Letters

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Deprivation and emergency admissions for cancers

Other possible explanations for findings need to be explored

EDITOR—The reasons for Pollock and Vickers's findings about the relation between deprivation and emergency admissions for cancers remain speculative.[1] To impute the differences in care to failures of primary care seems unfair at this stage. The authors discuss a range of possible explanations, but many other could also be relevant.

Day case treatment may require a certain level of facilities at home that are less commonly available in deprived areas. The presence of another adult at home may also be a prerequisite. Single people may be more likely to live in deprived areas; patients from deprived areas may be more likely to have a working partner who cannot afford to take time off work or who has a job where such absences would be unacceptable.

Patients with lung cancer due to smoking (more common in areas where smoking is more prevalent) may be less likely to have an operable malignancy because of concomitant disease related to smoking. The authors mention this in their discussion, but limiting the study to inpatient finished consultant episodes with a primary diagnosis of any of the three cancers of interest does not give any information about comorbidity.

I hope further research will be carried out to help elucidate the reasons behind the apparently inequitable access and treatment decisions that Pollock and Vickers have found. Both qualitative and quantitative research methods could be used to study patients' and professionals' experiences as patients pass through the system. Perhaps allocation of blame should wait until such results are available.

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1 Pollock AM, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. *BMJ* 1998;317: 245-52. (25 July.)

Social factors affect patterns of referral for breast cancer

EDITOR—Pollock and Vickers reported that deprivation did not affect the admission of women with breast cancer to units treating more than 100 cases a year.[1] We examined patterns of care in Scotland by studying referrals outside the local health board for initial treatment.

The Scottish breast cancer audit identified 3681 women from the Scottish cancer registry who underwent surgery for non-metastatic breast cancer diagnosed in 1987 and 1993.[2] Patients were allocated to the least deprived fifth of the population, the most deprived, or an intermediate group (2nd, 3rd, and 4th fifths), the Carstairs classification of social deprivation being used for this.[3] The 541 cases detected by screening were excluded from this analysis since their referral may have been determined by the screening programme.

In all, 257 women were operated on outside their health board of residence (132/1585 (8.4%) in 1987 and 125/1555 (8.0%) in 1993) whereas 2883 were first treated in their own health board area. Univariate analysis showed that women who lived in an area with a cancer centre were less likely to be referred externally than those living elsewhere (30/1729 (1.7%) *v* 227/1411 (16.1%); $P<0.001$, χ^2 test for association). The most deprived women, however, were less likely to be referred to another health board than those who were more affluent (16/467 (3.4%) *v* 241/2673 (9.0%); $P<0.001$).

Women aged ≥65 were referred to another health board less frequently than younger women (58/1124 (5.2%) *v* 199/2016 (9.9%); $P<0.001$). Clinical stage at presentation did not influence patterns of referral so cannot explain the effects of deprivation and age. Neither can these effects be explained by more of the older or more deprived women living in health boards with cancer centres, as they remained significant in an analysis restricted to women living in health boards without a cancer centre. A multivariate analysis supported these results.

Although social factors seem to influence patterns of referral, the importance of this finding is unclear. In the Scottish study the adverse effect of deprivation on survival was no longer significant after adjustment for clinical factors ($P=0.28$).[4] Women treated outside their health board were, however, significantly more likely to have their axillary node status and oestrogen receptor status defined ($P<0.001$). If deprived or elderly women are less likely to be referred outside their health board, the staging of their disease and the treatment they receive may be compromised.

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1 Pollock AM, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. *BMJ* 1998;317:245-52. (25 July.)
2 Scottish Breast Cancer Focus Group, Scottish Cancer Trials Breast Group, Scottish Cancer Therapy Network. *Scottish breast cancer audit 1987 and 1993.* Edinburgh: Scottish Cancer Therapy Network, 1996.
3 Carstairs V, Morris R. *Deprivation and health in Scotland.* Aberdeen: Aberdeen University Press, 1991.
4 Twelves CJ, Thomson CS, Gould A, Dewar J. Variation in the survival of women with breast cancer in Scotland. *Br J Cancer* 1998;78:566-71.

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Effect of flutamide on survival in patients with pancreatic cancer

Study needs to be repeated on a much larger scale

EDITOR—Studies in pancreatic cancer, such as that of Greenway,[1] are difficult to recruit into, and a review of the literature will confirm that they are unusual. During the

past three years two other national studies in advanced pancreatic cancer have been done (unpublished data). These were much larger, and histological or cytological proof was an entry requirement. This was not a requirement for inclusion in Greenway's study. Only 17 of the 49 patients entered into Greenway's study had confirmation of their disease, 12 in the flutamide group and five in the placebo group. Thirty two patients had evidence of only local disease at entry into the study; 11 of these had open surgery either before or after they entered the study. Presumably, histological proof of diagnosis was obtained in this group, which leaves a further six patients who had cytological proof of diagnosis obtained from ascitic fluid.

Two patients in the group treated with flutamide survived for over three years, compared with a maximum of just over one year in the group treated with placebo. This length of survival in someone with advanced ductal adenocarcinoma of the pancreas is unusual and brings into question the original diagnosis. Greenway comments that three of the patients in the flutamide group with histological or cytological proof of diagnosis were the longest survivors in the trial. We would be interested to know the exact diagnostic details of the two patients surviving for three years and whether they remain alive and well. It is also disappointing that there is no significant benefit in using the generalised Wilcoxon test when the whole group is analysed. Although use of the log rank test gives a significant result, this test gives greater statistical weight to differences in treatment at later time points. The two patients with longest survival times were both in the flutamide group, and the use of the log rank test necessarily skews the result.

