CORRESPONDENCE

Time for reflection after the Bristol case

Sir—Once again the reputation of the whole medical profession has been blackened by the action of two high-profile individuals, James Wisheart and Jaradan Dhasmana from Bristol, which you report on in your June 6 editorial,[1] Richard Horton's May 23 and June 27 commentary,[2,3] and Sarah Ramsay's news items on June 6 (p 1707)[4] and June 27 (p 1935)[5]. The failure of senior consultants in Bristol to police the activities of their colleagues and the subsequent closing of ranks is an ugly sight in a profession that is inherently based on trust and has the historical privilege of self-regulation. It is time that the profession as a whole took stock.

Medicine is a difficult job. It is not science but still very much an art, one that to be performed well requires a delicate balance of listening, examining, commonsense, compassion, knowledge, and, most importantly, the formation of a trusting relationship with the patient. Most of us achieve this balance, but some are unable to achieve this diagnostic balance and usually become the drop-outs from medical schools or the disgruntled doctors in later years. Others sadly become egotistical victims of their own success and forget the ethics of good practice. Most doctors, however, provide a first-class service to their patients and rarely enter the public domain. Good doctors do not attract attention and so, by definition, most doctors must be reasonably good.

The public, however, increasingly expect more from the National Health Service (NHS) and the medical profession. The inadequacies of the NHS, seen in the waiting room and on the ward, are mostly perceived to be the fault not of goverment underfunding but of the doctors. We have to listen to complaints from patients about the long waiting-lists, and inadequate level of staff. The media also, are only too ready to vilify doctors, which erodes the faith the public place in the profession. So when a scandal such as the Bristol case erupts, the public are only too willing to condemn, not just the individuals involved but also the profession as a whole.

Doctors need to decide exactly what their role is and how they wish to be perceived. First and foremost, we are medical practitioners: we diagnose, we prescribe, we operate, we treat. In doing this work we must make sure we do it well. There is no easy answer as to how we regulate our work, but we must not be seen to be an old boys network. We must be quick to condemn the poor performance of others and we must lose our veneer of silent reserve in the face of professional misconduct. We must be forthright in voicing our concerns about the state of the NHS, for if we are to provide a service in which the public have any faith, we must be allowed to work in an environment conducive to good medicine—ie, one that is well funded, is well run, and provides an equal service to all.

In the wake of the Bristol scandal, the public may well question the values of our profession. Let us not passively restore our trustworthiness by hoping that in time our past mistakes will be forgotten—rather let us actively restore the public's faith in us by being good at what we do.

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1 Editorial. First lesson from the "Bristol case". *Lancet* 1998; **351:** 1669.
2 Horton R. Doctors, the General Medical Council, and Bristol. *Lancet* 1998; **351:** 1525–26.
3 Horton R. How should doctors respond to the GMC's judgment on Bristol? *Lancet* 1998; **351:** 1900–01.
4 Ramsay S. Evidence against "Bristol case" doctors found proven. *Lancet* 1998; **351:** 1707.
5 Ramsay S. UK "Bristol case" doctors found guilty of misconduct. *Lancet* 1998; **351:** 1935.

Sir—The press coverage of the (GMC) General Medical Council's handling of the James Wisheart case has been so condemnatory that the pressure for the medical profession to be regulated by an external body is likely to be irresistible, unless action is taken quickly.

There is no doubt in my mind that the commercialisation of the NHS must have had some part to play in these awful events. By setting Trusts in competition with each other, the tendency of senior managers is to suppress any information that might harm their Trust and its ability to attract contracts—or worse, to lose contracts it had already secured. I have experienced this attitude when I was given information that a doctor was writing prescriptions for opiates for another member of staff. I voiced my concern to the then Medical Director of the Trust, thinking that he might advise me as to what should be done, only to be told in the strongest terms that it would not be advisable to proceed further on hearsay evidence in order that the reputation of the Trust could be protected from adverse publicity if the rumour went any further.

The Wisheart case has left three options for the regulation of the profession: Parliament gives the GMC whatever powers it presently lacks so that, in future, it can regulate all aspects of a doctor's practice; an outside body is established to undertake the task; or an office is established to audit medical practice, consisting of members of the appropriate specialty and such others as are deemed necessary. This office—Offmed—could have a permanent staff and the power to co-opt others for particular investigations. Reports of alleged bad practice could be reported to Offmed and would be investigated as thought necessary. In the Wisheart case, a report to, and an investigation by, such a body might very well have prevented at least some of the misery.

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Sir—In his May 23 commentary on the GMC and the Bristol doctors James Wisheart and Janardan Dhasmana, Richard Horton[1] raises several questions that are easily answered. Informed consent means telling a patient the mortality rate associated with the treatment of a particular condition. With any new treatment, it is inevitable that patients will be exposed to the so-called learning curve of a doctor or a hospital, and it is vital that doctors seek evidence of comparable performance between

centres to assure the public of equivalent standards in different centres. Audit must, therefore, be carried out between centres so that comparisons can be made and shortcomings addressed. We have applied this type of audit to the extracorporeal membrane oxygenation (ECMO) service at the Freeman Hospital. We report our methodology which can be used in a wide range of clinical services.

