

CORRESPONDENCE

Dissection of regional lymph nodes in cutaneous melanoma

Sir—Natale Cascinelli and colleagues (March 14, p 793)¹ confirm that elective block dissection of regional lymph nodes in cutaneous malignant melanoma confers no survival advantage: in short, it is excessive treatment adding morbidity and no benefit. They conclude that “multivariate analysis showed that routine use of immediate [elective] node dissection had no impact on survival”, and state that “node dissection [elective?] offers increased survival in patients with node metastases only”. The latter statement presumably implies that the observed 5-year survival of 48.2% of patients with occult regional metastases undergoing elective lymph-node dissection versus 26.6% of patients having surgery when metastases become clinically apparent, is due to treatment effect from elective surgery.

These workers comment on the significant ($p=0.04$) survival difference (figure 4) between elective and delayed surgery for histologically positive nodes. However, they do not provide the p value for survival difference of patients undergoing elective surgery with histologically positive versus negative nodes. The course of the respective graphs NO+ (patients with clinically negative, histologically positive nodes) and NO- (clinically and histologically negative) in figure 4, indicates no statistical difference. Therefore, an alternative interpretation is that elective surgery merely labels patients with occult metastases but has no impact on survival. In this case, the argument for sentinel-node biopsy becomes untenable. Dissection of regional lymph-node metastases—whether occult or clinically apparent—will not eradicate the disease. In fact, the WHO study reaffirms the long established fact that nearly 75% of patients with clinically apparent metastases in regional lymph nodes will succumb to their cancer.

Consequently, the question that patients ask, once regional lymph-node metastases have been resected, is, what else can be done to mitigate the prognosis? This question is of particular concern to the patient who may have been reassured that the

original primary melanoma had been completely removed, only to discover months or years later—occasionally as late as 20 years after excision of a primary lesion—a metastasis in the regional lymph-node basin.

Some answers are beginning to emerge from two studies that have recently addressed this issue^{2-5*}—ie, that treatment with adjuvant vindesine or high-dose interferon- α -2 β results in improved survival. In clinically apparent metastatic regional lymph nodes, the 5-year survival with adjuvant vindesine was 49% and with interferon- α -2 β approximately 37%. The 5-year survival for untreated patients was, respectively, 28% and 26%. The cost of treatment for these two drugs is about US\$5000 for vindesine and US\$30 000 for interferon- α -2 β . The encouraging observations from the use of these drugs in the adjuvant treatment of clinically apparent regional lymph-node metastases should now direct attention to the optimum use and further development of these treatments.

*A summary of the findings of the two studies is available from the author or *The Lancet*, on request.

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- 1 Cascinelli N, Morabito A, Santinami M, Mackie RM, Belli F, on behalf of the WHO Melanoma Programme. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *Lancet* 1998; **351**: 793–96.
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- 4 Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996; **14**: 7–17.

- 5 Retsas S. Adjuvant interferon alfa-2b for high-risk melanoma. *J Clin Oncol* 1996; **14**: 1968.

Sir—Natale Cascinelli and colleagues¹ rely too heavily on significance testing when they suggest that their trial may be interpreted as “finally settling the debate between advocates and opponents of elective lymphadenectomy” for melanoma of the trunk. This conclusion implies that their trial was merely a test to establish whether elective lymphadenectomy is better than delayed surgery.

This is too narrow a vision. Rather, we should regard their study as an estimate of the value of immediate surgery. Their results, unadjusted for covariates, show that we can be 95% confident that elective lymphadenectomy may, at worst, reduce 5-year survival by 2% but, at best, may improve it by 23% (I have calculated the 95% CI for the difference in survival from the published data). Thus, although we cannot be certain that elective lymphadenectomy improves survival, we cannot rule out the possibility that it will result in greater than 20% more patients surviving at 5 years, which hardly seems to settle the debate in favour of delayed surgery. In fact, adjustment for covariates, which the investigators do not provide for the 5-year survival data, should further favour immediate surgery. (The confidence interval for the adjusted hazard ratio which is reported is more difficult to translate into a clinically meaningful form.)

The hazards of interpreting negative studies² and the value of confidence intervals over significance testing³ have been well described. We should avoid the erroneous view that significance testing provides a yes or no answer to the question of a treatment's value. A significant p value only indicates that the difference between two groups is not likely to be zero. It does not tell us the magnitude of the difference, which is what we need to know in order to balance benefits and risks. To determine the clinical significance of a trial we need to look at confidence intervals.⁴ In this case, those confidence

intervals are wide enough, I am sure, to lead many readers to question the clinical significance of the results. Researchers need to consider carefully the sample size required to reduce confidence intervals to clinically meaningful proportions.⁵

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- 1 Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F, on behalf of the WHO Melanoma Programme. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *Lancet* 1998; **351**: 793–96.
- 2 Freiman JA, Chalmers TC, Smith H Jr, Keubler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized clinical trial: survey of 71 negative trials. *N Engl J Med* 1978; **299**: 690–94.
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Sir—The trial reported by Natale Cascinelli and co-workers¹ asked an important question regarding the management of regional nodes in truncal melanoma. Although the investigators conclude that their results may finally settle the debate between advocates and opponents of elective lymphadenectomy, it would seem that the trial has insufficient numbers to allow this conclusion.

The results of the multivariate analysis shows that the hazard ratio for the effect on survival of immediate versus delayed node dissection was 0.72 (95% CI 0.49–1.04). This hazard ratio is not significant because the 95% CI includes 1.00. However, because the point estimate (0.72) and almost all the 94% CIs are less than 1.00, the difference tends towards significance.² The fact that the confidence interval is so wide indicates that patient numbers are inadequate to exclude a clinically relevant benefit. If the study was larger the confidence intervals would be narrower, and the hazard ratio of 0.72 (which translates to an important survival gain) may well have been confirmed. The trial may even have indicated a greater benefit for elective node dissection (ie, a hazard ratio less than 0.72). Alternatively, a larger study might have shown no difference between the treatment arms, with a narrower confidence interval lending more credence to the result.

The results of this study indicate the immediate dissection of regional nodes

in patients with melanoma of the trunk may well provide a clinically important therapeutic benefit, but that such a benefit could not be demonstrated because of insufficient patient numbers.

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- 1 Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F, on behalf of the WHO Melanoma Programme. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *Lancet* 1998; **351**: 793–96.
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Authors' reply

Sir—Results of the updated analysis of WHO trial 14 are not intended to be interpreted as a final solution of the long running debate between those who advocate elective lymph-node dissection in melanoma and those who prefer to wait until there is clinically evident disease.

Our data strongly suggest that early detection of occult nodal metastasis may substantially affect the final outcome in these patients. Your correspondents' comments can be answered at least in part by the introduction of the sentinel-node biopsy technique. One useful way to use this technique is to limit full anatomical lymph dissection to patients who have pathologically proven metastasis in the appropriate draining lymph-node basin, and thus avoid unnecessary morbidity in those who are sentinel-node negative.

