possible—within a few days for light bleeding, or the same day for heavier bleeding—to see whether the fetus is still alive. If it is the woman may be reassured that she has only a one in 10 chance of subsequently losing the pregnancy.[2] If the fetus is dead and there are retained products of conception she may be admitted electively for evacuation within a few days to allow calm, daytime surgery, although if the bleeding is heavy she should be admitted immediately. This reduces the risk of septic abortion and other complications compared with that associated with emergency surgery later. If there is doubt about viability in a pregnancy of only a few weeks' gestation scanning may be repeated a week or 10 days later before proceeding to evacuation if appropriate. When she first presents we also check the woman's blood group and give anti-D immunoglobulin if she is Rh negative.

In general practice the woman's beliefs about the bleeding must be considered. It is worth explaining that the bleeding comes from the mother, not the baby; that in over 95% of cases the outcome is determined before the bleeding starts (as shown by scanning on the first day of bleeding); and that the bleeding does not itself harm the baby. It is dreadful for a woman to wait and see because she may be unwilling to commit herself to the pregnancy if she thinks that she is likely to lose it. The fact that a scan showing a viable fetus means that she has a better chance of having a successful pregnancy (nine out of 10) than she started the pregnancy with (four out of five) is reassuring. A pregnancy full of anxiety can lead to an over-anxious, overprotective approach lasting long into the baby's childhood.

It must be pointed out to the patient that there is no evidence at all that rest influences the outcome. Otherwise she may think that she is to blame if she cannot or does not rest and subsequently miscarries.

Finally, aftercare needs attention. The woman needs to know what to expect after evacuation of retained products of conception so that signs of retained products or infection are acted on early. She and her partner should be encouraged to allow themselves time to recover emotionally from the loss. Many women lose their libido and their interest in trying again for a baby after a miscarriage and should know that this is a normal grief-defence reaction, which usually passes quite quickly. They should be invited to come back to talk about it if they are not getting over their loss in a couple of months.

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## Prognosis of breast cancer associated with pregnancy

SIR,—Minerva states that many women and some doctors continue to believe that breast cancer has a poor prognosis if it is diagnosed during pregnancy or within one year of delivery.[1] She then quotes an article from the Memorial Sloane-Kettering Cancer Center, New York, suggesting that cancers associated with pregnancy are no more or less aggressive than others.[2] It should be recognised that this was a review of 56 patients, of whom only 12 were diagnosed and treated before delivery, and 80% of the 12 did not have spread to the lymph nodes. The numbers are small and the proportion of patients without spread to the lymph nodes surprisingly high.

In contrast, a series from the Princess Margaret Hospital, Toronto, which included 154 patients whose tumours were coincident with pregnancy and 96 whose tumours arose during the 12 months after parturition (conventionally termed "the lactation period"), showed a serious reduction in survival for these patients.[3] Patients whose tumours were coincident with pregnancy had a poor survival of 32% at five years and 25% at 10. Relapse free survival was 24% at five years and a dismal 18% at 10 years. Patients whose tumours arose during the lactation period fared a little better, with a five year survival of 39% and a 10 year survival of 35%. Among those whose tumours were coincident with pregnancy there was no difference in survival between patients with and without spread to the lymph nodes, and only 10% of these patients had tumours less than 2 cm in diameter.

The Sloane-Kettering series matched breast cancers that were associated with pregnancy with breast cancers that were not and were of the same stage and compared survival. This does not take into account, however, that patients with breast cancers associated with pregnancy have a strong tendency to present with more advanced disease, presumably because of the pregnancy itself. Such a comparison therefore becomes irrelevant as it is the effect of the pregnancy that is the dominant factor.

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1 Minerva. Views. *BMJ* 1991;**302**:798. (30 March.)
2 Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. *Cancer* 1991;**67**:869-72.
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## Breast cancer screening: the current position

SIR,—Dr J A Muir Gray and colleagues[1] refuse to accept the failure of the British randomised controlled trial of mammography and physical examination to show statistically sound evidence of benefit[2] and accuse unbelievers of "inappropriate use of epidemiology." Their argument, however, is based on the inappropriate use of meta-analysis.