In 1996, the UK collaborative ECMO trial[2] reported that ECMO can improve the outcome of severe respiratory failure in neonates. As a result, the Department of Health, through the National Specialist Commissioning Advisory Group financed a national ECMO service that includes Freeman Hospital, the Glenfield Hospital, Leicester, and Great Ormond Street Hospital, London.

In the 5 months before the start of this service in April, 1997, four of five children died during ECMO, which prompted us to examine our procedures and case selection. We invited an external assessment of our unit by an experienced team from another centre, to identify any specific failings in our techniques, management, and decision making that had not been disclosed by our continuing internal audit. We asked an external neonatologist (JW) and ECMO team (DM and ES) to look at the case notes of our recent deaths. Our senior medical staff and nurses met with the assessors for a day during which the preceding years throughput was reviewed and the deaths discussed. Senior nurses had taken part in a written survey of nursing views on the way the programme was run (organised by ES), the findings of which were used to inform a separate discussion during the day. We used the report by the external assessors to improve our service. In the year since the audit, we have introduced more guidelines on the care of these infants, and an internal training course has been introduced, and our overall services have improved.

Mortality from ECMO is about 33%. To track our progress, we looked at our death as a proportion of our survivors by cumulative sum analysis, in which mortality is plotted against the number of patients in the order they were treated.* After 34 cases in each of the three centres, there were 12 deaths (95% CI 7–18) at the Freeman Hospital, eight deaths (3–14) at Great Ormond Street, and nine deaths (4–15) at Glenfield Hospital. Thus, the three centres perform similarly with the proviso that the time scales for recruitment of patients differ. We believe that these methods of peer review and analysis should be used more frequently and can provide some measure of quality assurance to both purchasers and the public. Perhaps if this approach had been adapted in Bristol, events would have been different.

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* Details of analysis available from the authors, on request.

1 Horton R Doctors, the General Medical Council, and Bristol. *Lancet* 1998; **351:** 1525–26.
2 UK Collaborative Trial Group. UK collaborative trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996; **348:** 75–82.

Sir—I have followed Sarah Ramsay's news reports[1,2] on the case of James Wisheart and Jaradan Dhasmana. I write as an ex-patient of Mr Wisheart. It is my firm belief that had it not been for the skill of Mr Wisheart I would not be here today. In the years leading up to 1990, I had serious angina and suffered several heart attacks. After careful examination I was told that several blood vessels surrounding my heart were badly blocked and that some of them were in extremely difficult places to by-pass. I believe that my chances of surviving the necessary operation were slim. In 1990, James Wisheart performed five by-passes in one operation. Undoubtedly his skill, competence, and professionalism saved my life and I remain eternally grateful to him.

I consider that James Wisheart has taken on the more serious and complex cases during his career—cases that other surgeons may not have undertaken. I am sad that such an eminent man should find himself in the public eye in such circumstances, and wish to make my personal view of his extreme competence known.

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1 Ramsay S. Evidence against "Bristol case" doctors found proven. *Lancet* 1998; **351:** 1707.
2 Ramsay S. UK "Bristol case" doctors found guilty of misconduct. *Lancet* 1998; **351:** 1935.

Sir—In the aftermath of the Bristol case, which you raise in your editorial,[1] commentary,[2,3] and news pages,[4,5] the Secretary of State for Health announced that the medical profession will have its performance monitored in the future to provide better information to patients.

Despite the fact that that idea is not new and already rigorous monitoring of the profession exists in many parts of the UK, this action involves a profession with the highest entrance requirements, the longest and most stringent training period, continuous training and examinations, and in which the individual carries a huge responsibility.

The past years have deprived the medical profession of an environment conducive to imparting the best medical care to the patients, as a result of ill conceived and badly implemented economic sanctions within the health-care sector. I propose that before performance monitoring is implemented, it might be a good idea to establish a uniform environment for practising medicine in a hospital, so that the current situation of ill-equiped and poorly staffed hospitals is not the setting in which physicians are assessed.

Economic restraints on resources have gradually eroded quality in medicine, forcing instead minimum patient-doctor interaction, increased workload, and unacceptable working conditions. If the basic factors that affected the care of patients—ie, the environment—were clearly defined and implemented for all grades of hospital staff involved in clinical care, one might then have an even playing field on which to assess the performance of thoses with whom the real responsibility for the patient lies.

Without such changes, we will continue to see the decline in the public's perception of health care and a marginalisation of an already frustrated medical profession.

