CORRESPONDENCE

Autism, inflammatory bowel disease, and MMR vaccine

Sir—The controversy surrounding the paper by Andrew Wakefield and colleagues (Feb 28, p 637)[1] seems to stem from the inclusion of two ideas in one paper. That autism may be linked to a form of inflammatory bowel disease is a new idea worthy of discussion, and *The Lancet* was correct in its decision to publish this. The reply of Simon Murch and colleagues (March 21, p 908)[2] to criticism of their paper emphasises the importance of this part of the work, a message lost in the media reporting.

The second idea was the unsubstantiated reporting of an association between this new syndrome and measles/mumps/rubella (MMR) vaccine. This anecdotal reporting of a biased sample is poor science and has no place in a peer-reviewed journal. Nor was it new; the supposed association between MMR, autism, and inflammatory bowel disease has been published before by the same research group. Since no additional work was reported to substantiate this association and since considerable evidence has been collected by others to suggest that it does not exist, publishing it again lends further unwarranted credence to the hypothesis. Peer review seems to have failed to screen out this attempt to "piggyback" the cryptic suggestion of MMR as a causal factor onto a description of a new syndrome, and the criticism of this second idea obscures the important message of the first.

The anger of public health workers at this paper is not due to the challenge to public health dogma, as Wakefield suggests (March 21, p 908).[3] It is because children are being put at risk from potentially lethal infectious diseases not by new reliable evidence but by media coverage of another badly designed study by this group.

As a clinical researcher Wakefield has a responsibility to conduct his studies with scientific rigour. Listening to the patient is important but biased selection of patients will influence what you hear.

D R Walker
Department of Public Health Medicine, County Durham Health Authority, Durham DH1 5XZ, UK

1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive-developmental disorder in children. *Lancet* 1998; **351:** 637–41.
2 Murch S, Thomson M, Walker-Smith J. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 908.
3 Wakefield AJ. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 908.

Sir—I note significant inaccuracies in table 1 of the paper by Andrew Wakefield and colleagues,[1] a table that records "abnormal laboratory tests" and "normal ranges". The ranges given in the legend to this table are not age related, and those for the immunoglobulins vary markedly from the ones most laboratories use. For example, the normal range for alkaline phosphatase is given as 35–130 U/L. This is the adult range. Normal-growing children have activities up to 2·5 times the upper adult limit.[2] Patients 1, 4 and 6 (aged 4, 10, and 5 years, respectively) had normal alkaline phosphatases if the paediatric age-related range of 250–800 U/L is used.[3]

Care should be taken in interpreting marginal differences from normal in plasma immunoglobulin levels, but the ranges given by Wakefield et al also differ from common standards.[3,4] The normal range for IgA is given as 0·9–4·5 g/L but this too is an adult range. Patients 7, 8, and 12 appear to have significantly low levels of IgA but standard laboratory reference normal ranges appropriate for their ages[3,4] show that these children have normal IgA concentrations.

The normal range for patient 8, whose IgG level was 7·0 g/L, is given as 8–18 g/L. This sort of result bears repeating. Even so, the normal range for this child, aged 3·5 years, varies significantly from paediatric standards (5·0–15[3] and 4·9–16·1 g/L[4]).

Patient 7 had an Hb of 9·4 g/dL with a marginally raised erythrocyte sedimentation rate (ESR) of 16 mm. Had the ESR been corrected for packed cell volume it would have been normal.

Leonard Sinclair
34 Armitage Road, London NW11 8RD, UK

1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive-developmental disorder in children. *Lancet* 1998; **351:** 637–41.
2 Zilva JF, Pannall PR, Mayne PD. Clinical chemistry in diagnosis and treatment, 5th edn. London: Edward Arnold, 1989: 315.
3 Belton NR. Biochemical and physiological tables and reference ranges for laboratory tests. Campbell AGM, McIntosh N, eds. In: Forfar and Arneil's textbook of paediatrics, 5th edn. Edinburgh: Churchill Livingstone, 1998: 1928
4 Ward AM, Riches PG, Fifield R, Smith AM, eds. PRU (Protein Reference Laboratory) handbook of clinical immunochemistry. Sheffield: PRU Publications 1996: 335.

Sir—Andrew Wakefield and colleagues[1] dismiss selection bias because of the uniformity and significance of the gastrointestinal findings in a "unique disease process". However, the most striking and consistent endoscopic feature, lymphoid nodular hyperplasia in the terminal ileum, is not unusual in children. Walker-Smith et al have described this condition as "benign lymphoid hyperplasia due to the frequency of its demonstration in asymptomatic children", and state that the association of gastrointestinal symptoms such as abdominal pain and diarrhoea with this condition is "all too often circumstantial".[3] This view is shared by other authors, who describe lymphoid nodular hyperplasia as "essentially a normal finding".[4] It is not clear how the control children were selected for endoscopy. The clinical features described are thus far from unique, and the suspicion of selection bias remains.

IgA deficiency in four children is used to support the hypothesis that the consequences of an inflamed or dysfunctional intestine may play a part in behavioural changes in some children. However, the IgA concentrations in three of the four children are normal according to the UK age-specific reference range for immunoglobulins used to diagnose antibody deficiencies.[5] The reference ranges for immunoglobulins quoted in this study would appear to be derived from an adult range, and the IgG and IgG_1 values quoted as abnormal for four patients are also all within normal paediatric limits.

**Peter Richmond, David Goldblatt*
Immunobiology Unit, Institute of Child Health, London WC1N 1EH, UK

1 Wakefield AJ, Murch SH, Linnell AJ, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive-developmental disorder in children. *Lancet* 1998; **351:** 637–41.
2 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; **351:** 611–12.

3 Walker-Smith J, Hamilton JR, Walker WA. Practical paediatric gastroenterology. Norwich: Butterworth, 1983: 254–55
4 Williams CB, Nicholls S. Endoscopic features of chronic inflammatory bowel disease in childhood. *Baillièrés Clin Gastroenterol* 1994; **8:** 121–31
5 Ward AM, Riches PG, eds. PRU handbook of clinical immunochemistry, 4th ed. Sheffield: Hallmark: 1993: 157–66.

Sir—After reading Andrew Wakefield and colleagues' article[1] I did a simple Internet search and quickly found the *Society for the Autistically Handicapped.* (http://www.mplc.co.uk/eduweb/sites/autism/index.html) I downloaded a 48 page fact sheet produced for the society by Dawbarns, a firm of solicitors in King's Lynn.

It seems likely then that some of the children investigated by Wakefield et al came to attention because of the activities of this society; and information from parents referred in this way would suffer from recall bias. It is a pity that Wakefield et al do not identify the manner in which the 12 children investigated were referred (eg, from local general practitioners, self-referral via parents, or secondary/tertiary or international referral). Furthermore, if some children were referred, directly or indirectly, because of the activities of the Society for the Autistically Handicapped, Wakefield should have declared his cooperation with that organisation.

A Rouse

Department of Public Health Medicine, Wiltshire Health Authority, UK

1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive-developmental disorder in children. *Lancet* 1998; **351:** 637–42.

Author's reply

Sir—D R Walker states that "biased selection of patients will influence what you hear". Bias occurs in science when data are either wittingly or unwittingly concealed. Does he condone the exclusion of a potentially significant element of the history? He asks for virological evidence: we refer him to our abstract (*Gut* 1998; **42:** A86). Sadly, Walker casts the value of the medical history, the process of peer review, and this paediatric diaspora to the scrapheap of bad science and anecdote.

Leonard Sinclair and Peter Richmond and David Goldblatt correctly point out the inappropriate use of adult reference ranges. We stated that IgA levels were low in four out of 12 affected children. The normal range for IgA in this age group is 0·5–2·4 g/dL, and, only one child was outside the normal range. Similarly, the appropriate age-related range for alkaline phosphatase is 250–800 U/L. These errors do not affect the conclusions of the paper, particularly the identification of ileal lymphoid nodular hyperplasia and colonic inflammation in a group of children with developmental disorder.

A Rouse suggests that litigation bias might exist by virtue of information that he has downloaded from the Internet, from the *Society for the Autistically Handicapped.* Only one author (AJW) has agreed to help evaluate a small number of these children on behalf of the Legal Aid Board. These children have all been seen expressly on the basis that they were referred through the normal channels (eg, from general practitioner, child psychiatrist, or community paediatrician) on the merits of their symptoms. AJW had never heard of the *Society for the Autistically Handicapped* and no fact sheet has been provided for them to distribute to interested parties.The only fact sheet that we have produced is for general practitioners, which describes the background and protocol for investigation of children with autism and gastrointestinal symptoms. Finally all those children referred to us (including the 53 who have been investigated already and those on a waiting list that extends into 1999) have come through the formal channels described above. No conflict of interest exists.

The authors stand by their findings. We recommend that paediatric gastroenterologists investigate this problem further, since it is our belief that there is both a large unmet need in the community and a possible window-of-opportunity for some children with autism.

A J Wakefield

Departments of Medicine and Histopathology Royal Free Hospital School of Medicine, London NW3 2PF, UK

Sir—Letters in *The Lancet* and the letter of March 27, 1998 (PL/CMO/98/2) to all doctors by Sir Kenneth Calman, Chief Medical Oficer, Department of Health, on measles, mumps, and rubella (MMR) vaccine, Crohn's disease, and autism are in danger of completely obscuring the observation we made of an association between ileal lymphoid nodular hyperplasia, non-specific colitis, and autism in childhood. As the senior clinician on the study I would like to make several points.

