by smaller amounts in New Zealand, Switzerland, Finland, Belgium, and Israel.¹⁰ All cause mortality has fallen in these countries at the same time. By contrast, the countries of eastern Europe—for example, Hungary, Poland, and Czechoslovakia—have suffered large increases in coronary deaths accompanied by rises in total mortality. In an intermediate group of countries—for example, Sweden, Denmark, Ireland, England and Wales, Scotland, and Northern Ireland—changes in coronary mortality have been small or late.

Those who have examined these changes in contrasting countries conclude that dietary change seems to have been the most consistent variable in lifestyle—notably an increase in ω -6 polyunsaturated fatty acids in countries with falling mortality¹¹ and an increase in animal fat in countries with rising coronary and total mortality.¹² In England and Wales coronary mortality started to move downwards in about 1977¹³; this coincided with the start of an increase in the ratio of polyunsaturated to saturated fatty acids in the average household's diet.¹⁴

Oliver's group in Edinburgh found significant inverse and progressive relations between the linoleic acid content of adipose tissue and the risk of angina and myocardial infarction in a population based case-control study.¹⁵ Four other case-control studies have yielded similar findings. Other components of the dietary package first recommended for preventing coronary disease at the end of the 1950s may play important parts as well—namely, reduced total fat, reduced saturated and hydrogenated fats, and increased vegetable, fruit, and fibre intakes.

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- 1 Davey Smith G, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992;304:431-4. (15 February.)
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SIR,—One of the hazards of writing an editorial is that some do not trouble to read it with care or without prejudice. Thus M F Ryan and colleagues have decided¹ that my appraisal of the Helsinki trial is unsound because I suggested that some of the adverse effects 10 years after the end of the trial might be related to the use of hypolipidaemic drugs

during the trial.² But neither I nor the authors of the trial made any such suggestion. I did not even refer to these drugs in relation to the Helsinki trial.

Other correspondents have focused entirely on the Helsinki trial and have ignored the equally or more important negative results of other major trials.¹ The doubts about preventing coronary heart disease stem from the overview of all these studies. In short, multifactorial primary prevention of the degree generally recommended during the past two decades has failed to prevent coronary heart disease in middle aged men.

The more stringent approach to hypercholesterolaemic men used in the Oslo trial did lead to a reduction in the incidence of coronary heart disease: cigarette smoking was reduced by 45% and serum cholesterol concentration was 13% lower in the intervention group.³ A diet enriched in ω -6 polyunsaturated fat was used (polyunsaturated: saturated ratio ≥ 1.0), supporting A Stewart Truswell's emphasis on their importance. I fully agree with him.

Unfortunately, there is no simple explanation for the decrease in mortality from coronary heart disease in the United States, Australia, Canada, England, Wales and even Scotland as the downturns in the incidence of both coronary heart disease and stroke began before public health advice on prevention was widely put into practice.

I agree with Tony Winder and J P D Reckless that people at high risk must be identified and should receive aggressive treatment for their specific risk factors.¹ But we must now move on, and a renewed research effort is needed to study causes of coronary heart disease other than smoking, cholesterol, and blood pressure so that new initiatives in prevention can be established.

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SIR,—J P D Reckless and J A Tobert¹ disagree with the inclusion criteria for the studies in our review of cholesterol lowering and mortality.² Reckless suggests that we “look at only a third of relevant studies.” He may have missed the fact that our quantitative analysis was solely of the primary prevention studies. It is in primary prevention, as we made clear, that we suggest caution should be exercised before the use of cholesterol lowering drugs expands rapidly.

Tobert suggests that the expanded clinical evaluation of lovastatin (EXCEL) trial should not have been included as a primary prevention trial as 28% of the participants suffered from pre-existing ischaemic heart disease.³ Our definition of primary prevention trials was those studies for which previous ischaemic heart disease was not an entry criterion. Thus, for example, in the colestipol-Upjohn study 31% of participants had evidence of ischaemic heart disease at entry.⁴ The classification of studies we used follows that of other reviewers.⁵⁻⁷

We agree with Tony Winder that inappropriate use of cholesterol lowering drugs is the danger.¹ Our worry is that the current exponential increase in prescription rates, together with widespread promotion of guidelines for treatment which suggest that a substantial proportion of the British population is eligible, makes such inappropriate use likely. Current evidence of the effects of cholesterol lowering drugs on mortality cannot be viewed as favourable. Lovastatin is now the most frequently prescribed cholesterol lowering drug in

the United States,⁸ where its use was already widespread and rapidly increasing by 1988.⁹

