

# CORRESPONDENCE

## Breast cancer survival advantage with radiotherapy

Sir—An important finding of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview (May 20, p 1757),<sup>1</sup> which is not highlighted by the trialists, is that the survival advantage conferred by radiotherapy appears to be inversely proportional to the adequacy of locoregional surgical treatment. Their figure 1 shows that the benefit of radiotherapy was evident only in patients with positive lymph nodes on axillary sampling who had no further surgery (primarily the Danish trials). Assuming inadequate treatment of the axilla to be more hazardous than inadequate treatment of the breast, the trend for overall survival differences conferred by radiotherapy among the different surgical groups is exactly as one would expect: mastectomy with axillary sampling, plus 17%; lumpectomy with axillary clearance, plus 6%; mastectomy in clinically node-negative patients, plus 2%; and mastectomy with axillary clearance, minus 4%. Therefore, the Danish trials may prove only that adequate locoregional treatment is important to survival, irrespective of whether that treatment includes surgery or radiotherapy.

The EBCTCG note the heterogeneity of the effect of radiotherapy on survival with regard to the surgical treatment group, and then state: "there may, however, be more informative ways of subdividing the overall mortality findings". I disagree. Their suggestion that radiotherapy confers an early advantage by improving locoregional control and a late disadvantage by increasing cardiovascular mortality is certainly cogent and clinically useful, but it does not make the differences due to surgical treatment any less compelling.

The EBCTCG data give us no reason to believe that adding radiation therapy to modified radical mastectomy is of benefit and suggest that it may very well be detrimental. Given the potential for late cardiovascular mortality, and the known increase in the risk of arm oedema after the combination of axillary surgery and radiotherapy,<sup>2</sup> it would seem prudent to continue to treat patients with either of the current standard options—breast conserving surgery combined with axillary

dissection and breast radiotherapy, or modified radical mastectomy alone.

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- 1 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; 355: 1757–70.
- 2 Larson D, Weinstein M, Goldberg I, et al. Edema of the arm as a function of the extent of axillary surgery in patients with stage I-II carcinoma of the breast treated with primary radiotherapy. *Int J Radiat Oncol Biol Phys* 1986; 12: 1575–82.

Sir—Unfortunately, the analysis presented by EBCTCG<sup>1</sup> fails to fulfil its potential to answer major questions of clinical interest and need, because the authors do not address the most pertinent issues. What are the possibilities of modern treatment techniques to avoid vascular damage? Which patient groups will benefit from radiotherapy by improving their locoregional control? Which patients will also improve their survival chances?

The investigators say that old-fashioned radiotherapy may cause more late morbidity. The EBCTCG accumulation of clinical trials includes trials which, by today's standards, are clearly unacceptable. The paper represents a history rather than guidance for how patients should be treated. It is also questionable if the role of radiotherapy can be described in as simple terms as in the overview, namely in the form of dose, a crude target, and then a few prognostic parameters. The issue is much more complex, especially when it comes to cardiac involvement. It is obvious from several studies<sup>3–4</sup> that if the dose to the heart is reduced substantially, the excess non-cancer morbidity and death rate is reduced or avoided. Therefore, the radiation technique and target is of importance, but these areas were not assessed sufficiently. The investigators are not correct in their argument that the observation time is too short in the modern trials. The observation time in the Danish studies,<sup>3–4</sup> where a modern radiotherapy technique avoiding cardiac irradiation was applied, is now 10–18 years without excess non-cancer deaths.

The experience from the Stockholm trials clearly shows that the enhanced cardiac morbidity occurs within a much shorter time.

The pre-treatment assessment in the EBCTCG series is also incomplete. Some of the older trials are based on clinical assessment only in the axilla, which is no longer acceptable. The relevance of such trials in this context is therefore questionable. Information on tumour size, number of positive nodes, and nodes removed, together with menopausal and hormone receptor status, age, and the histopathology and grade of tumour are all needed to be able to describe the appropriate prognostic characteristics. Only then can clinical guidance be given for the treatment of patients today.

The investigators say that an improvement in survival should be comparable with a large improvement in local control. This issue may be much more complex. The patients who benefit in terms of survival are probably those at high risk, but with a small tumour burden (eg, few positive nodes and small tumour size). Whereas patients who have the large reduction in local failure are either insufficiently surgically treated or have high-risk characteristics (large tumour and/or many positive nodes). The questions to be addressed are: what is the role of radiotherapy in reduction of the locoregional failure rate? And, what is the role of radiotherapy in improvement of survival? Results from the Vancouver and Danish trials<sup>3–5</sup> indicate that the benefit may be in patients who are node-positive who received systemic therapy (chemotherapy/tamoxifen) after mastectomy with a sufficient number of lymph nodes removed. It appears from these trials that patients with few positive lymph nodes and small tumours may have the greatest benefit. This finding deserves to be addressed in the meta-analysis as well.

A meta-analysis can be a helpful tool, but unfortunately the EBCTCG overview does not appropriately address the current clinical situation in which late side-effects can be avoided by modern radiation techniques and equipment. Patients making treatment decisions on the basis of this information may refuse radiotherapy and run the risk

of a locoregional cancer recurrence and a reduced chance of survival. We urge the EBCTCG to look to their responsibilities and use their resources to provide a more detailed analysis which answers our questions. Such reanalyses would clarify the discrepancy between the EBCTCG analysis and several smaller, but more focussed overviews, and in turn guide modern radiotherapy.

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- 1 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; **355**: 1757–70.
- 2 Højris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. *Lancet* 1999; **354**: 1425–30.
- 3 Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999; **353**: 1641–48.
- 4 Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997; **337**: 949–55.
- 5 Ragaz L, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; **337**: 956–62.

Sir—The EBCTCG show that<sup>1</sup> at 20 years follow up, locoregional radiotherapy gives a significant improvement in recurrences of breast cancer, and in breast cancer survival. Non-breast cancer, deaths were, however, increased in the radiotherapy group. Taking all deaths, the overall survival benefit of radiotherapy was slight. The investigators conclude that “while the absolute benefit of the 20 year overall survival is about 2–4%, the excess deaths from non-breast cancer causes would reduce this benefit in young women, and reverse it in older women”.

