reabsorbed. It soon became clear, however, that intravenous administration of the drug did not induce a maximal urinary concentration. We therefore proceeded to try 4 µg given as an intramuscular injection. This gives satisfactory results when compared with the intranasal desmopressin test. The mean difference between the two tests performed on 24 patients is 4 ± 20 (SEM) mmol(mOsm)/kg, the results ranging from 500 to 1100 mmol/kg (regression line: $y = 0.86x + 90$, where y = concentration at intramuscular test and x = concentration at intranasal test; $r = 0.80$). We have adopted the procedure of using intranasal administration routinely, but if technical difficulties arise we check the test with an intramuscular administration.

Looking into the data, it is also obvious that urine samples taken immediately before the desmopressin administration—that is, urine produced during the last hour of thirst before the test—often have attained maximal concentration. Urine produced after overnight thirst could therefore be used in a screening test. The use of the desmopressin test has also been reported by Monson and Richards¹ and by Curtis and Donovan.²

K DELIN
M AURELL
H BENDZ

Department of Medicine,
University of Göteborg, Sweden

¹ Monson, J P, and Richards, P, *British Medical Journal*, 1978, 1, 24.

² Curtis, J R, and Donovan, B A, *British Medical Journal*, 1979, 1, 304.

Klebsiella, spondylitis, and uveitis

SIR,—We were interested in the report by Dr Roland Ebringer and others (10 February, p 383). At a recent meeting of the Heberden Society we reported a prospective study of faecal *Klebsiella* carriage in 89 outpatients with ankylosing spondylitis (AS) and in 82 patients with rheumatoid arthritis (RA) attending the rheumatology department of Westminster Hospital. Using ampicillin peptone water and a carbenicillin inositol indicator agar, *Klebsiella* spp was isolated from 24 patients with AS (27%) and 26 with RA (32%). In a three-month period (early in 1978), we found no correlation between the activity of joint disease and *Klebsiella* carriage at initial assessment. This study is being reported in full.¹

Since 1976, we have studied the faecal flora of patients with acute anterior uveitis (AAU) diagnosed at Moorfields Hospital and referred to Westminster Hospital for rheumatological assessment. Fifty-two patients with AAU were seen within one month of the start of their attack of AAU (mean 15 days). Twenty-nine (18 men) had no rheumatic symptoms and no associated disorder; 19 (17 men) had the New York criteria for AS. The remaining four patients were excluded because they had Reiter's disease, RA, or spondylitis associated with ulcerative colitis or Crohn's disease. Two patients with no rheumatic disease and one with AS had second episodes of AAU in this period; the second episodes have been excluded from our results. Without using ampicillin peptone water enrichment for *Klebsiella*, we isolated *Klebsiella* or *Enterobacter aerogenes* from 7/29 (24%) of patients with AAU alone and 4/19 (21%) of those with both AAU and AS. *Klebsiella* carriage was no commoner in females. We cannot, therefore, support the

observation of Ebringer *et al* that *Klebsiella* was carried in the faeces of 13/17 (76%) of cases of AAU associated with AS. Although we have no matched unassociated patients examined over the same period, in our 1978 study we isolated *Klebsiella* using carbenicillin agar alone in 21/114 (19%) of AS patients and in 22/89 (24%) of RA patients. We have therefore found no difference in *Klebsiella* isolation rates from the faeces of individual patients with AS alone, AS and AAU, AAU alone, and RA.

We have also sought any organism which cross-reacts with *Salmonella*, *Shigella flexneri* or arthritogenic *Yersinia enterocolitica* strains, and which either appears in faeces or is detectable by seroconversion on paired sera in relation to attacks of AAU. Paired sera (taken one month apart) from 22 patients with AAU were examined for agglutinating antibodies to formalinised or boiled formalinised suspensions of 83 strains of aerobic Gram-negative rods isolated from initial faeces cultures of each individual. In 17 of these patients we have further examined the paired sera for antibodies against 74 coliform strains isolated from a second faecal sample obtained one month later. We have found no change in agglutinin titre against any of these Gram-negative rods, including strains of *Klebsiella* and *Enterobacter aerogenes*. We have, however, previously demonstrated that a wide variety of biotypes, serotypes, and bacteriophage types of *Klebsiella* are recovered from AS patients.¹ Thus we were unable to find evidence of serological changes in individual AAU patients representing reactions to their normal Gram-negative bacterial flora. By analogy with the HLA-B27-associated acute arthritis (after intestinal infection with *Salmonella*, *Campylobacter*, and *Yersinia enterocolitica*), such seroconversion might be expected if the normal Gram-negative bacterial flora were a provocative factor in acute anterior uveitis. We have also been unable to implicate—by serology or culture—arthritogenic *Yersinia enterocolitica* serotypes 3 or 9 in any of our patients with AAU.