The diagnostic strategy used in Greenway's study would yield an accuracy of 95% in the diagnosis of pancreatic cancer. If, however, the two long surviving patients had chronic pancreatitis, giving an overall diagnostic accuracy of 96% in the study, their exclusion would remove any significant survival benefit for flutamide. Greenway's study provides some interesting observations but needs to be repeated on a much larger scale with more controlled inclusion criteria.

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1 Greenway BA. Effect of flutamide on survival in patients with pancreatic cancer: results of a prospective, randomised, double blind, placebo controlled trial. *BMJ* 1998;316:1935-8. (27 June.)

Results are impressive

EDITOR—Greenway reports a doubling of survival in patients with pancreatic cancer who were treated with the antiandrogen flutamide compared with those treated with placebo.[1] These results seem more impressive than those of any of the larger randomised controlled trials of tamoxifen or cyproterone acetate that have previously attempted to address the question of whether ductal pancreatic cancer is hormonally driven.[2 3] Interpretation of the results presented by Greenway is, however, difficult. He has included 17 patients (35% of the study population) with tumours of 2-3 cm diameter, which, in the absence of dissemination, might be considered suitable for surgical resection by many centres. It is not clear from the paper whether it was these patients who underwent laparotomy and whose tumours were found to be unresectable. If this is not the case then staging methodology needs to be addressed. The inclusion of these patients almost certainly prolongs the absolute survival in both groups and makes comparison with trials of drugs given to patients with more conventionally defined unresectability difficult.

Comparison of the treatment and placebo groups is difficult because little information is given about their relative composition. How many patients in each group had undergone endoscopic stenting or surgical bypass, and how many had undergone laparotomy and biopsy? More detailed information on the tumour stage of patients and the presence or absence of an acute phase protein response would be useful to enable comparison with previous trials.

The failure to establish histology in 50% of patients taking flutamide and 80% of patients taking placebo is of concern, and Greenway devotes much of the discussion to this issue. The unwitting inclusion of two or three patients with neuroendocrine tumours or distal cholangiocarcinomas could bias the results in a trial with such small numbers, and we would be interested to know whether any survival difference existed when only patients with confirmed histology were included.

The results presented by Greenway are impressive and seem to support the notion of a treatment benefit from flutamide. Meaningful interpretation of this study, however, and the potential implications for our own practice are almost impossible to establish on the basis of the information given.

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1 Greenway BA. Effect of flutamide on survival in patients with pancreatic cancer: results of a prospective, randomised, double blind, placebo controlled trial. *BMJ* 1998;316:1935-8. (27 June.)
2 Bakkevold KE, Pettersen A, Arnesjo B, Espehaug B. Tamoxifen therapy in unresectable adenocarcinoma of the pancreas and the papilla of vater. *Br J Surg* 1990;77:725-30.
3 Keating JJ, Johnson PJ, Cochrane AM, Gazzard BG, Krasner N, Smith PM, et al. A prospective randomised controlled trial of tamoxifen and cyproterone acetate in pancreatic carcinoma. *Br J Cancer* 1989;60:789-92.

No recommendations can be made

EDITOR—Greenway's study into the use of flutamide in pancreatic cancer presents many problems. His eligibility criteria are unclear, and there is no evidence that "randomised" patients were matched for critical prognostic variables—for example, performance status, histology, tumour size or stage, or number of patients undergoing potentially beneficial or curative interventional procedures.[1] Certain "alcoholics" were randomly excluded, which implies a selection bias.

Despite the author's difficulties with the "objective bias" of the performance status, which is incorporated in many studies,[2] a baseline assessment is reported but without the relative distribution of the 20% of patients "requiring considerable assistance." Despite the stated 10-fold one year survival benefit surprisingly no consistent improvements in performance status were detectable.

One can extrapolate that 10-20 potentially curative operations for tumours of <1 cm diameter may have been performed and that 35% of patients had tumours <3 cm. Even if ampullary tumours are excluded, these proportions could bias the results, as one fifth of this subgroup may be cured. Conversely, any operative deaths may also explain the survival differences. Suspicion of surgical bias between the groups is highlighted by the lack of conventional response data and by the "chance" imbalance of 50% of patients with histological confirmation taking flutamide compared with only 20% taking placebo. This suggests that there were more operative procedures, and therefore biopsies, in the treatment arm. Were the patients treated with flutamide therefore fitter if more were eligible for surgery?

Altogether 65% of patients had no histological diagnosis and were still ethically randomised; 22% had open palliative procedures; 35% had liver metastases or ascites, or both; 65% had biliary stents; 95% died; and an unconfirmed number had potentially curative surgery. Yet only 35% had a definitive diagnosis. Not only is this a low figure for a tertiary referral centre, but a definitive diagnosis is also a prerequisite for ethical randomisation when treatments could have serious toxicity. Flutamide can contribute to fatal hepatotoxicity or weight loss (antiandrogen) in an already debilitated population. A probability, no matter how high, of a suspected clinical diagnosis is not a surrogate for definitive pathology, particularly when studies have shown only a 42% concordance for diagnoses of malignancy.[3] Rarity of alternative diagnoses is not a valid reason to disregard them, particularly when there were only two long term survivors. Paradoxically, the difficulty in excluding cholangiocarcinoma is highlighted.

From this clinical study, no recommendations are given as to which patients might benefit from treatment. Instead, mechanistic scientific conclusions about the androgen hormone pathway are made, which have not even been assessed. If, for example, any "responders" had negative androgen receptor status in their (probable) pancreatic cancers, it would lead to a different set of conclusions.