Spyros Retsas makes suggestions concerning postoperative adjuvant therapy involving vindesine and interferon. He no doubt is aware that the melanoma community keenly awaits the publication of the Eastern Oncology Group's trial 1690 by Kirkwood and colleagues, which is the study designed to confirm the encouraging results reported in their earlier trial.¹ We are not aware of any published randomised controlled trial reporting the value of adjuvant vindesine in a similar setting.

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- 1 Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996; **14**: 7–17.

Vein compliance for preoperative assessment in vascular bypass surgery

Sir—Gerard Stansby's April 4 commentary¹ on vein quality in vascular surgery correctly highlights the importance of the functional quality of veins as a factor that may affect the success of bypass grafts. Although endothelial function is likely to be of importance, one functional factor he does not mention is the compliance or distensibility of the graft wall.

Studies suggest that non-invasive-compliance measurements of veins can be a useful preoperative indicator of risk of subsequent graft stenosis. For example, Davies and colleagues² measured the compliance of the long saphenous vein by non-invasive venous occlusion in patients before femorodistal bypass surgery. Follow-up was with colour duplex ultrasonography and intra-arterial digital subtraction angiography to diagnose graft stenosis. Preoperative vein compliance was significantly reduced in 11 of 88 patients who subsequently developed graft stenosis—a sensitivity of 91% and a specificity of 94% as a predictor of later graft stenosis.² Kidson and Abbott³ also reported a significant positive relation between compliance and graft patency. Furthermore, the hypothesis that a mismatch in compliance between a vascular graft and its host artery could be detrimental to graft patency has been tested in animal studies. After 3 months, cumulative patencies were 85% and 37% for compliant and stiff grafts, respectively, suggesting that compliant grafts are more likely to remain patent.⁴ Because vein grafts are exposed to arterial high pressure and flow, it is relevant that in the native arterial circulation there seems to be a positive relation between arterial stiffening and the presence of advanced vascular disease.⁵

These data suggest a clear rationale for further studies into the use of preoperative non-invasive compliance measurements of candidate veins, since patients with stiffer veins may be at risk of developing subsequent graft stenosis.

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- 1 Stansby G. Vein quality in vascular surgery. *Lancet* 1998; **351**: 1001–02.
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- 5 Lehmann ED, Riley WA, Clarkson P, Gosling RG. Non-invasive assessment of cardiovascular disease in diabetes mellitus. *Lancet* 1997; **350** (suppl 1): 14–19.

Chimerism in scleroderma

Sir—J Lee Nelson and colleagues' report (Feb 21, p 559)¹ presents evidence from PCR experiments that some women with scleroderma who have given birth to sons have male cells in their peripheral blood. Possibly these invaders cause scleroderma, and getting rid of them would cure patients with scleroderma.²

Their hypothesis that autoimmune diseases are characterised by, indeed caused by, cell lines acquired during pregnancy—either mother-to-child or child-to-mother—is not original. Nor is the finding of male-cell determinants in the peripheral blood of patients with scleroderma by PCR. We have presented the hypothesis and PCR findings.^{3,4}

In 1972, I was asked to see a 13-year-old boy with systemic lupus erythematosus and nephritis. Because of Rh erythroblastosis fetalis he had received an exchange transfusion at birth. Had the donor's cell line persisted and caused his lupus by a graft-versus-host reaction? I located the donor and found that our patient's serum contained antibodies specific for a donor HLA class I antigen. This finding suggested that 13 years after his exchange transfusion the donor's cell line had persisted and was responsible for his disease.

But what of other patients with lupus who did not get an exchange transfusion? Perhaps the mini-exchange from mother or child during pregnancy or delivery had left in them a permanent cell line that produced graft-versus-host disease—ie, lupus.

A second such patient was a 25-year-old woman seen in 1988 because she had developed scleroderma and hypertension during the seventh month of pregnancy. Had her child's cells caused her scleroderma? 3 years after her son was born, we prepared DNA from her peripheral blood and analysed it for Y chromosome elements by PCR. They were found. Apparently, the patient with scleroderma harboured a male cell line from her son.

These findings led me to the thought that transplacental cells may be generally responsible for autoimmune

diseases: both multisystem and organ-specific diseases. In addition, the route of cell passage (mother-to-child or child-to-mother) may affect disease expression.

It is possible that patients would be cured by getting rid of the foreign cells. If so, it would be a tribute to Ray Owen, who in 1945 set the stage by reporting that cattle twins, known to share blood vessels, share blood groups with their twins and are thus chimeras. The field is fertile. Everyone has a mother.

The quantitative PCR test for chimerism used by Nelson et al¹ requires comment/question about the technique. "Results are expressed as the number of male DNA equivalents in 16 mL whole peripheral blood." In this technique,⁵ the purified DNA from 16 mL whole blood is taken up in 2 mL of buffer and 1/200th (10 μ L) is used in the PCR test. A positive test for a Y amplicon requires at least one Y chromosome as template. Therefore a positive result indicates that at least 200 male cells were present in the whole (16 mL) sample. Yet Nelson and colleagues report that no patient was found to have more than 61 "male cells equivalents" in 16 mL whole blood. Are detected sequences all on the Y chromosome?

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- 1 Nelson JL, Furst DE, Maloney S, et al. Microchimerism and HLA-compatible relationships of pregnancy in scleroderma. *Lancet* 1998; **351**: 559–62.
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- 5 Bianchi DW, Williams JM, Sullivan LM, et al. PCR quantitation of fetal cells in maternal blood in normal and aneuploid pregnancies. *Am J Hum Genet* 1997; **61**: 822–29.

Sir—J Lee Nelson and colleagues¹ report a significant increase of male cell DNA in whole blood of female patients with scleroderma as compared with controls. These original and interesting results will certainly give rise to a renewed interest in the domain of chimerism and its consequences.

In their introduction, these workers state that "scleroderma is an autoimmune disease that has clinical similarities with graft-versus-host disease, a chimeric disorder that occurs

in recipients of allogeneic stem-cell transplants". This statement seems to be an important rationale for the design of the study and the conclusions drawn from the results. However, this claim should be viewed with caution.

Patients with chronic sclerotic graft-versus-host disease (GvHD) display indurated localised or disseminated shiny plaques, but these involve mainly the trunk and the proximal limbs, usually with no sclerodactyly or Raynaud's phenomenon,² by contrast with what is found in scleroderma. Cutaneous histological and ultrastructural findings of these two conditions are also quite different. In chronic GvHD, epidermal colloid bodies, fibrosis of papillary dermis sparing vessels, and normal collagen fibrils are found.³ In scleroderma, fibrosis of reticular dermis with pericapillary fibrosis is found and the collagen fibrils are thin.³ Granular IgM deposits at the dermal-epidermal junction are seen in 86% of the biopsies of chronic GvHD, but this is found between 10% and 42% in scleroderma. In chronic GvHD, oesophageal fibrosis is rare and does not involve the musculature, as in scleroderma.⁴ Renal dysfunction, a common consequence in scleroderma is not a feature of chronic GvHD.⁴ Finally, the circulating auto-antibodies usually target topoisomerase in scleroderma but not in chronic GvHD.⁵

Altogether, these clinical, histological, and immunological differences point out that different events occur in these diseases. If, indeed, chimerism plays a part in scleroderma, as in GvHD, one may suspect that other yet unidentified factors will also contribute to its pathogenesis, leading to these differences.

