Letters

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Referral and diagnostic process in suspected colorectal cancer needs to be improved to achieve two week target

EDITOR—In response to the government initiative to improve the diagnosis of cancer, and using the recently published referral guidelines for suspected colorectal cancer, we have completed a three month pilot study looking at the introduction of the two week target at the North West London Hospitals NHS Trust.

Consultation occurred with general practitioners in the pilot area's primary care group. The general practitioners were asked to use a specific two week target form, which contained six symptom categories, when they referred patients. The completed form was faxed to St Mark's Hospital, and an outpatient appointment was then given within the two week target time. Each patient was seen by a consultant surgeon or surgical specialist registrar. The hospital specialist, blinded to the general practitioner's form, completed a similar form, which had an additional category—"patient does not fulfil any of the above criteria."

Altogether 364 clinic slots were reserved for patients referred under the two week target scheme, on the basis of calculations for projected appropriate referrals for a population of 500 000. However, just 20 patients were referred during the three month pilot period. General practitioners and specialists categorised five patients identically (two of these patients had a letter attached to the fax, which the specialist read in the clinic despite the protocol). Six patients were categorised by specialists as not fulfilling any of the criteria for urgent referral. All patients were seen within two weeks. Thus far, four cancers have been diagnosed—three adenocarcinomas and one squamous cell carcinoma. During the pilot period a further seven cases of cancer from the pilot area were diagnosed that had not been referred via the two week target process.

This preliminary experience suggests that, despite close liaison with the primary care group, the referral process will take time to be adopted and implemented. Despite clear referral guidelines there was massive underuse of the facility, considerable variance between the general practitioner's and specialist's assessments of symptoms, and a high rate of apparently inappropriate urgent referral. Unless these outcomes are improved dramatically, the efficiency of the referral and diagnostic process in suspected colorectal cancer would not improve for most patients. The audit is continuing.

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Effect of screening programme on mortality from breast cancer

Benefit of 30% may be substantial overestimate

EDITOR—Blanks et al have attempted to model the decline in mortality from breast cancer in England and Wales and to estimate the proportion of this decline due to screening.[1] Unfortunately, even their estimate of a modest effect may be too large: the effect of tamoxifen at ages 55-74 may be larger than that at ages 50-54, as many of these younger women may be premenopausal and have oestrogen negative cancers, gaining less benefit from tamoxifen.

Blanks et al do not comment on the unexplained rise in mortality from breast cancer in the United Kingdom from about 1965 to 1990. The recent fall in this mortality in the United Kingdom may have been partly due to the removal of the factor that caused the rise. Such a rise was not seen in North America, where mortality from breast cancer was stable until about 1990, since when similar falls in both Canada and the United States have occurred, of the same order as that in the United Kingdom.[2]

Blanks et al perpetuate the unproved assumption that falls in mortality from breast cancer are due to the early detection by mammography of cancers when they are small and impalpable. It was always impossible to explain the rapid fall in mortality from breast cancer in women aged 50-64 in the health insurance plan trial[3] by such an effect; recently published Canadian data cast further doubt on this assumption.[4]

Gøtzsche and Olsen have suggested that imbalances in many of the breast screening trials cast doubt on the evidence that Blanks et al rely on to expect an eventual 30% reduction in mortality from breast cancer through screening.[5] As colleagues and I have pointed out, such a relatively large effect will be seen only if the effects of improved treatment of breast cancer are additive to the effects of screening.[2 4]

Quite possibly, improvements in treatment will reduce the effect of screening, if not abolish it altogether. It is relevant that we do not know whether in the two county trial in Sweden equivalent treatment was given to the screened and control groups. If it was not, and the treatment in the control group was inferior (as it could have been then in rural areas geographically separate from the screened areas), then 30% may be a substantial overestimate of the eventual benefit to be seen in all screening programmes for breast cancer.

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Women might not accept mammography if benefit is lower than is currently thought

EDITOR—Regular mammographic screening has been vigorously promoted by several guidelines on the basis of an expected reduction in mortality of as much as 25-30%.[1 2] Blanks et al also concluded that such screening reduced mortality, although they cited a much lower rate (6.4%).[3] Nevertheless, a recent critical review and meta-analysis of the Cochrane database by Gøtzsche and Olsen has provoked a debate, which is currently unresolved; these authors found that the mortality benefit of screening may be overrated, and thus there may be no justification for it.[4]

To assess what minimal expectations women undergoing mammographic screening had, we conducted a written anonymous survey about the perception of mammographic screening among 457 women who underwent mammography at a public university hospital. Screening was the only reason for undergoing mammography for most of the women (n = 329). For 64 of the women it was the first time they had had mammography. Altogether 201 of the women were aged 50-70 and 146 were aged

Opinion of women undergoing mammography about its benefit and their willingness to undergo examination in event that benefit is reduced. Values are numbers (percentages); some women gave more than one answer

	No (%) of women
I believe that mammography increases the likelihood of earlier detection of breast cancer and therefore increases the chances of cure (n=450):	
Very much	204 (44)
Much	154 (33)
Moderately	48 (10)
Slightly	8 (2)
Very slightly	4 (1)
Not at all	4 (1)
I have no clear opinion	46 (10)
I would only undergo mammmography if the likelihood of cure of cancer is at least (n=411):	
Very much increased	50 (10)
Moderately increased	24 (5)
Very slightly increased	147 (31)
Not increased but the chance of preserving my breast is increased	117 (24)
Not at all increased	108 (23)
I have no clear opinion	29 (6)

41-50. The table shows their opinion about mammography's benefit and their willingness to undergo this examination in the event that the benefit is reduced.