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1 Editorial. First lessons from the "Bristol case". *Lancet* 1998; **351:** 1669.
2 Horton R. Doctors, the General Medical Council, and Bristol. *Lancet* 1998; **351:** 1525–26.
3 Horton R. How should doctors respond to the GMC's judgment on Bristol. *Lancet* 1998; **351:** 1900–01.
4 Ramsay S. Evidence against "Bristol case" doctors found guilty of misconduct. *Lancet* 1998; **351:** 1707.
5 Ramsay S. UK "Bristol case" doctors found guilty of misconduct. *Lancet* 1998; **351:** 1935.

Sir—I believe that important points are not addressed in Sarah Ramsay's news piece[1] and your editorial in the same issue.[2]

I had the responsibility of recommending disciplinary action against physicians when I was the head of a large tertiary-care cardiac centre in upstate New York for 7·5 years. I am well aware of the differences between operator skills and need for self audit. In our institution, we did almost 6000 invasive cardiac procedures and over 1400 cardiac surgical procedures a year. We did monthly audits on our complication rates. Our cardiac-surgery programme received the national 1998 Quality Cup Award. The New York State Health Department makes annual public disclosure of the mortality data of all cardiac-surgery programmes in the state and includes hospitals and individual operators by name. The publication includes observed mortality and expected risk-adjusted mortality.

In Ramsay's news piece[1] there is no mention of the risk-adjusted mortality on the procedures done by the surgeons involved. I should also point out that in cardiac surgery, the skill of the anaesthetist makes a huge difference. Our surgeons work with only those expert anaesthetists with a background in cardiac anaesthesia. Ramsay's news piece does not include the background and performance record of the anaesthetists who left the UK to find a position in Australia. Did he leave because his competence was being questioned? The GMC should review the performance of the anaesthetists who administered anaesthesia to cardiac patients at the Bristol Royal Infirmary to assess whether there are differences in the surgical mortality between different practitioners. The GMC should also look at the difference in the cardiac surgical mortality during the time when the anaesthetist worked at the Bristol Royal Infirmary and after he left.

Cardiac surgeons alone should not be made to bear the responsibility of the unfortunate excessive mortality at the Bristol Royal Infirmary during 1988–95. The case mix, severity of illness, and the anaesthetist's competence in cardiac anaesthesia should all be carefully analysed before making a final recommendation.

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1 Ramsay S. Evidence against"Bristol case" doctors found proven. *Lancet* 1998; **351:** 1707.
2 Editorial. First lessons from the "Bristol case". *Lancet* 1998; **351:** 1669.
3 Morrison J, et al. "Physicians disciplined by a state medical board". *JAMA* 1998; **297:** 1889–93.

Renal dysfunction accompanying oral creatine supplements

Sir—I have concerns about N R Pritchard and P A Kalra's (April 25, p 1252)[1] report. These workers conclude that they have "strong circumstantial evidence that creatine was responsible for the deterioration in renal function". They recorded in their patient a moderate decrease in renal function over time, which apparently coincided with a period of creatine supplementation, but he had recurring renal failure, which they largely ignore. Furthermore, to intimate that the decline in renal function was the direct result of creatine ingestion is exaggerated. Since they present no data for dietary creatine intake or urinary creatine output, and offer no rational explanation for their finding, how can they conclude that a direct cause and effect relation existed? The 2 g per day creatine maintenance dose ingested by the patient for 7 weeks before diagnosis probably contained only slightly more creatine than found in an average meat-eater's diet.

Pritchard and Kalra also choose to ignore published data showing that short-term oral creatine supplementation has no effect on renal function in healthy individuals.[2] Oral creatine supplementation would be expected to cause a rise, not a fall, in urinary creatinine output in healthy individuals. This increase correlates well with the increase in muscle creatine noted during supplementation and indicates an enhanced rate of muscle creatine degradation to creatinine.[3]

The regimen of ingesting 20 g of creatine per day for 5–6 days has shown no obvious health risks in healthy volunteers, provided that the creatine is dissolved before ingestion[2] (undissolved creatine may cause slight gastrointestinal discomfort). Longer high-dose creatine supplementation (20 g per day for 5 days followed by 10 g per day for 51 days) has no effect on serum markers of hepatic and renal function and routine clinical chemistry in healthy volunteers.[4] These data also invalidate Pritchard and Kalra's conclusion that tubular damage could have arisen "due to muscle pigment, or . . . increased creatine [presumably they meant creatinine] production".

Finally, the recent death of three American wrestlers has not been attributed to creatine supplementation as these workers imply. It is now accepted that the excessive weight loss procedures undertaken in an attempt to meet weight categories was responsible for the untimely deaths of these athletes.[5] Indeed, it seems that two of the athletes had never used creatine supplements.

Creatine supplements are now used worldwide by healthy individuals to attain maximum performance and training adaptations during intense exercise and by patients who have compromised muscle energy metabolism and function. Published work indicates that acute creatine ingestion is not a health risk. However, although there seems little cause for concern, it should be emphasised that no scientific data have yet been published that have specifically addressed the long-term health risks of chronic creatine ingestion. Clearly, this question needs to be investigated so that informed conclusions about its safety can be made.