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Authors' reply

Sir—That chimerism from an exchange transfusion might cause systemic lupus is supported by a study we discussed in which female lymphocytes were found in males who had received exchange transfusion from their mothers. The ideas from Franklin Mullinax and from our group, although independent, have some overlap and are complementary. We do not agree, however, with his statement that the previously published hypothesis by one of us¹ is not original.

Clearly, there are reports that describe chimerism in animals and in man. The second patient Mullinax describes had onset of scleroderma during pregnancy, and he has proposed that chimerism is responsible for the expression of autoimmune disease during pregnancy. However, the frequency of scleroderma is not increased during pregnancy, but, rather, peaks in women aged 45–54 years.² Thus the earlier hypothesis is not limited to autoimmune disease with onset during pregnancy.

It is only recently that long-term persistence of fetal cells has been recognised, and a central feature of the proposed hypothesis is that persistent fetal microchimerism contributes to the development of some autoimmune diseases long after pregnancy completion. Although a previous adverse pregnancy outcome might potentiate risk,³ pregnancies with normal outcomes are included. It was also proposed that having given birth to an HLA-compatible child may increase risk of subsequent autoimmune disease in the mother. Our study is the first to describe a significant difference in microchimerism between patients with an autoimmune disease and controls. Finally, although non-host cells might be direct effectors of disease, as we discussed, autoimmunity may occur due to disruption of host immunoregulatory mechanisms, for example, by non-host peptides. Non-host DNA could also be incorporated into host cells.

It should be emphasised that low levels of persistent microchimerism are common in normal parous women. The preliminary study by Mullinax and Mullinax did not describe a significant difference between healthy women and patients. In our preliminary studies, done in collaboration with Jeff Hall in 1995, we found microchimerism in peripheral blood samples from patients with scleroderma, and in DNA extracted from a lung-biopsy specimen. However, some peripheral blood samples and three of four lung samples from controls were also positive (unpublished).

Mullinax correctly points out that the quantitative PCR assay is not absolute, but relative. Stochastic variation is seen in each 10 µL reaction sample; this is why results are expressed as an average of ten reactions. However, Mullinax's point that one Y signal equals at least one male cell is not wholly correct. The fetal DNA remaining in maternal blood may not be derived from intact cells, the copy number may be polymorphic, and fragmented DNA may be distributed across several samples. The results are accurate because the intensity of the signal is always related to a standard reaction run simultaneously, with a known number of male cells. It is noteworthy that neither this assay, nor those used for HLA typing, bear any resemblance to nested PCR, as erroneously stated by Ken Welsh, in his commentary.⁴

We agree with Sélim Aractingi that there are clinical and pathological differences between chronic graft-versus-host-disease (GvHD) and scleroderma. However, some of the differences outlined should be considered with caution because all but the earliest studies describe patients in whom regular prophylaxis and immunosuppressive therapy have been instituted. Among the early descriptions of chronic GvHD, a 1978 report from our institution described widespread cutaneous involvement with hidebound skin, taut facies, and cutaneous involvement of fingers resulting in contractures. Thus, such manifestations may be characteristic of untreated chronic GvHD. Also, antibodies to topoisomerase I have been described in sclerodermatous chronic GvHD, contrary to Welsh's⁴ suggestion. Their true incidence in untreated chronic GvHD will probably remain unknown because earlier studies did not investigate these antibodies. Antibodies to topoisomerase I are present in about 30% of patients with scleroderma.

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- 1 Nelson JL. Maternal-fetal immunology and autoimmune disease. Is some autoimmune disease auto-alloimmune or allo-autoimmune. *Arthritis Rheum* 1996; **39**: 191–94.
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Specificity of antinuclear antibodies in scleroderma-like chronic graft-versus-host disease: clinical correlation and histocompatibility locus antigen association. *Br J Dermatol* 1996; **134**: 848–54.

Stopping the Breast Cancer Prevention Trial

Sir—Your April 18 editorial¹ defends the decision of the data safety monitoring board of the Breast Cancer Prevention Trial to stop the study based on an interim analysis conducted 14 months before the close of this 6-year trial. With the aid of *The Lancet* Interactive (website), I was able to track down all of the relevant data from the April 11 news item by Alicia Ault and Jane Bradbury (April 11, p 1107,² and the press release). With simple statistical calculations and a few assumptions (eg, distribution of patients between treatment groups was 1:1), I was able to ascertain that the odds ratio for development of breast cancer in the treated versus control groups was 1.8 ($p < 0.001$). These data are consistent with typical stopping rules of $p < 0.001$ used when a single interim analysis is done, and supports the correctness of the decision to stop the trial. Was there only one such analysis? Had the sponsor of the study revealed the stopping rule under which the decision was made, clinicians could more readily have interpreted this decision and its applicability to their own practices.

Some of the safety data are more disturbing. Since there seemed to be a higher incidence of endometrial cancer in the treated group (odds ratio=2.4, $p < 0.01$, based on my assumptions), might not the data have stopped the trial equally from safety concerns? If I were a woman at risk of breast cancer, I might reasonably want all of the data available in a form that could readily be interpreted. Given the median survival of breast versus endometrial carcinoma, I expect that the decision to use or forgo tamoxifen is not as straightforward as a simplistic analysis might suggest.

If one calculates the risk of cancer with the data available, the odds ratio still favours tamoxifen over control (1.4), but the level of significance $p < 0.001$ is not achieved. If risk of adverse outcome (breast cancer, endometrial cancer, pulmonary embolism, and deep-vein thrombosis) as defined by the Breast Cancer Prevention Trial is analysed, the difference between groups is not significant (odds ratio 1.2, $p > 0.05$).

I admit that my seat-of-the-pants statistical analysis is not solidly

grounded. Nor, do I believe, was the decision to abort this critical trial. We have yet another prematurely terminated clinical trial that has failed to answer the question it asked, and leaves women and physicians without a solidly grounded basis on which to decide whether or not to use tamoxifen.

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- 1 Editorial. Defending data-monitoring committees. *Lancet* 1998; 351: 1143.
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Mortality of hepatitis A in adults with hepatitis C antibodies

Sir—In their March 28 commentary, Marina Berenguer and Teresa Wright¹ suggest hepatitis A vaccine for patients with chronic hepatitis C as a consequence of Vento and colleagues² finding² of a 35% mortality among cases of hepatitis A in such patients.

