cancer and for those who took it for more than 10 years the relative risk was virtually neutral (relative risk 1.03).² Furthermore, it seems that, even if the incidence of breast cancer is increased in current long term users, the risk of death is decreased.³

Those of us who advocate hormone replacement therapy would agree with McPherson's sentiments that on balance the current evidence continues to suggest that such therapy will probably give rise to a net gain in years of life. The American nurses' study recruited 121 700 female registered nurses aged 30 to 55 in 1976; it will be several years yet before such studies can provide us with conclusive answers.

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- 1 McPherson K. Breast cancer and hormonal supplements in postmenopausal women. *BMJ* 1995;311:699-700. (16 September.)
- 2 Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589-93.
- 3 Brinton LA, Schairer C. Estrogen replacement therapy and breast cancer risk. *Epidemiol Rev* 1993;15:66-79.

Likely mode of death may be a consideration

EDITOR,—Klim McPherson uses net loss of or gain in years of life as a criterion in discussing the balance between the risks and benefits of hormonal supplements in postmenopausal women.¹ Another criterion, however, is the mode of death. A patient might choose to risk an earlier, but "easy," death from coronary heart disease rather than a later, but possibly lingering and traumatic, death from breast cancer.

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Increase in risk of breast cancer is small

EDITOR,—I am confused over how Klim McPherson reaches some of his conclusions, particularly the conclusion that long term use of hormonal supplements in postmenopausal women may be responsible for an average net loss of years of life.¹ Far more studies have been done that show benefits of hormone replacement therapy on coronary heart disease and osteoporosis than that show benefits on breast cancer. The figures for coronary heart disease, of a 50% reduction in overall mortality,² and the preventability of osteoporosis and fractures are reasonably believable.³ The studies of breast cancer show variable results, some with a small increase in incidence from long term use. If we accept the figures quoted—that for a 50 year old postmenopausal woman the lifetime risk of coronary heart disease is 45%, of fracture of the hip is 15%, and of cancer of the breast is 8%—then with the reduction in the incidence of coronary heart disease and fractures there would need to be a huge increase in breast cancer of the order of 400-500% to produce a negative net loss of years of life.

Henderson *et al* carried out a prospective study in 8881 postmenopausal residents of a retirement community who had used oestrogen for a mean of 10 years.⁴ They found that subjects with a history of use of oestrogen had a 20% reduction in all cause mortality adjusted for age compared with non-users, and current users had a 40% reduction. This included a 20% reduction in the incidence of

carcinoma, including carcinoma of the breast, although a rise in endometrial carcinoma was noted with oestrogen only treatment.

The prevention of endometrial carcinoma by the addition of a progestogen is well recognised, but the overall effects of progestogen are less well defined. Long term use (for 22 years) of combined oestrogen and progestogen was not associated with an increase in the risk of breast cancer in a study by Nachtigall *et al*.⁵

Long term use of combined oral contraceptives has been intensively studied by the Royal College of General Practitioners, among others, and only a small increase in the risk of breast cancer has been suggested. While this is in a younger age group, many of the women who started taking combined oestrogen and progestogen long term in the early 1960s must be well over 50 by now; as far as I am aware, no appreciable increase in breast cancer in this age group has been reported.

The lack of evidence for anything other than a potentially small increase in the risk of breast cancer associated with long term (15 years) use of hormone replacement therapy is far outweighed by the large benefits and reduction in overall mortality associated with hormone replacement therapy.

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- 2 Bush TL, Barrett-Connor E, Cowan LD, Criqui MH, Wallace RB, Suchindran CM, et al. Cardiovascular mortality and non-contraceptive use of oestrogen in women: results from lipid research clinics follow-up study. *Circulation* 1987;75:1102-9.
- 3 Royal College of Physicians. *Fractured neck of femur, prevention and management*. London: RCP, 1989.
- 4 Henderson BE, Paganin-Hill A, Ross RK. Decreased mortality in users of oestrogen replacement therapy. *Arch Intern Med* 1991;151:75-8.
- 5 Nachtigall MJ, Smilen SW, Nachtigall RD, Nachtigall RH, Nachtigall LE. Incidence of breast cancer in a 22 year study of women receiving estrogen-progestin replacement therapy. *Obstet Gynaecol* 1992;80:827-30.