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1 Pritchard NR, Kalra PA. Renal dysfunction accompanying oral creatine supplements. *Lancet* 1998; **351:** 1252–53.
2 Poortmans JR, Auquier H, Renaut V, Durussel A, Saugy M, Brisson GR. Effect of short-term creatine supplementation on renal responses in men. *Eur J Appl Physiol* 1997; **566:** 566–67.
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4 Earnest C, Almada A, Mitchell T. Influence of chronic creatine supplementation on hepatorenal function. *FASEB J* 1996; **10:** 4588.
5 Center for Disease Control and Prevention. Division of media relations, Atlanta: CDC, News, Feb 20, 1998.

Authors' reply

Sir—We did not overlook the patient's "recurring renal failure" because he simply did not have it. At no stage before the use of creatine did the patient have renal failure; as we stated, his creatinine clearance had been 91–141 mL/min which is normal. We are surprised that Greenhaff confuses frequently relapsing nephrotic syndrome and renal failure.

We maintain that strong circumstantial evidence exists linking creatine supplements to deterioration of renal function in our patient. Although we are aware that more information would probably be collected in a clinical trial than in this case, this is a problem often encountered in case reports which are, by their very nature, written after the clinical event. The absent information

outlined by Greenhaff does not alter the fundamental points of the case. We reiterate that the patient had previously normal renal function, then took creatine and was shown to have deterioration in renal function confirmed by isotopic glomerular filtration rate (GFR). On stopping the compound his renal function returned to baseline (normal). In the absence of alternative explanations, as in this case, one could be forgiven for suggesting a cause and effect relation.

The claim that we ignored published data showing the apparent safety of creatine supplements is inaccurate. We had actually stated that there had been no reports of severe side-effects with creatine used at these doses. However, it should also be acknowledged that the evidence relating to the long-term effects of creatine on renal function is far less conclusive than Greenhaff implies. For example, in Poortmans and colleagues' study creatine was only taken for 5 days, whereas in Earnest and co-workers' abstract, the markers used to assess renal function were only serum creatinine and blood urea/nitrogen. In a person with normal renal function, a change in these indices would only have been recorded if a reduction in GFR of at least 50% had occurred.

Even Greenhaff himself admits in his conclusion that "no scientific data have yet been published that have specifically addressed the long-term health risks". Indeed, as shown by our patient, the situation is even less clear outside the laboratory, where there is a distinct possibility that some individuals taking creatine supplements may not benefit from normal health, or may be taking excessive creatine doses or other drugs in combination. We do not claim to be experts in creatine metabolism, but we do not feel that any of the above considerations invalidate either our findings or the conclusions that we have drawn from them.

We think that the robust case made by Greenhaff for the safety of creatine supplements is not warranted on the basis of the evidence. In fact, the conclusion that he draws in his final paragraph more accurately reflects the real situation; we do not know.

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Sir—N R Pritchard and P A Kalra[1] report renal dysfunction with oral creatinine supplements. The widespread use of this diet product among sportsmen and women[2] means that this report will have an impact on the use of creatinine since the safety of this substance has been questioned. However, we have previously shown[3] that creatine supplementation has no adverse effect on kidney function at a dose of 20 g creatine monohydrate daily for 5 consecutive days.

20 men (21 [SE 1·7] years, weight 71·0 [7·9] kg) were given oral creatine supplements or maltodextrine (placebo) supplements. Each participant in the creatine group was told to take 21 g creatine monohydrate daily, distributed in 7 g doses in the early morning, at noon, and in the evening for 5 consecutive days. Then they took 3 g of individual dose daily for 58 additional days. The placebo-group participants followed the same protocol but took maltodextrine. We collected blood and 24 h urine samples before the supplementation (baseline), and at days 5, 20, 51 and 63. Creatinine, urea, and plasma albumin were assayed and their clearance assessed by conventional methods. Non-parametric methods were applied to test the statistical significance of the results.

Table 1 shows the results obtained throughout the study. There were no between-group differences at any time.

Our results show that oral creatine supplementation, has no adverse effects on the renal responses of healthy individuals. These findings do not accord with those of Pritchard and Kalra; their only participant had glomerulosclerosis for several years which may explain the further impairment in renal function in this specific case of creatine supplementation.

We believe that medium-term oral creatine supplements do not affect kidney function in healthy individuals. Physicians should however, measure, under resting condition, the albumin excretion rate, which should remain under 20 μg min^{-1}. This rapid and accurate method is not invasive or expensive and could be applied to estimate early renal dysfunction.[4]

We thank the Direction Générale des Sports (Communauté Française de Belgique) for their support and Flamma SpA (Italy) who provided the creatine monohydrate.