Women who accept surveillance by mammography probably do so because they expect a benefit from it. A vast majority of the women (87%) thought that mammography increased, at least moderately, their chances of cure from breast cancer. In the event that no proved benefit exists, about half (46%) would not accept it; a quarter (24%) would accept it provided that detection on mammography at least increased the chance of breast preservation. There was no difference in opinion between women who were having mammography for the first time and those who had undergone it previously; neither was there a difference in relation to age distribution.

Schwartz et al have drawn attention to the potential harm of mammography, such as false positive results and the detection of cancers that may never progress.[5] They found that women show a high tolerance to false positive results. This may partly be due to the expected benefit of mammography. If the benefit of mammographic screening is lower than is thought, many women might not accept this examination,[3] which is not free of stress and may even be harmful in the case of false positive results.[5]

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Investment in treatment would be more cost effective

Editor—We emerged from the fifth world overview of breast cancer trials elated by the impact of recent improvements in treatment.[1] Appropriate surgery, cytotoxic chemotherapy, and hormonal treatment (tamoxifen or ovarian suppression) produces around a 25% reduction in the relative risk of disease-specific mortality *across all age groups and stages*. An average baseline 10 year mortality of 40% in 1985 translates into an absolute survival benefit of 10% by 2000. In other words, in addition to helping prevent uncontrolled local disease, modern treatment now ensures that 100 more women out of 1000 treated are alive today than might have been 10 years ago.

Compare this with the results of breast screening described by Blanks et al and widely reported in the national press.[2,3] Over the same time screening has produced a *relative* risk reduction in breast cancer mortality of 6.4%. However, this applies to a population of asymptomatic women in a limited age range and not to those who actually have the disease. In addition, "we cannot … be completely sure whether the estimate [of benefit] is biased and thus whether the goal of the screening programme has been achieved."[4]

It is informative to calculate the absolute chance of benefit from screening for a given woman using the number needed to treat, as is often used for adjuvant systemic therapy. The incidence of breast cancer in women aged 50-64 is 2 per 1000 per year. Over a decade 2% of women will develop the disease, but for simplicity let's assume that 2% of women presented with the disease in 1990. Without systemic therapy, mortality might be 40%, so the number needed to treat is calculated as 2%×40%×6.4%=0.052%—1 in 2000 in the age group invited for screening. Improvements in treatment have therefore been 200 times more efficient than the screening programme in saving lives—and screening only applies to a third of the population at risk.

The figures are self evident, yet it is galling how the political spin from government agencies suggests that the best way of reducing deaths from breast cancer lies in trawling through the asymptomatic population. We suggest that greater investment in quality of care and research related to treatment could be much more efficient.

Screening regularly captures the headlines—so much so that to question even the concept of a national screening programme is tantamount to attacking an unusually well protected example of the species *Vacca sacra* [sacred cow]. Anyone can see that detecting a disease early might be good for you; it is more difficult to appreciate the rationale, importance, and contributions of adjuvant systemic therapy and to recognise the negative impact of unnecessary anxiety, false positive readings, and repeated negative biopsy results among the worried well, who attend regularly for screening but for marginal benefit.[5]

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Pitfalls of pharmacoepidemiology

Editor—Farmer et al cited several "crucial differences" between a study they published and our recent study on the risk of venous thromboembolism associated with third generation oral contraceptives compared with oral contraceptives containing levonorgestrel using the same data source, the General Practice Research Database.[1–3] We agree that it is worth while to consider how the differences Farmer et al allude to might affect the findings of our studies.

Firstly, Farmer et al point out that over the years of our using the database to conduct pharmacoepidemiological research at the Boston Collaborative Drug Surveillance Program we have restricted our studies to a subset of practices that have provided reliably high quality data.[1] They imply that this may introduce selection bias (at the level of general practice rather than individual subjects). This is not, however, a plausible explanation for the difference between our findings. If there were truly no difference in the risk of venous thromboembolism with third generation oral contraceptives and oral contraceptives containing levonorgestrel, our finding of a twofold risk in the practices we studied means that we must have excluded practices that would collectively show an equally strong association for the incidence of venous thromboembolism with third generation oral contraceptives and oral contraceptives containing levonorgestrel but in the opposite direction from what we found. No one has postulated that third generation oral contraceptives might be associated with a lower risk of venous thromboembolism than those containing levonorgestrel; moreover, it is diffi-

cult to see how we could have identified practices in which such a supposed protective effect would be observed before carrying out our study (so that these practices could be systematically excluded). On the other hand, when the exposure under study is dichotomous (as in our study) it is comparatively easy to obscure a true association—that is, to produce bias towards the null—by introducing misclassification of either the exposure or the outcome, even when such misclassification is non-differential. To minimise this common potential bias, we always exclude practices that we have found to provide incomplete or otherwise inadequate data.