During an outbreak of 144 cases of hepatitis A among intravenous-drug users in Oslo in 1995–96, we found that 101 (81%) of 125 examined patients also had hepatitis C antibodies. Of this group, about two-thirds would be expected to have chronic active hepatitis. Seven of the hepatitis-C-antibody-positive patients developed severe but reversible acute hepatitis, but only one of them died.³ This patient had a previous liver cirrhosis, and heavy alcohol abuse may have contributed to her liver damage.⁴

Oslo has fairly complete data for hepatitis among drug addicts, and it seems unlikely that any person could have died from hepatitis A without being notified. Our findings do not indicate any alarming mortality of hepatitis A among individuals who are positive for hepatitis C antibody.

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- 1 Berenguer M, Wright TL. Are HCV-infected individuals candidates for hepatitis A vaccine? *Lancet* 1998; 351: 924–25.
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- 3 Grinde B, Stene-Johansen K, Sharma B, Hoel T, Jensenius M, Skaug K. Characterisation of an epidemic of hepatitis A virus involving intravenous drug

abusers—infection by needle sharing? *J Med Virol* 1997; 53: 69–75.

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MRSA and minimally invasive treatments for benign prostatic hypertrophy

Sir—Urologists need to be aware of the potential threat of infective complications, when comparing transurethral resection of the prostate (TURP) and the minimally invasive treatment alternatives for benign prostatic hypertrophy (BPH). The increased incidence of urinary-tract infection and epididymo-orchitis after the earlier laser techniques is well recognised.¹ More recently, there have been reports of postoperative urinary-tract infections after electrovaporisation surgery, including Mark Feneley's April 1 commentary.^{2–4}

Bacterial colonisation of the urinary tract with sensitive coliform species after prostatic surgery rarely causes serious morbidity. When the organism involved is methicillin-resistant *Staphylococcus aureus* (MRSA), colonisation may be symptomless, but serious life-threatening sepsis, responsive only to the glycopeptide antibiotics, can result.

Since 1993, our urology department has been involved in the development and evaluation of laser techniques (Neodymium Yttrium Garnet [Nd:YAG] and a vaporising Potassium Titanyl Phosphate [KTP] laser) for BPH. We initially used a hybrid operating technique of tissue coagulation and vaporisation. Between December, 1994, and November, 1996, an outbreak of MRSA occurred in our urology ward. We found that when compared with TURP, patients who had Nd:YAG laser treatment of the prostate had an increased risk of acquiring MRSA. The retained necrotic tissue, after coagulation laser treatment, required long-term catheterisation for the removal of tissue debris, which probably predisposed the patients to colonisation with MRSA leading to an unacceptable increase in morbidity due to infection.

The minimally invasive alternative treatments for BPH rely on the delivery of sufficient heat to the prostate so that coagulative necrosis or frank vaporisation occurs.³ Enhancement of tissue removal by vaporisation with diminution in the coagulative necrosis will assist in reduction of postoperative

infection. At the end of 1996, a rapid decline in the incidence of MRSA occurred. Around this time, a laser technique based on tissue vaporisation had been adopted. Improvements in the handling of urinary-drainage systems with strict implementation of the hospital policy on hand-washing and use of alcohol hand wipes had also been introduced. The control of the postoperative acquisition of MRSA was attributed to all these factors.

Our experience suggests that the prevalence of MRSA in the ward needs to be considered when choosing the optimum operative technique for a patient. Electrovaporisation of the prostate with appropriate electrodes used at power levels necessary to ensure immediate tissue removal and a minimal zone of tissue coagulation should limit the risk of the infective complications.³

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Postoperative cognitive dysfunction in the elderly

Sir—J T Moller and colleagues' report, for the SIPCOD investigators (March 21, p 857),¹ adds greatly to our knowledge of postoperative cognitive dysfunction. They note that delirium was not a risk factor for cognitive dysfunction after surgery. However, postoperative complications and chest infections, which are common causes of delirium after surgery, were associated with early postoperative cognitive dysfunction. Were standardised diagnostic criteria used to define delirium in this study? Daily assessment with the orientation section of the mini mental state examination would probably be reasonably sensitive but non-specific as a screening test for the clinical syndrome of delirium.

Was early postoperative cognitive dysfunction predictive of long-term dysfunction in this study? Investigations

in elderly patients with medical illnesses suggest that delirium is commonly associated with longlasting cognitive deficits, even after resolution of the acute syndrome.^{2,3} There is also evidence that this effect is true for elderly patients who develop postoperative delirium.⁴ For example, in their study of elderly patients undergoing elective knee replacement, Williams-Russo and colleagues⁵ noted long-term cognitive deterioration in three (13%) of 24 delirious patients and nine (5%) of 198 non-delirious patients, although this difference was not significant.

In clinical practice, diagnosis of delirium after surgery suggests the need for careful search for precipitating factors, such as infection. It seems likely, although not proven, that early treatment of such complications might prevent subsequent long-term cognitive dysfunction.

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- 1 Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 Study. *Lancet* 1998; **351**: 857-61.
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- 3 O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc* 1997; **45**: 174-78.
- 4 O'Keeffe S, Ni Chonchubhair Á. Postoperative delirium in the elderly. *Br J Anaesthesia* 1994; **73**: 673-87.
- 5 Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME. Cognitive effects after epidural vs general anaesthesia in older adults. *JAMA* 1995; **27**: 44-50.

Sir—The probability that a member of a group will come to help an individual in trouble is inversely related to the number of individuals in the group. This bystander effect, whereby the presence of others inhibits helping, may have withheld the many co-investigators of the ISPOCD1 study¹ from correcting errors in the reported data on postoperative cognitive dysfunction in the elderly.

Of the original 1218 patients, 271 (22%) are reported not to have completed the assessment at 3 months, but 118 refusals and 57 deaths do not equal 271, nor does 1218 minus 271 equal 910—ie, the number of remaining patients at 3 months (table 3)—but, rather, 947 (table 1, n=949 according to the male/female ratio). The investigators recorded cognitive dysfunction at 7 days after surgery in 266 patients, but table 3

unexpectedly shows lower numbers for age, duration of anaesthesia, and education. The number of patients tested at 7 days remains a constant n=1011, whereas the text reads that “four patients could not complete the test at 1 week and were excluded from the study”. Thus one would expect n to be 1214. More serious errors show up in table 3 in the columns referring to testing at 3 months. A constant number of 910 patients were tested but the entries for “patients with POCD” can hardly be correct. Odds ratios in table 4, based on table 3, also contain errors—eg, for education (second entry, where no p value is given): 0.73 (=420*31/114*156) instead of 0.5.

Important as the results of this report may be—they received widespread media coverage in the Netherlands—its bystander researchers may have been victims of pluralistic ignorance.² By noticing that many co-authors had left the data unchanged, other investigators perhaps thought that the data must be correct. Possibly as a result of this bystander effect, the investigators have inadvertently put a burden on their shoulders to verify that their results, which may have far reaching consequences, are reliable in every respect.

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- 1 Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 Study. *Lancet* 1998; **351**: 857-61.
- 2 Brehm SS, Kassir SM. Social psychology. Geneva, Illinois: Houghton Mifflin Company, 1996.