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1 Greenway BA. Effect of flutamide on survival in patients with pancreatic cancer: results of a prospective, randomised, double blind, placebo controlled trial. *BMJ* 1998;316:1935-8. (27 June.)
2 Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for

patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-13.
3 Engel LW, Strauchen JA, Chiazze L, Heid M. Accuracy of death certification in an autopsied population with specific attention to malignant neoplasms and vascular diseases. *Am J Epidemiol* 1980;111:99-112.

Author's reply

EDITOR—My study was a small single centre study to support laboratory data showing that pancreatic cancer may be responsive to testosterone. Knowledge of the histology, acute phase reactants, and androgen receptor status in every patient would have improved the study, but feasibility, cost, and the fact that it was a single centre, single clinician study came into consideration.

Tremendous reliance is placed on histological diagnosis, but even in the best centres this is often not possible. Fine needle aspiration will only yield cells that are suitable for cytological diagnosis, which, in the case of adenocarcinoma, could easily come from cholangiocarcinoma, carcinoma of the ampulla of Vater or the duodenum, or even secondary tumours. The better option of Trucut biopsy may be equivocal in specimens with poor differentiation. Histology must be supported with computed tomography and endoscopic retrograde cholangiopancreatography.

Over 95% of carcinomas are advanced at diagnosis. The best chance of long term survival is by resecting tumours of 1 cm diameter or less. As Wigmore states, some centres operate on 2-3 cm tumours; these will be associated with neurolymphatic dissemination with its negative effect on long term survival. All patients in my study had advanced pancreatic cancer.

All 40 patients with tumours in the head had either a stent (32) or a surgical bypass (8), with equal distribution between the treatment groups. Eleven patients had operations; these were for palliative procedures.

Tamoxifen had no effect on survival in the original animal studies or the clinical trials. Cyproterone acetate is not a pure androgen receptor blocker, having androgenic activity, which is why, I assume, it had no effect.

Both patients with long survival times, who are now dead, had macroscopic and microscopic confirmation of adenocarcinoma as they had palliative surgery during their disease.

In reply to Wasan, there was no statistically proved consistent improvement in performance status as numbers were small initially and patients died, reducing numbers for comparison. Anecdotally, who was being treated with flutamide became obvious to both clinicians and nursing staff as they showed improved appetite, together with feeling better and weight stabilisation.

It is planned to introduce a national study once pharmaceutical and ethical committee approval has been sought to compare flutamide with flutamide plus gemcitabine and gemcitabine alone.

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Bulimic eating patterns should be stabilised in polycystic ovarian syndrome

EDITOR—Hopkinson et al have reviewed the polycystic ovarian syndrome and emphasised that it represents more than a purely gynaecological disorder.[1] They also emphasised the link between insulin resistance and obesity in its pathogenesis. They made no mention, however, of the role of bulimia nervosa. McCluskey et al found that three quarters of 34 patients with bulimia nervosa had polycystic ovaries[2] and roughly one third of 153 patients with the polycystic ovarian syndrome attending an endocrinology clinic had scores on a self rating scale for bulimia indicating disordered eating.[3] It was stated that fluctuations in carbohydrate intake associated with bulimia may facilitate the phenotypic expression of the polycystic ovarian syndrome via altered insulin resistance.

Hopkinson et al have highlighted the multiple benefits of weight reduction in the management of women with the polycystic ovarian syndrome. This, however, may simply amount to unsupervised dieting, which runs the risk of escalating cycles of binge eating and purging, potentially contributing to the pathogenesis of the syndrome and certainly contributing to the patient's distress.

More work is needed to examine the causal relations between bulimia nervosa and the polycystic ovarian syndrome. On the available evidence, women with the syndrome should be routinely screened for abnormal eating behaviour; where appropriate, bulimic eating patterns should be stabilised by cognitive behavioural therapy before dieting is recommended. Such treatment can lead to a reduction in the frequency of purging and bingeing of over 70%.[4] Cycles of feast and famine have always modulated reproductive cycles, and an appreciation of this is crucial.

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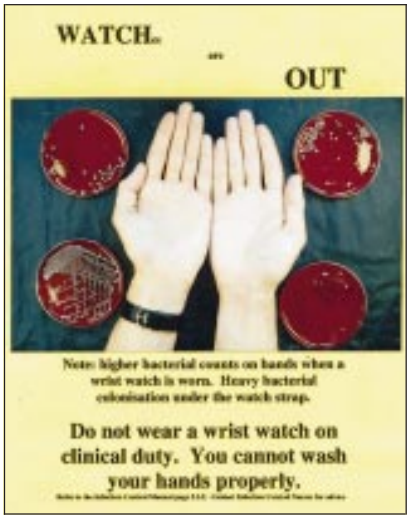
1 Hopkinson ZEC, Sattar N, Fleming R, Greer IA. Polycystic ovarian syndrome: the metabolic syndrome comes to gynaecology. *BMJ* 1998;317:329-32. (1 August.)
2 McCluskey SE, Lacey JH, Pearce JM. Binge-eating and polycystic ovaries. *Lancet* 1992;340:723.
3 McCluskey S, Evans C, Lacey JH, Pearce JM, Jacobs H. Polycystic ovary syndrome and bulimia. *Fertil Steril* 1991;55:287-91.
4 Fairburn C. Short term psychological treatments for bulimia nervosa. In: Brownell KD, Fairburn CG, eds. *Eating disorders and obesity.* London: Guilford Press, 1995:344-9.