Secondly, Farmer et al assert that they reviewed individually all records of potential cases and suggest that some of the discrepancy between our reports may be due to our "underidentification" of cases.[1] We studied cases that were well documented and idiopathic (not due to an identifiable proximal cause such as recent surgery or fracture) among women currently exposed to one of the classes of oral contraceptives under study. If there were additional similar cases that we did not study, this would not bias the effect estimate we reported, although an effect estimate calculated from a subset of cases would be less precise—that is, it would have wider confidence intervals. However, our study showed a significant association[3] while that of Farmer et al did not.[2] Hence, an explanation of the difference between our findings must lie elsewhere.

Thirdly, Farmer et al note that we studied women aged 15 to 39[3] while they studied women up to the age age of 49.[2] Again, this would not explain why we observed an association between a dichotomous exposure variable and the outcome (venous thromboembolism) unless an equally strong inverse association exists—that is, a protective effect for venous thromboembolism of third generation oral contraceptives compared with oral contraceptives containing levonorgestrel—among women aged 40-49, who were included in the study of Farmer et al but not ours. In fact, the number of women aged 40 to 49 in the database who had an episode of idiopathic venous thromboembolism while taking oral contraceptives is too small for us to be able to estimate reliably the relative risk of different classes of oral contraceptives among women in this age range.

Finally, Farmer et al seem to acknowledge that their time series analysis[2] did not control adequately for confounding due to obesity and smoking. As pointed out in our discussion,[3] more precise control of confounding is possible in a nested matched case-control study than in a cohort study, especially when prescription patterns change rapidly over time (as was the case after the Committee on the Safety of Medicines issued its warning in 1995 about the higher risk of venous thromboembolism associated with third generation oral contraceptives). This is exactly why we conducted and presented the results of a matched case-control analysis in addition to reporting a cohort study.

We leave it to the epidemiological and medical scientific communities to assess the relative merits of our case-control study[3] and the time series (cohort) study of Farmer et al.[2]

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Competing interests: The study on use of oral contraceptives based on the General Practice Research Database that was conducted by the Boston Collaborative Drug Surveillance Program in 1996 was funded by NV Organon.

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Primary care is natural place for clinical research and practice

Editor—In his editorial Thomas pointed out that primary care, because of its complexity, is not an easy place to conduct research, despite the great need for more research to be carried out.[1] In Italy collaborative groups of general and paediatric practitioners have been performing observational studies for some time but cannot, by law, organise or participate in randomised clinical trials. A few studies reported in the literature have therefore to be considered illegal for doctors in Italy.[2 3]

The voluntary participation of practitioners in formal clinical research is a core resource for independent and qualified research, but a recognised body of legislation is fundamental for defining mechanisms and for stimulating participation. More efforts, especially those that are characterised by a more formal participation, are needed in every country. In Europe these should take into account the new European health strategy recently proposed in an attempt to harmonise the delivery of health care and to overcome political and economic misinterpretations.[4] Unfortunately, once again, primary care is hardly considered; proposed networks seem more oriented towards arranging guidelines and statements than harmonising different priority issues in different settings.

The challenge of carrying out clinical research in primary care while creating networks of general practitioner researchers should be one of the priorities at regional, national, and European levels. Since most patient contacts with health professionals occur in primary care this is the natural laboratory of clinical research and practice, where effectiveness, efficacy, and safety of care can be assessed and guaranteed to all.[5]

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Giving medicine a fair trial

Patients' preferences should be assessed

Editor—Ashcroft in his editorial calls for trials that do not second guess what patients want.[1] We agree that sometimes the search for the perfect design of a clinical trial is impractical. Ashcroft argues that if we are uncertain about treatments then the best treatment for the patient is the trial.

Although trials should be simple, timely, and well designed to answer well posed questions, we cannot agree that they should not assess what patients prefer. The preference of a patient deserves special emphasis when diseases or treatments affect quality of life, when the treatment entails risks or side effects, or when the choice between treatments is a "close call."[2] This is particularly relevant in chronic diseases where a particular symptom such as pain is the problem. The balance between the efficacy and the profile of side effects of the treatment in relation to the overall pain experience is one that only patients can judge and may be more accurate than pain measures alone. Preference for a particular treatment may promote compliance and contribute to its success. We understand Ashcroft's difficulty that endpoints relevant to patients—for example, quality of life—make trials harder to run and take longer to implement, but we cannot agree that the results are harder to generalise and apply.

Those who apply a true evidence based approach include only studies that are randomised, double blind, and placebo controlled in systematic reviews. The goal of good clinical trial design is to eliminate chance and bias. Without randomisation, treatment effects are exaggerated up to 40%; without effective blinding, exaggeration may reach 20%.[3] The larger the sample population the more likely the results are to be credible; small trials overestimate treatment effect by as much as 30%.[4] These facts constitute a hierarchy that has not yet been recognised in levels of evidence attributed to quality. Trials attempting perfect design

may fail to yield clinically useful results, raising ethical questions of enrolling patients into studies doomed to fail.

