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 there 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. The 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.

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 CSII patients nearly six times that in normal subjects, and nearly twice that observed in subcutaneous injection patients. These observations are not surprising, since any insulins 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 CSII *vs* UCT patients. This difference 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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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 might be modified to limit aggregation. 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.

Americans love gadgets. Predictably, therefore, the very governmental agencies in the United States that are so conservative in controlling the availability of new drugs tend to be quite the opposite when a new mechanical device appears on the scene. Insulin pumps, for example, are available to any physician in the USA who wants to equip his patient with the latest of more than a dozen models—if and only if that patient can meet the considerable expenditure necessary to secure a pump and can afford all the accoutrements necessary for its continuing use.

Tight blood sugar control is the holy grail of American diabetologists, despite the fact that more objective reviews of the evidence that tight control delays the ravages of microvascular disease have concluded that the verdict must be "not proved".[1,2] More to the point are the results of short-term studies of insulin pumps which show that they do not retard retinopathy or nephropathy[3-5] and even that retinopathy may be more likely to progress in patients on pumps than in patients treated conventionally.[6]

Although the Centers for Disease Control[7] have concluded that the incidence of death in patients using insulin pumps is not significantly increased (35 deaths out of 3500 users over a short period), there does seem to be a large number of patients who die with pumps in place—deaths which in some cases at least would be totally unexpected had they been on conventional therapy (bacterial endocarditis from an infected infusion site, for example). The greatest threat from pumping insulin is the same as that with other forms of tight control—namely, life-threatening hypoglycaemia.[8]

So Brownlee et al have demonstrated yet another potential hazard to be added to the long list of those associated with pumping insulin. Yet they circumvent the issue and conclude by revering the attainment of tight control. To the man whose only tool is a hammer, all problems are nails. At the very cornerstone of scientific medicine lies the dictum that, despite our fond wishes and hopes, we recommend for our patients only treatment proved to be safe and proved to be effective. All other therapies must be regarded as experimental. US clinicians should insist that the insulin pump be withdrawn from general use and studied intensively in a limited number of centres, as in the UK.

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CHOLESTEROL LOWERING AND THE RISK OF CORONARY HEART DISEASE

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.[1]

Dr Cottrell, from the British Nutrition Foundation, writes that "High plasma low-density lipoprotein cholesterol levels may in some individuals be an early symptom of atherogenesis" 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 or that not wearing a seat belt is an early manifestation of incipient brain damage.

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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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[2] and can be changed by altering the 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.[3] 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 cholestyramine. In the trial there were 57 cancer cases in the placebo group (and 15 deaths) versus 57 cancer cases in the cholestyramine 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 cholestyramine 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 cholestyramine group. These figures are the basis for Pinckney's statement that there were "800% more deaths from cancer" in the cholestyramine 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 cholesterol-lowering diet, there does not seem to be good evidence from the trial that either the diet or the cholestyramine 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 cholestyramine 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*,[4] 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. While correspondence columns tend to attract controversy, there is more agreement on the fundamentals of coronary heart disease prevention than may appear on the surface.[5]

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HUGH TUNSTALL-PEDOE

SIR,—On the whole, we agree with your assessment of the Lipid Research Clinics Program (LRCP) statistics. We would add, however, the following caveats.

(1) For the combined end-point of death definitely due to coronary heart disease and/or definite myocardial infarction, the results were significant ($p<0.05$ for a one-sided test) but the difference in event rates was only 1·6% (8·6% in the placebo group and 7% in the cholestyramine group).

(2) There was an excess of 12 deaths in the control group for definite or suspected CHD mortality; there was an excess of 11 non-CHD deaths in the treated group. The LRCP considered only the latter difference to be due to chance alone.

(3) In the design phase a 1% one-sided level of significance was used for sample size estimation, to allow sufficient power for extrapolation to the population as a whole. Yet, the trial data attained only a 5% one-sided level of significance.

Of even greater significance is the omission from the report of the LRCP, the National Heart, Lung, and Blood Institute (NHLBI) press conference on the findings, and from your Feb 11 editorial, of a clear distinction between the efficacy of primary intervention versus secondary. The LRCP was a primary intervention trial—ie, none of the participants had overt atherosclerotic cardiovascular disease on entry. Thus, any conclusions drawn from this trial are applicable only to primary intervention. Although Oliver has cast a pall over the merits of secondary intervention,[1] the jury is still out with respect to the validity of efforts to lower cholesterol late in the atherosclerotic process. The health care community will have to wait until about 1990 for a definitive answer for secondary intervention; that is the scheduled termination date for the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial.

