- exposures are measured imprecisely. *J Clin Epidemiol* 1991;**44**:1223-31.
- 8 Barker DJP, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986;*i*:1077-81.
- 9 Ben-Shlomo Y, Davey Smith G. Deprivation in infancy or adult life: which is more important for mortality risk? *Lancet* 1991;**337**:530-4.
- 10 Davey Smith G, Shipley MJ, Rose G. The magnitude and causes of socio-economic differentials in mortality: further evidence from the Whitehall study. *J Epidemiol Community Health* 1990;**44**:265-70.

Treatment of hypertension in older adults

SIR,—The recent report on the principal results of the Medical Research Council trial of treatment of hypertension in older adults will provoke considerable interest and discussion. One conclusion was that the trial “found no primary cardioprotective effect of β blockers.” I suggest that a more precise conclusion would be that the trial found that atenolol did not show a cardioprotective effect and that it confirms the lack of data on cardioprotection derived from studies on the hydrophilic β blockers. This group includes atenolol, nadolol, and sotalol. This should not detract from reports suggesting that lipophilic β blockers—that is, drugs like metoprolol, propranolol, and timolol—do have cardioprotective actions. The relevance of intrinsic sympathomimetic activity is not certain; some consider it a disadvantage.

The heart attack primary prevention in hypertension (HAPPHY) trial did not find that β blockers have a primary prevention role,¹ but this result was the overall conclusion derived from a beneficial effect of metoprolol and a slightly adverse effect of atenolol.² The Medical Research Council trial of 1985³ is usually regarded as a negative study, but it included a large number of patients with very mild hypertension; about half the patients were female and at very low risk of having a coronary event; and it did not include data on silent infarcts.⁴ When the data for non-smoking men are considered⁴ and those with silent ischaemic episodes are included, the potential benefits of propranolol are revealed.⁵

The literature on β blockers in secondary prevention is extensive and includes a number of positive results from trials in which lipophilic β blockers were used. The best known are the Norwegian timolol trial,⁶ the Gothenburg metoprolol trial,⁷ and the β blocker heart attack trial of propranolol.⁸ In each of these investigations the β blocker had a significant impact on sudden death, a major cause of death in post-infarct patients, but also the way in which one third of coronary events present in people with hypertension.

For the patient with angina and hypertension the most common major complication and the most common cause of death is coronary artery disease. The drug treatment most likely to reduce the risk of death, particularly sudden death, is a lipophilic β blocker. It would be a tragedy if conclusions based on studies in which hydrophilic β blockers have been used were to cast doubts about the potential value of the other β blockers.

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- 1 MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;**304**:405-12. (15 February.)
- 2 Wilhelmssen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosc J, *et al.* Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 1987;**5**:561-72.
- 3 Steering Committee of the HAPPHY Trial. MAPHY and the two arms of HAPPHY. *JAMA* 1989;**262**:3273-4.
- 4 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985;**291**: 97-104.
- 5 Green KG. British MRC trial of treatment for mild hypertension

—a more favourable interpretation. *Am J Hypertens* 1991;**4**: 723-4.

- 6 Norwegian Multicentre Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;**304**:801-7.
- 7 Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Malek I, Nyberg G, *et al.* Effect on mortality of metoprolol in acute myocardial infarction. *Lancet* 1981;*ii*:823-7.
- 8 Beta Blocker Heart Attack Trial Research Group. A randomised trial of propranolol in patients with acute myocardial infarction. *JAMA* 1982;**247**:1707-24.

SIR,—As one who took part in both of the Medical Research Council's trials of hypertension^{1,2} I have some observations regarding K Beard and colleagues' study of managing sustained hypertension in elderly patients.³

Epidemiologically there seems to be good evidence for treating hypertension in elderly patients.³ From general practitioners' point of view, this would generate an enormous amount of hard work, which should not be underestimated. Some of the advice given by Beard and colleagues on the practicalities of assessment, treatment, and follow up represent consultants' points of view and may not be feasible let alone cost effective in the community.

What of the patients' point of view? According to the worst profile in table IX of the Medical Research Council's report of its trial in older patients, I can expect a one in 11 chance of benefit if I take a diuretic for five years.² Against that, there is a one in six chance of getting an important side effect over five years with the same treatment, and the odds substantially worsen if I am one of the 50% who require additional treatment. If my general practitioner was good enough to explain these facts to me I might well be prepared to take a gamble and not take any tablets at all.⁴ Furthermore, as the chances of a longer life seem improbable I would want some kind of guarantee that my life would be improved.

Until intervention trials take note of the participants' quality of life,⁵ the costs may well outweigh the benefits.^{6,7} I probably won't live the 200 or so years that are necessary to reap the benefits that the trials have to offer, but it may just feel like it.