Tobert suggests that in the EXCEL trial differences in mortality “did not approach significance ($p > 0.2$ by the Kaplan-Meier method)”; we assume a log rank test is meant. With the small number of deaths in this study, survival analysis closely approximates to a simple χ^2 test. A global comparison across the four lovastatin groups and the placebo group produces a similar statistic ($\chi^2 = 5.21$, 4 df, $p = 0.27$). Combining the four lovastatin groups and making the comparison of active treatment versus placebo, however, gives a different picture ($\chi^2 = 3.15$, 1 df, $p = 0.076$). Perhaps the more than twofold increase in mortality among the patients treated with lovastatin should not be dismissed so lightly. Certainly, more powerful data should be obtained before doubts about the wisdom of widespread promotion of these drugs are dismissed.

On the principle of first do no harm we find it difficult to see how expanding the use of cholesterol lowering drugs in the primary prevention of ischaemic heart disease in patients other than those with severe familial hyperlipidaemias can be justified, even though these drugs apparently protect against non-fatal ischaemic heart disease. As Rose pointed out,¹⁰ in primary prevention of disease a small adverse effect can often outweigh any benefit; thus there should be stringent requirements for the acceptable level of evidence regarding safety. A large enough randomised clinical trial should be carried out to examine the effects of pharmaceutical lowering of cholesterol concentrations on all cause mortality, and therapeutic restraint should be maintained until this is completed.

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Age associated memory impairment

SIR,—Thomas H Crook and Steven H Ferris accuse us of arguing against the investigation of possible pharmacological treatment of age associated memory impairment.¹ We do nothing of the sort. Our editorial was subtitled “Too broad an entity to justify drug treatment yet” and emphasised the

need for long term follow up to determine whether the entity that they have defined represents an early manifestation of dementia or a benign if inconvenient consequence of growing old.¹ The National Institute of Mental Health's working group of which they were members published its criteria in 1986,¹ and yet six years later we still do not know the answer. This information is of more than academic interest as it is bound to affect the risk:benefit ratio of any drug advocated to improve memory in elderly people.

Crook and Ferris argue by analogy to presbyopia and its correction by means of lenses. A closer parallel might be the decline in physical prowess with age and its boosting with hormones. Both analogies are likely to be imperfect, and the issue is complex and unlikely to be resolved in the current state of knowledge. We do not automatically oppose the investigation of drugs to improve memory. What we want is more information about the baseline so that a more informed judgment may be made about the risks and benefits of their use.

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Medical abortion

SIR,—In their letters Peter Doherty and A P Cole allude to possible teratogenic effects of mifepristone.^{1,2} They refer to the sole case of multiple abnormalities seen at late abortion in a woman who had received mifepristone in early pregnancy in France in 1987. This case has been investigated and reported previously. No conclusion was possible as to whether the abnormalities were related to mifepristone or coincidental.^{3,6}

Women may change their mind and decide to continue their pregnancy to term despite exposure to mifepristone and prostaglandins. In fact, the incidence is very low, with only five known cases in over 100 000 uses. No abnormalities occurred.

The responsible approach is to advise women clearly of the potential risk, as is done in the information leaflets on mifepristone, and for prescribers to follow rigorously the stated protocol, covering assessment, dosage, treatment schedule, and follow up.

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SIR,—Medical abortion using mifepristone (RU 486) in combination with a prostaglandin is a safe and effective alternative to surgical abortion in the early first trimester.¹ Although no rigorous economic evaluation has been reported, it has been

suggested that this new treatment would lead to considerable financial savings to the NHS. We have recently completed an economic analysis as part of a wider study investigating the medical and psychological sequelae of medical and surgical abortion. As many purchasing authorities are currently negotiating contracts for abortion services, an interim report may be useful to decision makers.

Our analysis is based on a pragmatic randomised trial of 363 women, 172 of whom underwent medical abortion and 191 surgical abortion. Medical abortion was undertaken using mifepristone 600 mg followed 36-48 hours later by gemeprost 1 mg vaginal pessary. Surgical abortions were performed by vacuum aspiration under general anaesthesia. Ninety nine per cent of medical abortions and 91% of surgical abortions were completed as day cases. There were no significant differences in complete abortion or complication rates, which were consistent with previously reported studies.^{2,3} There were no persisting pregnancies.

We estimate that costs to the health board, including all outpatient services, investigations, inpatient services, and the management of complications occurring up to eight weeks after abortion were £400 for medical abortion and £480 for surgical abortion. Costs to the patients and to community health services are not included. Preliminary analysis suggests that there was little difference between the two groups in patients' perceptions of outcome in general, and acceptability in particular.

