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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[1] Whitehead TP, Clark CA, Whitfield AGW. *Lancet* 1978;i:978-81.

**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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[1] Levine HB, ed. *Ketoconazole in the management of fungal disease.* Balgowlah, NSW: Adis Press, 1981.
[2] Petersen EA, Alling DW, Kirkpatrick CH. *Ann Intern Med* 1980;**93**:791-5.
[3] Farrow LJ, Steward JS, Stern H, Clifford RE, Smith HG, Zuckerman AJ. *Lancet* 1981;i:982-4.

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.