Authors' reply

Sir—Áine Chonchubhair and Shaun O'Keeffe question our finding that delirium is not associated with long-term postoperative cognitive dysfunction and ask whether standardised diagnostic criteria were used. Delirium was diagnosed according to DSM-III criteria¹ by daily screening with the orientation part of the mini mental state examination, information from the medical record, and observation from the nurses taking care of the patient. Delirium was noted in 99 (8.1%) of our study population. Delirium was not a significant risk factor in the logistic regression analysis at the 7-day or 3-month test. Our study does not support their assertion that early treatment of postoperative delirium will prevent late cognitive dysfunction.

We thank Benno Bonke for this comments on the importance of our findings. He is correct in his observation that there were some numerical errors in table 3 (see department of error, June 6, p 1742) but incorrect in his suggestions as to cause of those errors. Percentage values, which are correct, were submitted by us to *The Lancet* but without the actual numbers of patients. These numbers were added by *The Lancet* and we failed to note several errors during proof reading, for which we apologise.

The other apparent errors in numbers of patients result from incomplete datasets for some patients. Such patients may be included in calculations of frequency of occurrence, but must be excluded from the logistic regression analysis. The number of drop-outs is correct (271), of which 118 were refusals, 57 deaths, and 96 due to other reasons.

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- 1 American Psychiatric Association, Committee on Nomenclature and Statistics. Diagnostic and statistical manual of mental disorders, third edition. Washington, DC: American Psychiatric Association; 1987: 100-03.

Safety guidelines for exercise during pregnancy

Sir—D M Bailey and colleagues (April 18, p 1182)¹ report a case-study of an elite female marathon runner who continued high-volume training (107 km per week at a heart rate of 130-40 beats/min) throughout a twin pregnancy. Although she trained below the 150 beats/min heart rate safety limit, as recommended by the American College of Obstetricians and Gynecologists, the investigators imply that these guidelines may be too cautious.

There is no firm evidence in human beings that exercise intensities at the upper limits of what is mechanically and metabolically still possible during pregnancy would produce a rise in temperature, which is critical for the fetus. A decrease in fetal oxygen and availability of carbohydrate has been documented, but this reduction is accompanied by fetus-protective physiological adaptations, such as an increase in oxygen extraction, haemoconcentration, and intrauterine redistribution.

No doubt, the relation between exercise and pregnancy has been investigated extensively; a recent search of Medline identified 1065 papers. Several investigators have argued in favour of a liberalisation of what many believe to be stringent recommendations. Indeed, there are other reports of pregnant high-level competitive athletes who approached and even exceeded the recommended maximum heart rate without any apparent harmful effects on the fetus.²⁻⁵ It is unlikely that the American College of Obstetricians and Gynecologists meant to establish the 150 beats/min limit as a rigid criterion, with 149 beats/min being safe, and 151 beats/min representing a hazardous exercise intensity. That being said, there is evidence that at 170 beats/min even in elite athletes, the limits of tolerance for the fetus appear to be reached.² Whether those limits too can be extended by further training at such raised heart rates is not known.

Cited recommendations are literally safety guidelines. Athletes commonly have a more realistic view as to how far they can go in their exercise; this approach seems more of a problem for non-athletes. Arguably, suggesting that every pregnant woman should do as much exercise as she finds "reasonable", may in itself not constitute a reasonable recommendation. More important perhaps, aerobic running has a low injury rate as far as the anatomy involved in pregnancy is concerned, compared with, for example, rowing or horseback riding. The possible effect of the low caloric intake of high-level endurance athletes also warrants attention—this issue may represent more of a risk for the fetus than the actual exercise itself.

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- 1 Bailey DM, Davies B, Budgett R, Sanderson DC, Griffin D. Endurance training during a twin pregnancy in a marathon runner. *Lancet* 1998; **351**: 1182-83.
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Fluticasone propionate for chronic obstructive pulmonary disease

Sir—Pier Paggiaro and colleagues (March 14, p 773)¹ studied the effect of high-dose inhaled fluticasone in chronic obstructive pulmonary disease (COPD). Although theirs is essentially a negative study in that the primary endpoint, reduction in exacerbations of COPD, was not altered significantly, they claim significant effects on secondary endpoints such as lung function, symptoms, and walking distance. I believe that these observations are questionable because of a fundamental flaw in the study design.

As N C Barnes points out in his accompanying commentary,² inhaled steroids have numerous actions on the airways, and the time course of onset and offset of these actions differ. Paggiaro and co-workers have chosen to study patients who may have been taking inhaled steroids before the start of the study and although the number of such patients is not reported, they infer that it is a large proportion of those recruited. Is a 2-week washout before the start of the study adequate? There is evidence that it is not. Lung function declines with time in COPD. The median decline in placebo group is between -20 and -11%, equating to a mean fall in FEV₁ greater than 50 mL at week 16 (figure 3). This rate of decline is far in excess of that seen even in susceptible patients who continue to smoke. The most likely explanation for this and most of the positive effects seen in the study is that controls are withdrawing from their previously administered inhaled steroids. The difficulty is compounded in that no trial of steroid responsiveness was undertaken and so we do not know what proportion of patients had chronic asthma as opposed to COPD. The bronchodilator test used is inadequate to exclude steroid-responsive asthma.

Although there was little change in the number of patients with exacerbations or in the number of exacerbations, there was a shift in the observed severity, with a greater number of physician interventions and admissions in the placebo group. This shift may be due to regular inhaled medication; however, I offer an alternative hypothesis. We know that oral steroids are effective in acute COPD and that high-dose inhaled fluticasone propionate seems effective as prednisolone in acute asthma.³ Is fluticasone propionate acting as a

treatment for the exacerbation and thus causing a reduction in severity? If true, the drug could be important as a cost-effective treatment for patients liable to exacerbations.

I presume that the study was financially sponsored and supported by the company that manufactures fluticasone (although this is not stated). If so, this interest may explain why we are told that fluticasone propionate has a better therapeutic ratio than other inhaled steroids; a statement that could occupy many column inches of debate. What is most surprising is that Paggiaro et al dismiss evidence for that statement in their study. Fluticasone propionate caused important adrenal suppression and yet this effect is described as being without clinical importance. We are treated to an extensive analysis of beneficial activity but only given access to the mean data for serum cortisol, itself an insensitive marker of suppression. I challenge these investigators to provide us with data on the distribution of adrenal suppression in a fashion analogous to their figure 4; this is important since unlike change in FEV₁ there seems to be great variation in individual sensitivity to corticosteroid-induced systemic side-effects. If we are to fairly consider the therapeutic ratio, we need similarly detailed reporting of both effect and side-effect.

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- 1 Paaggio PL, Dahle R, Bakran I, et al. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. *Lancet* 1998; **351**: 773-80.
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- 3 Levy-ML, Stevenson C, Maslen T. Comparison of short courses of oral prednisolone and fluticasone propionate in the treatment of adults with acute exacerbations of asthma in primary care. *Thorax* 1996; **51**: 1087-92.