Wrist watches must be removed before washing hands

EDITOR—The select committee on science and technology's seventh report states that "Adequate and appropriate hand washing is well recognised as the single most important measure in infection control."[1] All doctors and nurses who have a role in infection control will have been disappointed to see the illustration in the *BMJ* of a lumbar puncture[2] being performed by a doctor who cannot have washed her hands adequately because she is still wearing her wrist watch.



Wearing a wrist watch prevents proper hand washing, which should always be done before an aseptic procedure such as a lumbar puncture. Infection control manuals in our healthcare trust and throughout the country include removing wrist watches and rolling up the sleeves as the first stage of hand washing. We emphasise the importance of removing wrist watches with a poster on the wards depicting the lower bacterial counts achieved by following this policy (figure).

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1 House of Lords Select Committee on Science and Technology. *Seventh report.* London: Stationery Office, 1998.
2 Berger A. Amyloid clearly implicated in Alzheimer's disease. *BMJ* 1998;317:102. (11 July.)

Intravenous β blockade in acute myocardial infarction

Doubts exist about external validity of trials of intravenous β blockade

EDITOR—Owen's perception that intravenous β blockers are less commonly given after acute myocardial infarction in the United Kingdom than elsewhere[1] is confirmed by data from the European secondary prevention study.[2] Clinical management was examined in a representative sample of over 4000 patients admitted to hospital with confirmed acute myocardial infarction in 11 European regions. Intravenous β blockade was given to 13% of patients overall, but this proportion varied from 0.5% (United Kingdom) to 54% (Sweden) in the regional samples. This 100-fold range, larger than the range for any other treatment or procedure studied, is particularly striking for an aspect of management that has been subjected to at least 28 randomised trials in over 27 000 patients.

Variation in practice on this scale has important messages for proponents of evidence based medicine and cannot be

explained by lack of awareness on the part of clinicians. The key issue is the generalisability of the evidence from trials in highly selected low risk patients. In the largest trial, the first international study of infarct survival, fewer than a third of patients admitted to coronary care units were considered to have been eligible for randomisation.[3] The primary end point of vascular mortality in the first week was low in both the atenolol and control groups (3.9% *v* 4.6%; $P<0.04$). The pooled estimate of treatment effect on one week mortality in all available trials remains of borderline significance, and definition of the relevant patient group is even more difficult when meta-analysis is used.

No evidence from clinical trials exists to indicate whether intravenous β blockade would be more or less beneficial in haemodynamically compromised patients or those with hypotension induced by thrombolytics. All observational data are invalidated by the confounding of treatment selection and haemodynamic status. The highly significant increase in the use of inotropic support seen after treatment with atenolol in the first international study of infarct survival gives grounds for caution.

The observed variation in practice probably reflects the widely differing judgment of clinicians on the external validity of the published trials of intravenous β blockade. For long term oral β blockade the evidence is stronger and patient selection less problematic. Correspondingly, use of this treatment was more common in the European study (46% at six months after discharge) and rather more consistent between regional samples (range 27-72%).

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2 Woods KL, Ketley D, Lowy A, Agusti A, Hagn C, Kala R, et al. β Blockers and antithrombotic treatment for secondary prevention after acute myocardial infarction. Towards an understanding of factors influencing practice. *Eur Heart J* 1998;19:74-9.
3 ISIS-1 Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986;ii:57-66.

Case for intravenous β blockade for patients given thrombolysis is still uncertain

Editor—The debate about the value of acute β blockade in myocardial infarction is interesting, partly because of the lack of randomised data in the "thrombolytic era."[1] Owen's statement that evidence for the use of intravenous β blockade is "even more overwhelming" than in the prethrombolytic era is not supported by the studies that he references in his editorial[1] or by the world literature.

The thrombolysis in myocardial infarction (TIMI) II-B study is the only randomised comparison in patients receiving thrombolysis.[2] The effect of acute intravenous metoprolol versus deferred oral metoprolol (started at 6-8 days) was assessed in 1434 patients who had been treated for acute myocardial infarction with recombinant tissue-type plasminogen activator. Though this was a relatively small study, the results are widely recognised to have been disappointing. There was no benefit in left ventricular function and no reduction in mortality. Furthermore, the incidence of myocardial rupture was not reduced. Though the incidence of recurrent chest pain and of reinfarction fell (18.8% *v* 24.1%; $P<0.02$ and 2.7% *v* 5.1%, $P=0.02$; respectively), this difference was not maintained at one year follow up. It should be emphasised that the GISSI-2 (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio-2) trial, which Owen cites, was not a randomised comparison but a description of what happened to two very different groups of patients; it should not be used as evidence for either safety or efficacy.

The case for intravenous β blockade in patients who do not receive reperfusion treatment is secure, but for those treated with thrombolysis or primary angioplasty the data are far from overwhelming.

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2 Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) II-B study. *Circulation* 1991; 83:422-37.

In one health district, only 0.2% eligible for intravenous β blockade received it

Editor—Owen discusses how rarely intravenous β blockade is used in trials in acute myocardial infarction in Britain,[1] citing the fourth international study of infarct survival (ISIS-4) trial, in which intravenous β blockade was given to only 5% of patients enrolled in Britain compared with 30% of those enrolled in Italy and the United States.[2] He says that this is consistent with anecdotal evidence that few British hospitals routinely use intravenous β blockade in acute myocardial infarction. We agree.