Although we embrace the gold standard of evidence based medicine, we must employ some common sense. Jadad, a well known proponent of evidence based medicine, recently published 10 challenges for clinical trials in pain relief.[5] These emphasise that more trials should be clinically relevant and more collaboration used over sample size, acknowledging the importance of integrating the findings from clinical trials with other types of research that must be balanced by individual values, preferences, and circumstances. This pragmatic approach requires unprecedented commitment from clinicians, research funders, journal editors, policymakers, journalists, and patients.

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Patients' altruism should be appreciated

Editor—Ashcroft in his editorial argues for wider acceptance of the need for randomised clinical trials.[1] His case is founded on the idea of uncertainty, and herein lies both the strength and the weakness of the argument. Not only does the rest of Ashcroft's argument flow from this central point, but it also limits the argument to very few clinical trials.

Clinical trials are not conducted in a vacuum of knowledge about the treatment options available. In the case of diabetes doctors already have a fair amount of trial based information about what can be expected from each of many treatment options. A patient may be reasonably stabilised if treated with one of them. Into this scenario a proposed clinical trial is brought, of a new hypoglycaemic agent, with either a placebo or a current drug as the comparator. Is the best option for the patient to enter this trial, as Ashcroft suggests?

Most trials that come before research ethics committees are of this nature. Each involves a chronic condition (asthma, diabetes, epilepsy, hypertension, hypercholesterolaemia, depression, and psychosis) and a potential new wonder drug and is the latest in a series. Patients have to balance the relative certainty of current best treatment against the unknown potential benefits and harms of entering the trial. The harm is not all hypothetical either. Promising new hypoglycaemic agents have been withdrawn because of liver toxicity, and much vaunted antipsychotic drugs have been discovered to have serious cardiac toxicity.

Seldom do patients have everything to gain and nothing to lose by entering a trial. Future patients, on the other hand, would certainly benefit from the knowledge gained from a trial, whatever the outcome. For this reason I do not accept Ashcroft's contention that it is misleading to believe that trials are run to benefit future patients, nor that the trial is the treatment. The only clinical situation when this is true is when we are dealing with a serious condition for which there is no treatment of any degree of efficacy and doing nothing means either certain death or serious disability. In all other situations, patients who volunteer are trading a degree of certainty under the current best practice regimen for an uncertain balance of risk versus benefit under the trial protocol. This is altruism at its best, and we ought to recognise it.

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Patients' perspective must be acknowledged

Editor—We have been using Ashcroft's arguments for 20 years, trying to convince clinicians to start randomised trials instead of using unproved treatments.[1] In recent years, however, we have come to realise that things are not that simple. The argument "either you know or you don't" often does not work, since for many new (and old) treatments some evidence of efficacy is available, albeit imperfect, inconclusive, and unreliable.

Patients' decisions on treatment cannot be based solely on the results of "perfect" studies, but take into account also the size of the potential benefit associated with each therapeutic option, modulated by the personal attitudes. This was best illustrated a couple of years ago by the brother of a patient with terminal cancer, who was seeking the Di Bella treatment[2] for his sister. He said that he knew that the chances that this treatment works are almost none—but might we not all be wrong? If we were to realise in a few years from now that the treatment can save lives, it would be too late for the sister. There are patients who claim they have been cured by the Di Bella treatment.

Many patients cannot wait for definitive evidence, and they want to select their treatment on the basis of whatever evidence is available, including reports on the media, patients' stories, and such like. The widespread use of unproved treatments outside randomised trials should not be labelled as entirely irrational: in many progressive diseases for which treatments of proved efficacy do not exist or are unsatisfactory (for example, many rare or advanced tumours), the randomised trial implies the possibility of not receiving the experimental treatment—that is, of not exploiting the only chance, small as it may be, of a substantial benefit.

The case of high dose chemotherapy in breast cancer, routinely used while the clinical trials that eventually showed its lack of efficacy were still ongoing, is paradigmatic.[3] What can we do to protect patients from false (and often expensive) hopes and useless or even harmful treatments, while assessing promising treatments? We are not proposing to abandon the randomised trial as the model for the assessment of medical procedures and to give up evidence based medicine. We should, however, start to reflect critically on the current methods of clinical trials from the patients' perspective, which often may differ from, and yet be as rational as, the scientific perspective.

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Blanket enthusiasm for trials won't help

Editor—Ashcroft in his editorial argues that patients in well designed and timely clinical trials do better than those not participating in trials, and—considering also the inherent uncertainty medicine is built on—trials in themselves are therefore treatments for patients.[1] This means that there is a moral obligation for doctors and investigators to offer trials to all patients since it is unethical to offer an inferior treatment—namely, the currently accepted standard treatment. If we find a medical condition for which there is no alternative (experimental) intervention that could serve as a control in a trial, our task is simply to find one to enable patients to be enrolled in trials.

What does that all mean?

Research ethics committees may be disbanded since there is no extra risk that research subjects should be protected from. Instead, those patients who do not have the choice to participate in trials need additional protection; therefore committees for protecting the rights and interests of getting standard treatment need to be established. The standards for informed consent for regular treatment must be higher than those for trials from now on.

