistry returned to normal.