So what does a general practitioner do now? I for one will continue to inform my patients to the best of my ability and allow them to make up their own minds.⁸ At least that way I can give back to patients the freedom that they deserve.

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- 1 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985;**291**: 97-104.
- 2 Medical Research Council Working Party. MRC trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;**304**:405-12. (15 February.)
- 3 Beard K, Bulpitt C, Mascie-Taylor H, O'Malley K, Sever P, Webb S. Management of elderly patients with sustained hypertension. *BMJ* 1992;**304**:412-6. (15 February.)
- 4 Bursztajn HJ, Feinbloom RI, Hamm RM, Brodsky A. *Medical choices, medical chances: how patients, families, and physicians can cope with uncertainty*. New York: Routledge, 1990.
- 5 Bowling A. *Measuring health: a review of quality of life measurement scales*. Buckingham: Open University Press, 1991.
- 6 Stoate HG. Can health screening damage your health? *Br J Gen Pract* 1989;**39**:193-5.
- 7 Marteau TM. Psychological costs of screening. *BMJ* 1989;**299**: 527.
- 8 Tuckett D, Boulton M, Olson C, Williams A. *Meetings between experts: an approach to sharing ideas in medical consultations*. London: Tavistock, 1985.

SIR,—It was ironic that in the issue of the *BMJ* detailing the cardioprotective value of diuretics in elderly hypertensive patients^{1,2} and the doubtful value of lowering serum cholesterol³ and triglycerides⁴ a statement should appear in the paper by Keith Beard and colleagues that “adverse lipid changes induced by thiazides may be important in younger [hypertensive] patients.”⁵ The reasons for this conclusion, the vagueness of the statement, and the fact that it was not referenced are puzzling. Given the available evidence in this issue of the

journal and information published over the past 15 years might I suggest the following revision: “There is little or no evidence that thiazide diuretics have long term adverse effects on plasma lipids^{6,7} and no evidence whatsoever that these supposed changes have any detrimental effects on cardiovascular mortality.”^{8,9,10,11}

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- 1 Medical Research Council Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;**304**:405-12. (15 February.)
- 2 Beard K, Bulpitt C, Mascie-Taylor H, O'Malley K, Sever P, Webb S. Management of elderly patients with sustained hypertension. *BMJ* 1992;**304**:405-12. (15 February.)
- 3 Oliver MF. Doubts about preventing coronary heart disease. *BMJ* 1992;**304**:393-4. (15 February.)
- 4 Hulley SB, Avins AL. Asymptomatic hypertriglyceridaemia. *BMJ* 1992;**304**:394-6. (15 February.)
- 5 Smith GD, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992;**304**:431-6. (15 February.)
- 6 Williams WR, Borhani NO, Schnaper HW. The relationship between diuretics and serum cholesterol in HDFP participants. *J Am Coll Cardiol* 1983;**1**:623.
- 7 Veterans Administration Co-operative Study Group on Antihypertensive Agents. Comparison of propranolol and hydrochlorothiazide for initial treatment of hypertension. Result of short-term titration with emphasis on racial differences in response. II. Results of long term treatment. *JAMA* 1982;**248**:2004-11.
- 8 Multiple Risk Factor Intervention Trial Research Group. Mortality after 10½ years of hypertensive participants in the multiple risk factor intervention trial. *Circulation* 1990;**82**:1616-28.
- 9 Johnston GD, Wilson R, McDermott BJ, McVeigh GE, Duffin D, Logan J. Low dose cyclopentiazide in the treatment of hypertension: a one-year community based study. *Quart J Med* 1991;**78**:135-43.
- 10 Collins R, Peto R, MacMahon S, Herbert P, Fiebach NH, Eberlein KA, *et al.* Blood pressure, stroke and coronary heart disease. Part 2. Short-term reduction in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;**335**:827-38.
- 11 New trials in older hypertensives [editorial]. *Lancet* 1991;**338**: 1299-300.

Monoclonal antibodies in sepsis and septic shock

SIR,—C J Hinds's editorial discusses the use of monoclonal antibodies in sepsis and septic shock.¹ Though the relative merits of different antibodies to endotoxin will no doubt continue to be debated, we think that, in addition to the cost, there are other issues that should be considered.

By giving antiendotoxin only after admission to the intensive care unit, we may miss the “therapeutic window” when it can be of most benefit. The onset of signs of sepsis seems to coincide with the release of cytokines such as tumour necrosis factor, which occurs 90 minutes after the administration of endotoxin.² So a delay has already been established before clinical signs appear. Giving antiendotoxin after the cascade has started may not halt its progress. This partly explains the inconsistencies in the studies Hinds mentions.