We did not describe any increase in Crohn's disease or ulcerative colitis in children with autism so the observations of Eric Fombonne (March 28, p 255)[1] are not surprising. What we did describe was non-specific colitis with ileal lymphoid nodular hyperplasia. The colitis we described was ignored in Robert Chen and Frank De Stefano's commentary accompanying our *Lancet* paper. Calman seeks to dismiss our findings concerning lymphoid hyperplasia and also makes no mention of colitis. Indeed, he selectively quotes from my own publications on this topic since 1983 but makes a number of false assumptions. Because our *Lancet* paper was a preliminary report we did not expand on the diagnostic term "ileal lymphoid nodular hyperplasia". This is a term often used inexactly by radiologists and endoscopists to describe both a normal finding in children and a pathological finding which may be accompanied by abdominal pain and diarrhoea requiring therapy.

The 1983 Walker-Smith, Hamilton, and Walker reference cited by Calman does indeed state that ileal lymphoid nodular hyperplasia "has been termed benign" but we went on to say that recurrent abdominal pain and diarrhoea often prompt a diagnostic barium study to permit this radiological diagnosis. We also stated that symptoms could be so severe that steroids may be used and even that surgery might be contemplated (although is this not recommended owing to uncertain knowledge concerning outcome). Calman also cites a 1990 radiological study[3] which indicated that 24% of children referred for investigation of inflammatory bowel disease had a form of lymphoid nodular hyperplasia with a disorganised mucosal fold pattern. What was new was that this report distinguished two patterns of lymphoid hyperplasia. Lymphoid hyperplasia causing small nodular defects about 2 mm in diameter is considered a normal variant but there is a more exaggerated change, probably reflecting enlargement of Peyer's patches. This latter pattern can occur in yersiniosis and it could represent an early lesion of Crohn's disease. That paper referred back to our 1987 endoscopic study describing lymphoid follicles in the ileum of 23 children of whom only seven children had identifiable disease. Three cases were described as lymphoid nodular hyperplasia with recurrent abdominal pain and diarrhoea. This proportion (13%) accords with the 12% found in the endoscopic study of Lindley and Milla.[4] In their endoscopic study Williams and Nicholls[5] referred to the radiological diagnostic confusion.[3] They describe "1–5 mm nodules, usually pink and shiny . . . dotted singly or in coalescing masses. Localised conglomerations around 10–15 mm diameter are described as Peyer's

patches". They published a photograph identical with the findings in our *Lancet* paper. Williams and Nicholls did indeed warn "against misdiagnosis of ileal Crohn's disease" but, incredibly, Calman left out the phrase "of ileal Crohn's disease" so that his subsequent phrase "inappropriate medication", which applies only to Crohn's disease, has a wholly different meaning.

I must also further address the issue of why we published this preliminary study. Our observation had been presented at the First International Symposium on Pediatric Neurogastroenterology (1997) and an expanded series of 30 children, with two scientific studies of the mucosal lesion, was presented to the British Society of Gastroenterology in March, 1998. (*J Pediatr Gastroenterol Nutr* 1997; **25** [suppl 1]: S47,S48 and *Gut* 1998; **42** [suppl 1]: A24, A85, F93). We would not have published this preliminary report without knowledge of all these further studies.

It is one thing for the Chief Medical Officer to defend MMR vaccination but quite another to criticise so severely and be so dismissive of gastrointestinal findings that have been published after peer review in *The Lancet* and selected for presentation, also by peer review, at an international and a national meeting.

J A Walker-Smith

University Department of Paediatric Gastroenterology, Royal Free Hospital, London NW3 2QG, UK

1 Fombonne E. Inflammatory bowel disease and autism. *Lancet* 1998; **351:** 955.
2 Walker-Smith J, Hamilton R, Walker WA. Practical pediatric gastroenterology. London: Butterworth 1983: 254.
3 Lipson A, Bartram CI, Williams CB, Slavin G, Walker-Smith JA. Barium studies and ileoscopy compared in children with suspected Crohn's disease. *Clin Radiol* 1990; **41:** 5–8.
4 Lindley KJ, Milla PJ. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 907.
5 Williams CB, Nicholls S. Endoscopic features of chronic inflammatory bowel disease in childhood. *Baillières Clin Gastroenterol* 1994; **8** (no 1): 121–31.

Sir—Andrew Wakefield and colleagues[1] suggest that functional deficiency of vitamin B_{12} through chronic malabsorption of enterohepatic vitamin B_{12} caused by non–specific ileal–lymphoid–nodular hyperplasia following MMR vaccination, may contribute to neuropsychiatric damage and autism. Their hypothesis, vitamin B_{12} and methylmalonic acid (MMA) testing, and data interpretation are confused.

The onset of autism was acute when the children did not have any documented B_{12} deficiency or inflammatory bowel disease. Adverse reactions to the vaccine were immediate or acute in seven and delayed in four but developmental regression was noted in all 11 boys aged 12–21 months. Gut symptoms occurred at age 18–30 months and inflammatory bowel disease was proven histologically in seven cases only.

MMA production, implied from its urinary concentration (reference range 0–0·38 mg/mmol creatinine)[2] seems to have been raised in eight patients and three to four controls; it was not measured in the other four patients. The statistical difference between means for patients and controls, for incomplete data, is invalid and is wrongly attributed to functional B_{12} deficiency.[3–5] Other causes of B_{12} deficiency or MMA production were not excluded, and abolition of MMA excretion with B_{12} treatment, which is essential to sustain the hypothesis, was not shown in any patient.

Unlike the patients, the controls did not receive any restrictive diets, alternative therapies, or megadose vitamin C. Details of the treatments in patients were not stated. However, B_{12} deficiency can occur after megadoses of ascorbate,[3] which are given routinely with folate to diet–restricted autistic children over many years.

Serum total vitamin B_{12} was measured with an obsolete non–specific protein–binder isotope assay, urinary MMA concentrations were measured in single random specimens, and no reference values for children aged 3–10 years were provided.

Functional vitamin B_{12} deficiency in the brain cannot be diagnosed unless MMA is increased in the serum, cerebrospinal fluid, and urine after valine loading, and cobalamins are measured in CSF and plasma.[2-5]

Ray Bhatt

39 Rickmansworth Road, Pinner, HA5 3TE, UK

1 Wakefield AJ, Murch SH, Linnell J, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive-developmental disorder in children. *Lancet* 1998; **351**: 637–41.
2 Linnell JC, Bhatt HR. Inherited errors of cobalamin metabolism and their management. *Baillière's Clin Haematol* 1995; **8**: 567–602.
3 Herbert V. Etiology of vitamin B_{12} (cobalamin) deficiency and staging of B_{12} status. In: Bhatt HR, James VHT, Besser M, Bottazzo GF, Keen H, eds. Advances in Thomas Addison's diseases: vol II *J Endocrinol* 1994; **2:** 139–48.
4 Lindenbaum J, Savage DG, Stabler SP, Allen RH. Neuropsychiatric disorders in cobalamin deficiency. *J Endocrinol* 1994; **1:** 269–80.
5 Chanarin I. The megaloblastic anaemias. Oxford: Blackwell Scientific, 1990: 34–44.

Author's reply

Sir—The previously normal children we investigated all had developmental regression and undoubted intestinal abnormalities. All those from whom we were able to obtain urine had MMA concentrations above 1·5 mg/mmol creatinine, the upper limit in our age and sex matched controls (p=0·003). None was receiving megadoses of vitamin C or was on a restictive diet.

John Linnell

Inflammatory Bowel Disease Study Group, University Department of Medicine, Royal Free Hospital, London NW3 2QG, UK

Sir—The report by Andrew Wakefield and colleagues[1] confirms the clinical observations of several paediatricians, including myself, who have noted an association between the onset of the autistic spectrum and the development of disturbed bowel habit. Many of these children also have other symptoms that might be associated with a food intolerance, including nasal congestion, eczema, excessive thirst, dark shadows under the eyes, and swollen tonsillar lymph glands.[2]

Wakefield and colleagues refer to the concept of increased gut permeability and associated allergy/intolerance.[3] They will be aware of the theories surrounding the links between altered bowel flora, increased gut permeability, and food intolerance. I do not have the results of double-blind studies but I have found a consistent pattern of children with disturbed bowel function, and autistic spectrum symptoms improving both intellectually and physically, on treatment with an antifungal preparation (nystatin, amphotericin, or fluconazole). The symptoms recur if the treatment is discontinued prematurely. One feature that suggests that this is not just a placebo effect is that these children often show a pattern of increased symptoms before they improve.

M A Tettenborn

Frimley Children's Centre, Frimley, Surrey GU16 5AD, UK

1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive-developmental disorder in children. *Lancet* 1998; **351:** 637–42.
2 Anthony A, Birtwistle S, Eaton K, et al. Environmental medicine in clinical practice. Southampton: BSAENM Publications, 1997: 263–307.
3 Jackson PG, Lessof MH, Baker RSR, et al. Intestinal permeability in patients with eczema and food allergy. *Lancet* 1981; **1:** 1285–86.