R E WARREN

Addenbrooke's Hospital,
Cambridge

DERRICK BREWERTON

Westminster Hospital,
London SW1

¹ Warren, R E, and Brewerton, D A, *Annals of the Rheumatic Diseases*, in press.

Male sexual dysfunction and cimetidine

SIR,—In a recent report (10 March, p 659) Dr N R Peden and others claim that a prima facie case has been made against cimetidine as a cause of male impotence. The experience of the following patient may partly redress the balance.

A 57-year-old man with a 20-year history of dyspepsia presented with a severe relapse of symptoms. Endoscopy confirmed the presence of a duodenal ulcer, and cimetidine was started in a dose of 1600 mg/day for six months. His ulcer symptoms disappeared within two weeks of starting treatment and endoscopy at three and six months confirmed ulcer healing. Four weeks after starting cimetidine he requested referral for vasectomy. Further inquiry established a sustained increase in libido accompanying the improvement in ulcer symptoms. This unexpected

bonus from his cimetidine treatment was confirmed by his wife.

Most of the reported adverse effects of cimetidine have been in the form of anecdotal reports, and the recent report from Dundee is no exception. These are to be expected after the introduction of any new drug¹ and occasionally may give a useful indication of serious toxicity. Nevertheless, undue importance should not be attached to poorly validated reports.

JOHN WEBSTER

Department of Clinical Pharmacology,
Royal Postgraduate Medical School,
Hammersmith Hospital,
London W12 0HS

¹ Laurence, D R, *Clinical Pharmacology*, p 411. Edinburgh, Churchill Livingstone, 1973.

Fats and atheroma

SIR,—Dr John Vane (17 February, p 484) emphasises views put forward many years ago^{1,2} concerning the putative importance of dietary essential fatty acids (EFAs) in the pathogenesis of ischaemic heart disease, and his letter stimulates me to speculate on the possible relevance of these ideas to the extraordinarily high mortality in Scotland. Sinclair¹ suggested that atherosclerosis might be due to a chronic deficiency of arachidonic acid when diets are high in saturated fat or unnatural fats and fairly low in EFAs. Are such diets encountered? he asked. We have some evidence that in Scotland they are:

(1) The linoleic acid (C18:2w6) content of plasma cholesterol esters, plasma triglycerides, and adipose tissue in 40-year-old healthy Edinburgh men is significantly lower than that of comparable 40-year-old healthy Stockholm men.³ (2) There is also a lower arachidonic acid (C20:4w6) content of adipose tissue in Edinburgh men. (3) The polyunsaturated:saturated ratio in adipose tissue of Edinburgh men was 0.30 compared with 0.44 in Stockholm men ($P < 0.001$). (4) The fatty acid content of a seven-day weighed dietary survey is still being analysed, but the correlation between dietary linoleic acid and adipose tissue linoleic acid in both cities is in the region of 0.8. (5) Adipose tissue fatty acid composition reflects long-standing dietary fatty acid consumption, because of a very slow turnover rate, and is not influenced by day-to-day or even week-to-week dietary changes. Thus the differences between the Edinburgh and Stockholm populations appear to establish a real difference in EFA consumption.

A significantly lower proportion of linoleic acid has previously been reported in the adipose tissue of two populations dying suddenly. It was 6% lower in Japanese dying in Tokyo than in Americans dying in Cleveland, and the latter showed a higher incidence of myocardial infarction or coronary occlusion as the cause of death.⁴

Most of the work suggesting a balance⁵ between prostacyclin and thromboxane A_2 in relation to platelet aggregation is based on the effects of the addition of precursors of prostaglandins, such as arachidonic acid. An interesting question is whether a longstanding deficiency of certain EFA precursors for prostacyclin, other prostaglandins, and thromboxanes might lead to a low-grade thrombotic tendency. Recent evidence indicates not only that arachidonic acid stimulates the formation of a prostacyclin-like material from human endothelial cells but also that it results in less inhibition of platelet aggregation in the presence of long-chain saturated fatty acids.⁶

The bearing of this on mortality from ischaemic heart disease in Scotland might be that there is a greater thrombotic element to its clinical presentation than in communities where the EFA precursors of prostaglandins are more "in balance" with the saturated fat composition of the diet. No excess in

extent or degree of coronary atheroma was found at necropsy in Glasgow men compared with London men,⁷ but mortality from ischaemic heart disease is much greater in Scotland, particularly around Glasgow, than in the south of England.⁸ Preliminary observations indicate that platelet aggregation to thrombin, collagen, and arachidonic acid is greater in farmers in the south-west of Scotland, where the mortality is high, than in farmers in the central east of Scotland, where the mortality is lower.⁹ Furthermore, the highest mortality from stroke in the UK is also in Scotland and particularly in the central-west and north-west regions.⁸

More data are needed to confirm or refute the longstanding views of an important association between a deficiency of EFAs and ischaemic heart disease. This may be mediated through prostaglandin-related thrombogenesis rather than the development of coronary atheroma. We now need to collect evidence to determine whether the addition of certain EFAs to the diet reduces indices of hypercoagulability in man. If so, such specific dietary supplementation should be tested formally to see if it is preventive in communities with a very high vascular mortality.