In the two main trials quoted treatment with antiendotoxin was delayed further: by a mean of 14.3 hours from diagnosis in one³ and within eight hours in the other.⁴ By this time about half of those without shock who are likely to develop this complication will already have done so.⁵ This seemingly excessive delay probably reflects the ordinary clinical situation, considering possible hold ups in transfer to, and initial treatment in, the intensive care unit. If good haemodynamic control is obtained the temptation will be to avoid using an expensive and controversial drug; if not, the prognosis may already be poor.

We are not suggesting that antiendotoxin should be given indiscriminately as patients enter hospital. What is necessary is the ability to predict who is likely to develop sepsis, as we have recently shown⁶ in patients undergoing endourological manipulation of urinary calculi, in whom the incidence of

postoperative endotoxaemia is 32%.⁶ Further work should be directed at identifying those who are at risk and assessing their innate immunity in different clinical situations. If antiendotoxin is then given early, rather than after sepsis is established, the results are likely to be superior to those obtained in the trials published so far.

Comparisons can be made with the published trials of steroids in sepsis. For them to be beneficial it was thought necessary to administer steroids in the very early stages. They were deemed ineffective, though confirmatory studies were not performed. Although these two drugs are not comparable, by performing similar studies with antiendotoxins without fully understanding the events leading up to sepsis we run the risk of condemning this potentially useful treatment for the wrong reasons, spending millions in the process.

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- 1 Hinds CJ. Monoclonal antibodies in sepsis and septic shock. *BMJ* 1992;304:132-3. (18 January.)
- 2 Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello CA, *et al.* Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 1988;318:1481-6.
- 3 Ziegler EJ, Fisher CJ Jr, Sprung CL, Straube RC, Sadoff JC, Foulke GE, *et al.* Treatment of Gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. *N Engl J Med* 1991;324:429-36.
- 4 Greenman RL, Schein RMH, Martin MA, Wenzel RP, MacIntyre NR, Emmanuel G, *et al.* A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of Gram-negative sepsis. *JAMA* 1991;26:1097-102.
- 5 Bone RC, Fisher CJ, Clemmer TP, Slotman GS, Metz CA, Balk RA, *et al.* Sepsis syndrome: a valid entity. *Crit Care Med* 1989;17:389-93.
- 6 Rao PN, Dube DA, Weightman NC, Oppenheim BA, Morris J. Prediction of septicemia following endourological manipulation for stones in the upper urinary tract. *J Urol* 1991;146:955-60.

Low protein diets in chronic renal insufficiency

SIR,—D Fouque and colleagues report a meta-analysis of the effect of low protein diets on rates of renal death in patients with renal failure of various severities.¹ They conclude that the beneficial effect, if genuine and free of bias, might be due to a reduction in the rate of progression of renal failure induced by diet or to delayed institution of renal replacement therapy consequent on an improvement in symptoms of uraemia. Although low protein diets have long been recognised to alleviate uraemic symptoms, their effects on quality of life and general physical fitness in less severe renal failure have not been adequately addressed in the papers analysed by Fouque and colleagues or elsewhere. These are crucial to the prescription and tolerance of such diets.

We assessed quality of life with the Nottingham health profile and aerobic fitness by low work cycle ergometry in 25 adults with stable renal failure (serum creatinine concentration >350 µmol/l) prescribed 0.6 g protein/kg desirable body weight/day with an energy intake of 125-145 kJ/kg/day for three months. Assessed dietary compliance was good but energy intake remained about two thirds of that prescribed. The mean (SD) baseline respiratory exchange ratio, used as an indicator of fitness, was consistent with weakness, ranging from 0.86 (0.05) at zero watts to 1.02 (0.04) at 60 W. After three months of the low protein diet a consistent improvement in respiratory exchange ratio was evident at all workloads and was significant at 20 W (0.87 (0.03) at three months *v* 0.96 (0.05) at baseline, *p*<0.05), suggesting a beneficial effect on aerobic fitness. The subjects' perceived energy, emotional reaction, and sense of social isolation as determined by the Nottingham health profile also improved significantly.

The results imply that low protein diets improve quality of life and fitness in subjects with renal failure who do not have overt uraemic symptoms. These results will be reported in detail later.

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- 1 Fouque D, Laville M, Boissel JP, Chifflet R, Labeuw M, Zech PY. Controlled low protein diets in chronic renal insufficiency: meta-analysis. *BMJ* 1992;304:216-20. (25 January.)