Sir—The pre-emptive strike by US vaccine policymakers on Andrew Wakefield and his colleagues'

investigation into the immunopathology of children with chronic enterocolitis and regressive developmental disorder[1] brings into sharp relief the inappropriate intervention of politics into what should be an apolitical scientific examination.[2] It is perhaps understandable that health officials are tempted to discredit innovative clinical research into the biological mechanism of vaccine-associated health problems when they have steadfastly refused to conduct this kind of basic science research themselves. However, it should not be accepted without protest.

Condemning research of the kind undertaken by Wakefield et al will only ensure that no scientific progress is made toward identifying children genetically or otherwise at high risk of immune and neurological dysfunction after vaccination. Such children could be screened out of the vaccination programme. And there will be no scientific progress made toward developing therapies to restore children who have been injured to good health.

In their commentary, US Centers for Disease Control employees Robert Chen and Frank DeStafano[2] take a cheap shot at the intellectual integrity of British physicians, the British public and *The Lancet* when they imply that reports in British medical journals and in the British media in the 1970's concerning pertussis-vaccine associated neurological damage were unfounded and led to a "painful history" that could be repeated if Wakefield's report is taken seriously "because passion would then conquer reason and the facts again in the UK". US public health officials will not accept any independent thinking or scientific investigation into vaccine-associated health problems that does not carry their imprimatur. In the words of Herbert Spencer, "There is a principle which is a bar against all information; which is proof against all argument; and which cannot fail to keep a man in everlasting ignorance. That principle is contempt prior to investigation."

Barbara Loe Fisher

National Vaccine Information Center, 512 W Maple Avenue, #206, Vienna, VA 22180, USA

1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive-developmental disorder in children. *Lancet* 1998; **351:** 637–42.

2 Chen RT, DeStefano F. Vaccine adverse effects: Causal or coincidental? *Lancet* 1998; **351:** 611–12.

Sir—I am surprised that Andrew Wakefield and colleagues[1] and your correspondents[2] have not pointed out that an MMR vaccine that we were using in the early 1990s has already been withdrawn from the market. This followed reports by general practitioners of adverse reactions that seemed to be related to that vaccine. Since that time, I have not seen or heard about any child having a reaction to MMR vaccine, whereas before then I was aware of several children having adverse events after MMR vaccination.

Looking at the ages of the children in Wakefield's study,[1] it seems that most of them would have been at an age when they could well have been vaccinated with the vaccine that has since been withdrawn.

In some cases the parents associated MMR vaccination with autism, and there seems nothing in Wakefield's report, or in the subsequent correspondence that gives any firm evidence to reject these views of the parents. The only sensible suggestion about a solution comes from Payne and Mason[2]—to look at primary-care computer held records—which has also been suggested by the chairman of the Primary Care Virology Group. However, such a method is unlikely to be able to detect an association, if it arises from a vaccine that had been taken off the market 4–5 years earlier.

The most important task now falls (as usually seems to be the case in such situations) on those working in primary care: it is to get the message across to parents that MMR vaccination carries a much lower risk than their children not having the vaccine. This message is especially pertinent because the media and public interpretation of the safety of MMR vaccine was probably the complete opposite of what it should have been. Wakefield and colleagues' report did not show an established link between MMR vaccine and autism. The very strict standards demanded for vaccine safety had already caused the removal of one MMR vaccine because of reported possible adverse events. Knowing this, we and parents should have even more, not less, confidence in the safety of present MMR vaccine and the benefits of vaccination.

One cannot really blame the public and media for their interpretation of the recent MMR concerns, because if we do not provide all the information, how can we expect the media to produce balanced articles, and more importantly, how can we expect parents to make a sensible fully informed choice?

M R Kiln

Rosendale Surgery, 103a Rosendale Road, London SE21 8EZ, UK

1 Wakefield AJ, Murch SH, Antony A, et al. Ileal-lymphoid nodular hyperplasia, non-specific colitis, and pervasive-developmental disorder in children. *Lancet* 1998; **351:** 637–41.

2 Payne C, Mason B. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351:** 907.

Questions on breast-implants study

Sir—In 1991 the Committee on Appropriations of the US Congress was sufficiently concerned about the risk of breast cancer in women having breast implants to fund the National Cancer Institute "to develop a strategy for conducting longitudinal studies on women on the various types of silicone breast implants, with particular attention to those used for breast reconstruction after mastectomy or injury."[1]

The result was the Follow-up Study of Women with Augmentation Mammoplasty, an intramural project of the National Cancer Institute. The initial protocol was released in November, 1993. Findings will be reported soon. We do not know what the results will be, but we have some questions about the methods, the fieldwork, and the questions this study will be able to answer.

(1) Why was reconstructive surgery an exclusion criterion in the protocol if the intent of Congress was "particular attention to [implants] used for breast reconstruction after mastectomy or injury"?

(2) What are the key hypotheses of the NCI study?

(3) Given the large number of questions about arthritic and rheumatic symptoms and conditions in the study questionnaire, has the emphasis of the study changed? Are arthritic and rheumatic conditions and symptoms now a primary endpoint?

(4) What statistical power can be expected for arthritic and rheumatic conditions and symptoms?

(5) Why were women having breast reduction surgery not used as the "unexposed" controls?

(6) How will the investigators deal with response rates among women screened and deemed eligible to participate if they are below 85% as specified in the protocol? Is a difference in response rate expected between the group of women exposed to breast implants and the control group? How are denominators used to calculate response rates defined?

(7) Women who had plastic procedures other than breast augmentation may be considerably younger or much older than those who had breast implants. Does the necessary

age adjustment leave adequate statistical power for the main contrasts in the analysis?

(8) Were the endpoint/outcome measures (particularly arthritic and rheumatic findings) formally validated before the fieldwork began—or before the definitive analysis plan was adopted?

(9) Members of a follow-up cohort are classified and then assigned or recruited by exposure status at "zero time", before the specified outcome becomes manifest. They are then followed up. Documents and correspondence obtained by Freedom of Information mechanisms from the coordinating office at the NCI suggest that recruitment of women was done extensively in plaintiffs' lawyers' practices and among advocacy groups of women with adverse events (ie, women who considered themselves already affected by an outcome of interest). How will the investigators contain major biases introduced, almost certainly, by such recruitment methods?

(10) Have there been any formal protocol revisions? If so, how were they reviewed and approved?

The NCI Follow-up Study of Women with Augmentation Mammoplasty is considered by some to be very objective because it is governmentally funded. But the absence of sponsorship by plastic surgeons, implant manufacturers, and other interest groups does not guarantee lack of bias on methodological grounds.

After five years and several million dollars of public funds the NCI study has the potential to bring important new evidence to bear on the controversies surrounding breast implants and women's health. However, unless the above questions are answered—and none, surprisingly are resolvable via the protocol—the findings may be uninterpretable.

WOS has consulted with one defendant in breast-implants litigation. None of the other authors have had any involvement with any aspect of the controversy.

*Patricia Clark, Edeltraut Garbe, Brian Habbick, Valerie Lawrence, *Walter O Spitzer*

Faculty of Medicine, Universidad Autonoma Nacional de Mexico, Mexico City, Mexico; Potsdam Institute of Pharmacoepidemiology and Technology Assessment, Potsdam, Germany; Departments of Epidemiology and of Community Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; Department of Medicine, University of Texas at San Antonio, San Antonio, TX, USA; and *Phylax Biomedical Sciences Integrity (USA) Inc, Palo Alto, CA 94301, USA

1 US Congress. Departments of Labor, Health and Human Services and Education and Related Agencies Appropriation Bill. US 102nd Congress, July 11, 1991.

Survival of patients with breast cancer and *BRCA1* mutations

Sir—L C Verhoog and co–workers (Jan 31, p 316)[1] found that 5-year survival rates for women with breast cancer and *BRCA1* mutations were similar to those for patients with sporadic disease. Their results are surprising, given that *BRCA1*-associated breast cancers are more likely than sporadic cancers to be high grade,[2] oestrogen-receptor negative,[2] and p53 positive.[3]

Accurate estimates of survival for patients with hereditary cancer based on clinic records is difficult, and the results of all such studies must be questioned. Difficulties arise because living affected women are preferentially referred to the clinic and offered genetic testing. Once a mutation is known in a family it may be possible to assess the mutation status of deceased cases with stored histological samples, but this technique does not always succeed and is not usually offered when there is no living affected case.

Verhoog and colleagues analysed the dataset twice: first with all 49 patients and then after the exclusion of 13 probands. As expected, these exclusions negatively affected the observed survival rate. However, exclusion of the proband is insufficient to correct for ascertainment bias in clinic-based genetic studies. This fact is often overlooked; for example, if each living woman with familial breast cancer in Holland were equally likely to be referred to a cancer clinic for assessment, then a family with three living affected women would be three times more likely to be included in a clinic-based study than a family with only one living affected woman. So, the differences in survival between patients with or without the *BRCA1* mutation in the Dutch breast cancer cohort may be even greater than that reported.

An unbiased way to estimate relative survival is to ascertain *BRCA1*-mutation status on an unselected sample of pathology breast specimens in a hospital tumour bank, and to compare survival for women with and without mutations. We analysed 187 tumour blocks from unselected Ashkenazi Jewish women with breast cancer, aged 28–65 years, diagnosed between 1986 and 1996. We reviewed the medical records of each case to determine tumour stage and grade and survival.