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Article increased uncertainty

EDITOR,—Klim McPherson's editorial on breast cancer and hormonal supplements in postmenopausal women is important both for patients taking hormone replacement therapy and for general practitioners prescribing it.¹ But what are we supposed to do now? McPherson presents the statistics as irrefutable facts. Are they? Should we ask our patients whether they want to die of breast cancer or ischaemic heart disease? What is the actual decrease in the risk of ischaemic heart disease in women taking hormone replacement therapy? Should a family history of breast cancer become a contraindication to hormone replacement therapy? Do we now have to get consent forms signed before patients start taking hormone replacement therapy?

Perhaps McPherson should have written a review article rather than an editorial, so that he could proffer the full implications and necessary advice to practising doctors. As a profession we should be grateful that the media had other things to concentrate on at the time.

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Author's reply

EDITOR,—In general I agree with David A Viniker. The finding of an apparent deficit in the case fatality from breast cancer among women who take supplements when there is evidence of an increased incidence is to be expected early in a study because of likely selection and surveillance biases.¹ Proving a real effect is therefore difficult.

Jules Alterman points out that patients might prefer an easy death from coronary heart disease rather than a traumatic death from breast cancer. Probably for this reason, breast cancer is more feared than coronary heart disease despite its being a less common cause of death after age 55, and this is important.

With regard to C J Mugglestone's comments, if supplements affect the risk of breast cancer for a prolonged period after they are stopped and the attributable effects on coronary heart disease are less than observational studies (which might suffer from important selection bias) seem to show, then a net loss of years of life could result. Mortality from breast cancer is currently higher than that from coronary heart disease until around age 55. A 50% reduction in coronary heart disease is almost certainly largely a consequence of some selection bias.² The problem with breast cancer, as I tried to point out, is that the effects of a recent common exposure (combined hormonal supplements, for example) might be systematically underestimated until sufficient patients have been followed up long term.³ Exposure to stilboestrol during pregnancy affects the risks of breast cancer, but not at all until 20 years after exposure.⁴ Mugglestone's calculations do not take into account the differing age specific mortality patterns. What was observed during long term follow up in the United States among selected users of unopposed supplements may not be true for combined supplements, possibly taken more generally. There is, of course, a considerable increase in the incidence of breast cancer among women aged over 50,⁵ but this is due neither to oral contraceptives nor to hormone replacement therapy. And Mugglestone's confidence in only a small increase in risk with 15 years of use of hormone replacement therapy is not supported by recent data.

Finally, in answer to D J Plews's comments, I hope that I did not present the statistics as irrefutable facts; I said that "reliable information . . . is still lacking."

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- 1 Hunt K, Vessey M, McPherson K. Mortality in a cohort of long term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol* 1990;97:1080-6.
- 2 Petitti DB. Coronary heart disease and estrogen replacement therapy. Can compliance bias explain the results of observational studies? *Ann Epidemiol* 1994;4:115-8.
- 3 McPherson K. Latent effect of oral contraceptives on breast cancer. *JAMA* 1988;260:1240-1.
- 4 Greenberg ER, Barnes AB, Resseguie L, Barrett JA, Burnside S, Lanza LL, et al. Breast cancer in mothers given diethylstilbestrol in pregnancy. *N Engl J Med* 1984;311:1393-7.
- 5 Quinn M, Allen E, on behalf of the United Kingdom Association of Cancer Registries. Changes in incidence of and mortality from breast cancer in England and Wales since introduction of screening. *BMJ* 1995; 311:1391-5. (25 November.)

Thrombolytic treatment

Pulse spray infusion works faster but is more expensive

EDITOR,—We were surprised by Marc Verstraete's comment that "thrombolytic drugs are now usually given locally with a pulse spray technique" in less than two hours.¹ The British Thrombolysis Study Group has collected information prospectively from several hospitals in Britain on the use,

technique, and outcome of peripheral thrombolysis for the past two years.² This is a continual process to provide a system for the national audit of peripheral arterial thrombolysis, and so far over 450 events of thrombolysis have been recorded. In these, only 13% of infusions were given with a pulse spray technique, in a median time of six hours (range 1-78 hours).