Authors' reply

Sir—In all, 31.3% (43 placebo, 45 fluticasone propionate) of patients were taking inhaled steroids up to 2 weeks before the start of the study. The numbers were well balanced between the two groups and patients were taking only moderate doses of up to 500 µg daily. Previous use of inhaled steroids had no effect in terms of the benefit of fluticasone propionate on FEV₁. In addition, at the end of the 2-week washout period, only patients who had no important change in their lung function or symptoms were allowed to proceed to randomisation.

Mean FEV₁ in the placebo group declined by 0.04 L (from 1.52 to 1.48 L) over the 6 months' treatment, which is well within the range of decline seen in COPD patients.¹ It is misleading and statistically unsound to select the decline in FEV₁ at one time point mid study and suggest that this is representative of the whole curve.

Differentiation between chronic asthma and COPD is often challenging clinically. We selected patients on the basis of slowly progressive loss in lung function, current or ex-smoking, and symptoms of chronic bronchitis. Patients with features of chronic asthma (eg, largely episodic or seasonal wheezing, bronchodilator reversibility in FEV₁ \geq 15%) were excluded by clinical history and a detailed atopy questionnaire. Steroid trials are not wholly reliable in differentiating chronic asthma from COPD. Moreover, bronchodilator responsiveness has proved a useful guide to steroid responsiveness in COPD patients.^{2,3}

Many fewer patients had moderate to severe exacerbations in the fluticasone propionate group than in the placebo group. Although the total number of exacerbations did not differ between the two groups, there was a strong trend in favour of fluticasone propionate, with 111 exacerbations in the placebo group and only 76 in the treatment group. The shift in exacerbation severity is probably best explained by fluticasone propionate damping the underlying inflammatory disease process, both during exacerbations and chronically.

The statement regarding the better therapeutic ratio of fluticasone propionate than those of other inhaled steroids was based on several large, randomised, controlled clinical trials (reference 4 for meta-analysis and summary). In our study, the mean serum cortisol concentration fell by only 9.7% in the fluticasone propionate group and remained well within the normal range. Additionally, only seven patients on the drug and six on placebo had cortisol values below the normal range at the end of treatment. However, in none of these patients were there any signs, symptoms, or laboratory findings of clinically important adrenal suppression. Alyn Morice's suggestion of providing a distribution histogram for serum cortisol changes would be of little value, because the relation between falls in serum cortisol and clinical effects are generally poor in patients taking corticosteroids, especially within the normal range. Other more clinically important

markers of corticosteroid-related systemic activity are likely to be of greater value, and Egan and colleagues⁵ have shown prospectively that fluticasone propionate 1 mg daily has no effect on spinal bone density after 2 years of treatment.

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A selective policy in follow-up for bowel cancer

Sir—In his April 11 commentary,¹ John Northover summarises the results of follow-up studies in bowel-cancer patients and is realistic in his conclusion that such studies are "high cost" with "low evidence of effectiveness". The evidence to-date, however, is derived from studies with low power that are unable to detect potential differences in selected small groups of patients undergoing resections for recurrence. Non-randomised studies have shown a consistent pattern of better survival, with at least as good a quality of life, after second surgery for hepatic metastases or isolated rectal recurrences.^{2,3} There is also evidence from small randomised trials that early chemotherapy for advanced disease improves survival compared with delaying chemotherapy until required for symptom relief.⁴ Because the proportion of patients in whom potentially curable recurrences are detected is small (<5% overall), very

large studies are required to show a significant oncological advantage. In the largest published randomised trial on colorectal cancer follow-up, 325 patients were recruited to detect differences of greater than 15%.⁵

An alternative approach is to adopt a selective policy that uses investigative tools with proven effectiveness and distinguishing disorders in which survival advantages could materialise. Rather than a blanket process of follow-up for all patients, our endeavours should be aimed at research to identify biological and molecular characteristics that best predict resectable and curable recurrences. Once detected, these patients should be managed within the framework of a multidisciplinary team, with low morbidity and perioperative mortality as essential prerequisites.

We cannot exclude the possibility that discriminating intensive follow-up with reoperation may improve outcome. Colorectal cancer remains one of the few solid tumours for which re-resection offers a chance of cure, and hence Northover's "minimalist" approach is too nihilistic.

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- 1 Northover J. Realism or nihilism in bowel cancer follow-up? *Lancet* 1998; **351**: 1074-76.
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- 5 Schoemaker D, Black R, Giles L, Tououli J. Yearly colonoscopy, liver CT, and chest radiography do not influence 5-year survival of colorectal cancer patients. *Gastroenterology* 1998; **114**: 7-14.

Sir—John Northover's April 11 commentary¹ on follow-up for patients with colorectal cancer does not address the benefits of chemotherapy in the management of recurrent colorectal cancer. Randomised comparisons have established the benefits of palliative chemotherapy in the management of advanced colorectal cancer and that these are greatest when patients are symptom free. Scheithauer and colleagues² showed a doubling of survival (11 months *vs* 5 months, $p=0.006$) with systemic 5-fluorouracil compared with best supportive care,

with a trend towards improved quality of life in the chemotherapy-treated group of patients. A Nordic group trial³ reported improved survival from immediate chemotherapy compared with delaying chemotherapy until symptoms develop (14 months *vs* 9 months, $p < 0.02$); symptom-free survival was also increased with immediate chemotherapy (10 months *vs* 2 months, $p < 0.001$). Another randomised trial of hepatic artery infusion floxuridine versus best supportive care in 100 patients,⁴ showed that survival was significantly increased with regional chemotherapy (405 days *vs* 226 days, $p = 0.03$), with similar significant increases in normal scores for physical symptoms ($p = 0.04$), anxiety ($p = 0.04$), and depression ($p = 0.04$). The most recent trials emphasise the benefit of chemotherapy in the palliation of symptoms of metastatic disease.

Metastectomy may be feasible after early detection of recurrence in the liver or lung. Resection of liver and lung metastases has resulted in long-term survival. In their study of the benefits of hepatic metastectomy in 150 patients with potentially operable liver metastases on radiological criteria and no extra-hepatic disease, Steele and colleagues⁵ found that 69 patients underwent curative resection, 18 non-curative resection, and 63 were found to have unresectable disease. Survival was significantly better in the patients who had curative resection (37.1 months) than in those who had non-curative resection (22.1 months) or unresectable disease (16.5 months) ($p < 0.01$). Increasingly, patients with potentially resectable liver and lung metastases are being treated with 3–6 months preoperative chemotherapy. Encouraging results are being reported with this approach, including patients previously judged unsuitable for resection proceeding to metastectomy after preoperative chemotherapy.

On the basis of these studies, we recommend palliative chemotherapy for patients with metastatic or inoperable locally recurrent colorectal cancer who are capable of all self-care and up and about at least half the day. Follow-up is indicated for all patients treated for colorectal cancer with potentially curative resection alone or in conjunction with adjuvant chemotherapy or chemoradiation. We advise that patients are reviewed every 3 months for 1 year, every 6 months during the second year, and then once a year for a further 3 years. Early recurrences with potentially curable metastatic disease can be detected

by computed-tomography scanning 1 and 2 years after surgery.