36 women had died by the end of 1997. The median length of follow-up was 4·5 years. 25 (13%) women were carriers of *BRCA1* mutation. Death from breast cancer was more common in the *BRCA1*-mutation carriers than in controls. Eight of the nine deaths in carriers were attributed to breast cancer. Kaplan-Meier actuarial survival methods showed that the 5-year survival rate was worse for carriers than for non-carriers (70·8% *vs* 85·9%, log-rank test p=0·05). The difference was especially striking for node-negative patients. Only 58·3% of node-negative carriers survived for 5 years, compared with 94·1% of the node-negative controls (p=0·0001). The *BRCA1*-mutation carriers were younger on average, but restricting the analysis to premenopausal cancer had little effect on the survival differences. The result was equally strong for the node-negative cases diagnosed before age 50 (37·5% survival for carriers *vs* 87·5% non-carriers, p=0·0013). Positive-node status was an adverse prognostic factor among the *BRCA1*-negative cases (94·1% of node-negatives cases survived 5 years *vs* 73·9% of node-positive cases, p=0·003). By contrast, *BRCA1*-mutation carriers had poor survival, independent of nodal status.

We believe that previous investigators may have come to different conclusions because of the biases inherent in studying survival historically, in clinic-based populations. Although our data are preliminary and our sample size is small, our findings call into question the practice of relying on lymph-node status to grade early-stage breast cancer in *BRCA1* carriers.

We thank L Bégin, M Pollak, P Tonin, and S Karp for assistance.

**William D Foulkes, Nora Wong, Florence Rozen, Jean-Sebastien Brunet, Steven A Narod*

*Cancer Prevention Research Unit, Sir Mortimer B Davis–Jewish General Hospital, Montreal, Quebec, Canada H3T 1E2; Departments of Medicine and Human Genetics, Montreal General Hospital, McGill University, Montreal, Quebec; and Centre for Research in Women's Health, University of Toronto, Toronto.

1 Verhoog LC, Brekelmans CTM, Seynaeve C, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of *BRCA1*. *Lancet* 1998; **351:** 316–21.

2 Johannson OT, Idvall I, Anderson C, et al. Tumour biological features of *BRCA1*-induced breast and ovarian cancer. *Eur J Cancer* 1997; **33:** 362–71.

3 Sobol H, Stoppa-Lyonnet D, Bressac-De Paillerets B, et al. *BRCA1*-p53 relationship in hereditary breast cancer. *Int J Oncol* 1997; **10:** 349–53.

Authors' reply

Sir—William Foulkes and colleagues' explanation of ascertainment bias in our study resulting in selection for longevity is too simple. The assumption that we selected families with high proportions of surviving patients is incorrect. This assumption might only hold if all

probands were living breast-cancer patients. But this is not the case since healthy women also consult our family cancer clinic, and these families were also included in our study. At our clinic, we offer DNA-analysis to families without a living affected case with histological samples stored in paraffin of deceased patients or blood from living relatives who have a 50% risk of carrying a mutation.

We agree with Faulkes that a population-based study of patients with breast cancer is the best way to calculate relative survival. Nevertheless, we think that their selection procedure did not exclude the risk of any bias, chance, and inappropriate comparisons within their own and other studies. In their initial hospital-based study[1] Foulkes and colleagues investigated mainly Jewish patients, excluded patients older than 65 years, and those with long-term follow-up and proven long-term survival. They selected patients with a recent diagnosis of breast cancer (initially 1990–96,[1] later 1986–96), and most patients (about 94%) were treated with breast-conserving surgery. Their control group had an excellent survival rate, suggesting a specific reference pattern to their hospital, which is not representative and could indicate increased awareness of breast cancer. In their initial study[1] in 12 *BRCA1*-positive and 100 *BRCA*-negative tumours, Foulkes and co-workers showed a significant difference in tumour size in favour of the control group, but this difference disappeared after the addition of 75 other patients (13 *BRCA1* positive). After that, the tumour size in the *BRCA1*-positive group dropped from 2·41 cm to 2·07 cm and increased from 1·71 cm to 1·99 cm in the controls. The between-group difference in breast-cancer-specific death rate dropped from 31·4% (p=0·002) in their initial study[1]—to 15·1% (p=0·05) in their present extended study. This difference reflects the impact of potential bias by small sample size and the selection of time for years since breast cancer diagnosis.

The small mutation spectrum in their study differs from the broad spectrum in our study and might per se explain the difference in conflicting results of the two studies. The site of both *BRCA*1 mutations (185 delAG, 5382 insC) specific for the Ashkenazi Jewish population have been associated with highly proliferating undifferentiated hereditary breast cancer.[2] However, there are no major differences in death rates between the *BRCA1*-positive patients in their and our study whereas there is a great between-study difference between the control groups (14·1% *vs* 29%). This difference could result from Faulkes and colleagues' selection procedure and small subgroups that were not matched adequately for age, which is an independent prognostic factor. In addition, the results of two recent age-matched studies[3,4] confirm out findings.

We conclude that there was no ascertainment bias towards lengthy survival in our study, but differences in populations, small sample size, and selection criteria are responsible for the discrepant results. The findings of Faulkes and co-workers in the node-negative subgroup and their hypothesis that *BRAC1*-mutation carriers may be especially prone to develop distant metastases without evidence of axillary lymph-node involvement are intriguing, but their subgroups and number of events are too small to allow definitive conclusions.

*Leon C Verhoog,
Cecile T M Brekelmans,
Hanne J Meijers-Heijboer, Jan G M Klijn
Family Cancer Clinic, Rotterdam Cancer Institute (Daniel den Hoed Kliniek), University Hospital Rotterdam, 3075 EA Rotterdam, Netherlands

1 Foulkes WD, Wong N, Brunet J-S, et al. Germline *BRAC1* mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer. *Clin Cancer Res* 1997; **3:** 2465–69.
2 Sobol H, Stoppa-Lyonnet D, Bressac-de-Paillerets, et al. Truncation at conserved terminal regions of BRAC1 protein is associated with highly proliferating hereditary breast cancers. *Cancer Res* 1996; **56;** 3216–19.
3 Watson P, Marcus JN, Lynch HT. Prognosis of *BRAC1* hereditary breast cancer: a commentary. *Lancet* 1998; **351;** 304–05.
4 Johannsson OT, Ranstam J, Borg A, Olsson H. Survival of BRAC1 breast and ovarian cancer patients: a population-based study from southern Sweden. *J Clin Oncol* 1998; **16:** 397–404.

Prenatal exposure to famine and health in later life

Sir—A C J Ravelli and colleagues' (Jan 17, p 173)[1] observations on adults born around the time of the Dutch famine add further support to the notion that prenatal conditions might contribute to metabolic programming. Insulin resistance might be the main determinant of the resulting adverse metabolic profile,[1-3] but Ravelli and co-worker's insulin data raise questions about their conclusion regarding the critical timing of prenatal exposure to famine. On the basis of their 2-h glucose observations, these investigators have implicated late gestational exposure in higher insulin resistance later in life. However early gestation could be the critical time window, as the unadjusted data on fasting insulin, fasting 32-33 proinsulin, and 2-h insulin suggest (Ravelli's table 2). We are informed that insulin and proinsulin concentrations, controlled for sex and body-mass index, did not differ significantly according to the timing of famine exposure, but it may not be appropriate to control for an obesity variable that could be intermediate in the causal pathway. It would be of interest to examine insulin concentrations according to time of exposure and strata of body-mass index. Similarly, data on insulin concentrations stratified by birthweight and according to time of exposure might shed further light.

Ravelli's data also suggest that there may have been reduced survivorship in men exposed to famine during early or mid gestation. There were 70 men and 93 women among those exposed to famine during early or mid gestation, whereas on the basis of the sex distribution of unexposed individuals, one would have expected about 83 men and 80 women (p=0·07). The sex distribution among those exposed in late gestation (56 men and 60 women) was what might have been expected (p=0·69).

Insulin resistance is a predictor of coronary heart disease, the illness that largely accounts for the lower survivorship among men than women in middle age.[4] Thus, if our interpretation is correct regarding the reduced male representation among famine-exposed individuals in Ravelli and colleagues' study, the reduced survivorship in men may also point to early or mid gestation (rather than late gestation) as the critical period for determining insulin resistance in later life. Consistent with this view is the higher rate of obesity noted earlier among young men exposed to the Dutch famine during the first half of pregnancy.[5]

More evidence about the mechanism(s) by which prenatal circumstances may determine later metabolism and health is needed. At the same time, we must attempt to clarify the gestational time window (late *vs* early), and the exact nature (eg, nutritional deprivation *vs* stress hormones) of the implicated prenatal exposure

*Henry S Kahn, K M Venkat Narayan, Rodolfo Valdez
*Department of Family and Preventive Medicine, Emory University School of Medicine, Atlanta, GA 30303, USA; and Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta.