Pulse spray lysis is certainly faster than conventional low dose techniques, but it requires expensive catheters and infusion systems. Other methods, such as high dose bolus thrombolysis and six hourly dose infusions, have also been reported to reduce infusion times without expensive equipment.^{3,4} Personal communications with the manufacturers of pulse spray infusion catheters also suggest that relatively few hospitals in Britain use the pulse spray technique.

Little information is available on many of the techniques for peripheral thrombolysis, and low dose infusions remain the gold standard for many hospitals in Britain.

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- 1 Verstraete M. Thrombolytic treatment. *BMJ* 1995;311:582-3. (2 September.)
- 2 Braithwaite BD, Ritchie AWS, Earnshaw JJ. NATALI—a model database for national computer databases in the investigation of new therapeutic techniques. *J R Soc Med* 1995;88:511-5.
- 3 Braithwaite BD, Birch PA, Poskitt KR, Heather BP, Earnshaw JJ. Accelerated thrombolysis with high dose bolus t-PA extends the role of peripheral thrombolysis, but may increase the risks. *Br J Surg* 1994;81:619.
- 4 Decrinis M, Pilger E, Stark G, Lafer M, Obermosterer A, Lammer J. A simplified procedure for intra-arterial thrombolysis with tissue-type plasminogen activator in peripheral arterial occlusive disease: primary and long term results. *Eur Heart J* 1993;14:297-305.

Streptokinase is more economical than alteplase

EDITOR,—Marc Verstraete cites streptokinase and alteplase as alternative thrombolytic drugs for the management of myocardial infarction.¹ His guidance on choice is confined to the statement that use of streptokinase, aspirin, and heparin saves 26 lives per 1000 patients treated, whereas use of alteplase, aspirin, and heparin saves 35-37 lives per 1000 patients treated. The implication is that he recommends alteplase. He omits to mention that the cost of treating a single patient with alteplase (£750, all inclusive) is over nine times higher than that of using streptokinase (£81.50, including the cost of the diluent, transfer device, and infusion bag). An annual budget sufficient to treat 1000 patients with streptokinase could therefore save 26 lives whereas the same budget would allow only 108 patients to be treated with alteplase and could save only three lives.

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Timing is more important than choice of agent

EDITOR,—Marc Verstraete states incorrectly¹ that the accelerated tissue plasminogen activator regimen used in the global utilisation of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) trial² "lowered the 30 day mortality to 6.3%, compared with 7.2% achieved with streptokinase, aspirin, and

intravenous heparin." The 30 day mortality for the latter combination was found to be 7.4%. The figures quoted are for the combination of aspirin, streptokinase, and subcutaneous heparin in the same trial.

To quote this trial without mentioning the discussion that it has generated is misleading. By doing so Verstraete implies that streptokinase is good but that tissue plasminogen activator is better. This has by no means been proved to be the case. Many of the controversial issues surrounding the trial were summarised in a recent review.³ The authors helped put the debate in perspective by emphasising that the timing of thrombolysis is much more important than the choice of thrombolytic agent.

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- 1 Verstraete M. Thrombolytic treatment. *BMJ* 1995;311:582-3. (2 September.)
- 2 GUSTO Investigators. An international randomized controlled trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.
- 3 McMurray J, Rankin A. Recent advances in cardiology. 1. Treatment of myocardial infarction, unstable angina, and angina pectoris. *BMJ* 1994;309:1343-51.

Are second opinions a right or a concession?

An important political issue

EDITOR,—Granting patients an unqualified right to a second opinion about their diagnosis or treatment would set in motion much needed cultural changes in medicine.¹ It would be a nail in the coffin of medical paternalism and of the "like it or lump it" health service. Giving patients the power to "vote with their feet" would flush out many poorly performing doctors.² It could generate sensitive new performance indicators—for example, for each individual consultant, the proportion of referrals that led to requests for a second opinion initiated by the patient and the proportion of these that resulted in changes of diagnosis or treatment.