The EBCTCG analyses influence policies of breast cancer management across the world, so the results must be interpreted in the context of their clinical relevance. As contributing trialists, we also feel that they should be easily understood by clinicians lacking expertise in statistics.

Close to half of the patients in this

overview were in radiation trials done before 1975 (equipment and planning techniques considered obsolete according to current standards, with greater non-breast cancer mortality); and almost 50% of all patients were lower risk subsets (ie, node negative). Therefore, it would be essential to determine the overall cost-benefit of radiotherapy in newer radiotherapy trials (ie, after 1975) and in patients at higher risk of recurrence (ie, node positive). Information for these cohorts is provided only separately for breast cancer and non-breast cancer deaths, with no data on overall survival for each of these subsets. We projected the results of the ERCTCG meta-analysis in each cohort as the net sum of all avoided versus excess deaths due to radiotherapy (see table). We calculated a total of 29 deaths per 1000 radiotherapy-treated patients avoided due to radiotherapy in the node-positive subsets ( $p=0.0006$ ), compared with an overall 3.3 excess in deaths in the node-negative group ( $p=0.55$ ). In trials started after 1975, there were 33 deaths per 1000 patients avoided ( $p=0.001$ ), compared with an excess of 10 deaths per 1000 treated in trials before 1975 ( $p=0.34$ ).

Our data allow a more forceful interpretation of this meta-analysis. Even the suboptimum radiotherapy, as given in most trials in the EBCTCG overview, confers a substantial benefit in node-positive cohorts, and to patients treated after 1975. These conclusions are also reflected in several randomised trials,<sup>2–4</sup> with close to 70–90 avoided deaths per 1000 treated, as in the meta-analysis restricted to trials with systemic therapy.<sup>5</sup>

Our comments emphasise the potentially large problems when heterogeneous trials are compared in meta-analyses. These will require appropriate analysis of clinically relevant subcategories, as done by the EBCTCG group for the 1998 tamoxifen overview. In that analysis, subgroups with more substantial treatment benefit were identified, such as patients who are

oestrogen positive treated for 5 years. The same careful examination needs to be made for the radiotherapy meta-analysis, because radiotherapy given with obsolete equipment given to patients at low risk of recurrence may not be cost-effective and may be counterproductive. In those, the cost benefit may overshadow the significant mortality reduction of modern radiotherapy applied to high-risk subsets. Without such scrutiny, radiotherapy benefits may be missed, and hundreds or thousands of lives may be lost unnecessarily each year as a result of breast cancer.

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- 1 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer. *Lancet* 2000; **355**: 1757–70.
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- 3 Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node positive premenopausal women with breast cancer. *N Engl J Med* 1997; **337**: 956–62.
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- 5 Whelan TJ, Julian J, Wright J, Jadad AR, Levine M. Does logoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000; **18**: 1220–29.

Sir—The method used by the EBCTCG<sup>1</sup> to define cause of death: “all deaths after recurrence were classified as breast cancer deaths”, is potentially flawed. This assumes that no recurrences are salvageable, which may be untrue, especially for the breast conservation trials. Patients who develop a local recurrence within a conserved breast, have a quite different outlook to women who develop

Category	Deaths						p†
	Breast cancer		Non-breast cancer			Observed-expected*	
	Radiotherapy	Control	Radiotherapy	Control	Net/1,000		
<b>Time of radiotherapy</b>							
Before 1975 (n=9489)	43.5%	46.8%	18.3%	14.0%	+10.0	+15.6	0.34
After 1975 (n=10 686)	33.8%	37.9%	5.6%	4.8%	-32.8	-104.5	0.001
<b>Node positivity</b>							
Positive (n=10 307)	47.1%	51.6%	8.6%	7.0%	-29.2	-121.6	0.0006
Negative (n=9868)	29.2%	32.2%	14.7%	11.4%	+3.3	+23.5	0.55

\*Observed and expected numbers of all deaths (overall mortality), and their variances (not shown), were taken from EBCTCG 2000, table 8, as the sum of breast cancer and non-breast cancer deaths, separately for each category of interest. †Approximate p values were derived from the ratio of O-E to the standard deviation of O-E (estimated from the square root of the sum of the separate variances). --avoided. +=excess deaths of radiotherapy versus control expressed as net overall deaths per 1000 treated patients.

#### Categories of EBCTCG radiation meta-analysis

metastatic disease as their first relapse. Because radiotherapy reduces the recurrence rate by a third, the proportion of patients in the control groups whose cause of death is misclassified by this assumption is much larger than in the radiotherapy groups. Because the percentage difference in breast cancer deaths was relatively small (18.6% vs 21.3%), this classification procedure alone could account for the difference.

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- 1 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; **355**: 1757-70.

#### EBCTCG Secretariat's reply

Sir—From our meta-analysis we found that radiotherapy slightly reduced mortality from breast cancer, particularly during the first decade or so of follow-up, but slightly increased mortality from vascular and other causes, particularly after the first decade of follow-up. As yet, the trials started after 1975 have an average of only about 10 years of follow-up, so they include the main period of any benefit but not the main period of any risk (especially for women who were still premenopausal when randomised and whose main period of vascular risk will come when they are older). Hence, longer follow-up of their results may well change the apparent balance of risk and benefit.

Unduly selective emphasis on the recent trials, on results for women with node-positive disease, on results for women also receiving systemic therapy, or just on any particular part of the totality of the randomised evidence may lead to mistaken conclusions. The average effect of radiotherapy on breast cancer deaths was not large, so some trials will, by chance, yield results that are appreciably better or appreciably worse than this average.

It is reasonable to hope that the main life-threatening side-effects of radiotherapy can be substantially reduced by careful technique (especially if this spares the coronary, carotid, and other intrathoracic arteries). It is, however, less reasonable to hope that there were substantial differences between these trials in the main benefits of radiotherapy (at least for women who were at substantial risk of local recurrence). The proportional reduction of about two thirds in local recurrence

that is produced by radiotherapy did not appear to differ much from one trial to another, or between older and newer radiotherapy techniques. Hence, the real extent to which radiotherapy can reduce breast cancer mortality may well be assessed more reliably by a meta-analysis of all the trials (which suggests an absolute benefit of only a few per cent) than by unduly selective emphasis only on the more promising studies. Carl Atkins correctly re-emphasises that only if there is a substantial risk of local recurrence can radiotherapy produce a substantial decrease in that risk.