1 Ravelli ACJ, van der Meulen JHP, Michels RPJ, et al. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998; **35:** 173–77.
2 Phillips DIW, Barker DJP, Hales CN, Hirst S, Osmond C. Thinness at birth and insulin resistance in adult life. *Diabetologia* 1994; **37:** 150–54.
3 Fall CHD, Osmond C, Barker DJP, et al. Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 1995; **310:** 428–32.
4 Donahue RP. The insulin resistance syndrome (syndrome X) and risk factors for coronary heart disease: an epidemiologic overview. *Endocrinologist* 1994; **4:** 112–16.
5 Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med* 1976; **295:** 349–53.

Sir—During the past year, three reports have addressed the influence of prenatal exposure to famine on health in later life. We studied 161 744 individuals born during the 1866–68 Finnish famine and found, on the basis of a comparison with more than 600 000 individuals born before and after the famine, that nutritional deprivation in utero has no effect on survival in adult life.[1] Stanner and colleagues[2] investigated a broad range of coronary heart disease and diabetes mellitus risk factors among 169 people exposed to malnutrition in utero during the siege of Leningrad in 1941–42 and nearly 400 born before or outside the area of the siege. They found no association between intrauterine malnutrition and glucose intolerance, dyslipidaemia, hypertension, or cardiovascular disease in adulthood. Finally, A C J Ravelli and colleagues[3] studied 279 individuals who were exposed to malnutrition in utero during the Dutch hunger winter 1944–45 and nearly 425 controls born before and after. They found an association between intrauterine exposure to famine and decreased glucose tolerance in adults aged around 50 years. Surprisingly, these workers do not take the two previous negative studies into consideration in the interpretation of their results.

All three studies were motivated by the intriguing fetal origins hypothesis proposed by Barker[4] and co-workers, which asserts that a baby's nourishment before birth and during infancy programmes its susceptibility to cardiovascular diseases as well as several other diseases and adverse outcomes, ranging from diabetes mellitus to cancer and suicide. Concerns have been raised about the numerous indirect indicators of fetal nourishment used by the Barker group,[5] and therefore the famine studies were anticipated with great interest, especially the Dutch famine study.[1] However, it is disappointing that Ravelli and colleagues, among all the suggested outcomes related to fetal nourishment, only report glucose tolerance. Presumably other outcomes were also readily available in the Dutch famine study—eg, blood pressure, which is among the most studied outcomes in relation to fetal nourishment. Only if these other key outcomes show the predicted association with fetal nourishment, will the study provide evidence for the fetal origins hypothesis.

*Kaare Christensen, James W Vaupel

*Odense University Medical School, Danish Centre for Demographic Research, DK-5000 Odense C, Denmark; and Max Planck Institute for Demographic Research, Rostock, Germany

1 Kannisto V, Christensen K, Vaupel JW. No increased mortality in later life for cohorts born during famine. *Am J Epidemiol* 1997; **145:** 987–94.
2 Stanner SA, Bulmer K, Andrés C, et al. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. *BMJ* 1997; **315**: 1342-49.
3 Ravelli ACJ, van der Meulen JHP, Michels RPJ, et al. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998; **35:** 173–77.
4 Barker DJP. Mother, babies, and diseases in later life. London: BMJ, 1994.
5 Kramer MS, Joseph KS. Enigma of fetal/infant origins hypothesis. *Lancet* 1996; **348:** 1254.

Sir—By contrast with A C J Ravelli and colleagues'[1] findings during the Dutch winter famine, we found no difference in glucose concentration, or in any of the insulin-like molecules, between individuals whose mothers were exposed in utero to the siege of Leningrad hunger winter and those exposed during infancy or born outside the siege limits.[2] We have further analysed the data according to the stage in pregnancy at which the exposure occurred. The food ration for dependents fell below 1000 kcal with the imposition of rationing on July 18, 1941, and remained below 1000 kcal for the duration of 1942, by contrast with the restoration of adequate nutrition in the Netherlands within 3 weeks of the end of the siege. Thus children born after Oct 18, 1941, until the end of our study period, were exposed to an average maternal food intake of under 1000 kcal for at least one trimester of pregnancy. This period was divided to define those exposed during late, mid, and early gestation—although, because of the duration of the siege, those exposed in early or mid gestation remained in utero during maternal starvation throughout the rest of pregnancy, and all neonates were exposed to at least 6 months' postnatal malnutrition.

There was no difference in glucose concentrations by trimester of exposure (table). Only 2-h insulin concentration differed between groups, being significantly lower in those exposed in late gestation than in those born before the siege (p=0·049). Adjustment for gender and BMI had little effect on the analyses. By contrast, 2-h glucose and insulin concentrations reported by Ravelli were significantly higher in the exposed individuals, particularly the late gestation group.

We feel that the differences between the two studies are real. Numbers in our study provided 91% of the power of the Dutch Study, and we have outlined our reasons for discounting selection bias to account for our results.[2] Two possible explanations are proposed. First, birthweight has been inversely related to the maternal carbohydrate-to-protein ratio in the first trimester,[3] and although protein was virtually absent from the diet in both situations, the average calorie intake, predominantly from carbohydrate, was nearly twice as high in the Netherlands as in Leningrad. A more likely suggestion is that growth retardation is of greater impact when followed by a high nutrient intake postnatally—a situation that would have prevailed in the Netherlands, where the Siege ended after less than 6 months, by contrast with the 28-month Leningrad siege. Preliminary data in animals have implicated catch-up growth in the postnatal period after a maternal protein-deficient diet in both increasing blood pressure and shortening lifespan of the exposed animals.[4]

This interpretation may be of some importance. If catch-up growth contributes to the aetiology of diabetes in growth-retarded babies, it may have more relevance to the practice of

	Exposure to famine				
	Born before Siege (n=192)	Late gestation (n=64)	Mid gestation (n=75)	Early gestation (n=58)	p*
Fasting glucose (mmol/L)	5·26	5·18	5·15	5·28	0·84
Fasting insulin (pmol/L)	35·0	35·4	34·7	34·3	0·98
Fasting proinsulin (pmol/L)	2·90	2·52	2·76	2·70	0·63
Fasting des 31,32 proinsulin (pmol/L)	1·21	0·99	1·65	1·22	0·18
120 min glucose (mmol/L)	6·0	5·93	6·09	6·06	0·97
120 min insulin (pmol/L)	149·8	117·5	167·5	128·3	0·05

*ANOVA.

Effect of siege exposure on glucose and insulin concentrations in Leningrad

neonatologists than to understanding the epidemic of diabetes in the Indian subcontinent.[5]

*John S Yudkin, Sara Stanner

Centre for Diabetes and Cardiovascular Risk, Whittington Hospital, University College London Medical School, and Royal Free Hospital School of Medicine, London N19 3UA, UK

1 Ravelli ACJ, van der Mejlen JHP, Michels RPJ, et al. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998; **351:** 173–77.
2 Stanner SA, Bulmer K, Andrés C, et al. Malnutrition in utero as a determinant of diabetes and coronary heart disease in adult life: the Leningrad siege study. *BMJ* 1997; **315:** 1342–49.
3 Godfrey K, Robinson S, Barker DJP, Osmond C, Cox V. Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. *BMJ* 1996; **312:** 410–14.
4 Hales CN. Fetal and infant growth and impaired glucose tolerance in adulthood: the "thrifty phenotype" hypothesis revisited. *Acta Paediat* 1997; **422** (suppl): 73–77.
5 Ramaiya KL, Kodali VRR, Alberti KGMM. Epidemiology of diabetes in Asians of the Indian Subcontinent. *Diab Metab Rev* 1990; **3:** 125–46.

Authors' reply

Sir—The results of the Dutch famine study showed that prenatal exposure to famine in late and mid gestation is associated with a decreased glucose tolerance in adults aged about 50 years. Henry Kahn and colleagues focus on insulin resistance as the main determinant of poor glucose tolerance. They refer to our finding that the unadjusted means of fasting insulin, 32–33 split proinsulin, and 2-h insulin are highest in those exposed to famine in early gestation, and they suggest therefore that this period may be the critical time window. Insulin concentrations are strongly related to obesity, and exposure to the Dutch famine in early pregnancy resulted in higher rates of obesity.* We presented all results adjusted for body-mass index, because our aim was to study the effect of prenatal exposure to famine on insulin-glucose metabolism, independently of its effects on body fatness and weight.

Kahn and colleagues also presumed a higher mortality in men exposed to famine during early or mid gestation; this is not true. Mortality until 1996 was, in men and women, respectively, 18·5% and 14·2% in those born before the famine, 20·3% and 10·2% in those exposed during late gestation, 12·7% and 11·3% in those exposed during mid gestation, 12·5% and 9·2% in those exposed during early gestation, and 9·7% and 5·7% in those conceived after the famine period. Obviously, mortality was higher in men than in women, and the highest mortaility was in men exposed to famine during late gestation.

Kaare Christensen and James Vaupel point out that prenatal exposure to the Finnish famine 1866–68 did not affect survival in those who survived at least up to 17 years,[1] and that prenatal exposure to famine during the siege of Leningrad 1941–44 was not associated with glucose intolerance, dyslipidaemia, hypertension, or cardiovascular disease in adult life.[2] We think that the Finnish famine and the Leningrad siege are hardly comparable with the Dutch famine. The Dutch famine happened abruptly and lasted only 5–6 months, took place in a highly organised society, and was preceded and followed by periods of adequate nutrition. Furthermore, those born around the time of the Dutch famine grew up in a time of increasing affluence. We think that the Leningrad study cannot be regarded as a negative study. After all, this study showed a mean of 120 min glucose plasma concentration after a standard oral glucose tolerance test of 6·1 mmol/L (95% CI 5·8–6·4) in 169 people who were exposed to famine in utero and 5·7 mmol/L (5·4–6·0) in 188 unexposed people born outside the famine area.

