group than did the 2 high SAA patients on subcutaneous injections of their group. We explained in the Subjects and Methods section how infection and inflammation were excluded and discussed their physical examination, and determination of the acute-phase proteins, fibrinogen and haptoglobin. The question raised about syringe-aggregated insulin can be most simply answered by referring to the text and to reference 6 cited therein.

Both the references cited by Pickup et al as showing no evidence of amyloidosis in diabetic animals or in patients differ importantly from our study. By Koivisto et al differed in three significant ways, which are plainly addressed in the sixth paragraph of our Discussion. The experiments described by Mauer et al support, rather than contradict, our findings; the insulin used in these experiments was rendered non-aggregable by the addition of the detergent SDS.

Intravenous insulin administration has produced generalised amyloidosis in animals and that localised amyloid was found in the tissue of a patient at the site where insulin was delivered by pump. They conclude that insulin used in pumps may be modified and would be more aggregable. It would seem more logical to recommend that the use of insulin pumps in the USA be severely restricted until this and other hazards, potential and real, are further defined and until any benefits of pumping insulin are established.

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Most of Dr Deckert and Dr Lauritzen's comments reiterate statements made in our paper (eg, the fourth paragraph of our Discussion). The original data presented by Deckert and Lauritzen appear to confirm our observation of increased SAA concentration in patients receiving insulin. We found a mean level in SII patients, nearly six times that in normal subjects, and nearly twice that observed in subcutaneous injection patients. These observations are not surprising, since any insulin available commercially already have a significant particulate content (discussed in the first paragraph of our Introduction, and cited in reference 3).

The only point of disagreement appears to be on the relative levels of SAA in SII vs UCT patients. This discrepancy may be more apparent than real, however, since our data are expressed in arithmetic means while Deckert and Lauritzen use medians. It would be interesting to compare data from our two groups expressed in a similar fashion.

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Michael Brownlee

Sir,-Dr Brownlee and colleagues have demonstrated the excessive production of amyloid-A in diabetic patients using insulin pumps. They note that intravenous insulin administration has produced generalised amyloidosis in animals and that localised amyloid was found in the tissue of a patient at the site where insulin was delivered by pump. They conclude that insulin used in pumps may be modified and would be more aggregable. It would seem more logical to recommend that the use of insulin pumps in the USA be severely restricted until this and other hazards, potential and real, are further defined and until any benefits of pumping insulin are established.

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SIR,-I would like to answer the letters published in your March 3 (p 520) and March 17 (p 633) issues commenting on the Lipid Research Clinics Trial. I am mainly referring to Food, whose low-density lipoprotein cholesterol levels may in some individuals be an early symptom of atherogenesis3 and that "high LDL-cholesterol levels cannot be considered causal except in the sense that high levels appear to exacerbate a pre-existing condition in these individuals". Why then, if cholesterol is not causal, did treatment prevent coronary events in previously healthy subjects and to the extent predicted by the level and change in serum cholesterol? You might as well argue that cigarette smoking is an early symptom of lung cancer and insist that wearing a seat belt is an early manifestation of incipient brain damage.

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Dr Le Fanu has reservations about the cost-effectiveness of treatment with cholestyramine, which I share, but he also quotes some data from the trial on the effectiveness of diet which are misleading. The 14 100-man-years of cholestyramine treatment, involving 82 tonnes of cholestyramine, would cost £8 million at today's NHS prices. The 8 fatal coronary events prevented would, as Le Fanu calculates, cost about £1 million each. The equivalent figure for all definite coronary events would be £240 000. The cost of cholestyramine would have to change by several orders of magnitude to make it a best-buy, even if it were desirable on all other grounds. However, Le Fanu then suggests that dietary manipulation of the serum cholesterol was ineffective because the mean cholesterol fell from 279 to 277 mg/dl over 7 years. The figure of 279 mg/dl was achieved after introduction of the diet, and the mean cholesterol level in these men before this had been 292 mg/dl. Also, anyone whose cholesterol fell sharply with diet alone was eliminated before randomisation—ie, the men whose serum cholesterol fell from 292 to 279 mg/dl were the comparative non-responders to diet. The American population shows a modest increase in cholesterol levels with age so that a few more mg/dl of presumed benefit might be added for the expected rise over 7 years.