Hospitals not offering clinical trials should be forced to change their practice, and those not willing or able to do it need additional supervision and permanent monitoring from governmental and professional organisations. The Helsinki Declaration should be revised or eliminated, and guidelines for protecting patients from the

risks associated with standard treatment must be formulated.

Our whole way of thinking must be changed with regard to standard and trial treatment. And certainly, those who suffered or even died just because they participated in well designed and timely trials must be forgotten.

These are absurd consequences of Ashcroft's statement. Although it might be true that some patients do better in trials, this does not mean that all patients do so. Why this is so and how it may improve the standard of care may be the subject of future research. But a blanket enthusiasm for trials won't help.

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It needs to be established whether patients really fare better in trials

Editor—Ashcroft in his editorial argues that individual patient outcomes are improved as a consequence of being treated as part of a randomised trial, and this alone is a reason why patients should consent to such treatment.[1] Although the outcomes of participants of trials are often better than those of non-participating patients, probable explanations for this include selection bias (patients with a poorer prognosis are less often offered, or accept, randomisation).[2]

Recently the Cancer Foundation of Western Australia ran a full page advertisement in the state's newspaper, taking Ashcroft's arguments directly to the public.[3] Beneath an eye catching photo of shark fins circling in a petri dish, the text states that patients participating in trials usually do better than those who are not. The other text of the advertisement uses such similar format and words to the recent *BMJ* commentary that it is almost certainly the source. As the public is likely to accept such statements at face value this may raise ethical concerns.[4,5]

Whenever I have obtained a patient's consent for treatment on a trial I have reassured them that their treatment was not going to be worse if they declined to participate. Are there people who believe that oncologists should tell patients that it will be?

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Improving patients' access to information may help

Editor—We respond to the debate on clinical trials prompted by the editorial by Ashcroft.[1] At the Cancer Foundation of Western Australia we believe that progress in the management of cancer depends in part on the participation of greater numbers of patients in clinical trials. In conjunction with the Western Australian Clinical Oncology Group we are therefore enthusiastic to see improvement to the current poor rate or accrual into trials.

As part of our public education initiatives an annual cancer update campaign is conducted, during which invited speakers address community and professional audiences on issues of relevance to cancer control.

As part of this year's campaign in July 2000 we aimed to increase awareness of and knowledge about clinical trials. Part of the programme entailed placing a full page advertisement on the value of clinical trials in the largest selling newspaper in the state.[2] Other electronic and print publicity was generated. This coincided with the release of a patient brochure and booklet aimed at improving patients' access to information on clinical trials.

These measures attracted substantial attention. Over 220 people attended the lecture, presented by Professor Konrad Jamrozik from the University of Western Australia, and several said afterwards that they had changed their attitude towards clinical trials as a result of attending the lecture.

The advertisement also attracted 146 telephone enquiries to our cancer helpline. Fallowfield has reported that doctors included clinical trials among a list of the five most difficult areas of discussion during patient consultations.[3]

If we are able to prompt further discussion between clinician and patient about the issue of clinical trials, we believe we have made a contribution towards our cancer control objective. The outcome of this discussion is a matter for patients and their doctors.

With regard to Bydder's reassurance to his patients that their treatment would not be worse if they declined to participate in a trial[4] our question is: how does he know?

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Increased high risk sexual behaviour in homosexual men

There is no evidence for a decreased incidence of HIV infection

Editor—Dodds et al began their paper[1] with the statement that the incidence of HIV infection among homosexual men in the United Kingdom is increasing despite efforts to reduce high risk behaviour and supported the statement of increasing incidence by referencing a report from the Public Health Laboratory Service.[2]

This report, which featured national surveillance data on HIV infection acquired through sex between men, does, however, not suggest that the incidence in homosexual men is rising. Rather, together with the more recent update,[3] it highlights the number of new diagnoses of HIV infection acquired through sex between men, which have remained fairly constant at around 1500 a year throughout the 1990s. The published erratum clarifies the situation (16 September, p 675), but the statement caused us to re-examine our data to see what we are able to say about recent trends in HIV among homosexual men.

Although trends in the diagnosis of HIV relate more closely to the uptake of HIV testing than to the underlying incidence of infection, the fact that there has been little change in the median age or median CD4 lymphocyte count at diagnosis in this group over the past 10 years suggests that new infections have occurred at similar rates to diagnoses, through most of that period at least.[4]

At best, however, such indicators provide only a broad measure of past incidence, and more sensitive and timely markers of likely changes in HIV incidence may be found in the surveillance of acute sexually transmitted infections and the type of monitoring of high risk sexual behaviour covered in the paper by Dodds et al.

Increases in markers of HIV transmission risk may not, however, be directly translated into increased transmission. The annual survey of prevalent diagnosed HIV infections shows that in 1999 67% of homosexual men with diagnosed HIV infection in England, Wales, and Northern Ireland were receiving multiantiretroviral therapy.

Widespread use of treatment that is successfully reducing viral load might well offset any increases in risky behaviour. Although measures of the recent incidence of HIV infection are imprecise, there is clear evidence that the numbers of prevalent HIV infections that are diagnosed are increasing,[5] and the messages concerning safer sex practice among men who have sex with men need to be further strengthened. The fact that we have no evidence of a decrease in the incidence of HIV infection is a cause for concern at this stage in the epidemic.