John Yudkin and Sara Stanner reanalysed some of the data of the Leningrad study while attempting to use definitions of exposure during late, mid, and early gestation similar to those used in the Dutch famine study. But as they have indicated, this attempt falls short, because people born in Leningrad exposed to famine in mid or early gestation were also exposed during the remaining part of gestation. Furthermore, people born before or during the Leningrad siege were also exposed during infancy, whereas children younger than 1 year were fairly protected during the Dutch famine, because their official daily rations never fell below 1000 kcal.[3] Prenatal malnutrition might indeed be of greater impact when postnatal nutrition is sufficient.

* Data available from authors or *The Lancet*, on request.

*A C J Ravelli, *J H P van der Meulen*

Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, PO Box 22700, 1100DE Amsterdam, Netherlands

1 Kannisto V, Christensen K, Vaupel JW. No increased mortality in later life for cohorts born during famine. *Am J Epidemiol* 1997; **145**: 987–94
2 Stanner SA, Bulmer K, Andrés C, et al. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. *BMJ* 1997; **315**: 1342-49
3 Burger GCE, Sandstead HR, Drummond JC. Malnutrition and starvation in Western Netherlands. The Hague: General State Printing Office, 1947.

Magnetic-resonance imaging in breast cancer

Sir—Michael Douek and co-workers (March 14, p 801)[1] report that small, enhancing foci detected by magnetic-resonance imaging (MRI) represent invasive and in-situ foci of breast cancer and suggest that MRI could be used to investigate prospectively the clinical significance of unresected breast cancer foci in the context of breast-conserving surgery.

With attention to detail during breast conserving surgery followed by radiotherapy to the breast, recurrence in the conserved breast in the Manchester breast unit is 7% at 10 years. Most undetected invasive foci never become clinically important after radiotherapy. Despite its better sensitivity Kramer and colleagues[2] reported an incorrect diagnosis of multicentric breast cancer by MRI in eight of 46 patients.

Before any clinical decisions are made on the basis of MRI findings, it will be necessary to find out whether the finding of extra enhancing foci in a breast during conservation therapy predicts for local recurrence in the breast. We are conducting such a study, in which patients with early mammographically unifocal breast cancer undergo MRI before surgery. The MRI findings are not revealed to the surgeon so the surgical procedure is not affected by the MRI findings. Correlation with histological findings is being undertaken and, provided surgical margins are clear, the patient undergoes breast conservation with radiotherapy All patients are being followed up for 5 years to assess whether MRI predicts local recurrence after surgical treatment of radiotherapy and chemotherapy. The project is supported by a grant from the North Western Research and Development Directorate with contrast medium supplied by Nycomed.

Breast MRI is an expensive procedure, in the UK £300–£400 per patient, and before its widespread introduction evidence of its value in clinical management needs to be established. Studies of MRI are expensive and are not usually fully funded, making it difficult to determine the role of MRI in the therapeutic process.

C R M Boggis, N J Bundred

Department of Surgery, South Manchester University Hospital, University of Manchester, West Didsbury, Manchester M20 8LR, UK

1 Douek M, Viadya JS, Lakhani SR, et al. Can magnetic-resonance imaging help elucidate natural history of breast cancer multicentricity? *Lancet* 1998; **351:** 801–02.
2 Kramer S, Döinghaus K, Schulz-Wendtland R, et al. The role of MR-mammography in the diagnosis of multicentricity in breast cancer. *Proc Radiol* 1997: 51.

Aboriginal health

Sir—Your March 14 editorial on aboriginal health[1] is timely. To find solutions, however, is not easy.

When I took up the chair of child health in Sydney in 1960, I found more pressing problems on my doorstep. At the Royal Alexandra Hospital for Children an official instruction to the nurses was that all children in low-sided cots up to the age of 6 years and in high-sided cots up to the age of 4 years had to be in restrainers. Such matters had to be coped with, and I decided that the problems of aboriginal health were in the too difficult basket.

Every few years, medical students would ask if I could help obtain admission to the medical school for some aboriginal students at a lower educational level than that required for white students. We would discuss this, and they soon realised the problems. Could the aboriginal students continue to be given conditional passes, and what evidence was there that an aboriginal medical graduate would want to work amongst his own people rather than join a lucrative practice on Sydney's North Shore?

When Gough Whitlam became prime minister; we had a government that truly desired to improve the health of the aboriginal population. He appointed a delightful, bumbling, kindly man with a big heart as the minister responsible, Gordon Bryant. An aborigine should get the same pay for the same work as a white man. Aborigines worked well as stockmen in the Northern Territory but they would periodically go "walk-about" for some weeks. The properties were mostly American managed and they lost their jobs. Aborigines should make their own decisions about what they eat and drink—so the consumption of beer rose. Child allowances should be the same; in no time families were so large and allowances so great that to take employment would be foolish. So the effects of the minister's well meaning moves were all bad.

There was an outcry at the infant mortality amongst aboriginal children in Alice Springs. The government built a new hospital, with white labour flown in. Not an hour of aboriginal labour was used despite over 90% unemployment. Furthermore, the hospital might have been suitable for whites but it was wholly unacceptable to aborigines. In Darwin, a new children's ward was opened. Many of the children admitted because of diarrhoea and malnutrition turned over and died after they had been resuscitated. Not, I believe, because of unrecognised potassium deficiency but because they woke up in an environment so alien that they could not cope with it.

Some dedicated doctors have set up appropriate, user-friendly clinics in the depressed aboriginal reserves outside towns but these are almost impossible to maintain on a permanent basis.

So, the problems are not easy to solve. I am, however, optimistic for there has been a sea-change in the attitudes of most young Australians and the first professor of aboriginal health (Michael Gracey) has been appointed, at the University of Western Australia, Perth.

Thomas Stapleton
The Foundry Cottage, Lane End,
High Wycombe, Bucks HP14 3JS, UK

1 Editorial. Aboriginal health, a missing dimension. *Lancet* 1998; **351:** 765.

Sir—We would like to comment on some of the issues you raise in your editorial[1] after working for 6 years in remote North West Queensland, where 20% of the population of 36 000 are indigenous people. The pattern of disease found in aboriginal people is different from that in other Australians. Life expectancy for aboriginal Australians falls short of fellow Australians by almost 20 years. Comparison with other indigenous groups such as native Americans or Maoris in New Zealand shows that aboriginal Australians have catastrophically poor health outcomes. The high incidence of disorders such as rheumatic fever, diabetes, ischaemic heart disease, and hypertension may reflect not only the present cultural and material destitution of many aboriginal people, but also a legacy begun in utero (maternal malnutrition compromising fetal pancreatic β-cell development, fetal alcohol syndrome).

To recruit aboriginal health professionals is laudable, and forms a necessary step towards the goal of autonomy for health services in aboriginal communities. However, progress has been slow and it may take 20 or 30 years to show results. Many aboriginal people are reluctant to travel to centres of traditional education—ie, metropolitan universities and colleges—and a consistent demand is for locally delivered education and training. Important progress towards locally based health worker training for aboriginal students is being made in Mount Isa, with local delivery of health education material supported by new distance education technologies. It is critical that this training, as well as providing a goal in itself, promises aboriginal health workers a mechanism to enter mainstream health education, whether nursing, medical, or allied health.

Other goals should be improved access to health services (overcoming both cultural and geographic barriers) and enhanced communication (helping people to understand that their health may be affected by their lifestyle). However, when a group of people in a society is concerned with the most basic aspects of life (obtaining food, water, and shelter), health becomes a luxury that is rapidly dispensed with. Poverty is perhaps the unifying theme, defining aboriginal health and disease. To argue for equity is insufficent when aboriginal people have been left so far behind in so many respects. A concerted government approach will be needed to improve substantially health outcomes for this group of Australians. Recognising native title to traditional lands is fundamental to any process of healing and reconciliation.

**Nikki Blackwell, Jeremy Hayllar*
PO Box 27, Mount Isa, Queensland 4825, Australia

1 Editorial. Aboriginal health, a missing dimension. *Lancet* 1998; **351:** 765.

Sexual ill-health among blacks in the UK

Sir—Your editorial on aboriginal health[1] revisits race, ethnicity, and ill-health objectively. The example you provide, of a high incidence of sexually transmitted diseases (STD) initially blamed on promiscuity but shown to be associated with inadequate access to services—and thus pointing to the need for cultural appropriate care rather than behaviour modification—to sexual ill-health in those of African descent in the UK.[2]

At a seminar on STDs organised by the African Caribbean Medical Society on March 14, 1998, I outlined the anthropological principles underlying the definition of race and ethnicity. Anthropology has two basic divisions: physical anthropology deals with differences in human physical characteristics (race) and cultural anthropology looks at language, behaviour, and beliefs (ethnicity). The danger when race and ethnicity are used by researchers in the analysis of STD data is illustrated by the Tuskegee syphilis study. Both distinctions, the racial and the ethnic, deal with minor differences among the human race, who belong to a single species for whom sex, recreational or for procreation, carries the risk of STD. Sexual transmission of an infection requires the agent to be present in one partner, the other partner to be

susceptible to infection with that agent, and the sex partners to engage in sexual practice able to transmit the infection.[1]

London, for example, is a melting-pot of various cultures, religions, level of educational attainment, and socioeconomic status and recent immigration. An epidemiological approach to the control of STD includes case-finding screening of susceptible partners, and ensuring adequate treatment and relevant behaviour modification with preventive counselling to truncate infectiousness. Ethnic or race data, should only be used to understand cultural mores inimical to appropriate behaviour modification. The emphasis should be on acquiring composite knowledge of behaviour science theory.[4] STDs pose difficult public-heath problems.[5] Sociocultural taboos related to sexuality are a barrier to preventive efforts. We must be careful lest messages in the mass media hinder effective control because the unreserved support of all racial-ethnic groupings is needed in the campaign. At the community level, partnerships need to be fostered between providers and service users to ensure a culturally sensitive service.