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- 1 Northover J. Realism of nihilism in bowel cancer follow-up? *Lancet* 1998; **351**: 1074–75.
- 2 Scheithauer W, Rosen H, Kornek G-V, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ* 1993; **306**: 752–55.
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First-ever stroke incidence

Sir—Gudrun Boyesen and Thomas Truelsen's April 11 commentary,¹ discusses comparisons of stroke rates between people of different ethnic origins, and possible reasons for the higher rates reported among blacks, focusing on Broderick and colleagues' study² of stroke incidence among blacks in Greater Cincinnati/Northern Kentucky. However, their description of that study as "population-based" is misleading because the incidence was based only on cases identified from hospital records and necropsies, and therefore, excluded most strokes in people who were not admitted to hospital.

In our recent overview of stroke incidence studies carried out worldwide since the early 1980s, only 11 fulfilled criteria for a comparable study, all in predominantly white populations in developed countries. The proportion of first-ever-in-a-lifetime strokes not admitted to hospital varied from 5% to 40%.³ Although several sources of out-of-hospital cases were monitored in the Greater Cincinnati/Northern Kentucky study, the results were not presented;² only when they are will we have some idea of the perhaps substantial proportion of strokes excluded from the current estimates. These data will provide the first community-based estimate of stroke incidence among

blacks, because previous studies comparing stroke rates in blacks and whites have either been hospital-based or have examined only mortality data, limited by the variations and inaccuracies of death certificates, and by the exclusion of non-fatal strokes.^{1,3}

Boyesen and Truelsen do not mention other important limitations of Broderick and co-workers' study, which will reduce the accuracy of its estimates of stroke incidence even when more data become available. The main sources of cases were hospital records, which are likely to be inaccurate, especially for information about history of stroke or transient ischaemic attack, duration of symptoms (the only way to distinguish strokes from transient ischaemic attacks), and ICD discharge codes. Furthermore, only records with specific cerebrovascular ICD codes were reviewed, and so cases with less specific diagnoses that could represent stroke (eg, collapse, headache, confusion, fits) were excluded. These inaccuracies can be avoided by active review by a study specialist of all potential cases within a few days of onset.³

There is still a real need for comparable community-based studies of stroke incidence among different ethnic groups in different parts of the world, especially developing countries where the burden of stroke is greatest, and increasing.⁴ Various measures of stroke rate in such studies can address different issues; we agree with Boyesen and Truelsen that all strokes (including recurrences) are useful for estimating the burden of stroke, but if comparisons are to help identify important aetiological factors, then incidence based on first-ever strokes is most appropriate.³

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- 1 Boyesen G, Truelsen T. Looking beyond first-ever stroke incidence. *Lancet* 1998; **351**: 1073–74.
- 2 Broderick J, Brott R, Kothari R, et al. The Greater Cincinnati/Northern Kentucky stroke study. Preliminary first-ever and total incidence rates of stroke among blacks. *Stroke* 1998; **29**: 415–21.
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Medical advocacy for the oppressed

Sir—I am astonished that in your April 25 editorial¹ you can seriously claim that the British Medical Association (BMA) rarely pronounces an opinion on matters outside domestic medical practice and politics.

Even the most superficial scan of the association's daily activities and its publications will reveal a mass of documentation and public statements about international issues. These range from the BMA's world renowned publication on medical involvement in human rights, *Medicine Betrayed*, to the association's very public campaign on landmines.

It was BMA representatives who, at last year's annual General Assembly of the World Medical Association, persuaded the association to approve a resolution urging governments employing economic sanctions against other states to respect the agreed exemptions for medicines, medical supplies, and basic food items.

In addition to all the BMA's public activities, is the mass of activity that never sees the light of day—making substantial support to refugee physicians, writing every week in support of detained doctors and other health professionals and other detainees reported to be in need of medical care. What is particularly heartening is when one of these detainees is released unharmed.

Although the BMA does not get involved in the internal politics of individual countries, we do give a great deal of support to Iraqi refugee doctors and their families to assist them to get settled in this country. In short, the BMA has a public record on these issues of which every UK doctor can feel proud.

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¹ Editorial. Medical advocacy for the oppressed. *Lancet* 1998; 351: 1219.

Sir—Your comments in the editorial¹ about the British Medical Association's (BMA) stance on economic sanctions affecting health reveal a misunderstanding of the way that organisation operates.

The BMA is a large, bureaucratic, but very democratic organisation. Its actions are guided by its policy, which is formulated by the annual representative meeting. The BMA cannot currently take a stance on economic sanctions that affect health because it has no policy on the matter. The BMA would no doubt

be roundly condemned by its members and others if its leaders and staff took stances on issues for which they had no mandate.

The bureaucracy of the BMA, whilst sometimes an encumbrance, does contain a clear mechanism by which BMA policy (and hence action) can be changed. At least two constituent organisations have sent motions on the health effects of economic sanctions against Cuba in particular, to be included in the agenda for this year's annual representative meeting (in Cardiff in early July). Concerned doctors should ensure that their local BMA divisions and Craft Committees do likewise. BMA members who attend the meeting must then ensure that these motions are debated and appropriate policy formulated, after which the BMA not only will be able to, but will be required to, take a stance on the issue.

Finally, your comment that the BMA do not usually announce an opinion on matters outside domestic medical practice and politics is unfair. The BMA's reports on the medical effects of nuclear war and on medical aspects of torture have been enormously influential. There are many other examples of international work of the BMA which could be given.

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¹ Editorial. Medical advocacy for the oppressed. *Lancet* 1998; 351: 1219.

Sir—The editorial¹ on medical advocacy for the oppressed should lead us to ask why organised medicine seems so reluctant to speak out against sanctions imposed on Cuba and Iraq. Physicians, after all, have been instrumental in pointing out the health hazards of smoking, landmines, and nuclear proliferation. There can surely be no question of the harmful effects on the health of the populations of the countries affected. The political decisions taken have deprived people of needed care.

The destruction of malignancy (including dictatorships) is a worthwhile objective, but not at the expense of the health of the whole body. The acronym PAUSE—Physicians Against Unnecessary Suffering Everywhere—might remind our political masters of the need to stop and reflect on the terrible consequences of some of their actions.

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¹ Editorial. Medical advocacy for the oppressed. *Lancet* 1998; 351: 1219.

Screening for HIV-1 in pregnancy

Sir—The ability to decrease the vertical transmission of HIV-1 from mother to fetus has been convincingly shown. The ACTG 076 trial of zidovudine given to mothers during pregnancy and during delivery and to the neonate showed a 67.5% reduction in the vertical transmission rate of HIV-1 from 25.5% to 8.3%.¹ Because of the clear benefits of this treatment, every effort should be made to detect mothers of previously unknown HIV-1 status so that they can be allowed to make informed decisions that will influence the health of the newborn infant.