We could soon expect the new arrangements to raise standards of diagnostic performance; promote both more considered choice of treatments and better monitoring of their outcomes; and reduce the frequency and scale of the costly, embarrassing, and tragic hospital blunders that have done so much in recent years to threaten patients' confidence that they are safe in the NHS's hands. This right would provide doctors with a powerful incentive to "accept that they could improve their practice and to work continuously to do so."³ In conjunction with the lifting of restrictions on patients' rights of access to their medical records, the unqualified right to a second opinion could be a powerful deterrent to clinical fraud.⁴

So much good would obviously come of this right that we need to look carefully at any reasons adduced for not establishing it. The view that resources must be conserved seems to be an excuse rather than a reason, since the cost implications both of granting the right and of not granting it remain unknown. Before considerations of possible harm to patients could be seriously entertained there would need to be good evidence of its occurrence, nature, and gravity to offset the accumulating evidence that going without a diagnosis is harmful to patients, even if the ultimate diagnosis lacks clear implications for treatment.⁴ If doctors are reluctant to countenance granting the right to a second opinion their reluctance needs to be acknowledged for what it is and the reasons for it examined openly and dispassionately.

Behind the smokescreen of contrived ethical debate and foregone economic conclusions lies a political issue. We can choose to acknowledge or

ignore it. The core values embodied in medicine in the 21st century⁵ may well hinge on the outcome of that choice.

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- 1 Pelosi AJ, McGinnis EB, Elliott C, Douglas A. Second opinions: a right or a concession? *BMJ* 1995;311:670-2. (9 September.)
- 2 Smith R. British government's proposals on poorly performing doctors. *BMJ* 1995;311:402. (12 August.)
- 3 Rippere V. Handling scientific fraud. *BMJ* 1995;311:262. (22 July.)
- 4 Woodward RV, Broom DH, Legge DG. Diagnosis in chronic illness: disabling or enabling—the case of chronic fatigue syndrome. *J R Soc Med* 1995;88:325-9.
- 5 BMA. Core values for the medical profession in the 21st century. Report of conference held on 3/4 November 1994. London: BMA, 1995.

Case history breached confidentiality

EDITOR,—I take issue with two points raised in the debate over whether second opinions are a right or a concession.¹

My first point relates to confidentiality in such an exercise. The doctors at Bethlem Royal and Maudsley Hospitals can easily be narrowed down to a shortlist of two or three, including me. If I am not one of those described then I have had an extraordinarily similar experience. I discussed the matter with a member of the *BMJ's* staff soon after the article appeared, and he said that there is sometimes a dilemma between protecting confidentiality and the need for open debate. Has the *BMJ*, which has an excellent reputation for issuing professional directives, now lurched towards the tabloid genre?

Secondly, I take issue with Anthony J Pelosi's polemic against tertiary referral centres. Having done most of his training at the Bethlem Royal and Maudsley Hospitals, Pelosi knows that patients do not sit around there being overresearched. The patient discussed in the article would immediately have had a trial of clozapine. E B McGinnis is incorrect in saying that tertiary referrals are not free: all such referrals to my unit will be free until at least 1997. This is not an ethical debate but the all too familiar tale of a patient being denied a superior modern treatment because of the inertia, prejudice, and protectionism that bedevil the psychiatric profession. If the *BMJ's* readers have any patients in whom clozapine should be tried, I and my colleagues, Dr Reveley and Professor Murray, will be happy to accept appropriate referrals. The patients will certainly not sit around for months having "expensive brain scans and well meaning attempts at psychological treatment"—our waiting list is far too long for that.

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New developments have transformed outlook for patients with schizophrenia

EDITOR,—In the debate on whether patients with schizophrenia should have the right to referral for a second opinion against the wishes of their local psychiatrist, Anthony J Pelosi attacks one of my lecturers (Dr B) for "bizarre behaviour" in advising a relative that my colleagues and I are willing to see patients in such circumstances.¹ While we much prefer to cooperate with local doctors, our experience has been that a small number of psychiatrists use ineffective or counter-productive treatments and yet oppose a referral. In such a situation where the patient continues unnecessarily to have hallucinations or crippling side effects of inappropriate drugs, his or her