As shown by Professor Nicholas Wald and colleagues,[3] three of the four randomised controlled trials of mammography failed to reach statistically significant benefit for women aged 50 and over. Professor Wald and colleagues suggest that the reason for the failure to show a clear benefit in the Malmö and Edinburgh trials was that both were small studies. If studies of 16 000 women in Malmö and 14 000 women in Edinburgh who accepted screening and were followed up for 10 and seven years, respectively, are "small" then the clinical benefits of such screening, if any, must also be small. As Dr Muir Gray and colleagues rightly point out, "doctors need to know the clinical benefits of such screening and not to be confused by statistical red herrings."

One of the red herrings is the combination of randomised controlled studies and case-control studies in an attempt to show the non-significant as significant. Gullberg *et al* showed that applying case-control methodology to their data from the Malmö randomised controlled trial "improved" the clinical benefit from a relative risk of 0·96 (not significant) to 0·42 (highly significant).[4] Case-control studies should thus not be combined in meta-analyses with prospective randomised trials. Dr Muir Gray and colleagues do not attempt to correct their meta-analysis for such biases.

Dr Muir Gray and colleagues express the opinion that "on the basis of the experience obtained in the early days of the NHS screening programme . . . the quality being achieved was adequate to ensure that this benefit was attainable across the country." In stark contrast, the authors of the report on the Edinburgh trial concluded with the statement that if the defects encountered in their trial "were to persist we would be only spending resources recklessly and to little or no effect."[2]

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1 Muir Gray JA, Vessey MP, Patnick J. Breast cancer screening: the current position. *BMJ* 1991;**302**:1084. (4 May.)
2 Roberts MM, Alexander FE, Anderson TJ, Chetty U, Donnan PT, Forrest APM, *et al*. The Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* 1990;**335**:241-6.
3 Wald N, Frost C, Cuckle H. Breast cancer screening: the current position. *BMJ* 1991;**302**:845-6. (6 April.)
4 Gullberg B, Andersson I, Janzon L, Ranstam J. Screening mammography. *Lancet* 1991;**337**:244.

SIR,—Dr J A Muir Gray and colleagues have taken issue with the statement that there is no statistically sound evidence that breast screening has ever saved a life in the United Kingdom.[1] This is difficult to reconcile with the fact that the only trials of screening in this country have been reported as statistically non-significant.[2,3] I suggest that it is an inappropriate use of epidemiology to discount these disappointing results by supporting unjustified meta-analyses of foreign trials which are, to a greater or lesser extent, unreliable or irrelevant, or both. For example, there is good evidence to suggest that the benefits indicated by case-control studies are partly[2] or even totally[4] factitious. Furthermore, the relevance of the more reliable randomised trials must be questioned—for example, there are several reasons why the results from the Swedish two counties study might not be reproduced here,[5] not least of which are the far superior attendance rates in Sweden.

Moreover, Dr Muir Gray and colleagues seem to be selective in their criticism of epidemiological integrity. They cite uncritically an overview by Professor Nicholas Wald and colleagues,[6] which (*a*) claims to describe the current position without any acknowledgment of the detractions of screening; (*b*) includes the breast cancer detection demonstration project, which, as its title admits, was no more than a demonstration project, on the same graph as the randomised trials; and (*c*) claims that randomised trials somehow underestimate benefit because they eliminate selection bias by including non-attenders in the study group.

I do not believe it is acceptable to say that screening saves lives when so many different factors—such as attendance rates; the method and frequency of screening; and input from radiologists, surgeons, pathologists, and community physicians—all contribute to the success of any individual programme. The fact remains that two of the finest centres in the United Kingdom failed to produce a statistically sound reduction in mortality at seven years using annual clinical examination and biennial mammography, and we have embarked on a national programme of triennial mammography alone. I agree that the weight of evidence suggests that screening probably will save some lives (and we could fill the letters column with arguments over how many), but I fear that the number will not be enough to outweigh the damage to the women traumatised in the process or the opportunity costs of the scheme. My original letter was a plea to keep screening in the age group that enjoys the maximum cost to benefit ratio,[7] and I stand by it.