Establishment of pregnancy after removal of sperm antibodies in vitro

SIR,—Carolyn E Grundy and colleagues report that two pregnancies occurred in three cases after sperm antibodies had been removed in vitro with immunobeads.¹

Antibodies bind irreversibly to sperm at ejaculation, so any laboratory procedure must either cleave the F_c fragment of the antibody—for example, by use of papain, which requires a pH of 2.2, making sperm non-viable—or prevent the attachment of antibodies at ejaculation. The immunobead procedure that Grundy and colleagues used allows sperm bound to antibodies to be sequestered from those that are free and is not a technique for removing antibodies from the surface of sperm. The technique is therefore unsuitable for cases in which almost all sperm in the ejaculate are bound to antibodies.

We have been using a procedure developed by Chantler *et al.*² and successfully tested by M Tucker *et al.* (meeting of the American Fertility Society, Atlanta, October 1990), which uses carbohydrate and enzyme moieties to competitively inhibit the attachment of sperm to antibodies at ejaculation. Briefly, semen is collected in 10 ml of culture medium buffered with hydroxyethylpiperazine-ethanesulphonic acid (HEPES) containing 0.2M D-galactose and 5000 IU α chymotrypsin and allowed to stand for 30 minutes. Motile sperm are collected by centrifuging the sample on a Percoll gradient, washed once in 0.2M D-galactose, and then washed twice in culture medium buffered with HEPES. The resulting pellet of motile sperm is free of antibodies. In this way we have prevented the attachment of antibodies to sperm in 70% of cases.

We have achieved pregnancies with in vitro fertilisation in two patients, in both of whom two previous attempts at in vitro fertilisation without treatment of semen for antibodies had failed.

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- 1 Grundy CE, Robinson J, Guthrie KA, Gordon AG, Hay DM. Establishment of pregnancy after removal of sperm antibodies in vitro. *BMJ* 1992;304:292-3. (1 February.)
- 2 Chantler E, Sharma R, Sharman D. Changes in cervical mucus that prevent the penetration of sperm. *Symp Soc Exp Biol* 1989;43:325-36.

Childhood mortality after a high dose of vitamin A

SIR,—In their paper on childhood mortality after a high dose of vitamin A in a high risk population Nils M P Daulaire and colleagues describe one of their objectives as determining whether periodic

community wide supplementation of vitamin A could be readily incorporated into an ongoing primary health care programme.¹

We agree with the conclusion that vitamin A supplementation improves survival in children from a harsh nutritional environment such as in Jumla, Nepal. We question the claim that the supplementation programme was readily integrated into the community health programme as the authors describe only their experience of integration with a large, single intervention research study.

The paper contains some indicators highlighting how different the community health programme is from the basic health service found elsewhere in Nepal.

Firstly, within a defined area (16 subdistricts) all households were visited every two weeks by a local lay health worker from a pneumonia case management programme. In contrast, a random cluster sample household survey in Baglung district found that only 41% of 680 households had been visited by the village health worker. A study of attendance at health posts in the same district showed that a quarter of children aged under 5 from the immediate catchment area were seen in a year and only 11% for the area as a whole.

Secondly, no nutritional services other than vitamin A supplementation were available from any source. The village health worker in the government health service, however, has the responsibility to provide health education and advise on nutrition as well as monitoring the growth of all children aged under 5.

Thirdly, 99% of all life events had been recorded. This is exceptional for any programme in rural Nepal other than an intense research programme.

We suggest that this kind of intervention is unlikely to have the same degree of protective effect elsewhere in Nepal other than in the remote mountain areas with exceptionally high levels of malnutrition. This programme could not be replicated in the present basic health service, especially in the same remote areas. An intervention of this kind should not be considered in the absence of a more comprehensive nutrition education programme in the community.

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- 1 Daulaire NMP, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR. Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992;304:207-10. (25 January.)

Risk of Down's syndrome and amniocentesis rate

SIR,—Charlotte Fleming and David J Goldie highlight the problem of choosing appropriate cut off limits for the risk of Down's syndrome and raise the question of patients' acceptance of such risk and their uptake of offers of amniocentesis.¹ They quote their own experience of using maternal serum α fetoprotein concentration and maternal age in screening women aged over 30: at a cut off risk of 1 in 200 only 39% of women offered amniocentesis took up the offer, while at a cut off of 1 in 300 31% took up the offer.

One of the difficulties in translating these data beyond the confines of their screening programme is that confidence in screening that uses only maternal serum α fetoprotein concentration as the biochemical marker with maternal age is low. Several studies have shown that maternal serum α fetoprotein concentration and maternal age at best can identify only 35% of cases of Down's syndrome for a 5% false positive rate. If a combination of markers that give superior detection rates at the