On statistical methodology, Sean Bydder and colleagues note that for breast cancer deaths, as defined in the EBCTCG meta-analysis (and for other deaths), a crude statistical analysis would yield biased results. For this reason, however, we did not use such crude methods, and the method of logrank subtraction that we did use avoids any such bias.

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### Sex ratio in the children of the Austrian chloracne cohort

Sir—Paolo Mocarelli and colleagues (May 27, p 1858)<sup>1</sup> presented their findings on the cohort in Seveso, Italy, and concluded that there is a significantly lower sex ratio if fathers had been exposed to dioxin when they were younger than 19 years. We reassessed the Austrian cohort in line with the findings of Mocarelli and colleagues.

The Austrian chloracne cohort consists of 159 workers (157 men, two women) who were exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the early

1970s when working in building 518 of a chemical plant in Linz, Austria. Exposure mainly occurred after May, 1971, during production of 2,4,5-trichlorophenol. The outbreak of chloracne led to technical improvements in May, 1972, and to a complete halt in production and closure of the building in August, 1973. After closure other people were exposed to dioxins during cleaning and reconstruction work and consequently developed chloracne. Only four people were exposed before 1971.

Nine people examined in 1990 had blood fat concentrations in the range of 98–659 pg/g.<sup>2</sup> In a larger sample of 46 men and one woman in 1996 the corresponding range was 19–2900 pg/g and has been correlated with individual work histories and long-term health effects.<sup>3</sup>

Live births to the exposed workers from 1969 until 1990 were documented. The two women of the cohort did not give birth to a child, so the data only comprise children of exposed fathers. No difference from the usual sex ratio was noticed in the complete group. Before the exposure of the fathers 19 boys and 12 girls were conceived. After onset of exposure the fathers sired 26 boys and 30 girls thus showing a tendency towards more girls. But no trend could be seen either concerning the amount of the dioxin-load or the duration between exposure and date of birth.

We found that most of the difference in the number of boys and girls is a result of more girls from fathers who were 20 years of age or younger when they were first exposed to dioxin (figure). In fathers older at exposure even high doses of dioxin had no apparent effect on the sex ratio of their offspring.

The number of young fathers at exposure to dioxin is low in the Austrian cohort, but the findings are consistent with the findings of Mocarelli and colleagues. There is an intriguing theory because it suggests a mechanism by which an exposure at a young age would lead to an effect on the cellular level even years later. The spermatogonia stay diploid during the whole sexual active life of a man. In meiosis shortly before the sperms are ready for conception four haploid spermatids (two bearing an X-chromosome and a Y-chromosome each) are generated from one diploid cell. Any mechanism that would reduce the number of Y-sperms or decrease their efficiency would have to act in the short time before the conception of the child. We recommend further studies into the cellular mechanism to better understand the effects of dioxin.



Numbers of boys and girls born to fathers exposed to dioxin

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- 1 Mocarelli P, Gerthoux PM, Ferrari E, et al. Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* 2000; **355**: 1858–63.
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## Pneumococcal vaccine and HIV-1 infection

Sir—N French and colleagues have documented the high degree of susceptibility of HIV-1-infected patients to invasive pneumococcal disease and their suboptimum response to 23-valent pneumococcal polysaccharide vaccine (PPV). More recently (June 17, p 2106)<sup>1</sup> they have reported that pneumococcal vaccine was not effective and possibly harmful in these patients.

Workers in the USA have shown that black patients with AIDS have a strong susceptibility to invasive pneumococcal disease, with risk 5.4 times higher than that of similarly infected white patients.<sup>2</sup> Furthermore, in a case-control study, pneumococcal vaccination was protective in white patients but not in black patients.<sup>3</sup> Why black people are not protected by pneumococcal vaccination is poorly understood. Thus, the lack of protection observed in the Ugandan trial is disappointing but not surprising.

French and co-workers believe that their results provide evidence of vaccine-associated harm because the frequency of all-cause pneumonia was significantly increased in the vaccine group. This observation has serious implications, since whether bacterial pneumonia accelerates the progression of HIV-1 infection or simply indicates virological and immunological deterioration that predisposes to bacterial pneumonia and eventual death is unclear.<sup>4</sup> Their findings provide some measure of reassurance: mortality rates in the vaccine and placebo groups were identical.

The finding of more cases of all-cause pneumonia in the vaccine group was unexpected. If PPV is harmful (or beneficial), its effects should be greatest for vaccine-serotype invasive disease, less so for all pneumococcal disease (including infection due to non-vaccine serotypes), and least of all for all-cause

pneumonia, only some of which is due to *S pneumoniae*. In the Ugandan trial, however, the hazard ratio for the least specific outcome did not move in the direction one would normally expect.

Randomisation of patients ensures equality in the distribution of variables (measurable or not) at the time, but not necessarily for the whole course of entry into a clinical trial. Moreover, randomisation is not sufficient or necessary for hypothesis testing. A causal interpretation of unexpected trial results based on a statistical analysis should be viewed as tentative and should prompt investigators to search for differences in intermediate outcomes that could have arisen during the trial. In the Ugandan trial, different rates of physician visits or of obtaining blood cultures and chest radiographs in the two study groups could have affected the results.

French and colleagues state that pneumococcal vaccination probably has little, or no public health value in sub-Saharan Africa. They overlook limited but persuasive evidence that pneumococcal infection is an important health issue for Africans who are not HIV-1 infected.<sup>5</sup> Such people include young mothers, most of whom are HIV-1-negative, who might be given PPV to protect their infants. Also included are older individuals, many of whom will be called upon to care for grandchildren who have been orphaned because their parents died of AIDS.

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- 1 French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet* 2000; **355**: 2106–11.
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### Authors' reply

Sir—David Fedson and Michael Watson suggest the failure of the pneumococcal polysaccharide vaccine

(PPV) in HIV-1-infected East Africans was not unexpected. Findings from retrospective, case-control studies or both, in North America have shown HIV-1-infected black adults to be at increased risk of invasive pneumococcal disease and to derive little protection from PPV.