We have recently concluded a retrospective study examining routine clinical care of patients with acute myocardial infarction in St Helens and Knowsley Health District. For three periods of four months in successive years (1994-6) we have complete data on use of intravenous β blockers in acute myocardial infarction and contraindications to this treatment for 717 of 989 patients. Altogether, 285 of these 717 patients had contraindications to intravenous β blockade: asthma, chronic obstructive pulmonary disease, acute left ventricular failure, severe hypotension, or severe bradycardia. Of the remaining 432 patients eligible for intravenous β blockade, only one received it; 205 received thrombolysis and presumably therefore had even more to gain from intravenous β blockade (it was not indicated for over half whether they received thrombolysis or not).

Our data strongly support Owen's impression that many eligible patients in Britain are being denied a lifesaving treatment at the time of acute myocardial infarction.

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1 Owen E. Intravenous β blockade in acute myocardial infarction. *BMJ* 1998;317:226-7. (25 July.)
2 Sleight P. What happened to intravenous atenolol in acute myocardial infarction? *Cardiology* 1994;85(suppl 1):13-7.

Storing methadone in babies' bottles puts young children at risk

Editor—On 28 January 1998, Dublin City Coroner's Court heard that a 3 year old boy had died after aspirating gastric contents secondary to the ingestion of methadone. The methadone had been stored in a baby's bottle. The jury recorded a verdict of accidental death.

We investigated the extent to which babies' bottles are used to measure and store methadone. Nine general practitioners agreed to participate in a study whereby they would ask three questions of each consecutive patient to whom they prescribed methadone in a nominated week: (1) Have you used a baby's bottle in the past month to measure methadone? (2) Have you used a baby's bottle in the past month to store methadone? (3) Do you have children aged under 14?

Altogether, 186 consecutive patients agreed to participate in the study. Forty eight had used a baby's bottle to measure methadone in the previous month, and 21 of this group stated that they had children aged under 14 in the home. Seven patients had used a baby's bottle to store methadone in the previous month, of whom four had a child aged under 14 in the home.

Roughly 3000 patients are prescribed methadone in Dublin, over half having it dispensed weekly. They then administer a prescribed dose each day. There is no provision for measuring devices to be supplied to patients either in the Republic of Ireland or in the United Kingdom.

We conducted a telephone survey of 10 pharmacists in Dublin and Manchester. Eight offered a measuring device to patients starting to take methadone (funded by either the pharmacist or the patient (charged 30p to 50p)). All provided a measuring device on request. Alternatively, the pharmacist provided a discarded measuring device from another product (normally baby food). The device was normally a graduated 30 ml plastic device and unsuitable for repeated use. Our finding that a quarter of patients use a baby's bottle to measure their methadone is therefore unsurprising. The bottle is readily available and clearly marked. Its use as a measuring device clearly presents a great risk of accidental overdose, particularly to children. Interestingly, in households

where a baby's bottle was used to measure methadone almost half had children aged under 14 living there.

The use of a baby's bottle to measure and store methadone seems to be common among patients prescribed the drug in Dublin. We recommend that all doctors who prescribe methadone should ask their patients how they measure their daily dose and that a measuring device should be issued, free, with each instalment of methadone dispensed.

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Standards in advertising

Has Didronel PMO been proved to protect against osteoporosis?

EDITOR—The clinical research edition of the 13 June issue of the *BMJ* contained an advertisement for Didronel PMO (between pages 1764 and 1765). The advertisement claimed that the combination tablet of disodium etidronate 400 mg and calcium carbonate 1250 mg "is proven and licensed to protect bones from corticosteroid induced osteoporosis." However, the data presented to support this statement—that is, that "initiating this treatment at the start of long-term corticosteroid therapy reduces the incidence of new vertebral fractures in postmenopausal women on high dose corticosteroids by 85% compared to control ($p=0.19$)"—does not provide evidence of benefit.[1 2] Although we recognise that a non-significant effect does not mean that there is no effect, the absence of confidence intervals does not allow clinical significance to be evaluated.[3]

The supporting references by Adachi et al[1] and correspondence in the *New England Journal of Medicine*[2 4] add further confusion. These references indicate that: the study was not designed to show the effect of disodium etidronate on the incidence of fractures (a secondary endpoint)[1 2]; a treatment effect was seen only in postmenopausal women[1]; and there seemed to be a greater frequency of vertebral fractures occurring among men in the group taking disodium etidronate (4 of 19 men in the etidronate group *v* 3 of 25 in the placebo group).[1 4]

Furthermore, in a post hoc logistic regression analysis which accounted for the disproportionately lower bone mineral density at baseline in the placebo group (making them more likely to have fractures) and the higher proportion of patients with rheumatoid arthritis (21 *v* 13 in the etidronate group), this finding of an 85% reduction in the proportion of postmenopausal women with new vertebral fractures in the etidronate group (1 of 31 women *v* 7 of 32 women in the placebo group) failed to reach the conventional level of statistical significance.[2]

Surely advertisements in the *BMJ* should be expected to meet the same rigorous standards that are applied to primary research papers.

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1 Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997; 337:382-7.
2 Adachi JD, Pack S, Chines AA. Intermittent etidronate and corticosteroid-induced osteoporosis [letter]. *N Engl J Med* 1997;337:1921.
3 Gardner MJ, Altman DG, eds. *Statistics with confidence.* London: BMJ Publishing Group, 1989.
4 Disla E, Tamayo B, Fahmy A. Intermittent etidronate and corticosteroid-induced osteoporosis [letter]. *N Engl J Med* 1997;337:1921.

Manufacturer's reply

EDITOR—Millson and Clark raise an important point about advertising standards. Fortunately, in the United Kingdom these are clearly defined,[1] and they are adhered to in letter and spirit by Procter and Gamble Pharmaceuticals. Millson and Clark challenge our claim that "only Didronel PMO is proven and licensed to protect bones from corticosteroid induced osteoporosis."