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Findings are similar in Manchester

EDITOR—Dodds et al report a significant increase in unsafe sexual practices among homosexual men in London.[1] However, such activity, which predisposes to a risk of HIV infection, is not confined to the capital. As the recent outbreak of infectious syphilis in Manchester has shown,[2] safer sexual practices seem to be less rigidly adhered to in this high risk group.

In a survey of attenders at a dedicated sexual health clinic for homosexual and bisexual men in south Manchester 70% of men had practised unsafe sex, 45% within the previous 12 months. A higher proportion of men under the age of 25 engaged in "at risk" sexual behaviour (67% of those under 25 *v* 31% of those over 40), and 69% of them had had casual sex in the previous three months.

Although rectal gonorrhoea has been cited as an indicator of at risk sexual behaviour for HIV infection,[3] we detected rectal chlamydial infection using DNA amplification techniques in 11% of attenders. We believe that rectal chlamydial infection could be equally reflective of such behaviour.

Safer sex messages, common in the 1980s and early 1990s, have lost their impact, especially among young homosexual and bisexual men. Failure to associate themselves with being in a high risk group for HIV infection may have contributed to unsafe sexual practices and the emergence of the outbreak of infectious syphilis and revalence of rectal chlamydial infection. Educational programmes specifically targeting young homosexual and bisexual man are needed, otherwise a new HIV epidemic is likely to ensue.

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Clarity may have been lost through including too much information

EDITOR—Dodds et al[1] offered evidence of increasing high risk sexual behaviour among homosexual men. This followed shortly after a polemical article in the *Guardian*.[2] That article, which drew on one in the *Pink Paper* (which is published by and for gay people),[3] seemed critical of an apparent rise in irresponsible sexual behaviour among homosexual men.

The research by Dodds et al is important. What a pity that in reporting it they are less clear than they might have been. The article seems to promote unprotected anal intercourse for all men, whether homosexual or not, as a way of reducing HIV, by saying that HIV transmission can be reduced by ensuring that men have unprotected anal intercourse only with partners of a concordant HIV status. This is surely a linguistic mistake. More worrying is the fact that this statement fails to take account of other possible infections and of the difficulty in knowing whether a potential partner has the same HIV status.

Even more concerning is the lack of clarity in the figures Dodds et al present. When they say, for example, that in every year high risk sexual behaviour (for example, unprotected anal intercourse in the previous year) was significantly associated with younger age (occurring among 108/252 (43%) of those aged under 25 and 103/340 (30%) of those over 40, $P < 0.01$ in 1998) and recruitment from a genitourinary medicine clinic (odds ratio 1.39, 95% confidence interval 1.13 to 1.71, $P < 0.01$ in 1998), this is unclear on many points. How many patients came from clinics for genitourinary medicine? Are the figures for participants aged under 25 totalled from all three years?

The method of selecting venues was undefined. The report claims to describe the behaviour of gay men, when the research sampled only those in London who attend genitourinary clinics and attend night clubs, saunas, etc. The sample was narrowly based and self selected. Gay men who do not frequent the selected social and clinical venues were excluded. The veracity of answers from men present at or queuing to enter a venue must be questioned. How much can be ascribed to bravado? How much to concealment? Dodds et al had to work within the limits of a short report. Clarity may, however, have been lost through including too much information. This survey is interesting and important, and we hope that they have the opportunity to produce a fuller report soon.

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Authors' reply

EDITOR—We agree with the letter from Macdonald et al. The incorrect statement at the beginning of our paper was the result of editorial changes at the proof stage [see editorial footnote below]. We are interested and concerned to hear of similar findings to ours among men attending a clinic for genitourinary medicine in Manchester.

We thank Fairburn et al for their appreciation of the difficulties of condensing such a large repeated cross sectional survey into a short report. More detailed methods are to be found in our third reference, and a full report is available from the authors. We disagree that our paper seems to promote unprotected anal intercourse for all men and are surprised that Fairburn et al should infer this conclusion. Recent health promotion campaigns have encouraged men who have unprotected anal intercourse to undergo HIV testing and reach agreements to have unprotected anal intercourse only with men of the same HIV status as themselves, as one method among many (including the use of condoms, reducing numbers of partners, and safer sexual practices) of reducing the transmission of HIV.

We appreciate that our population is a selected one, constrained by the methodological difficulties of obtaining a large random population sample of men who have sex with men. The crucial point is, however, that this allows repetition of the survey, among comparable groups, over time, permitting trends to be examined. Any self reported sexual behaviour may be subject to measurement error, but we attempt to reduce this by the use of a short, self completion questionnaire that is completely anonymous. Any measurement error is likely to apply equally to each year of the survey and is therefore an implausible explanation of the observed trends.

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⁂An error crept into this short report at the proof stage, for which we apologise. A correction has been published.[1]

1 Corrections and clarifications. *BMJ*;321:675. (16 September.)

Income inequality and mortality in Canada and the United States

Third explanation is plausible

EDITOR—Ross et al report that income inequality in the state or province and metropolitan area is associated with mortality in the United States but not in Canada.[1] They offer two explanations for this discrepancy. Firstly, this association is

observed only at levels of inequality present in the United States, not the lower levels observed in Canada. Secondly, the actual association of income inequality with mortality is modified by the social and political characteristics specific to a place.