Reasons for vaccine failure may or may not be linked to factors generating increased susceptibility. We are unaware, however, of any immunogenicity data of a difference in response to PPV by ethnic origin or skin colour. In addition, the reasons for failure of PPV in East Africa could be different from those in North America. To date, the universal recommendation for the use of PPV in HIV-1-infected adults in the USA is not qualified by ethnic origin. Whether the study of Breiman and colleagues will alter these recommendations remains to be seen. We stress, however, that we did not do our study to influence vaccine policy in North America, but to address an entirely different public-health issue in Uganda. It is difficult to base policy on the results of a single study, but our data give little encouragement for the widespread use of PPV in HIV-1-infected adults in sub-Saharan Africa.

In a randomised and (just as critical) blinded study, finding a difference in disease surveillance episodes and investigation requests between vaccine and placebo recipients will not discriminate between a by-chance difference in health-seeking behaviour and a biological effect of the vaccine. Nevertheless disease surveillance between vaccine and placebo recipients did not differ significantly. Although the results of the study were unexpected, we had allowed for them. We based sample-size statistics on two-tailed tests and, as such, the validity of the hazard ratio or p value is no more questionable than if vaccine had been effective. In addition, as we pointed out in the discussion, our results might not be as isolated and unexpected as we first assumed. We cannot comment on lack of trend in the hazard ratios. CI are wide and overlap.

Our statements about the limited public-health value of PPV in sub-Saharan Africa refer to its use in HIV-1-infected adults. We would welcome further support and research into pneumococcal vaccination of other at-risk groups in Africa, if done in a way relevant to each region's health-care needs. PPV might offer benefits to non-HIV-1-infected African adults. However, the possible increased risk of invasive pneumococcal disease we saw with HIV-1-infection may mean that individuals offered PPV might also

need HIV-1 counselling and testing. The cost-effectiveness of any such widespread intervention will, therefore, be severely compromised.

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## Response to the MMR question

Sir—Proponents of the belief that measles-mumps-rubella (MMR) vaccine causes autism quote two strands of evidence. First, that the apparent increase in autism coincided with the use of the vaccine and, second, that behavioural regression typically occurs within a few months of vaccination.<sup>1,2</sup> We were unable to substantiate either of these arguments.<sup>3</sup>

Raymond Gallup (July 8, p 161)<sup>2</sup> dismisses our findings on the grounds that they are biased, since some of the authors are employed by a public-health authority. Such dismissal is absurd and insulting, especially in view of our record in identifying other adverse events attributable to MMR.<sup>4</sup> His implication that we have something to hide by not immediately handing over our data to a US Congressional Committee is similarly ill informed. Ethical and legal issues surrounding patient confidentiality, data ownership, and data protection must be resolved before we could agree to such a request. Gallup asserts, without explanation, that our methods were flawed. We presume that he is quoting the false testimony that Andrew Wakefield gave to the US Congressional Hearing on Autism and Immunisation on April 6, 2000, alleging that the Royal Statistical Society (RSS) had pronounced our methods to be wrong. This claim is totally unfounded, and Wakefield should withdraw it.

J H Roger (July 8, p 161)<sup>2</sup> states that we used the wrong study design. This is a serious criticism, and we are surprised that he did not voice it at the RSS meeting he describes. We reject his allegation since he unreasonably criticises us for not setting out to test a hypothesis that had not been formulated. The data that generated the Wakefield hypothesis suggest an interval of 24 h to 2 months between MMR and first behavioural symptoms, typically regression.<sup>1</sup> This finding is supported by parental reports as typified by that of David Thrower (July 8, p 161).<sup>2</sup> It therefore

seemed imperative to test the hypothesis that there was a close temporal association between MMR and regression and other markers of autism. Our methods were entirely appropriate for this purpose.

Roger implies that we should have used a case-control design. We compared first-dose MMR-vaccine coverage in autism cases born after 1987 and in the denominator population: this design is akin to an unmatched case-control study, with the entire population as controls. The groups did not differ. Moreover, coverage was constant when autism incidence was apparently rising. These findings provide further evidence that the very large reported increases in autism quoted by Thrower and Gallup cannot reasonably be attributed to MMR vaccine.

Roger states that the case-series method is unsuitable for investigating longer-term associations. In this instance, at least, it is not. In response to his reformulation of the Wakefield hypothesis to accommodate longer induction times, we did new analyses of our data. The results are negative, providing no support for the hypothesis that MMR increases the risk of autism at any time after vaccination.

Finally, Roger wrongly states that regression occurred typically 6 months after parental concern. Of the 93 cases with the two dates recorded, parental concern predated regression in only 21. The median intervals from concern to diagnosis we quoted<sup>4,5</sup> are incorrect; the correct values are 19 months for core autism (n=198), 18.5 for atypical autism (n=100), and 48 for Asperger's syndrome (n=47).

At the RSS meeting, Roger began his talk by giving a moving personal account of what it is like to be a parent of a child with autism. We strongly endorse his and other parents' calls for more research into the cause of this disorder. However, those who, in the absence of any evidence of causality, condemn a vaccine that has saved countless children from premature death and disability, do no service to children, parents, or health professionals seeking to understand the causes of this distressing disorder.

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- 2 The MMR question. *Lancet* 2000; **356**: 160–62.
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## Palliative pain relief

Sir—Andrew Thorns and Nigel Sykes (July 29, p 398)<sup>1</sup> convincingly add evidence to the notion that increasing opioid dose is not followed by an increase in mortality in palliative care.<sup>2</sup>

Thorns and Sykes' results reinforce that cancer pain can be treated effectively with relatively simple measures—the mean morphine dose was 26.4 mg and only between 2.4 and 7.1% of cancer patients died in pain. These data should help to demystify cancer pain management.

Unfortunately, a cautious look at the actual translation of widely accepted cancer-pain management guidelines casts some doubts on a direct impact on patient management. The prescribing patterns for the use of opioids seem particularly refractory to change: in a report from Germany, all of 47 terminally ill patients suffered from unrelieved pain and in 43% pain management was judged unsuccessful.<sup>3</sup>

We<sup>4</sup> did a retrospective chart review of cancer patients receiving strong opioids on a medical ward at the University of Freiburg, Germany. Misunderstandings and shortcomings were still encountered, despite the WHO guidelines on cancer-pain management.