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1 Muir Gray JA, Vessey MP, Patnick J. Breast cancer screening: the current position. *BMJ* 1991;**302**:1084. (4 May.)
2 United Kingdom Trial of Early Detection of Breast Cancer Group. First results on mortality reduction in the UK trial of early detection of breast cancer. *Lancet* 1988;ii:411-6.
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4 Gullberg B, Andersson I, Janzon L, Ranstam J. Screening mammography. *Lancet* 1991;**337**:244.
5 Rodgers A. The UK breast cancer screening programme: an expensive mistake. *J Public Health Med* 1990;**12**:197-204.
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7 Rodgers A. Breast screening in women aged 65-79. *BMJ* 1991;**302**:411. (16 February.)

## Deaths certified as due to coronary artery disease

SIR,—Professor Denis Pereira Gray and his colleagues repeat what we all seem to hold to be self evident—that ischaemic heart disease is the commonest cause of death in British adults.[1] We also believe that it is commoner here than anywhere else. I think that many of the deaths ascribed to ischaemic heart disease in this country are so ascribed without good evidence.

Whenever a patient dies unexpectedly the case is referred to the coroner, under normal procedure, and a coroner's postmortem examination is performed. My partners and I have been struck by the frequency with which the coronary arteries are examined, atheroma is found, and the cause of death is recorded as myocardial ischaemia due to coronary artery disease, although the brain has not been examined. Does this happen in other areas? What if there had been a stroke or a subarachnoid haemorrhage? The presence of atheroma then would not justify the certified cause of death.

Recently my partner was called urgently to a patient who had had a stroke a few months previously; she had also had a below knee amputation for peripheral vascular disease, and this had broken open and had started to bleed. While he was with her she bled to death. After the postmortem examination the cause of death was given as myocardial ischaemia secondary to coronary artery disease. I suppose that the myocardium was ischaemic, but only because she had exsanguinated. How was this a coronary death?

Is it not likely that we certify far too many deaths as having been due to coronary artery disease, and is it not also likely that countries such as the United States, which have improved their position in the league table for this disease, certify deaths more accurately than we do?

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1 Pereira Gray D, Steele R, Sweeney K, Evans P. Asymptomatic hypercholesterolaemia. *BMJ* 1991;**302**:1022. (27 April.)

## Penicillin prophylaxis in children with sickle cell disease

SIR,—Dr David Cummins and colleagues report a study of prophylactic treatment with penicillin in children with sickle cell disease.[1] They found that 31 of the 50 children studied were said to be receiving penicillin every day and that the parents of 37 of the children understood that stopping penicillin could have serious consequences. They conclude that counselling of families of children with the disease needs to be improved if the advantages of neonatal screening for the disease are not to be diminished.

Their paper made me look again at the results of a similar study that I did in 1986.[2] This looked at the care received by young children with sickle cell disease at a teaching hospital in London. The carers of 26 children were interviewed, and the findings were similar to those of Dr Cummins and colleagues. Eighteen children were said to be taking penicillin at least once a day, and the carers of 13 children understood that the aim of penicillin was to prevent infection.

There are, however, problems with presenting results in this way. Firstly, it risks blaming patients inappropriately. In my study eight of the 26 children were taking penicillin less than once a day. Investigation showed, however, that penicillin had not been prescribed for five children and that the carers of another had simply misunderstood the doctor's instructions. In six of the eight cases, therefore, failure to take penicillin daily could not be ascribed to poor compliance.

Secondly, looking only at patients attending a clinic ignores those whose follow up is inadequate—an important group for any screening programme. In my study hospital screening records identified 13 children with sickle cell disease born at the hospital during 1984-5, whom I reviewed in mid-1986. Six had never been followed up; two had been followed up but penicillin had not been prescribed; in one case penicillin had been prescribed but the carer was not interviewed; in one case penicillin had been prescribed but had never been given by the carer; and three children were taking penicillin at least once a day. There was thus good evidence that nine of the 13 children were not taking penicillin; failures of management after screening were more important than parental noncompliance as reasons for inadequate protection.

These findings should be interpreted cautiously. The numbers are small and the study examined care given before evidence from randomised controlled trials of the benefits of prophylactic penicillin in young children with the disease[3,4] was circulated widely. Despite these caveats the central lesson—that the organisation and content of follow up need to be planned as carefully as screening itself—should not be lightly dismissed. Otherwise, neonatal screening is likely to fall short of its aim of reducing the morbidity and mortality associated with sickle cell disease.