M F OLIVER

Department of Cardiology,
Royal Infirmary,
Edinburgh EM3 9YW

¹ Sinclair, H M, *Lancet*, 1956, **1**, 381.

² Bronte-Stewart, B, *British Medical Bulletin*, 1958, **14**, 243.

³ Logan, R L, *et al*, *Lancet*, 1978, **1**, 949.

⁴ Insull, W, *et al*, *Journal of Clinical Investigation*, 1969, **48**, 1313.

⁵ Moncada, S, and Vane, J R, *British Medical Bulletin*, 1978, **34**, 129.

⁶ Nordoy, A, *et al*, *European Journal of Clinical Investigation*, 1979, **9**, 5.

⁷ Crawford, T, and Crawford, M D, *Lancet*, 1967, **1**, 229.

⁸ Fulton, M, *et al*, *British Heart Journal*, 1978, **40**, 563.

⁹ Renaud, S, personal communication, 1979.

SIR,—Before we rest on our laurels, satisfied that the decline in death rate from ischaemic heart disease in the USA, paralleled by changes in diet, at last gives us "overwhelming evidence for a nutritional aetiology of ischaemic heart disease" (Dr J I Mann, 17 March, p 732), may I make a plea for a more careful temporal analysis of this association before we pronounce judgment upon it?

I would be just as pleased as anyone else if this association were in fact causal, and if we were at last making inroads into the prevalence of this disease. In order to confirm this, however, and to avoid the trap of seeing only what we want to believe, we must demonstrate not just a parallel change in diet but the fact that the dietary change preceded the change in mortality. As we are dealing with a long-term degenerative process, it is naive to expect an instantaneous response to the modification of one of the many known risk-factors. If the dietary changes are indeed responsible for the decline in mortality, we would surely expect them to antedate the decline.

There has been a considerably accelerated decline in the mortality rate from ischaemic heart disease in the USA since the late 1960s, but what is equally significant is that the rate reached a plateau during the 1950s. In other words, there was a definite deceleration at least a decade earlier. The alteration in causal factors contributing to this deceleration must therefore have occurred at least in the early 1950s, if not in the late 1940s. Does this coincide with the dietary changes? Perhaps the dietary influence is merely accelerating an

already declining rate. If so, what is the cause of the original decline?

What I would like to see is an age- and sex-specific analysis of ischaemic heart disease rates in the USA since the 1940s, with cohort as well as cross-sectional analyses. When it is established just exactly which sectors of the population are contributing to the decline, and when this is tied to evidence of dietary changes in those sectors, perhaps we may then be a little more certain about the role of nutritional factors in this very important natural experiment.

DAVID ST GEORGE

London E5 9EF

SIR,—Dr J I Mann (17 March, p 732) obviously has a touching confidence in the two trials of polyunsaturated fat (PUF) diets which made the flimsy cornerstones of the Royal College of Physicians-British Cardiac Society report. Mitchell disposes of the Finnish mental hospitals trial in the EEC report. Mann objects to secondary prevention trials because "the subjects are no longer young" but puts his faith in the Los Angeles Veterans trial on subjects aged from 55 to 88. Were they free of arterial disease?

Secondary prevention trials cannot be brushed off and ignored. If a valid causal factor in a long-lasting progressive disease is identified its reduction should logically retard further progression in identified patients and delay or reduce mortality. All published efforts to help by drug or dietary reduction of blood cholesterol have uniformly and convincingly failed. In addition to those quoted, a trial for eight years in Bavaria¹ by Stocksmeier failed to improve prospects (and support from the food industry was reduced). A trial in patients under 60 in the University of New South Wales² showed that those on PUF diets did much worse than those left on a free diet.

Primary prevention trials of cholesterol reduction by clofibrate have failed to produce convincing evidence of benefit. An interim report on a primary multifactorial dietetic (plus smoking and blood pressure control) trial in North Karelia³ has shown in the first three years an increased incidence of acute myocardial infarction from 14.9 to 18.4 per 1000 men and no change in incidence in the 30 to 64 age group. Even Dr Ruth M Kay (3 March, p 6283) admits that proof of benefit may be impossible. If we accept this why proceed with such massive propaganda which can benefit only commercial interests?