Between April, 1996, and May, 1998, we reviewed the charts of 100 cancer patients receiving strong opioids on a medical ward. Cancer was advanced in most patients.

Morphine was most frequently used (oral sustained release 56%, oral instant release 16%, intravenous 47%), and to a lesser extent drugs such as pethidine and piritramide. Many patients received opioids as needed (sustained-release morphine 18%, buprenorphine 9%) or the intake

schedule differed from the duration of action of the opioid (sustained-release morphine 12%). Weak opioids (11% tramadol) and partial agonists or antagonists were used concomitantly with strong opioids (12%). Laxatives were prescribed in 21% of the patients. Thus, simple pharmacological principles of opioid use and cancer-pain management guidelines were ignored.

We could not assess palliation of pain because of the absence of records. Use of multiple adjuvants and breakthrough medications implied difficulties in pain management and unrelieved pain.

This survey indicates poor or absent pain documentation, misunderstandings about basic pharmacological principles of opioid use, and a lack of adherence to guidelines in Germany.

Thorns and Sykes suggest the consultation of a palliative-care team if opioid doses need to be increased more than 2.5-fold in 24 h. In Germany, even most university hospitals have no palliative-care specialist. A single chair in palliative care exists at the University of Bonn. University hospitals should establish palliative-care teams and chairs for palliative medicine for the benefit of patients, medical students, and physicians.

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## Nitric oxide in neonates

Sir—Tim Higenbottam and colleagues, in their Aug 5 commentary,<sup>1</sup> propose chronic inhaled nitric oxide as a treatment for various disorders. They neglect, however, to note that nitric oxide can inactivate vitamin B12 and lead to severe folate deficiency. The net result may be megaloblastic anaemia and neurological changes. This

complication does not preclude chronic nitric oxide therapy, but it should be taken into account.

Active vitamin B12 contains cobalt in its reduced form (Co+). Nitrous oxide irreversibly oxidises reduced cobalt to the Co++ and Co+++ forms and renders vitamin B12 inactive. This mechanism in turn reduces the activity of the cobalamin-dependent enzyme methionine synthetase, resulting in decreased production of methionine as well as tetrahydrofolate, which is required in DNA synthesis.

In one study, five patients with unsuspected vitamin B12 deficiency developed subacute combined degeneration of the spinal cord after nitrous oxide anaesthesia.<sup>2</sup> Patients with vitamin B12 deficiency are especially sensitive to neurological deterioration after nitrous oxide anaesthesia. If unrecognised, the neurological deterioration can become irreversible and result in death.

In another study of 40 patients and 12 controls, cobalamin-dependent methionine synthesis became seriously compromised during nitrous oxide anaesthesia, leading to raised plasma homocysteine.<sup>3</sup>

This marker might, therefore, be used for monitoring nitrous-oxide-induced cobalamin inactivation.

The secondary development of folate deficiency from nitrous-oxide-induced effects has occurred in some seriously ill patients and may in turn result in the persistence and possible progression of bone marrow abnormalities. R J Amos and co-workers<sup>4</sup> studied 48 patients admitted to an intensive-care unit and given nitrous oxide anaesthesia. They suggest that consideration should be given to early supplementation with folic acid in such patients. In 70 seriously ill patients admitted to an intensive-care unit, these workers saw no evidence of folate deficiency in patients who had not received nitrous oxide, but evidence of a disturbance in folate metabolism in a large proportion of patients exposed to nitrous oxide anaesthesia. The development of megaloblastic changes in patients in intensive care could depend on factors related to the acute illness in addition to nitrous oxide anaesthesia.<sup>4</sup>

Folinic acid seems to offset the effects of nitrous oxide and rapidly restore normal marrow activity, and is effective following nitrous oxide exposure for up to 24 h.<sup>5</sup>

In studies of chronic nitric oxide administration, these findings should be taken into account to avoid potential harm to study participants and to discover whether a safe long-term regimen can be devised.

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Sir—Tim Higenbottam and colleagues<sup>1</sup> describe how chronically inhaled nitric oxide (NO) is a very promising treatment for pulmonary hypertension. However, we would like to add a note of caution for the use of such treatment. Chronically administered NO may pass the blood brain barrier (BBB) and affect the central nervous system (CNS).

There is evidence that NO can alter the functional state of the permeability of the BBB.<sup>2</sup> Increased permeability of the BBB means that the medications that patients are on will pass more easily into the CNS and therefore may reach toxic concentrations. Therefore, extreme caution should be used in prescribing co-medications. However, long-term consequences of such NO treatment on the stability of the BBB needs to be clarified. NO may also alter the mental state of the patients. It is therefore difficult to predict what exactly will happen to the mental state of these patients; the preclinical data is controversial, and indicates that there could be the development or improvement of psychoses, depression, and anxiety.<sup>3</sup> Also, long-term treatment with NO may increase the susceptibility to stroke because NO-synthase inhibitors have been found to prevent development of stroke in preclinical experiments.<sup>4,5</sup> We suggest that during these clinical trials and in the future clinicians should closely monitor mental and neurological states of patients treated with NO inhaled chronically.

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## Influence of hysterectomy on pelvic-floor dysfunction

Sir—J S Brown and colleagues (Aug 12, p 535)<sup>1</sup> do not address post-hysterectomy dysfunction other than urinary incontinence, nor offer explanations for causation. Prolapse and abnormal bladder emptying can also occur after hysterectomy. All three dysfunctions can be explained by connective-tissue damage.<sup>2</sup>

Two menopausal groups undergoing suburethral sling surgery<sup>3</sup> for cure of stress incontinence, one with previous hysterectomy (n=27) and the other without, were prospectively assessed. Mean age was 61 years (range 50–79), parity three (range 1–9), and mean weight 66 kg (range 41–108). Age, parity, intercurrent disease, and previous operations were similar in the two groups. Though the objective cure rate for stress incontinence was 90% in the two groups, in the first 24 months, 12 of 27 patients from the hysterectomy group required further surgery for de novo vaginal prolapse, but only two of 23 in the non-hysterectomy group required such surgery.