The POSCH trial is an NHLBI-funded trial that completed randomisation in July, 1983, with 838 subjects, approximately evenly randomised to a standard dietary therapy control group and a partial ileal bypass treated group. Each patient had sustained a single myocardial infarction, was between the ages of 30 and 64, and was free of hypertension, diabetes, and obesity on entry. The qualifying cholesterol concentration for inclusion was 220 mg/dl, or 200–219 mg/dl with an LDL-cholesterol concentration greater than 140 mg/dl. These values are in the mean American range and not the rather high levels needed for selection into the LRCP trial (>265 mg/dl total cholesterol). Further, the lipid profile effects of the POSCH surgical intervention far exceed (essentially triple) those achieved in the LRCP. In POSCH, the extended total cholesterol reduction (test group minus controls) has been 25% (LRCP 8·5%), the LDL-cholesterol lowering 40% (LRCP 12·6%), the HDL-cholesterol elevation 8% (LRCP 1·6%), and the increase in the HDL/LDL ratio 80% (LRCP 16%).

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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SIR,—The consensus, following Dr Basil Rifkind's presentation of the results of Lipid Research Clinics Coronary Primary Prevention Trial[2,3] 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 (ICD8 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.[4] 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.[5]

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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 four 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,[6] surely constitutes sufficient grounds for reviewing public and health professional policies regarding advice to the public on reducing dietary cholesterol.

Most clinicians and community medicine specialists will endorse Prof M. F. Oliver's caveat about not estrapolating 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.[7] 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 Scottish population, particularly in the west if nowhere else, to their 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 agricultural and food industries the needs of their customers. These industries should be reminded again of their 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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STREPTOCOCCUS FAECALIS: GROUP D OR GROUP G?

SIR,—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 have 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 ('Streptex', Wellcome Diagnostics; 'Phadebact', Pharmacia Diagnostics) as well as by traditional Lancefield grouping 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 as the sole criterion for identification, especially since most of the cross-reacting strains are also strongly β-haemolytic. This could have important therapeutic implications because conventional group G streptococci are typically sensitive to a wide range of commonly used antimicrobial agents. In contrast, our cross-reacting *Strep faecalis* strains, as well as being relatively insensitive to penicillin appear to be resistant to tetracyclines, macrolides, lincosamides, sulphonamides, and trimethoprim. Details of their antibiotic susceptibility patterns and biochemical characteristics are to be published elsewhere.

We would be interested to hear from others who have encountered these strains, to determine their geographical incidence, and also to receive cultures which we can compare with our own isolates.

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TRAZODONE ASSOCIATED WITH PRIAPISM

SIR,—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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BETA ADRENORECEPTOR ANTAGONISTS IN ESSENTIAL TREMOR

SIR,—In the treatment of benign, familial, or essential tremor a beta-adrenoreceptor antagonist is now the drug of first choice, and propranolol, a non-selective (beta-1 and beta-2) adrenoreceptor antagonist, having effects on both the peripheral and central nervous systems, is the most effective. Comparative clinical trials[1,2] suggest peripheral beta-2 adrenoreceptor as the locus of the anti-tremor effect of these drugs. However, the picture is clouded by other studies showing benefit from the selective beta-1 adrenoreceptor antagonist metoprolol[3-5] and by the apparent absence of attenuation of essential tremor after intravenous or intra-arterial propranolol,[6] suggesting that a central mechanism is involved in the therapeutic response to oral propranolol. A *Lancet* editorial[7] asked for studies with a peripherally acting, selective beta-2 adrenoreceptor antagonist to evaluate more directly the role of the beta-2 receptor in the control of essential tremor. We report the preliminary findings of such a study, double-blind and placebo controlled, in which the tremolytic effect of a single oral 2 mg dose of the very hydrophilic (peripherally acting) selective beta-1 adrenoreceptor antagonist LI 32-468 (4-(3-tert-butylamino-2-hydroxypropoxy)spiro[cyclohexan-1,2-indan]-1-on hydrogen malonate) was compared with propranolol at a dose (120 mg) known to be superior to placebo in essential tremor.[8]

Twelve previously untreated patients with essential tremor received all three treatments in random order with intervals of at least a week. Tremor of the hands in pronated posture was recorded under standardised conditions, by accelerometers.[8] The amplitude of the dominant tremor peak was measured with a spectral analyser and the root mean square acceleration was computed. Recordings were made before and 2 h after drug or placebo administration when drug plasma concentrations were expected to be approaching a peak.

Tremor frequencies ranged from 5·7 to 9·6 Hz before treatment and did not change significantly after administration of either of the drugs or placebo. Pretreatment amplitudes ranged from 5·8 to $102 \cdot 7\ g \times 10^{-3}$ ($g = 981\ cm/s^2$). Mean reduction in tremor amplitude was 9·6% after placebo, 42·4% ($p < 0 \cdot 05$) after 2 mg LI 32-468 and 39·4% ($p < 0 \cdot 05$) after 120 mg propranolol. Significant decreases in standing tachycardia were observed after administration of propranolol ($p < 0 \cdot 01$), but not after placebo or LI 32-468. Thus 2 mg LI 32-468 had no measurable effect on cardiac (beta-) receptors.

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