The assessment of bone protection is multidimensional, and its evaluation may include measures of mass, density, structure, and quality. Of these, bone mineral density can readily be assessed in clinical practice and is one of the most important predictors of fracture at several sites.[2] The principal finding and primary outcome of the study by Adachi et al was the statistically significant and clinically relevant increase in bone mineral density in the lumbar spine in patients treated with etidronate as compared with those treated with placebo.[3] This proves that Didronel PMO has a protective effect against corticosteroid induced osteoporosis. Didronel PMO was the first drug for which such a positive effect in corticosteroid induced osteoporosis was shown in a prospective, double blind, placebo controlled study.[3]

As clearly stated by Adachi et al, and by Millson and Clark, the study was not powered to look at fractures. Fractures were analysed as a secondary outcome parameter, and the reduction in the proportion of postmenopausal women with new vertebral fractures was reported.[3] After a post hoc correction for baseline bone mineral density the statistical significance of this 85% reduction was reduced.[4]

The rate of new fractures, although subject to greater influence from outlying values, provides an alternative assessment of fracture outcome. The statistical significance for the 94% reduction in the rate of vertebral fractures in the subgroup of postmenopausal women was unaffected by the adjustment for baseline bone mineral density at the 5% level ($P=0.018$) (unpublished data, Procter and Gamble).

We accept Millson and Clark's point that even with these statistically significant data on vertebral fractures this study does not provide definitive proof of a reduction in the incidence of fractures. We will therefore use more appropriate wording to describe the reduction in the risk of fractures in future versions of this advertisement. Nevertheless, the protective effect of Didronel PMO in corticosteroid induced osteoporosis remains statistically and clinically proved.

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1 Association of the British Pharmaceutical Industry, the Prescription Medicines Code of Practice Authority. *Code of practice for the pharmaceutical industry.* London: ABPI, 1998.
2 Ross PD. Risk factors for osteoporotic fracture. *Endocrinol Metab Clin North Am* 1998;27:289-300.
3 Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;337:382-7.
4 Adachi JD, Pack S, Chines AA. Intermittent etidronate and corticosteroid-induced osteoporosis [letter]. *N Engl J Med* 1997; 337: 1921.

Editorial control over controversial contents?

EDITOR—I am dismayed that on a weekend when another boxer was recovering from surgery for an intracranial haemorrhage sustained during that "noble sport" (sic), the *BMJ* published an appeal from the National Sporting Club for support from the medical profession.[1] Given the BMA's stand against boxing, are we to infer that the editor has no control over the contents of the classified supplement? Or has no knowledge of its contents?

Or will he defend the right of such organisations to advertise freely (on payment of a sum, of course)? If this be the case, will he also permit organisations supporting the rights of smokers, for example, to pollute themselves and non-smokers?

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1 Noticeboard. *BMJ* 1998;317 (classified suppl): item 03912. (2 May.)

⁂Advertisements in the *BMJ* are not peer reviewed and do not carry the stamp of approval of the journal. Readers know this. It is just the same as with advertisements in magazines for holidays, alcohol, or any goods or services.

There was a time when we did review the claims made in all pharmaceutical advertisements, and the editors of the Indian edition of the *BMJ* still do. We don't do it in Britain because there are now British and European statutes governing pharmaceutical advertising as well as self regulation by the industry. In India there are no such systems. We urge any *BMJ* reader unhappy with advertisements in the journal to make a complaint to the Code of Practice Authority (12 Whitehall, London SW1A 2DY). Readers should also consider sending us a letter for possible publication. We publish criticisms of advertisements just as we do for papers.

By publishing the appeal from the National Sporting Club for support from doctors who are in favour of boxing we are not supporting the position of the club. The editorial pages of the *BMJ* have carried letters and articles from doctors who

support boxing just as debates at the council of the BMA have included speeches from doctors who support boxing. That's free speech. The *BMJ* is a forum for debate, and we are willing to consider for publication all views that are not illegal.—Editor, *BMJ*

Intensive cognitive behaviour therapy for chronic schizophrenia

Specific effect of cognitive behaviour therapy for schizophrenia is not proved

Editor—Tarrier et al's randomised controlled trial of intensive cognitive behaviour therapy for patients with chronic schizophrenia seems to show that cognitive behaviour therapy offers advantages over routine care alone. It is not clear, however, that the patients receiving cognitive behaviour therapy did better than a third group, which received non-specific supportive counselling. The outcomes in this group were intermediate between those for the cognitive behaviour therapy and routine care groups and apparently did not differ significantly from either, although the paper is not as clear as it could be on this point.

This study provides some evidence that the course of schizophrenia can be improved by psychological support, but we cannot conclude that cognitive behaviour therapy exerts any specific effect. This is important for two reasons. Firstly, understanding what interventions affect the course of the illness may help us to understand the pathological mechanisms involved. Secondly, cognitive behaviour therapy is likely to be substantially more expensive than supportive counselling. Many schizophrenic patients already receive supportive counselling as part of their routine care, perhaps as part of sessions with a key worker at a day centre or in their supported accommodation. Finally, the authors did not mention the fact that of the patients available for follow up, 8 of 32 receiving cognitive behaviour therapy dropped out or refused follow up while only 3 of 24 receiving supportive counselling did so. This difference is not significant, but it is as noteworthy as several of the results that the authors do draw attention to.