In another 163 patients<sup>2</sup> (mean age 54 years), 59 had undergone hysterectomy. Of these 59, 31 (52%) had abnormal residual urines (>50 mL), a significant association. 20 of the 59 patients underwent surgical tightening of posterior fornix laxity, which reduced mean residual urine from 91 mL to 24 mL (p<0.001) and symptoms of abnormal emptying were also improved.

A constant intraoperative finding in the studies was laxity and atrophy of the uterosacral ligaments, which may give a clue to causation. The descending uterine artery supplies the uterosacral ligaments, and ligation during hysterectomy may cause atrophy.

Transverse suturing of the circular defect in the vagina can loosen the uterosacral ligament supports. These ligaments are an important structural support of the uterus, help tense the vaginal membrane, and anchor the downward-acting muscle forces that stretch open the outflow tract during micturition.<sup>2</sup> Weakening of these forces by lax uterosacral ligaments explains the correlation between raised residual urine and prior hysterectomy. Weakened ligaments may loosen the vaginal tension at the bladder base, predisposing to premature firing off of the stretch receptors.<sup>4</sup> The concept of a critical vaginal tension explains why urge incontinence is frequently cured by vaginal operations such as cystocele repair, and Burch colposuspension.<sup>4,5</sup> These operations stretch the vaginal membrane below the bladder base.

Brown and colleagues' findings of increased incontinence with age, but not immediately, in patients with nerve damage after childbirth, supports a connective-tissue rather than a nerve-damage causation.<sup>2</sup> Connective tissue loses strength and elasticity with age. Conservation of the cervix<sup>1</sup> seems to prevent postsurgical incontinence, giving additional support to the hypothesis that posthysterectomy bladder dysfunctions are caused by mechanical loosening of the ligaments at the time of hysterectomy, through devascularisation of the connective tissue structure, transverse suturing of the vaginal vault, or both.

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## More on mammography

Sir—Peter Gøtzsche and Ole Olsen presented<sup>1</sup> a meta-analysis of ran-

domised trials testing the effects of screening mammography. They concluded that screening mammography does not reduce breast cancer mortality and is not justified. This finding was unexpected and at variance with earlier reviews.<sup>2,3</sup> Discussion and criticism ensued, in an accompanying commentary,<sup>4</sup> and elsewhere.

Although Gøtzsche and Olsen work at the Cochrane Nordic Centre, and listed this association in their report, theirs was not a Cochrane Collaboration systematic review, and has not been reviewed by Cochrane Breast Cancer Group editors.

Systematic reviews themselves have methodological strengths and weaknesses in the same way as any other study design. To minimise methodological shortcomings in its systematic reviews, the Cochrane Collaboration has in place formal structures of peer review (including consumer input), first of proposed protocols and then of the reviews themselves. Both protocol and review, if accepted, are then published in The Cochrane Library, which contains a mechanism for external comment and criticism.

As it happens, Gøtzsche and Olsen did submit a protocol to undertake a review of screening mammography trials to the Cochrane Breast Cancer Review Group. This was submitted to us before their *Lancet* publication, which we knew nothing about. The protocol was then peer-reviewed and formally accepted before the *Lancet* article was published.<sup>5</sup> This should not imply that the editorial committee supports a particular conclusion on the question of mammographic screening, and whether or not Gøtzsche and Olsen's Cochrane review will draw the same conclusions as their *Lancet* review remains to be seen. When it is received, it will be carefully reviewed. If it is accepted by the editorial group, it will be published in The Cochrane Library, where it will be open to comment and criticism from anyone.

We thank I Craig Henderson, Alessandro Liberati, Sue Lockwood, Kathleen Pritchard, and John Simes for their input into this letter.

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#### Authors' reply

Sir—We agree with Nicholas Wilcken and colleagues that our *Lancet* paper was not a Cochrane review, it was mainly a critical assessment of the randomised trials. We were rather surprised by what we found and felt it was important to communicate our findings. We informed the primary investigators in advance that the paper was forthcoming but forgot to inform the Cochrane Breast Cancer Review Group, which we regret. Our Cochrane review is close to completion and will be submitted to the review group soon.

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### Adjuvant chemotherapy

Sir—The dosage of fluorouracil used by the QUASAR Collaborative Group (May 6, p 1588)<sup>1</sup> in more than half the patients enrolled is lower than that previously shown to be active in the treatment of colorectal cancer.

The current recommended weekly schedule for fluorouracil plus folinic acid used in the adjuvant and advanced disease setting is fluorouracil 500–600 mg/m<sup>2</sup> combined with high-dose or low-dose folinic acid. By contrast, the weekly schedule of fluorouracil in the QUASAR trial is only 370 mg/m<sup>2</sup>; we wonder on what basis this dose was selected. The dose used could have important implications in the interpretation of the results of the QUASAR uncertain group, yet to be reported.

In this group patients were randomly assigned fluorouracil-based adjuvant treatment or no further treatment if the physician managing their care was uncertain as to whether they would benefit from adjuvant therapy. The results of this study could affect oncology practice for patients with resected Dukes' B colorectal cancer

since there is still no consensus on the correct management of these patients. If the outcome proves to be the same in the two treatment groups, results may be the consequence of inadequate treatment with fluorouracil. We urge caution before rejecting the use of adjuvant chemotherapy for patients with Dukes' B colorectal cancer on the basis of this study.

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- 1 QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; **355**: 1588–96.

#### Authors' reply

Sir—Somewhat jumping the gun, Justin Waters and David Cunningham are concerned that if no survival benefit is seen with adjuvant folinic acid and fluorouracil in the QUASAR study, this might be explained by an inadequate dose of fluorouracil in the once-weekly arm. We will be presenting separately the results for the once-weekly and 4-weekly schedules, with the prespecified hypothesis that the once-weekly regimen will be less effective. However, subgroup comparisons are notoriously unreliable and we believe that a better estimate of the benefits of chemotherapy will be obtained from the overall result, with the two treatment-schedule subgroups combined.