From data in unlinked testing, we know that we do not pick up all HIV-1 positive patients when screening is linked to disclosed risk factors. We therefore introduced, on Jan 1, linked screening for HIV-1 as part of the routine antenatal screen. At booking, signed consent is obtained for screening for rubella, *Treponema pallidum*, hepatitis B, and HIV-1, and the other routine antenatal blood tests. If requested by the patient, the benefits and advantages of each test is explained by a member of staff. The value of antiretroviral treatment in pregnancy with follow-up treatment of newborn babies in reducing vertical transmission is fully explained. This linked HIV-1 testing was introduced after widespread consultation within the hospital with medical, nursing, and medical-social work department personnel.

In the first 2 months of testing, 1104 women had booked for antenatal care at the Rotunda Hospital. Four women expressed reservations about HIV-1 testing. However, after full explanation of the benefits, two of these patients consented to testing. The refusal rate was 0.02%. Three women tested positive; two had risk factors and would have been detected with the previous policy; one would not have been detected.

This approach will allow us to deliver optimum care to the mother during pregnancy and should reduce vertical transmission of HIV-1 infection. Pretest counselling for patients identified as at risk is a vital component in this protocol. In our evaluation of the implementation of the protocol, some patients at risk clearly had not been referred for counselling. This error has been rectified. Other smaller adjustments to an established system may also be necessary. We think that the behaviour of our population shows that important changes can be

introduced provided that they are scientifically valid and have clearly demonstrable benefits for the mother or her baby.

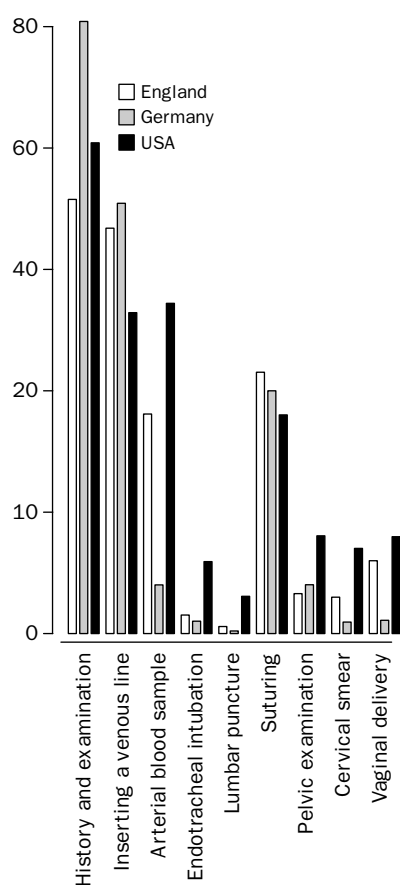
Mary Cafferkey, Margaret Philbin,
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1 Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine therapy. *N Engl J Med* 1994; 331: 1173-80.

Clinical experience of UK medical students

Sir—I McManus and colleagues (March 14, p 802)¹ report on a decline of clinical experience and skills among UK medical students. We asked final year medical students in England, Germany, and the USA to assess their experience with basic clinical skills. They were asked to comment on the number of times they have done a certain procedure (figure) and on how comfortable they felt in doing the procedure.

Although experience with inserting venous drips, suturing, history taking, and clinical examination were similar in all three countries, skills such as arterial blood sampling, endotracheal



Students' experience of medical procedures by country

intubation, pelvic examination, and deliveries varied significantly between countries. For example, endotracheal intubation was done at least once by all but one US student, compared with only five of 18 German students, and eight of 29 English students. Most German students had no experience with pelvic examinations (never done by nine of 18), taking a cervical smear (12 of 18), or vaginal deliveries (13 of 18). By contrast, almost all the students in the US and England had experience with these basic obstetric and gynaecological skills.

Although the number of students asked to take part in the survey is small, the data confirm our personal experience that the acquisition of clinical skills during medical school varies in different countries. We agree with McManus that the decline in clinical experience of UK medical students is of concern, but we like to stress that medical students in other countries, for example, Germany, will have even less opportunity to acquire essential and basic clinical skills before they qualify.

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1 McManus IC, Richards P, Winder BC. Clinical experience of UK medical students. *Lancet* 1998; 351: 802-03.

Israel's ban on Ethiopians' blood

Sir—Edward Kaplan (April 11, p 1127)¹ argues against the policy of the Israeli blood authorities to exclude Ethiopian donors on the basis that Ethiopian immigrants have an HIV-1 infection rate about 50 times that of all other Israelis. He argues that because there are so few Ethiopian blood donors, the removal of their blood from the total supply reduces the risk of HIV-1 contamination by about only 0.1 infected donation per year, from 0.34 to 0.24.

His argument is specious. To see why, I shall choose an extreme example, which requires changing the country to something the size of the USA, to increase the number of blood donations per year. Call this new country Arcadia. It has 10 million donations per year, of which 11 are estimated to be infected with undetected HIV-1, the same proportion as Kaplan derives for Israel. Suppose that in Arcadia, there is only one Presterian blood donor, who,

because of an undeclared needle-stick injury, has a 90% chance of being infected with HIV-1, which goes undetected in the screening process. Since this is an exercise, we (but not the Arcadians until well after the event) know that the estimated infection rate must increase to 11.9 out of 10 000 001 donors. The inclusion of this one donor represents an 8% increase in the risk of HIV-1.

Of course, if the Arcadians knew the HIV-1 status of the Presterian's blood, they would wish to remove it from the blood supply. But according to Kaplan's argument, we would not do so, because the risk is increased from 0.11 per million to 0.119 per million, still very small.

Clearly, the increased risk must be based on marginal calculations: the marginal (ie, incremental) risk of including the Presterian blood is 0.9. The incremental risk of including any other blood is 0.0000011. How the addition of the Presterian donation alters the average risk (the measure that Kaplan uses) is immaterial. The Israelis have made their decision on the basis of a correct criterion: the Ethiopian blood had a per-unit 50 times higher chance of being contaminated than other blood. Kaplan's average risk criterion, that the Ethiopian blood increases average risk by a factor of 1.41 (0.34/0.24), is not an appropriate measure. Whether the Israeli decision itself was the correct one to use depends on their estimate of the marginal benefit of the Ethiopian blood: in a national emergency, if there was no other blood available, presumably the risk would have paled in comparison. The Israeli authorities might also have handled their public relations with the Ethiopian immigrants better when they withdrew their blood from the supply, but that too is entirely another matter.

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1 Kaplan E. Israel's ban on the use of Ethiopians' blood: how many infectious donations were prevented? *Lancet* 1998; 351: 1127-28.

DEPARTMENT OF ERROR

Misuse of psychiatric epidemiology—In this Commentary by Eve Leeman on May 30 (p 1601), the finding of the National Comorbidity Study was that nearly 50% of almost respondents reported at least one lifetime disorder, with almost 30% meeting criteria in the previous year. Also, the 3rd and 4th sentences of the ninth paragraphs should read, "Robert Spitzer, and architect of DSM III, says not very. Although many would disagree, he postulates . . ."