	Baseline	Day 5	Day 20	Day 41	Day 63
Creatinine clearance (mL min^{-1})					
Creatine group	130 (16	138 (25)	130 (8)	146 (16)	143 (9)
Placebo group	145 (8)	148 (11)	150 (18)	147 (12)	145 (16)
Urea clearance (mL min^{-1})					
Creatine group	57 (4)	50 (4)	56 (4)	61 (6)	49 (8)
Placebo group	59 (3)	52 (4)	51 (6)	58 (5)	64 (4)
Albumin excretion rate (μg min^{-1})					
Creatine group	5·8 (0·7)	6·9 (0·9)	9·3 (2·7)	5·7 (0·7)	9·0 (1·5)
Placebo group	8·2 (2·1)	5·9 (1·0)	6·9 (1·6)	6·0 (0·9)	5·1 (0·7)

Mean (SD) values.

Renal responses to oral creatiine supplements or placebo

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1 Pritchard NR, Kalra PA. Renal dysfunction accompanying oral creatine supplements. *Lancet* 1998; **351:** 1252–53.
2 Mujika I, Padilla S. Creatine supplementation as an ergogenic aid for sports performance in highly trained athletes: a critical review. *Int J Sports Med* 1997; **18:** 491–96.
3 Poortmans JR, Auquier H, Renaut V, et al. Effect of short-term creatine supplementation on renal responses in men. *Eur J Appl Physiol* 1997; **76:** 566–67.
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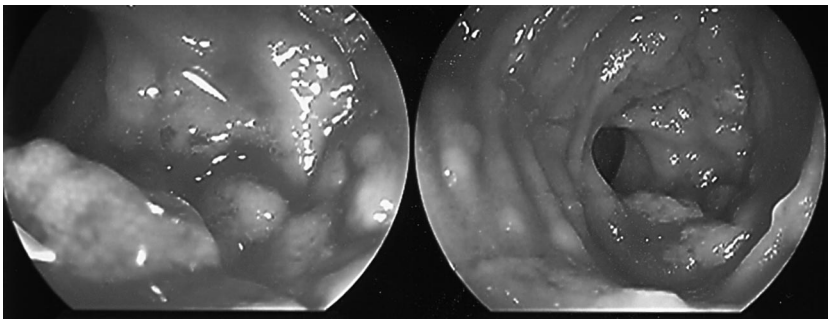
Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Sir—A J Wakefield and co-workers[1] have identified a new relation between gastrointestinal disease and developmental disorders in children; it opens a new avenue for the study of the gastrointestinal tract and other diseases that may be immunologically mediated. Their findings of ileal-lymphoid-nodular hyperplasia and non-specific colitis gastrointestinal manifestations in connection with autistic-spectrum disorders is the first description of this relation, with strong data suggesting the anatomical and histological alteration of the gut in such disorders. Although these workers suggest possible mechanism(s) of increased permeability for exogenous molecules they do not offer any explanation for these gastrointestinal alterations. The endoscopic and histopathological findings of ileal-lymphoid-nodular hyperplasia and non-specific colitis have so far escaped explanation and have evaded pathogenetic definition.

In support of the findings of Wakefield et al are several behavioural



Endoscopic view of terminal ileum in child with attention-deficit-hyperactive disorder

Greatly enlarged lymphoid nodules in both fields of view.

and clinical features known to be related to the central nervous system (CNS), such as migraine,[2] infantile colic,[3] abdominal epilepsy,[4] allergic-tension-fatigue syndrome, and attention-deficit-hyperactivity disorder,[5] which have been related to food allergy, although the precise relation is still unclear. IgE-mediated food allergy is plainly not the only mechanism of tissue injury, and these specific disorders could involve other mechanisms.

A major investigative effort of our laboratories has been directed to the study of food allergy and the immunological involvement of the gut as a central focus for injury of other target organs (skin, lungs, and gastrointestinal tract). We have noted a striking appearance of ileal-lymphoid-nodular hyperplasia in patients with non-IgE-mediated food allergy who present with asthma, atopic dermatitis, and attention-deficit-hyperactivity disorder. We have also studied two patients with this hyperactive disorder who were allergic to various foods, and our findings obtained by colonoscopy of their terminal ileum, shown in the figure, match with those reported by Wakefield and co-workers.

In our study, ileal-lymphoid-nodular hyperplasia is the hallmark lesion of the gastrointestinal tract, which allows entry of antigens across the inflamed mucosa of the bowel as a result of the reactive inflammatory response in the adjacent lymphoid tissue of Peyer's patches in patients with non-IgE-mediated food allergy. We propose that similar mechanism(s) may be involved in the pathogenesis of the CNS dysfunction in the patients described by Wakefield and co-workers.[1]

Although Wakefield's study, which suggests a connection between the CNS and the gut in patients previously immunised with measles, mumps, and rubella vaccine, did not prove an association, it has stimulated further discussion and opened unanticipated lines of investigation concerning the role of ileal-lymphoid-nodular hyperplasia as a predictive marker of gastrointestinal inflammation responsible for immunologically mediated tissue injury in other target organs sites.