There is, however, another possible explanation: confounding of the association of income inequality with health at the state level (or metropolitan area level) in the United States. This is not the same as confounding at the individual level by, for example, personal income, which varies between states.[2] State level confounding may occur when characteristics of the states are correlated with income inequality, remain associated with mortality within strata of states by income inequality, and hence cause a spurious association of income inequality with mortality. Two possible candidates are the extent of rurality and the welfare policies of the states. Both vary between states, are plausibly related to population health, and are probably correlated with the geographically biased distribution of income inequality.

The United States provides a rich natural experiment to study the association of income inequality with health, and several studies have now replicated the association of state level income inequality with health using different data sets.[3 4] But the use of different data sets in these studies is akin to reanalysing one cross sectional study of the same 50 people by using different measures of exposure and outcome; it is not akin to separate studies of a different 50 people each time. Thus, a spurious association of income inequality with health due to state level confounding will remain for each new analysis of the same natural experiment.

It seems likely and plausible that income inequality is associated with health.[5] Instead of examining the possibility of state level confounding, however, we propose two research strategies. Firstly, potential state level confounders are included as covariates in analyses. This will not be without difficulty, however, owing to the high probability of (multi)collinearity of ecological variables and challenging theoretical considerations—for example, causal ordering of ecological variables, such as income inequality and welfare policies. Secondly, many different natural experiments should be analysed to look for a consistent association of income inequality with health. From this perspective, the results from Canada and the United States are just two separate natural experiments to which we want to add results from many more natural experiments.

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Low mortality in Canadian cities may be driven by low mortality in immigrants

Editor—Ross et al compare the relation between income inequality and mortality in the United States and Canada.[1] They relate the proportion of income received by the less well off 50% of households to the mortality in all working age people. For Canadian metropolitan areas, they find no significant association between this indicator of income inequality and mortality; this is visible by the lack of slope in the respective weighted regression line (figure 2). For metropolitan areas in the United States, the association between income inequality and mortality is strong.

The findings from Canada are surprising. Typically, there is a strong inverse association between individual socioeconomic status and mortality, and also between overall distribution of wealth in a society and mortality. There is, however, one population group where this association tends to be absent: recent immigrants of working age frequently have an age-adjusted overall mortality that is considerably (20-30%) lower than that of the native born population.[2 3] This mortality advantage may persist 10-20 years after immigration[4]; it is present even where immigrants are a minority group and socioeconomically disadvantaged.

In Canada, recent immigrants form a considerable proportion of the total population, and they are not uniformly distributed in the country. According to the 1996 census, immigrants represent 17.4% of the total population; 85% of all immigrants—and 93% of those who arrived between 1991 and 1996—live in a metropolitan area.[5] This applies in particular to Toronto and Vancouver, which have 42% and 35% immigrants among their respective census populations (Montreal only 18%), half of whom have come to Canada since 1981. A 20-30% lower mortality among immigrants thus may have driven down the death rates in Toronto and Vancouver by as much as 10-20%.

Hence, the death rates in these two cities would be lower than what might be expected from the wealth distribution. This could be corrected for, for example, by restricting the analysis to Canadian born people. Once this is done, the overall mortality in Toronto and Vancouver would be higher. As these two cities are very populous, the slope of the regression line would become steeper, indicating some association between income inequality and mortality not only in the United States but also in Canada. In conclusion, Ross et al may wish to consider adjusting for the proportion of immigrants in future studies on social inequalities in health.

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Authors' reply

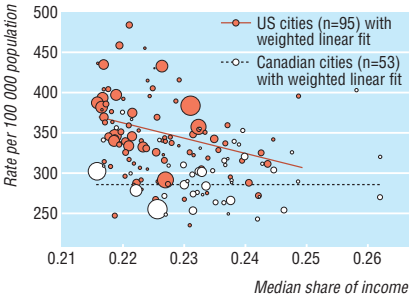
Editor—Our study has received two types of critique—that ecological variables in the United States and immigration in Canada confound the relation between income inequality and mortality and that the range of inequality in Canada was too narrow to draw conclusions about the relation between income inequality and mortality there.

Blakely and Woodward suggest that there are probably important variables at the level of the state or metropolitan area that are correlated with income inequality and cause a spurious association of income inequality with mortality. We have, however, always conceptualised our measure of income inequality of a particular place as a marker for a wide variety of social conditions and as reflecting the outcome of layers of political, social, and economic history of that place.[1] It is striking how strongly income inequality correlates with mortality at multiple geographic scales in the United States. In states income inequality is correlated (after adjusting for median income) with poverty, unemployment, incarceration, health insurance provision, and numerous educational outcomes.[2]

Our primary objective was to investigate the relation between income inequality and mortality in Canada compared with the United States, which has higher incomes but lower life expectancy. Our comparative analysis does not resolve causality. Instead, the results of this natural experiment provoke hypotheses about how differences in policies towards such things as health care, taxes and transfers, and urban structure in two otherwise culturally similar countries might influence population health.