In Grampian half of the 1200 women treated annually (virtually all in NHS premises) are managed before nine weeks' gestation. We have recently introduced a medical abortion service; this mirrors the experience in France, where about 20% of eligible women opt for medical abortion.¹ We estimate that this will result in an annual financial saving to the health board of nearly £10 000.

In England and Wales, although 79% of women first approach a doctor before eight weeks' gestation, only 21% of abortions in NHS premises are performed before nine weeks' gestation; 68% of these women are managed as day cases.^{4,5} Until more women are referred promptly, the financial savings offered by medical abortion will not be realised. As morbidity and mortality increase with advancing gestation,¹ it would be beneficial to all concerned for purchasing authorities to ensure that prompt referral is a high priority.

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5 Office of Population Censuses and Surveys. *Abortion statistics*. London: HMSO, 1989.

SIR,—We agree with Peter Doherty¹ that in up to 1% of cases mifepristone plus prostaglandin may not terminate a pregnancy. A P Cole wrongly states that 6% will not abort²; in both the French and English experience this larger percentage required surgical intervention for retained products or bleeding.

Although there have been several pregnancies

carried to term with no apparent abnormality, we also agree it should be presumed that mifepristone is capable of teratogenic effects in women. We made it clear in our article that a surgical termination should always follow if the process is either incomplete or the pregnancy fails to abort. Moreover, it is unlikely that there could be "1000 malformations resulting from 100 000 attempted abortions."³ This could be true only if 100% of fetuses in failed abortions had an abnormality (and none was identified in time to proceed to surgical abortion). The data available indicate that if pregnancies do continue only a proportion of fetuses have a malformation, though this risk is still unacceptable.

In practice, the most relevant circumstance will be when a woman changes her mind after receiving mifepristone. We recommend the initial consent includes a woman's agreement that she must take full responsibility for any outcome if the pregnancy continues as a result of any action or inaction on her part as there would be a risk of a birth defect.

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Functional iron deficiency during erythropoietin treatment

SIR,—We read with interest the paper by Ian C Macdougall and colleagues.¹ At our unit in 38 renal patients over the first 12 weeks of erythropoietin treatment, the haemoglobin concentration rose from 69 (SE 2) g/l to 104 (0.3) g/l ($p < 0.0001$, two tailed paired t test). The (geometric) mean serum ferritin concentration declined from 219 (1) μ g/l to 94 (1) μ g/l ($p = 0.014$), but the serum transferrin saturation did not change significantly (from 29.9 (3.4)% to 25.2 (2.2)%). The transferrin saturation correlated with ferritin initially ($r = 0.75$, $p < 0.001$) but not after the first four weeks. At 12 weeks, eight of 15 patients with iron deficiency (ferritin concentration $< 50 \mu$ g/l) had a transferrin saturation $> 20\%$ whereas two of five patients with iron overload (ferritin concentration $> 500 \mu$ g/l) had a transferrin saturation $< 20\%$. In 14 patients with iron overload the haemoglobin concentration rose from 67 (3) g/l to 99 (4) g/l ($p < 0.0001$) entirely by mobilising iron reserves, which were reduced from 1220 (73) mg to 739 (111) mg ($p < 0.001$). In the 24 other patients haemoglobin rose similarly (from 70 (8) g/l to 107 (4) g/l; $p < 0.0001$), partly by depleting iron reserves (from 224 (78) mg to -54 (83) mg; $p = 0.019$) and partly by utilising orally absorbed iron (297 (119) mg).

In a previous study Macdougall *et al* concluded that the transferrin saturation was superior to the serum ferritin concentration for detecting functional iron deficiency and that parenteral iron was superior to oral iron. These conclusions were based on five patients who initially had low serum ferritin concentrations ($< 50 \mu$ g/l). They received only 35 mg/day of elemental iron. In other words, the patients alleged to have functional iron deficiency were probably truly iron deficient before erythropoietin treatment and became more so subsequently. In the absence of adequate oral iron supplements their response to erythropoietin was impaired; hence their reported response to parenteral iron.

Use of the transferrin saturation has considerable limitations, as the authors concede; the serum ferritin concentration is the best available parameter of iron stores.^{1,4} High transferrin saturation usually indicates iron overload, but a low value in renal failure (and other chronic diseases) may coexist with any iron status.

Erythrocyte hypochromia may prove to be a