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1 Cummins D, Heuschkel R, Davies SC. Penicillin prophylaxis in children with sickle cell disease in Brent. *BMJ* 1991;**302**: 989-90. (27 April.)
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## Asymptomatic hypercholesterolaemia

SIR,—In their recent letter[1] Dr Denis Pereira Gray and colleagues state: "Peto estimated that a 1% reduction in serum cholesterol will lead to a 3% reduction in coronary heart disease. On this basis the average reduction of 7% that we are currently achieving through general practitioner advice without drugs is likely to lead to a 21% reduction in coronary disease."

Can they really believe this? Would they conclude that a 33% reduction in cholesterol concentration would be followed by a 100% reduction in coronary disease?

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1 Pereira Gray P, Steele R, Sweeney K, Evans P. Asymptomatic hypercholesterolaemia. *BMJ* 1991;**302**:1022. (27 April.)

AUTHORS' REPLY,—Dr Fogarty's neat reductio ad absurdum illustrates the difficulties in summarising complex statistical models in a single sentence.

Of course we agree with him that it is absurd to predict a 100% reduction in coronary disease, but we still understand that Peto's statistical analyses best represent the relation between the reduction in serum cholesterol concentrations and coronary heart disease. This is a summary of research work that has already been undertaken on the ranges of cholesterol concentrations that are found in Britain. The exact quotation from the Standing Medical Advisory Committee (1990) is:

The Working Party accepted a new analysis of existing data showing that the relationship between blood cholesterol levels and coronary heart disease is stronger than generally realised. This analysis was made available by Mr Peto. It has been presented at scientific meetings and so exposed to scrutiny (Peto, 1989). It is generally accepted that, in middle age, over the range of blood cholesterol concentrations observed in Britain, a 10 per cent reduction in blood cholesterol level is associated with a 20 per cent reduction in coronary heart disease, i.e. a "rule of two" applies. The new analysis suggests the rule of two is an underestimate which fails to allow for the effects of "regression-dilution" bias. It suggests that the true reduction is in fact about 30 per cent, therefore giving a "rule of three". Expressed in more formal terms the cholesterol "elasticity", the percentage change in coronary heart disease events following a one per cent change in blood cholesterol levels, is about three. Elasticity is a proportional rate of change, a unit-free measure of responsiveness.[1]

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1 Standing Medical Advisory Committee. *Blood cholesterol screening: the cost effectiveness of opportunistic cholesterol testing*. London: SMAC, 1990. (Para 2.2.)

## Epilepsy and disappearing lesions: adopting a wait and see policy

SIR,—Drs A Kennedy and F Schon recently recommended anticonvulsant treatment alone (that is, adopting a wait and see policy) in the management of epileptic patients in whom computed tomography shows a solitary space occupying intracranial lesions.[1] This policy may be acceptable in the United Kingdom but it is not necessarily suitable in places where computed tomography is not readily available and is expensive.

A 5 year old girl presented to our hospital with a right sided tonic-clonic seizure lasting about 15 minutes. Physical examination was entirely normal. Her full blood count, erythrocyte sedimentation rate, and a chest *x* ray film were all within normal limits. Cerebrospinal fluid contained $6\times10^6$ red cells/l, no white cells, and protein 0·14 g/l. Computed tomography showed a ring enhancing lesion in the left parietal lobe. Anticonvulsant and antituberculous treatment was started. After four months she had had no further seizures, her weight had increased from 13·2 kg to 15·4 kg, and repeat computed tomography showed near resolution of the lesion.

There is only one computed tomography scanner in Nepal. Few patients can afford the cost of travel to Katmandu and of scanning; fewer still can afford repeat tests. It would seem unjustified in Nepal, where tuberculosis is highly endemic and scanning expensive, to adopt a wait and see policy. Our patient was an exception in that her parents could afford multiple investigations. We think that, in our situation, if computed tomography shows a solitary lesion antituberculous treatment should be started.

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1 Kennedy A, Schon F. Epilepsy: disappearing lesions appearing in the United Kingdom. *BMJ* 1991;**302**:933-5. (20 April.)