There are two reasons for this belief. First, the once-weekly and 4-weekly schedules deliver the same planned cumulative dose of fluorouracil (30 doses at 370 mg/m<sup>2</sup>) and seem to be equally effective. Recurrence rates and survival among the 2370 QUASAR patients receiving the once-weekly schedule are almost identical to those among the 2559 patients receiving the 4-weekly schedule (3-year recurrence risk 35.6 vs 35.5%; 3 year survival 70.6 vs 71.0%).<sup>1</sup> The choice of treatment schedule was not randomised but was dictated by administrative rather than patient-related factors. As confirmation, recorded prognostic variables in the once-weekly and 4-weekly groups were closely matched (stage C, 73.3 vs 71.0%; colon, 68.0 vs 68.3%; women, 40.2 vs 41.7%; median age 62 vs 61 years). It seems likely, therefore, that unrecorded prognostic variables were also evenly distributed between groups, and that this comparison between schedules is not materially biased by patient selection factors. Thus, the

once-weekly schedule seems to be of comparable efficacy to the 4-weekly schedule. The 4-weekly schedule is known to significantly improve the survival of node-positive colon cancer patients.<sup>2</sup>

Second, the QUASAR chemotherapy regimen has good safety, and is suitable for patients with better outlook: only five chemotherapy-related deaths have occurred in 5000 patients receiving chemotherapy, all under the 4-weekly schedule.<sup>1</sup> Increasing the dose of fluorouracil (but not folinic acid) might increase the efficacy of the once-weekly, and 4-weekly, chemotherapy regimens, but treatment-related mortality increases with increasing dose of fluorouracil which raises concerns for node-negative (Dukes' stage B) patients. More effective chemotherapy would probably produce lesser absolute reductions in cancer-related deaths for such patients, because of the lower background risk. This reduction is more likely to be outweighed by an increase in the risk of treatment-related deaths than a similar proportional reduction among higher risk node-positive (stage C) patients.

Thus, until a higher dose of fluorouracil is reliably shown to be more effective, with acceptable toxic effects, the QUASAR regimen (in either the once-weekly or 4-weekly schedules) remains the gold standard adjuvant chemotherapy regimen. The results of QUASAR will provide a reliable basis for guiding future oncology practise.

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- 1 Kerr DJ, Gray R, McConkey C, Barnwell J, for the QUASAR Collaborative Group. Adjuvant chemotherapy with 5-Fluorouracil, L-Folinic Acid and levamisole for patients with colorectal cancer: non-randomised comparison of weekly versus four-weekly schedules—less pain, same gain. *Ann Oncol* 2000; **11**: 947–55.
- 2 International Multicentre Pooled Analysis of Colorectal Cancer Trials (IMPACT) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995; **345**: 939–44.

### Evidence-based practice

Sir—In his June 17 commentary, H L Halliday<sup>1</sup> suggests our findings on computer-assisted prediction of extubation failure in preterm neonates may be difficult to relate to normal

clinical practice since we did not follow evidence-based practice for certain neonatal-intensive-care-unit policies.

Clearly, this begs the question where do we derive evidence-based practice? The reviews in the Cochrane library have been helpful in this respect and several are referenced in Halliday's commentary. Yet, when interpreting any meta-analysis, it is important to be aware of heterogeneity in the details of the studies included and that findings may be overturned by a subsequently published large study.

Halliday suggests, referencing the pertinent Cochrane review, that we inappropriately placed infants on endotracheal continuous positive airway pressure (etCPAP) for 1 h before extubation. Yet, one of three studies included in the Cochrane review showed no difference in outcome between infants sequentially assigned extubation from a low intermittent mandatory ventilation (IMV) rate, nasopharyngeal tube CPAP after extubation, and CPAP administered via an endotracheal for 12 h before extubation.<sup>2</sup> A second study, which was of smaller sample size did show that extubation was more successful from a low IMV rate rather than from etCPAP before extubation, but the period of CPAP was 6 h.<sup>3</sup>

Apnoea is an important cause of extubation failure. We, therefore, expose infants to a maximum of 1 h of etCPAP before extubation to ensure they have adequate respiratory efforts. This effect cannot be fully assessed on low rates of IMV, since these are a potent stimulus to respiratory reflexes.<sup>4</sup>

Halliday also states that use of nasal CPAP after extubation is evidence-based practice, and describes its association in such a scenario with reduction in oxygen dependency at 28 days. The relevant review in the Cochrane library has, however, since been updated and no longer shows the reduction to be significant. We have also published a meta-analysis of CPAP trials<sup>5</sup> that includes a new trial, larger than those previously undertaken, confirming the lack of effect of nasal CPAP on oxygen dependency at 28 days (reported in six studies, relative risk 1.0 [95% CI 0.8–1.25]). We do agree that nasal CPAP can be beneficial after extubation. Although it does not significantly affect the need for reintubation (0.89 [0.68–1.17]), it significantly reduces the need for increased respiratory support, which includes a higher level of supplementary oxygen. It is important, however, to remember that it is not tolerated by all infants.<sup>5</sup>

We would, therefore, argue a more

appropriate conclusion to our results would be that calculation of the chest radiograph lung area could facilitate optimum use of nasal CPAP after extubation.

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## Drug related deaths—causes and numbers

Sir—In their July 1 commentary Wayne Hall and Deborah Zador<sup>1</sup> make the important point that “one factor which obscures the public health impact of drug related deaths is the poor quality of statistical data on these events”.

Improved ascertainment of drug-related deaths is vital to assess the contribution that illicit drug use makes to premature death. In the report from the UK Advisory Council on the misuse of drugs,<sup>2</sup> the possible routine use of toxicological investigation in coroners' inquiries into any deaths in which drugs are implicated is discussed. However, relating a death to drug use must be carefully distinguished from attributing a death to drug overdose. We are concerned that, especially for deaths in known drug users, routine toxicological investigation (irrespective of the clinical history) might bias the attribution of cause of death towards overdose and away from other causes, such as acute infections. This concern has arisen from our involvement with the investigation of the recent outbreak of serious illness and death in injecting drug users,<sup>3</sup> an outbreak believed to be the result of an acute infectious process.

We examined in detail the antemortem clinical features and test results for 15 deaths in heroin users in England and Wales, which met the

definition developed for definite or probable cases in this investigation,<sup>4</sup> and for which necropsy information was available. All 15 deaths were associated with rapid deterioration and death, with clinical features more consistent with an acute infectious process (severe localised and systemic inflammatory reactions with very high white cell counts), than with opiate poisoning. Where toxicology results were not available to the pathologist doing the necropsy, examination the cause of death was either not ascertained (two cases) or attributed to an acute infectious process (nine cases). In three of the four cases for whom morphine concentrations were available however, death was attributed to overdose. The importance of the concentrations detected is questionable; morphine induces tolerance and the concentrations associated with risk of fatality vary greatly in regular users. Despite the atypical clinical histories (and in one case identification of a likely causative organism) availability of toxicology results seemed to bias attribution of cause of death towards overdose.