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1 Tarrier N, Yusupoff L, Kinney C, McCarthy E, Gledhill A, Haddock G, et al. Randomised controlled trial of intensive cognitive behaviour therapy for patients with chronic schizophrenia. *BMJ* 1998;317:303-7. (1 August.)

Author's reply

Editor—As Curtis says, the direction of improvement reported in our trial was indicative of patients receiving cognitive behaviour therapy doing better than those receiving supportive counselling, who in turn did better than those given routine care alone in the intention to treat analysis. The significant differences, however, were for cognitive behaviour therapy over routine care in post hoc tests.

In a more detailed analysis of symptom types in patients who received the full treatment protocol, there were considerable differences between cognitive behaviour therapy and supportive counselling, mainly in greater improvement of hallucinations in those who received cognitive behaviour therapy. Furthermore, in the study supportive counselling had the same "therapy envelope" as cognitive behaviour therapy—that is, 20 hourly sessions delivered twice a week. I would be sceptical that this level of intervention currently takes place as routine care delivered by key workers, as Curtis suggests. My colleagues and I are currently investigating the effectiveness of supportive counselling more fully in a multisite trial comparing cognitive behaviour therapy, supportive counselling, and routine care alone in 320 acutely ill patients with schizophrenia of recent onset.

Reasons why patients drop out of treatment are always of interest, and we have reported the reasons that patients gave for dropping out.[1] There was no evidence that the relatively small and non-significant difference between groups in the number of patients who dropped out was related to the type of treatment to which they were allocated.

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1 Tarrier N, Yusupoff L, McCarthy E, Kinney C, Wittkowski A. Some reasons why patients suffering from chronic schizophrenia fail to continue in psychological treatment. *Behav Cogn Psychother* 1998;26:177-81.

Implementing research findings in developing countries

Skills for appraising evidence must be taught

Editor—The paper on implementing research findings in developing countries sets out a clear framework for getting research findings into practice.[1] With the creation of systematic reviews and guidelines, and implementation programmes through workshops and published work, the framework is in line with the process in Western countries. However, one element that we would add is the development of skills to find and appraise the scientific evidence.

We know that on its own the dissemination of guidelines and other educational materials has only a small impact on practice[2] and that approaches have to be multifaceted to work. Yet for many parts of the developing world access to evidence will be through literature in one form or another, and there may be little opportunity for getting together with colleagues.

This means that the acquisition of skills to find and appraise evidence must be central to all programmes designed to help get research into practice. Even in the United Kingdom many clinical staff have not got the basic skills in finding and appraising evidence, and this is now being remedied through comprehensive educational programmes in many parts of the country. To ensure clinicians are equipped with skills to find and appraise evidence is an enormous challenge for developing countries, but it has to be tackled. Methods will have to be tailored to the particular needs of clinicians in developing countries and no doubt have to include distance learning techniques.

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1 Garner P, Kale R, Dickson R, Dans T, Salinas R. Implementing research findings in developing countries. *BMJ* 1998;317:531-5. (22 August.)
2 Freemantle N, Harvey EL, Wolf F, Grimshaw JM, Grilli R, Bero LA. Printed educational materials to improve the behaviour of healthcare professionals and patient outcomes. In: Cochrane Collaboration. *Cochrane Library*. Issue 3. Oxford: Update Software, 1998.

Medical curriculums need changing

Editor—Few people who have worked in developing countries would argue with Garner et al's summary of how to encourage research in such areas and the difficulties and obstacles encountered.[1] However, experience from Ukraine shows that the solution may not just be providing the finance but may lie deeper in basic medical education.

The Royal College of General Practitioners has been working, through its international fellowship programme, on the facilitation of a system of primary care in Ukraine that is based on the European model. This programme is now in its fourth year, and substantial progress has been made.[2] We have been able to observe the delivery of health care, and although the numbers are small, interesting observations are emerging which may affect long term planning.

Observation of consultations in primary care suggests that there is a strong tendency to medicalise non-clinical problems. Multidrug prescribing is often the rule, and health promotion is rarely discussed. Neither the undergraduate nor the postgraduate medical curriculums teach health promotion or the diagnosis and management of psychosocial disorders (unpublished data). This has to be taken into the context of Ukraine having the worst morbidity and mortality figures in the whole of eastern Europe, with most illness being a result of a poor understanding of personal and social effects on disease.[3]

Ukraine is ready for the introduction of primary care research and evidence based medicine, but this must be accompanied by a change in medical education. This change has to be driven by a central government order with its associated complexities.

Ukraine shares with other developing countries the perception that a good doctor is judged by the items of equipment and

number of tests he or she performs. Hence computers are becoming increasingly common in medical practices and should be accessible for research. However, since there are no educational initiatives to encourage the wider use of information technology, specifically to access data or to collect data, facilities are unused and become items of status rather than practicality. Medical staff must recognise that this deficiency in basic medical education will impede the development of standard and progressive medical care and research, even if accompanied by vast financial resources.

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1 Garner P, Kale R, Dickson R, Dans T, Salinas R. Implementing research findings in developing countries. *BMJ* 1998;317:531-5. (22 August.)
2 Gibbs T, Mulka O, Zaremba E. The Royal College of General Practitioners Ukraine fellowship programme 1993-1997. *Eur J Gen Pract* 1998;4:84-7.
3 Kromhout D, Bloemberg B, Doornbos G. Reversibility of rise in Russian mortality rates. *Lancet* 1997;350:379.