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1. Bondy PL, Felig P. Relation of diabetic control to development of vascular complican-


had no special diet been taken. However, the trial was not designed as a trial of diet in cholesterol lowering; there is plenty of evidence that cholesterol levels are culturally determined and can be changed by altering dietary norm. The problem in changing cholesterol is in getting individuals to behave radically differently in their diet from their peers. As an example of the effectiveness of dietary control, 54 volunteers in North Karelia in Finland were switched from their traditional atherogenic diet to a Southern European substitute and back again. Mean serum cholesterol levels fell from 263 mg/dl to 201 in men and from 239 mg/dl to 188 in women; a fall occurred in every individual.

Dr. Pinckney raises the question of cancer and cholesterylamine. In the trial there were 57 cancer cases in the placebo group (15 deaths) versus 57 cancer cases in the cholesterylamine group (and 16 deaths). Colon cancer is of some interest from other studies: there were 6 cases in both groups with no deaths in the placebo group and 2 in the cholesterylamine group. For all gastrointestinal cancers together there were 11 cases (1 death) in the placebo group and 21 cases (not 29) and 8 deaths in the cholesterylamine group. These figures are the basis for Pinckney's statement that there were "800% more deaths from cancer" in the cholesterylamine group. A rough estimate of the expected number of gastrointestinal cancers in 14 100 man-years in American men aged 45-54 would be 11 cancers (and 6 deaths). Since both groups were on a cholesteryl lowering diet, there does not seem to be good evidence from the trial that either the diet or the cholesterylamine is dangerous, although, of course, there is no completely untreated control group for comparison. If cancers at one site are to be singled out, why not others? One could equally argue that cholesterylamine reduced the frequency of lung cancer (10 to 6), skin cancer (from 10 to 3), and prostatic cancer (from 11 to 7).

Dr. Patel restates the barrage of conflicting advice given to general practitioners on this subject, typified by the editorials in *The Lancet* (Feb 11, p 317) and the *British Medical Journal,* the former seemingly written by a mass interventionist and the latter by a known advocate of high-risk intervention only. It is the old contrast between the lumpers and the splitters. The former strategy is more popular with epidemiologists; the latter is preferred by clinicians, who like to distinguish patients from others and find the idea of population-based control frightening. However, the high-risk salami strategy does pose the problem of where to make the cut. Even the BMJ's editorialist, while warning that the trial was a controlled trial of a drug used only in the top 5% of risk, seemed ready to extrapolate to the top 20% and to use dietary means first.

We believe that, even though the results of a primary intervention trial cannot be applied to secondary intervention, the findings of a secondary trial, if demonstrating an improvement in prognosis with cholesterol lowering, would logically be transferable to the primary situation. Therefore, the POSCH trial will not only give a conclusive answer for secondary intervention but also may well strengthen the implications made by the LRCP.

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**HUGH TUNSTALL-PEDOE**

**SIR,—The consensus, following Dr. Basil Rifkind's presentation of the results of Lipid Research Clinics Coronary Primary Prevention Trial to the 24th Annual Conference on Cardiovascular Disease Epidemiology of the American Heart Association here last month, was that there was clear evidence that reducing very high plasma concentrations of cholesterol and of low density lipoprotein lowered the incidence of coronary heart disease (CHD). An earlier cohort study of five-year CHD mortality (ICDS 390-358) in 5616 males examined in Paisley, Scotland, showed a higher absolute risk, relative risk ratio, risk difference, and population attributable mortality for 377 males under 50 years of age in the range 6-8 to 7-5 mmol/l compared with 2667 males with less than 6-7 mmol/l (p = 0-07), and with 165 males with baseline cholesterol levels greater than 7-5 mmol/l.**

**1. Oliver M. Serum cholesterol: the knave of hearts and the joker. Lancet 1981; ii: 909-10.**


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This observation is but one of many arising in the study of the various risk factors for CHD supporting the view that the reduction of multiple small risks distributed widely over a defined population has the potential of contributing much more to the reduction of mortality than the complete and effective treatment of the small number at very high risk in the same defined population.
A recent review of changes in risk factors over time in Renfrew, Scotland, of a cohort of 3000 males and females aged 45 to 64 years, examined in 1972 and 1977 in the same study, showed a rise in cholesterol in this interval in all age and sex groups. This finding contrasts with a decline in systolic and diastolic blood pressure and cigarettes consumed per day (the latter except for younger women). That this should occur while the trend in CHD mortality in Scotland continued upwards, and when cholesterol levels were even higher in the Scottish cohort than for those in each age and sex matched group of the Tecumseh, Michigan, USA, cohort, surely constitutes sufficient grounds for reviewing public and health professionals' policies regarding advice on the public on reducing dietary cholesterol.