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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 Egger G, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? *Lancet* 1983 ii: 865–69.
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Low-dose spiral computed tomography for lung-cancer screening

Sir—Shusuke Sone and colleagues (April 25, p 1242)[1] conclude that their study of mass screening for lung cancer, "clearly showed the superiority of low dose spiral CT [computed tomography] for detection of small peripheral lung cancers". This may be so but the results (and any future data from this study) tell us little about the effectiveness of low-dose CT as a screening procedure.

In evaluating screening tests, sensitivity and specificity need to be shown. In calculating these, we have assumed that all 223 patients undergoing further diagnostic work-up on the basis of the results of the low-dose CT had a positive test result. This includes patients with "non-cancerous but suspicious lesions", "lesions suspicious of lung cancer", and "indeterminate small nodules less than 3 cm". 19 had histologically and surgically confirmed lung cancer. This gives a provisional sensitivity of 95% (though this will fall as missed cancers become apparent between screening scans). The specificity is 95%. The positive predictive value is 8·5%, in this population. Thus, 204 of 223 patients underwent unnecessary, extensive, and often invasive investigation for lung cancer.

Until the false-negative rate and the outcome of treatment in screen-detected cancer are known, we can say little about the effectiveness of CT as a screening test. Sone et al propose comparing outcomes after 1 year, but this analysis is unlikely to advance knowledge greatly because the length of follow-up is so short and the allocation has not been random (the screened groups are volunteers). Only well designed, randomised, controlled trials can show whether low-dose CT is an effective screening procedure for lung cancer.

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1 Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with a mobile spiral computed tomograph scan. *Lancet* 1998; **351:** 1242–45.

Sir—Shusuke Sone and colleagues[1] report that spiral computed tomography (CT) was more accurate in mass screening for lung cancer, and led to early detection and an accurate diagnosis of lung cancer, and should be considered in the future health plans. They also claim that CT identified almost ten times as many cancers (0·48%) as standard mass screening (0·03–0·05%) in the same area. Clinically the positive predictive value (PPV) is more important than the cancer detection rate, and the PPV was only 8·5% (19 cancer cases from 223 with suspicious lesions, indeterminate nodules, and suspicion of lung cancer). 91·5% of patients referred for work-up by chest radiography and high resolution CT (some with trans-bronchial biopsy), proved not to have the disorder. A previous study, with chest radiography and sputum cytology found a greater PPV (19%)[2] and fewer false positives than Sone et al did.

Randomised trials at a population level and looking at survival or quality of life should be done before spiral CT screening is introduced. Widespread

implementation of unproven screening methods makes subsequent rigorous evaluation much more difficult—indeed, it may be impossible to correct the original mistake.

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1 Sone S, Takashima S, Feng L, et al. Mass screening for lung cancer with mobile computed tomography scanner. *Lancet* 1998; **351:** 1242–45.
2 Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection. *Am Rev Respir Dis* 1984; **130:** 561–65.

Sir—Shusuke Sone and colleagues[1] attribute to the small sample size of smokers the fact that 0·52% of smokers versus 0·48% of non-smokers had cancers detected by spiral CT scanner. We calculate that this study had at least 95% power to detect even a 5-fold increased risk among smokers; since the risk among smokers is expected to be in the range 10–20-fold, this study should have certainly detected the difference, assuming there is no selection bias and that non-smokers are neither ex-smokers nor heavy passive smokers. The discrepancy between the similar frequency among smokers and non-smokers in this study and the fact that 95% of lung cancers normally diagnosed are in smokers, suggests that these subclinical cancers are not clinically relevant. Even the fact that only two of the 19 cancers found were squamous-cell cannot explain this equivalence of risk.

The incidence reported for non-smokers is too high. Let us conservatively assume that the findings of one in every 200 of non-smokers having a lung cancer is a 2-year incidence. The life-time (40 year) risk, would be 1 death from lung cancer in every 20 non-smokers; in the UK one in every 200 non-smokers dies from lung cancer.[2] This further suggests that most cancers detected by spiral CT are not clinically relevant.

The finding is very interesting, however, biologically. Perhaps lung cancer (especially adenocarcinoma) is similar to breast and prostate cancer—ie, normal lung harbours multiple subclinical cancers, many of which will never surface in life. This might mean that the critical inhibition of angiogenesis goes on continuously in all of us and is more important in homoeostasis than previously supposed.[3]

**Jayant S Vaidya, Michael Baum*

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2 Wald NJ, Hackshaw A. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; **52:** 3–11.
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Author's reply

Sir—Sarah Conolly and her colleagues and Yasuharu Tokuda argue that our study of spiral CT reveals little about the method's effectiveness as a screening procedure. It is argued that the follow-up is too short and the lack of randomisation is noted. We are conducting this Nagano project on lung-cancer screening with a mobile spiral CT scanner in a 5-year programme to investigate the medical applications of satellite communications, from 1995 to 1999, and we cannot, unfortunately, extend the follow-up. Although the follow-up will be too short to reveal the outcome for patients treated in the project we will be able to establish the radiological diagnoses for almost all those receiving CT screening.