Tubonye C Harry
Bure Clinic, James Paget Healthcare NHS Trust, Great Yarmouth, Norfolk NE31 6KA, UK

1 Editorial. Aboriginal health, a missing dimension. *Lancet* 1998; **351:** 765.
2 Low N, Daker-White G, Barlow D, Pozniak AL. Gonorrhoea in inner London: results of a cross sectional study. *BMJ* 1997; **314:** 1719–23.
3 Harry TC, Clark SL. Are race and ethnicity in analyses still of relevance? *Sex Transm Inf* (in press).
4 Gandelman AA, Dolcini MM, Volle SJ, Vogan S, Bolan GA. Assessing STD/HIV prevention provider knowledge of behaviour science theory: building on existing intuitive experience. 12th meeting of International Society of Sexually Transmitted Disease Research/14th regional meeting of International Union Against Sexually Transmitted Infections (Oct 9–22, 1997, Seville); abstracts: 568.
5 Harry TC. Are health of the nation targets attainable? *Int J STD AIDS* 1998; **9:** 185–86.

World health

Sir—As a new boy at WHO I have followed the *Lancet* series that ended in March with great interest. I feel I must defend WHO from some of the very unfair criticisms made about it. Indeed I am surprised that the editor allowed so many unsubstantiated statements which mix facts with personal prejudices to be written so uncritically in such a prestigious journal.

Of course we must rethink global health strategies and face up to the challenges that lie ahead. The Four Horsemen of the Apocalypse have been with us since the beginning of medicine and will ride on into the new millennium. We must get the right balance between centralised and devolved resources at a time of communication revolution. We have to be able to respond to inequities in social justice and be the world's health conscience. We must work closely with the many international agencies and charities that try to improve global healthcare. And persuading governments to implement proven preventive public health strategies for non-communicable diseases is crucial at a time of health transition and the export of unhealthy lifestyles from richer to poorer countries. But above all we must possess and provide high level expertise across a wide range of clinical topics. Knowledge is the key to effective action. Through its regional offices WHO has a remarkable global network and in certain technical areas is a world leader with collaborating centres and experts well recognised in their field.

There are too many armchair philosophers who, never having treated a single patient, are willing to share their views on how things should be done in medicine. I am afraid your series on World Health was written by such a group, most of whom I note were social scientists rather than clinicians. Getting international cooperation in health is not an easy business. Developing effective strategies for health requires knowledge and persuasive power not trendy, cliché-ridden political invective.

Karol Sikora
WHO Programme on Cancer Control, International Agency for Research on Cancer, 69372 Lyon, France

Sir—2 years ago I resigned my position as an international health bureaucrat in Canada and became an independent public health consultant in Ghana. I have now seen two sides of WHO. Endless meetings in the boardrooms in Geneva full of jargon, diplomatic courtesy, and backroom politics. And visits to WHO country offices trying to get useful information for a health sector review, a programme evaluation, or a feasibility study. My impressions may be drawn from a biased sample, they certainly have an African bias because of where I live. The experience, however, is surprisingly uniform, although there are both positive and negative outliers.

Extra-budgetary programmes of WHO, especially multiagency cosponsored programmes such as the tropical diseases research (TDR) and the onchocerciasis control programme (OCP), generally have a clear strategy, transparent operation, and high performance standards. They are monitored by their donors and work under pressure to produce results, which are instantly rewarded by annual funding pledges. There are two serious drawbacks to this type of operation. Funding is unstable, creating a tendency to concentrate on short-term objectives, and programmes are pressured by the political agendas of their donors. How well a programme performs under these constraints depends on the skill of the top management. The failure to negotiate this maze led to withdrawal of donor support to the WHO global programme on AIDS (GPA); this may sound like harsh judgment, which should be softened by the fact that AIDS is probably the most political of all health issues, and WHO may have faced a near impossible task. Whether UNAIDS can do any better remains to be seen.

WHO country offices present a different picture. The lights are usually on but there is rarely anybody at home. Biennial country programme plans, if at all obtainable, read like a smorgasbord of parochial interests and opportunistic positioning. I have seen many, some printed on a single page, none presenting an acceptable health-sector analysis. Unholy alliances between WHO staff trying to maintain their international status and national health officials striving to be in line for the next appointment undermine the claim for technical leadership that is so vehemently asserted by every WHO representative. This small-scale politicking is overshadowed by the organisational politics of regional offices trying to build alliances for the next election of the director general.

The call for WHO to concentrate on its "normative functions" quoted by Lucas[1] is based on the fact that these functions are politically neutral and generally well executed under the guidance of competent staff at WHO headquarters. Some extrabudgetary programmes still provide valuable technical cooperation. But until WHO can rid itself of its internal political morass and show that its country support is based on technical competence, it will continue to see itself marginalised to a ceremonial role. The WHO representative holds the opening speech, but the substantive external contribution to national health policy, the critical analysis, the strategic planning, and the technical support is provided by UNICEF, the World Bank, and the bilateral co-operation agencies.

Josef Decosas
Box 947 Kaneshie, Accra, Ghana, West Africa

1 Lucas A. WHO at country level. *Lancet* 1998; **351:** 743–47.

Clinical experience of UK medical students

Sir—I C McManus and colleagues (March 14, p 802)[1] argue for a decline in medical training in the UK, based on a trend of decreasing exposure of medical students to medical conditions, surgical operations, and practical procedures. I will not comment on the surgical cases or the procedures, but wonder whether the downward trend they show with regard to "acute medicine" would apply if the medical conditions were more appropriate to what we actually see referred to a tertiary care hospital.

I would argue the category of acute medical conditions should include ventricular failure, exacerbation of chronic obstructive airway disease, pneumothorax, status asthmaticus, drug overdose, central chest pain, altered mental state, syncopal attack, stroke, acute gastrointestinal bleed, unilateral swollen leg, acute oliguria, acute arthritis, and complications of drug addiction.

The spectrum of medical disease is changing. Can one expect an average medical student to see meningitis, diabetic ketoacidosis, hypothermia, subarachnoid haemorrhage, and acute glaucoma these days? I think not. Possibly, the goal posts should be changed before we use the data provided by McManus and co-workers to argue for a decline in medical training in the UK.

Leon G Fine

University College London Medical School and Royal Free Hospital School of Medicine, London NW3 2PF, UK

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

Number-needed-to-treat to prevent one death

Sir—In addition to the difficulties that Anton De Craen and colleagues describe in their Jan 31 commentary,[1] the use of the number-needed-to-treat (NNT) in clinical practice could lead to a decrease in therapeutic acceptance and compliance.

Most conventional measures of the effect of an intervention, such as reduction in relative or absolute risk, suggest that all patients who receive an efficacious treatment will inevitably benefit because it reduces their risk of disease, though the benefit may prove greater in some than in others because of their respective clinical profiles and so-called individual variability. NNT, however, underscores the fact that the benefit is actually obtained by only one patient of several treated.

The twin concepts of evidence-based medicine and NNT have enjoyed great success, and they may eventually reach the general population via such things as health supplements issued by the media. In the near future, physicians may have to provide patients with NNT-related information as to the different results of treatment on offer. What effect will such information have on therapy acceptance and compliance?

Many patients believe that there is always an individual benefit to be obtained in, for example, treating high blood pressure, and therefore, that they will always benefit by reducing their cardiovascular risk. Thank to NNT, the patient might have a better understanding of the fact that any treatment benefit may not reach him or her, because the NNT for many treatments, especially cardiovascular diseases or cancer, is far in excess of 10.[2] Although the NNT for each type of patient can be narrowed down somewhat depending on his or her clinical characteristics,[3,4] even here it is not possible to ascertain which patients will benefit, just as it is impossible to ascertain which patients will have adverse effects of exposure to risk factors for many chronic diseases.

Physicians can help patients to take a decision on the basis of: the efficacy of the intervention in terms of reduction in risk; their preferences based on the possible consequencs of an intervention; and their aversion for or acceptance of the risk. We can also ensure that patients gain keener insight into the problem benefits of a recommended intervention, benefits which, in certain cases, may also reach them.