Razum suggests that large immigrant populations in Canadian cities lower the death rates for those places beyond what would be expected for their income distributions. Although the healthy migrant effect could contribute to lower mortality in Toronto and Vancouver, if we were to exclude immigrants, hypothetically raising mortality in Toronto and Vancouver, this would actually flatten the relation between mortality and income inequality in Canada (figure 2).

The second critique, which is not articulated above, is the claim that the Canadian range of income inequality was too narrow



Mortality among people of working age by proportion of income belonging to less well off half of households, United States (1990) and Canadian metropolitan areas (1991) over range of Canadian median share values. Mortality is standardised to Canadian population in 1991

to allow any significant relation to emerge. We selected the subset of United States cities with income inequality measures in the same range as the Canadian cities and fitted weighted linear regression lines to the respective sets of points (figure).

A significant negative slope remained for the metropolitan areas in the United States. Thus the relation appears consistently in the United States but not in Canada. Our preliminary analysis of income inequality and mortality for Australian metropolitan areas (with comparable income distributions to Canadian metropolitan areas) has yielded similar results to the Canadian analysis, suggesting that this "Canadian paradox" may not be so paradoxical at all.

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Could fewer islet cells be transplanted in type 1 diabetes?

EDITOR—At a meeting in Bristol Dr James Shapiro presented the most recent data on islet cell transplantation in type 1 diabetes mellitus,[1] which White et al referred to in their editorial.[2] Islet cell transplantation has now been successfully carried out in 12 patients, with the longest follow up being 17 months. We need more evidence from longer follow up and larger numbers, as called for in the editorial, but results look promising.

Demand, though, will far outstrip supply. Perhaps we should think about what the aims of transplantation are and whether more people with type 1 diabetes could be helped. The aims are presumably threefold:

- To relieve patients from unpleasant acute complications such as hypoglycaemia and thereby improve quality of life
- To improve diabetic control and prevent long term complications, thereby improving both quality and quantity of life
- To allow patients to stop insulin injections

Two donor pancreases are needed to achieve all three aims in one patient. But could we benefit more patients if we had only the first two aims and accepted that patients would still need to inject some insulin? If we had two donor pancreases, how many patients could achieve the first two aims by transplantation of fewer cells? If the answer was four to six, then would that not be a better use of resources—both islets and funds—than allowing one patient to stop taking insulin altogether?

For individual patients, the answer may depend on the balance of benefits and risks between better control and long term immunosuppression. For health services, the dominant factor is probably the high cost of long term complications. Islet cell transplantation might be a cost effective investment, depending on how long the islets survived. The cost per quality adjusted life year may well be much less than that for whole organ transplantation, which is cost effective in selected patients.[3]

Perhaps as part of the multicentre trial a group of patients should be randomised to transplantation of a reduced number of islets, sufficient to achieve the first two aims but not the third. The trial could tell us what the best dose was. For individual patients the benefit would be less, but perhaps four times as many patients could benefit.

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In praise of mercury sphygmomanometers

EDITOR—O'Brien writes about replacing the mercury sphygmomanometer with other blood pressure measuring devices.[1] Far from agreeing with him, I would prefer to have all electronic devices banned from the general surgical wards of our hospitals.

Non-invasive pressure devices are designed for the management of hypertension. The emphasis is on the mean blood pressure and diastolic pressures at the upper end of normal. These devices are useless for patients in whom an indication of cardiac output is important. The relation between blood pressure and cardiac output is non-existent ($r = 0.2$).[2]

Some idea of cardiac output can be obtained from the pulse pressure. The true systolic, diastolic, and pulse pressures can be determined with a mercury sphygmomanometer. A wide pulse pressure indicates a good cardiac output, and a narrow pulse pressure a poor cardiac output. (Wide pulse pressure equates to low peripheral vascular resistance; low peripheral vascular resistance equates to large stroke volume and cardiac output = stroke volume × heart rate.) This is also an argument for not recording blood pressures as a mean. Two patients with vastly different cardiac outputs may have the same mean blood pressure.

The close physical contact required to auscultate Korotkoff sounds successfully from a hypovolaemic patient ensures that the clamminess of the skin, tachypnoea, thready pulse, sunken eyes, body odour, and frown are not missed. The very difficulty of measuring the blood pressure is a clinical sign. Automated devices keep mindlessly repeating until a value falls within the manufacturer's algorithm. Ridding the wards of non-invasive pressure devices ensures that the job of measuring blood pressure cannot be assigned to untrained staff. Non-invasive pressure devices encourage the cuff to be applied, the button to be pressed, and the staff to go off to perform another task. The numbers are charted, and the whole thing is over with another opportunity lost.

Once the blood pressure measured by a non-invasive pressure device has fallen to below 100 mm Hg the device may consistently over-read by 20-25 mm Hg. If use of non-invasive pressure devices is unavoidable then systolic pressures below 90 mm Hg should prompt the device to read "pressure unobtainable; seek trained staff."

When you discover that your patient from the previous day's list has had a stroke because the untrained staff do not realise that 70 mm Hg systolic for eight hours is not normal for 80 year olds you will realise that it is important not to put machines between staff and patients.

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