To challenge Hall and Zador's<sup>1</sup> view that “death is an unavoidable hazard of illicit drug use” we need to know not only how many deaths are associated with drug use, but also what drug users die from. Thus, any toxicology results require careful interpretation in the context of the duration of use of the implicated drug and the antemortem clinical history and investigations. But it also means that other causes, such as acute infection, should be routinely considered and sought—eg, by microbiological examination of necropsy specimens from foci of inflammation. There have been two instances of drug users who have survived wound botulism in England.<sup>5</sup> Unless such diagnoses are considered at necropsy we will have no information on how many others have not survived. Without such information targeted action to reduce drug-related deaths will be difficult.

The members of the PHLS CDSC/CPHL team are T Djuretic, R George, N Gill, V Hope, J Jones, A Liefucht, G Nichols, J Salmon, and A Weild.

\*J Jones on behalf of the PHLS CDSC/CPHL team investigating unexplained severe illness and death in injecting drug users

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- 5 Anonymous. Wound botulism in injecting drug users: second case in England. *Commun Dis Rep CDR Wkly* 2000; **10**: 221.

## Diagnostic errors

Sir—Your editorial<sup>1</sup> rightly states that “although the frequency of major diagnostic errors may be declining it is still a considerable toll”.

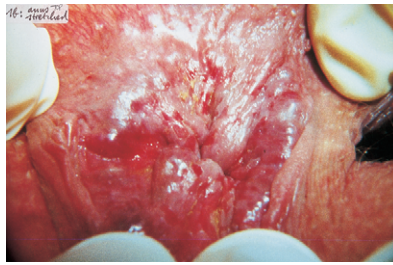
One major diagnostic error is the assumption that anal bleeding is usually from haemorrhoids.<sup>2,3</sup> The exact incidence of haemorrhoids is unknown and estimates vary.<sup>3,4</sup> Are proctologists especially biased when they claim that almost everyone suffers from haemorrhoids at some time in their lives?<sup>4</sup> Do all patients with haemorrhoids experience bleeding? Doctors may see haemorrhoids, but do they see them actively bleeding? If a patient reports anal bleeding but neither haemorrhoids nor any other lesions are found why are haemorrhoids so often assumed to be the cause?

Internal haemorrhoids are not painful because they are covered with non-sensitive epithelium and they can be treated without an anaesthetic.<sup>4</sup> Haemorrhoids are painful only when they thrombose.<sup>3</sup> Patients find palpation or anoscopy of the anal canal painful because of stretching of inflamed tissue of the extremely sensitive anal skin below the dentate line.<sup>2</sup> In my proctological clinic various types of anal and perianal dermatitis were found more frequently than haemorrhoids in patients examined for rectal bleeding. In the first quarter of the years 1996–99 I found haemorrhoids in only 15% of such patients, 5% had both haemorrhoids and a perianal dermatitis, and 80% had perianal dermatitis.

Such lesions of the anus are overlooked because of: incomplete examination with failure to find tiny superficial anal lesions which may hurt and bleed; too weak a light for examination; failure to use finger-tips to carefully stretch the anal skin to look for lesions hidden in the irregular crevices (figure); use of the left-lateral Sims' position which prevents careful stretching of the anal skin with the finger-tips of both hands; and, most importantly, you can only see what you know.

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Careful anal skin stretching to allow examination for lesions

- 1 Editorial. When primum non nocere fails. *Lancet* 2000; **355**: 2007.
- 2 Rohde H. Routine anal cleansing, so called “hemorrhoids”, and perianal dermatitis: cause and effect? *Dis Col Rec* 2000; **43**: 561–62.
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## Patient empowerment and coronary heart disease

Sir—Holt and colleagues (July 22, p 314)<sup>1</sup> tried to improve secondary prevention for patients with coronary heart disease who had been admitted under their care by asking them to have a serum cholesterol test from their family physician after discharge. They sent patients reminder letters after 3 months if a test had not been done. A higher proportion of patients had cholesterol checks after discharge than in a previous audit, but only a small proportion of patients eligible for lipid-lowering drugs were prescribed these agents.

This finding agrees with our randomised trial of postal prompts to patients and their family physicians after discharge for a coronary event.<sup>2</sup> We sent prompts at 2 weeks and 3 months after hospital discharge. A higher proportion of participating patients in the intervention practices than in the control practices had serum cholesterol concentrations measured (odds ratio 2.9 [95% CI 1.5–5.5]) and there were more consultations for coronary heart disease, increased recording of risk factors, and advice given in intervention practices. Family physicians did not, however, prescribe more  $\beta$ -blockers (1.7 [0.8–3.0]) or cholesterol-lowering drugs (1.7 [0.8–3.4]). Whether a hospital-based secondary prevention clinic improves secondary prevention, as Holt and colleagues hope, needs to be tested taking into account secular trends in increased prescribing of lipid-lowering therapy.<sup>3</sup>

We did a qualitative study simultaneously with our trial.<sup>4</sup> Although family physicians had some concern about prescribing budget limitations, probably the most important factor in not implementing secondary prevention in primary care was the lack of explicit understanding by those doctors that this task was their responsibility.

We believe that the idea of patients' empowerment entails a shift of power towards the patient and greater partnership between patients and clinicians. Interventions that achieve this effect may improve outcomes in patients with chronic disease.<sup>5</sup> Asking a patient to visit their family physician for a blood test is not necessarily empowering, even if it does increase the rate of serum cholesterol. We should avoid conflating the giving of responsibility to patients for particular activities with patient empowerment.

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## DEPARTMENT OF ERROR

Comparison of trends in prostate-cancer mortality in England and Wales and the USA—In this Research Letter by S E Oliver and colleagues (May 20, p 1788), figure 2 incorrectly showed the age-standardised incidence of prostate cancer to be falling in the Northern region in 1995 and 1996. The correct figure is shown below.