Using research findings in clinical practice

Doctors advocating evidence based medicine may be out of touch with real medicine

EDITOR—Is it possible that the evidence based medicine lobby is so busy reviewing the literature that it has lost touch with the rather disorderly world of real medical practice? Certainly Straus and Sackett provide convincing evidence of that in their article telling us how to use research findings in practice.[1] Having decided that the most important of several questions that a casualty officer could ask when faced with an alcoholic, confused man with cirrhosis who is bleeding is "Does treatment with somatostatin reduce the risk of death?", they conclude that the answer is unknown. The correct course is therefore to form a therapeutic alliance with the patient, discuss the potential risks and benefits, and then reach a decision.

Although confused alcoholic patients in Oxford may be more able to discuss clinical pharmacology than those from Middlesbrough, I doubt that that is the explanation for this strange approach to this medical emergency. I can conclude only that there are no trials in the literature that prove that a discussion of the risks and benefits of somatostatin with a confused man who may be bleeding from oesophageal varices is not only pointless but associated with a poor outcome.

What Straus and Sackett are suggesting may be a useful learning exercise for a junior doctor but is nothing to do with the practice of medicine. The correct response from the casualty officer in this case would be a rapid telephone call to someone who already knows how to deal with such problems without scurrying off to the ward computer.

Until those advocating evidence based medicine have a better understanding of what actually happens when patients and doctors meet, their scrupulous search for the truth will provide a disappointingly small input into the practice of medicine.

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1 Straus SE, Sackett DL. Getting research findings into practice: Using research findings in clinical practice. *BMJ* 1998;317:339-42. (1 August.)

Authors' reply

EDITOR—In case other readers made the same mistakes as Main in reading our paper, we would like to re-emphasise four points.

Firstly, practising evidence based medicine begins and ends with clinical expertise. In our clinical service (we admit about 200 patients a month) unstable patients therefore receive immediate care from a team that comprises staff with as many sorts of expertise as required; that's not what the paper was about.

Secondly, a typical inpatient generates five questions for clinicians who are willing to admit that they don't have all the answers. We therefore decided that our most useful contribution would be to describe how busy clinicians can pare these down to one answerable question by balancing various factors. These factors might be: which question is most important to the patient's wellbeing; which is it most feasible to answer in the time available; which is most interesting to the clinician; and which answer is most likely to be applicable in subsequent patients?

Thirdly, as we have published elsewhere, pre-appraised evidence often can be accessed by busy clinicians in seconds.[1]

Finally, we would suggest (as does every professional body we know about) that doctors' duty includes establishing an alliance (not to describe clinical pharmacology, but to discuss the benefits and risks of treatment) with every patient (or his or her surrogate).

Main's final sentence is wrong, too. Audits in medicine,[2] surgery,[3] psychiatry,[4] and general practice[5] have all shown that clinical services that strive to provide evidence based care can do so for about four fifths of their patients.

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1 Sackett DL, Straus SE. Finding and applying evidence during clinical rounds: the "evidence cart." *JAMA* 1998; 280:1336-8.
2 Ellis J, Mulligan I, Rowe J, Sackett DL. Inpatient general medicine is evidence based. *Lancet* 1995;346:407-10.
3 Kenny SE, Shankar KR, Rentala R, Lamont GL, Lloyd DA. Evidence-based surgery: interventions in a regional paediatric surgical unit. *Arch Dis Child* 1997;76:50-3.
4 Geddes JR, Game D, Jenkins NE, Peterson LA, Pottinger GR, Sackett DL. What proportion of primary psychiatric interventions are based on randomised evidence. *Qual Health Care* 1996;5:215-7.
5 Gill P, Dowell AC, Neal RP, Smith N, Heywood P, Wilson AK. Evidence based general practice: a retrospective study of interventions in our training practice. *BMJ* 1996; 312:819-21.

Safety of genetically engineered foods is still dubious

EDITOR—The editorial by Derek Burke, former chair of the government's Advisory Committee on Novel Foods and Processes (ACRE), certainly had a reassuring tone about it, but it also suffered from a fairly major dose of complacency.[1] It would be surprising if a man who had for nine years chaired the committee that authorised the release of genetically engineered seeds for testing in trial plots had any serious doubts about the decisions he made. Most consumers now think otherwise. His article certainly covered the ground, but it did not do justice to many of the serious concerns about the potential risks of this new and unproved technology. For example, Burke describes the transfer of genes from one species into another as a well tried and tested and precise science, whereas much about it is still random and hit and miss. As a result, there have been a number of unpredicted consequences arising from the transfer of genes into unrelated species.

To say that "the public has accepted some [genetically modified foods] without hesitation" is misleading, to say the least. Most consumers were totally unaware of genetic engineering until very recently. Many of the foods containing genetically engineered ingredients or their derivatives have never been labelled, including much of the hard cheese that is produced using the genetically modified enzyme chymosin.

On the subject of safety, Professor Burke says that genetically engineered foods are safe because his committee says so. The Soil Association is not convinced and has written to each chairperson and chief executive of Britain's leading multiple retailers, suggesting that they should set a date after which they should no longer use genetically engineered ingredients in the manufacture of their own-label products.

The premise on which most modern medical science has been based is that health is the product of the absence of disease and can be achieved through use of a vast array of drugs and, more recently, medicines derived from genetic engineering. The opposing view is that health is not merely the absence of disease but is in fact a dynamic equilibrium, which occurs when an organism is in a harmonious balance with its environment. Healthy plants, animals, and people are the result of sound husbandry and management, not the product of prophylactic doses of pharmaceuticals and genetically engineered drugs. The medical world would do well to entertain these types of ideas more seriously.

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1 Burke D. Why all the fuss about genetically modified food? *BMJ* 1998;316:1845-6. (20 June.)