**Fernando Rodríguez Artalejo, José Ramón Banegas, Antonio Rodríguez Artalejo, Pilar Guallar-Castillón*

*Department of Preventive Medicine and Public Health, University of the Basque Country, 01006 Vitoria, Spain; and Department of Preventive Medicine and Public Health, Autonomous University of Madrid, Madrid
(e-mail: osproarf@vc.ehu.es)

1 De Craen AJM, Vickers AJ, Tijssen JGP, Kleijnen J. Number-needed-to-treat and placebo-controlled trials. *Lancet* 1998; **351:** 310.
2 Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine. How to practice and teach MBE. London: Churchill Livingstone, 1997.
3 Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995; **310:** 452–54.
4 Chatellier G, Zapletal E, Lemaitre D, Menard J, Degoulet P. The number needed to treat: a clinically useful nomogram in its proper context. *BMJ* 1996; **312:** 426–29.

China's trade in human organs

Sir—César Chelala's March 7 news item (p 735)[1] describes the arrest in New York of a Chinese trader in human organs. He and those who sponsor him deserve all the rigours of the law.

I think that most of us will want to dissociate ourselves entirely from the attitude of the European Union (EU) mentioned in the same article. You report that the EU will not introduce or support a resolution on human rights in China in the forthcoming UN Commission on Human Rights. I wonder whom the EU thinks it represents in making such a cowardly decision. It certainly does not represent the views of anybody I have talked to about this matter.

A J Eisinger

South West Thames Renal and Transplantation Unit, St Helier Hospital, Carshalton, Surrey SM5 1AA, UK

1 Chelala C. China's human-organ trade highlighted by US arrest of "salesmen". *Lancet* 1998; **351:** 735.

Retraction: Is Kaposi's-sarcoma-associated herpesvirus in semen of HIV-infected homosexual men?

SIR—In 1995 we reported the detection of Kaposi sarcoma associated herpesvirus (human herpesvirus 8) DNA by nested polymerase chain amplification in the semen of seven (23%) of 30 artificial insemination donors and of 30 (91%) of 33 homosexual AIDS patients.[1] On subsequent analysis, we have been able to reproduce only a subset of those observations and have evidence, based on single-stranded conformation polymorphism and DNA sequencing, suggesting that most of the amplimers came from the same source and are probably the result of contamination. We retract the results in their entirety and apologise for any confusion associated with them.

**Jung-Chung Lin, Seh-Ching Lin, Eng-Chun Mar, Philip E Pellett, Felicia R Stamey, John A Stewart, Thomas J Spira*

Centres for Disease Control and Prevention, Atlanta, GA 30333, USA

1 Lin J-C, Lin S-C, Mar E-C, Pellett PE, Stamey FR, Stewart JA, Spira TJ. Is Kaposi's-sarcoma-associated herpesvirus in semen of HIV-infected homosexual men? *Lancet* 1995; **346:** 1601–02.

Hereditary breast cancer, circa 1750

SIR—The Broca family[1] is often cited as the earliest documented instance (1866) of hereditary breast cancer. In *Mémoires de l'Académie Royale de Chirurgie*[2] in 1757 a French surgeon named Le Dran related the experience of a colleague from Avignon, who had diagnosed a 19-year-old nun with cancer of the right breast. The surgeon had advised mastectomy but that the nun ("fearing its extirpation more than death") refused consent. Her decision was shaped not just by the pain of surgery but also by the belief that the operation would be futile. Her grandmother and a grandmaternal uncle had died with the disease and she was convinced that this malady was hereditary, and that "her blood was corrupted by a cancerous ferment natural to her family". She was doomed by familial inheritance, and surgery could not save her. Yet within a year, she was suffering such "insupportable pains" from her condition that she asked for the operation. After a mastectomy she was restored to "perfect health".

The claim of cure is questionable: we are not told how much time had elapsed since the operation. What is certain, however, is that she understood her condition to be inherited whereas the specialist (Le Dran) was unpersuaded, referring to the "hereditary ferment" as "supposed". Indeed, the woman's family history fits a *BRCA2* germline mutation, with male and female breast cancer aggregation. Le Dran's report may well be the first paper leading to the notion of the breast-cancer-prone family.[3]

The woman's interpretation of her illness as hereditary shaped her attitude to treatment. The approach of the surgeon, excision of the tumour, was rejected because it conflicted with her view of the disease as non-local: it was in her blood, which is as clear an interpretation of the meaning of inherited characteristics as one could form before the end of the 19th century. By her understanding, the disease permeated her body, frustrating any attempt by the surgeon to separate it out with his knife.

There is a striking resonance here between the nun's refusal of treatment and the inclination of some women in cancer-prone families today to request prophylactic mastectomy. Whether a woman resigns herself to the loss of disease-free breasts or to the loss of life once disease is manifest, thinking of cancer as hereditary engenders a fatalistic acceptance of inevitability that persists in defiance of medical progress.

The modern reader is also struck by the 18th century surgeon's readiness to respect the patient's autonomy,[4] and by the clash of interpretations of cancer as a local or a systemic disease.[5]

François Eisinger, Hagay Sobol, Daniel Serin, James C Whorton

*Department of Prevention and INSERM CRI 9703, Institut Paoli-Calmettes, 13009 Marseille, France; Clinique St Catherine, Avignon; and Department of Medical History and Ethics, School of Medicine, University of Washington, Seattle, WA, USA

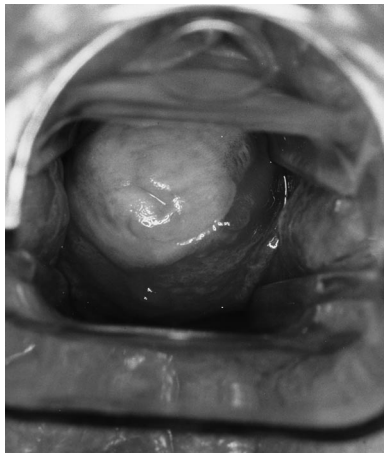
1 Broca P. Traité des tumeurs. Paris: Asselin, 1866.
2 Le Dran H. Mémoire avec un précis de plusieurs observations sur le cancer. *Mém Acad R Chir* 1757; **3:** 1–54.
3 De Moulin D. A short history of breast cancer. Boston: Martinus Nijhoff, 1983.
4 Quill TE, Brody H. Physician recommendations and patient autonomy: finding a balance between physician power and patient choice. *Ann Intern Med* 1996; **125:** 763–69.
5 Jatoi I. Breast cancer: a systemic or local disease? *Am J Clin Oncol* 1997; **20:** 536–39.

Pyoderma gangrenosum

Sir—Jeffrey P Callen's excellent seminar on pyoderma gangrenosum,[1] prompts us to report the rare occurrence of pyoderma of the cervix in a patient who attended our hospital over many years. Pyoderma gangrenosum of the vulva[2] and of mucosal membranes of the mouth in patients with inflammatory bowel disease[3] are well recognised, but our patient had cervical lesions.

In 1982, a 58-year-old woman presented with a 5-year history of chronic, non-healing skin lesions that first developed suprapubically, and then elsewhere. These were ulcerated lesions with a violaceous edge that were occasionally painful. Our investigations found no evidence of inflammatory bowel disease, arthritides, haematological/immunological disorders, or malignant disease. Biopsy samples and tissue cultures from four lesions over the years excluded infection, vasculitis, and cancer and showed neutrophilic infiltration, suppurative granulomas, and epidermal necrosis consistent with the diagnosis of pyoderma gangrenosum.

The skin lesions were resistant to treatment, but after several stays in hospital and trials of different regimens the lesions eventually healed with courses of minocycline and systemic and topical steroids. Some recurrences occurred and scarring was evident, but by 1993 she did not have any acute skin lesions.



Cervical lesion after 1 month of prednisolone treatment

In 1996, she developed blood-stained vaginal discharge. Speculum examination revealed an erythematous thickened lesion of the posterior vaginal vault and cervix. Two biopsy samples showed no evidence of infection or malignant disease, but review of all her histology showed changes identical to those seen in the skin biopsy samples taken years before.

She was treated with prednisolone as sodium phosphate suppositories and enemas inserted into the vagina. The figure shows the appearance of the cervix after treatment for 1 month. The vaginal discharge slowly resolved and the lesions gradually disappeared over 6 months. We believe that this disorder was pyoderma gangrenosum of the cervix, although it has not been previously reported at this site, and were relieved that it responded so well to treatment with topical steroids.

J Powell, F Wojnarowska, M Charnock, P Millard

Departments of *Dermatology, Gynaecology, and Cellular Pathology, Oxford Radcliffe Hospital, Oxford OX3 7LJ, UK

1 Callen JP. Pyoderma gangrenosum. *Lancet* 1997; **351:** 581–85.
2 McCalmont CS, Leshin B, White WL, Greiss FC Jr, Jorizzo JL. Valvar pyoderma gangrenosum. *Int J Gynecol Obstet* 1991; **35:** 175–78.
3 Van Hale HM, Rogers S, Zone JJ. Pyostomatitis vegetans: a reactive mucosal marker for inflammatory disease of the gut. *Arch Dermatol* 1994; **121:** 94–98.

DEPARTMENT OF ERROR

Mortality differences between black and white men in the USA: contribution of income and other risk factors among men screened for the MRFIT—In this article by George Davey Smith and others (March 28, p 934) for the MRFIT Research Group, the figure legend should have read Black/white age-adjusted and income-adjusted relative risks of death by clinical site, and the key should have been ● Age adjusted ▲Income adjusted.