Most clinicians and community medicine specialists will endorse Prof M. F. Oliver's caveat about not extrapolating too far from a study of treatment in a group judged to be at the highest risk from cholesterol to recommendations about changes in diet for the general population. However, grounds for caution are one thing, inanition in the present epidemiological situation is another altogether. It would seem timely to call for a campaign to alert the media and public to the need for dietary change. If that approach seems too inanition in the present epidemiological situation is another altogether. It would seem timely to call for a campaign to alert the public to the need for dietary change. If that approach seems too immoderate, then perhaps an immediate start might be made by bringing to the attention of the public health industries the needs of their customers. These industries should be reminded again of the responsibilities for at least a proportion of present high CHD mortality and morbidity through failure to do anything to reduce the cholesterol content and increase the polyunsaturated:saturated fat ratio of the Scottish diet.

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VICTOR M. HAWTHORNE

STREPTOCOCCUS FACAELIS: GROUP D OR GROUP G?

Sr,—We wish to report on the high incidence of Streptococcus faecalis strains which apparently possess the Lancefield group G, as well as the group D antigen. We first observed this cross-reaction in streptococcal grouping sera about six months ago but, in a current survey, 17 out of 36 strains (47%) isolated over a three week period reacted with both groups D and G antisera. The strains described have arisen from four separate hospitals in the Salford district, as well as from outpatient departments and general practice, making a common source seem highly unlikely. The cross-reactions can be demonstrated in two widely used commercial grouping kits ('Strepex', Wellcome Diagnostics; 'Pylococcus', Pharmacia Diagnostics) as well as by traditional Lancefield techniques.

Although most of the strains show equally strong reactions with both groups D and G antisera, several have demonstrated a significantly stronger reaction with group G. We feel that this could lead to a misidentification of these strains if Lancefield grouping is used to a misidentification of these strains if Lancefield grouping is used to a misidentification of these strains if Lancefield grouping is used.

Sr,—In the treatment of benign, familial, or essential tremor a beta-adrenoceptor antagonist is now the drug of first choice, and propranolol, a non-selective (beta-1 and beta-2) adrenoceptor antagonist, having effects on both the peripheral and central nervous systems, is the most effective. Comparative clinical trials suggest peripheral beta-2 adrenoceptor as the locus of the anti-tremor effect of its potential therapeutic efficacy. Its reluctance to be published elsewhere.

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B. R. BIRCH
M. G. L. KEANEY
L. A. GANGULI


TRAZODONE ASSOCIATED WITH PRIAPISM

Sr,—The new antidepressant drug trazodone ('Desyrel', Mead-Johnson; 'Molipaxin', Roussel) may have a significant side-effect. One of my patients (a physician) acquired priapism as a direct result of the use of trazodone. He required urological surgery and there may be permanent sequelae. I suggest that until this matter is better understood we avoid using trazodone in male patients (and, perhaps, all patients), because of the potential for serious complications, which seems to be greater than that of many of the more widely used and accepted antidepressants. On Nov 22, 1983, Dr Gordon McKinney, of Mead-Johnson Laboratories, told me that, as of March, 1982, there had been twenty official reports of priapism linked with trazodone.

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GERALD M. ARONOFF

BETA ADRENOCEPTOR ANTAGONISTS IN ESSENTIAL TREMOR

Sr,—In the treatment of benign, familial, or essential tremor a beta-adrenoceptor antagonist is now the drug of first choice, and propranolol, a non-selective (beta-1 and beta-2) adrenoceptor antagonist, having effects on both the peripheral and central nervous systems, is the most effective. Comparative clinical trials suggest peripheral beta-2 adrenoceptor as the locus of the anti-tremor effect of its potential therapeutic efficacy. Its reluctance to be published elsewhere.

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