Since efforts at blood cholesterol reduction have failed interest is now shifting to high-density lipoprotein (HDL), alleged to be protective, and low-density lipoprotein (LDL), alleged to be damaging. The evidence quoted by Dr Kay that a PUF diet will favourably affect this ratio is equivocal.

Drs K G Taylor and D J Betteridge (17 February, p 485) believe that cholesterol feeding produces "atheroma," but experts like Benditt and Armstrong believe that the fatty lesion thus produced is a very poor model of the human disease. Impurities in cholesterol have vitiated many animal experiments.⁴ Purified cholesterol produces only xanthomatous lesions that never thrombose.⁵ Even in the rare homozygous form of familial hypercholesterolaemia the disease is quite different from the common form of coronary artery disease. It affects only the mouths of the coronary arteries, leaving the main vessels and their subepicardial branches unaffected. Dr Mann might consider this important difference in the cause of angina.

The Belgian report proved nothing, as the mortality in 1947 in North Belgium was already lower than in South Belgium before preference for margarine occurred. Furthermore comparisons are hardly acceptable between two different ethnic groups.

The Blumgart report⁶ on induced myxoedema is

criticised by Mann and Dr P B S Fowler (10 March, p 681). The method of cholesterol estimation at that time gave much lower values. The upper limit was taken as 230 mg (today >300 mg). All patients showed a rise in cholesterol, and five out of eight reached concentrations of 338 to 524, which were very gross. After many years of this induced hypercholesterolaemia there were no coronary occlusions. I give priority to Blumgart for this most meaningful result of a planned therapeutic experiment which does not require statistics to prove its validity.

We must not confuse correlations or risk factors with causes. The Framingham study showed that 82% of those with all four risk factors (cholesterol, smoking, blood pressure, and sedentary lives) were still alive after 10 years, so the predictive value of any one risk factor is very limited. Cigarette smoking indeed has the strongest correlation and demonstrations of damage to the vascular endothelium by cigarette smoke encourages recognition of this hazard.

Norum's poll of 214 doctors (only a limited number of whom were critical scientists) was answered by 85%. As 92% of those who answered were already following the diet the result was only an indication of wishful thinking.

I agree that death rates from coronary heart disease in different countries are difficult to compare. That France has been under-recording its deaths from this cause by more than half⁷ owing to different diagnostic habits is a salutary reminder of the fallibility of these figures. But a rise from the baseline may be meaningful in an individual population (for example, Sweden). It is certain that the high PUF diet of Israelis does not prevent a high incidence of the disease.

Dr J R Vane's approach (17 February, p 484) gives a rational twist to the story. Rather than concentrate on cholesterol reduction there are hopes that certain fatty acids may be precursors of anti-thrombotic substances, and this is to be pursued. It might even be relevant to plaque formation if Duguid's work⁸ is right. The real cause of coronary obstruction is thrombosis.

We need a fresh approach to the problem at scientific level and should avoid further public speculation and confusion by repeated propaganda through the media until we have clarified our own professional minds and shaken off what most critical doctors are likely to regard as an untenable hypothesis of causation.

J M McMICHAEL

London, NW11 7AA

¹ Stocksmeier, U, *Influences of Saturated and Polyunsaturated Fats on Blood Lipids and some Socio-medical Variables*. National Dairy Council, London, 1978.

² Woodhill, J M, *et al*, *Drugs, Lipid Metabolism and Atherosclerosis*. New York, Plenum, 1979.

³ Milmo, S, *Doctor*, 9 February, 1978.

⁴ Imai, H, *et al*, *Archives of Pathological Laboratory Medicine*, 1976, **100**, 565.

⁵ Duguid, J B, *The Dynamics of Atherosclerosis*. Aberdeen, Aberdeen University Press, 1976.

⁶ Blumgart, H L, Freedburg, A S, and Kurland, G S, *American Journal of Medicine*, 1953, **14**, 665.

⁷ Richard, J L, *et al*, *INSERM*, 1973, **21**, 11.

Return to work after coronary artery surgery for angina

SIR,—Drs P G F Nixon and N G Weinstock should not be astonished (27 January, p 265) at the successful results published by Mr J Wallwork and others (16 December, p 1680). Not only do these results accord remarkably with other transatlantic experience but also with results in England.

From the United States, Cannon¹ reports that 63% of 375 survivors of saphenous vein bypass grafting for angina were working post-operatively, while a further 16% were angina free but not working. Similarly, Rimm² reports that 83% of 893 men (mean age 52.3 years) returned to employment.

At the meeting of the Society of Thoracic