To improve outcome in lung cancer we must detect and treat it much earlier—eg, Sagawa et al[1] reported 5-year-survival rate of 83% for patients with lung cancer measuring 2 cm or less and no lymph-node metastasis. Because most of the cancers found by CT alone were smaller than 2 cm with no lymph-node metastasis, yet showed no evidence in the chest radiograph, we would expect a better outcome than for those found in the chest radiograph.

We are now accumulating data on sensitivity and specificity; however, there is a question about how to define the presence of lung cancer before interpretations can be classed as false negative or false positive. There seems to be no consensus, from a clinical standpoint, about size of tumour;[1] 3 mm or 5 mm may be the clinically significant threshold because lung cancers less than 3 mm are very difficult to detect even on conventional CT and nodules less than 5 mm are difficult to establish radiographically or by biopsy-based histology. 5 mm seems an appropriate threshold and we allocated a case to false negative when a tumour of 5 mm or more was missed in the CT image—but other professionals may hold different opinions. We cannot pursue high specificity when interpreting screening CT images because that will increase missed cancers. We must maintain a high sensitivity while at the same time avoiding cursory interpretation of screening CT images, to keep the numbers needing further work-up exams within a reasonable range.

The X-ray dose used in the CT screening is relevant here. The low exposure dose means that the image quality reveals lung nodules but is inadequate for a precise differential diagnosis. We prefer a low dose in screening symptomless individuals, reserving higher-dose diagnostic examinations for those with suspicious or indeterminate nodules. In other words, the role of CT screening is to check the presence or absence of a lung nodule not to test for lung cancer. Therefore we do not feel it appropriate to talk of specificity for CT screening in detecting lung cancers (rather than lung nodules). By the way, our diagnostic work-up is not as expensive or invasive as your correspondents imply. We do further CT scans without contrast and rarely recommend bronchoscopy. Nor were all the work-ups on non-cancer patients unnecessary; some patients had non-cancer lung lesions that demanded medical consultation or treatment.

Jayant Vaidya and Michael Baum argue that the incidence of lung cancer (mainly adenocarcinoma) among non-smokers was too high and they suspect that most cancers detected by spiral CT are not clinically relevant. I agree that more needs to be known about the growth characteristics of this type of cancer if we are to manage patients on a sound scientific basis. In the meantime, however, we should look for early (preclinical) cancer and treat it;[2] most patients with lung cancer die because of delay in diagnosis, and we do not yet know how to discriminate the preclinical but life-threatening cancer from indolent one. The prevalence rate of CT-screening-detected cancer was nearly 5 per 1000 screened (males 10 cases in 2115 screenees, females, 11 in 1852). The age and sex-adjusted expected cancer incidence in the screened population was 4·57 (male 3·85, female 0·72) for 3967 screenees based on the data in the Cancer Registry of Japan. This means that we have detected nearly 4·6 times as many cancer patients as expected (2·6 times in males, 15·7 in females). I suspect that our high detection rate was due to the inclusion of lung cancers missed by the general health survey of the previous year, and adenocarcinoma of the lung in the female may lie undetected by conventional chest radiography for over 15 years on average.

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1 Sagawa M, Saito Y, Takahashi S, et al. Clinical and prognostic assessment of patients with resected small peripheral lung cancer lesions. *Cancer* 1990; **66:** 2653–57.
2 Noguchi M, Morikawa A, Kawasakii M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995; **75:** 2844–52.

Angina pectoris caused by microvascular spasm

Sir—Masahiro Mohri and colleagues' (April 18, p 1165)[1] suggestion that angina pectoris may be caused by coronary microvascular spasm deserves some comment. We believe that the proposal of microvascular coronary spasm as a clinically relevant pathogenetic mechanism of angina should be accompanied not only by more stringent diagnostic criteria, but also by a more careful clinical and electrocardiographic (ECG) characterisation of affected patients.[2]

In Mohri's report, patients without evidence of occlusive or subocclusive epicardial artery spasm were grouped according to the presence or absence of anginal pain and ECG changes during intracoronary acetylcholine infusion: one group of 29 patients with microvascular spasm and another of 25 patients with atypical chest pain. Such distinction, made a posteriori on the basis of test results, is incorrect. Anginal pain should be classified as typical or atypical on the basis of clinical features, independently of ECG, angiographic, and coronary sinus findings.

The possibility that myocardial ischaemia can be caused by microvascular coronary constriction is not at issue; previous studies showed that intense microvascular constriction can cause massive ischaemia after neuropeptide γ infusion in human beings[3] and after endothelin infusion in dogs.[4]

A key question in the interpretation of Mohri's results is the normal range of the response of coronary arteries to increasing doses of intracoronary acetylcholine. In Mohri and co-workers' study, the angiographic response to acetylcholine in the 29 patients with microvascular spasm was similar to that of the 25 patients with atypical chest pain, although lactate production was detected in the coronary sinus of nine of 11 patients in the first group, but in none of the ten patients in the second group. In a previous study in a series of patients with normal coronary arteries and atypical chest pain, we observed that low doses of acetylcholine caused coronary dilation, whereas higher doses caused constriction of the same segments, and a further increase of the dose caused diffuse microvascular constriction with severe ischaemia, chest pain, ST segment changes, and impairment of left-ventricular function.[5] Therefore, the distinction between patients with microvascular spasm and those with atypical chest pain proposed by Mohri may be arbitrary, and their results may be simply related to differences in the individual coronary smooth muscle dose-response to intracoronary acetylcholine and, possibly, in pain sensitivity among patients.[2]

There is limited information in their study about the relation between the features of chest pain and ECG changes observed during acetylcholine infusion and those developed by patients during their daily life, which makes it difficult to understand the actual clinical relevance of their observations. Thus, although the evidence for the occurrence of microvascular constriction as a cause of myocardial ischaemia seems fairly established, its prevalence and clinical correlates remain elusive.

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1 Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998; **351:** 1165–69.
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Author's reply

Sir—As Attilio Maseri and Gaetano Lanza state, we grouped our patients on the basis of the results of acetylcholine testing a posteriori. However, two points should be noted. First, our aim was to find evidence for a possible contribution of coronary microvascular spasm to the pathogenesis of angina. Thus, there were two subgroups: patients with and those without chest pain and ECG changes during acetylcholine testing.

Our results suggest that the patients who developed chest pain and ECG changes had myocardial ischaemia as evidenced by production of myocardial lactate, whereas patients without chest pain or ECG changes had no myocardial ischaemia. These results indicate that microvascular spasm may be the cause of angina in a subgroup of patients with microvascular angina.

Atypical chest pain was a diagnosis given to a group of 25 patients who had no coronary artery disease, no epicardial spasm, no chest pain or no ECG changes during acetylcholine infusion. The type of chest pain in patients with microvascular angina (including those caused by microvascular spasm) is generally atypical compared with effort angina.[1]

We found that the clinical features of angina and ECG changes in patients with microvascular spasm did not differ greatly from those in patients with spasm of epicardial coronary arteries, so that the diagnosis requires coronary angiography to exclude epicardial coronary artery spasm.

We disagree with Maseri and Lanza's comments on the clinical relevance of our findings. As described in our report, in 25 of 29 patients acetycholine induced chest symptoms that were similar to the patients' previous ones. Furthermore, in seven of nine patients it reproduced ischaemic ECG changes that had been documented during spontaneous attacks.

It should be noted that 100 μg acetylcholine is about 10^{-4} mol/L if left-coronary blood flow is assumed to be 150 mL/min. This dose is 10–100 times lower than that adopted in the Newman study.[2] Acetylcholine infusion at 100 μg is widely used to induce epicardial coronary spasm. The sensitivity and the specificity of this test in diagnosis of epicardial spasm are greater than 90%. We do not know how specific this testing is in diagnosing microvascular spasm, but some of our patients with microvascular angina developed myocardial ischaemia at the lower dose of 5–30 μg, or even spontaneously without acetylcholine. Such high sensitivity for coronary small vessels to constrict to a small dose of acetylcholine may be termed as spasm and the cause of microvascular angina, as we already discussed in our report.

We believe that our study offers evidence that coronary microvascular spasm does cause myocardial ischaemia and is clinically relevant to patients' symptoms in a subgroup of patients with chest pain and normal

coronary arteriograms. The prevalence of coronary microvascular spasm is not known, as Maseri and Lanza correctly point out.

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1 Kaski JC, Rosano GMC, Nuhoyannopoulos P, Collins P, Maseri A, Pool-Wilson P. Cardiac syndrome X: clinical characteristics and left ventricular function: a long-term follow-up study. *J Am Coll Cardiol* 1995; **25:** 807–14.

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HSV-1 and risk of Alzheimer's disease

Sir—We were surprised that Beffert and colleagues (May 2, p 1330)[1] conclude that their results contrast with ours.[2] In fact the values in their table show exactly the same trend as ours did: a higher apoE-ϵ4 allele frequency for the herpes simplex virus 1 (HSV-1)-positive patients with Alzheimer's disease (AD) than for those who were HSV-1-negative, or the HSV-1-positive or HSV-1 negative non-Alzheimer's although their data, unlike ours do not reach statistical significance. Possibly the non-significance relates to their low number of controls and, as they suggest, to the difference in prevalence of apoE ϵ4 between the two AD populations. (We have recently examined brain specimens from further AD patients and age-matched HSV-1 negative, non-Alzheimer controls, and have obtained apoE-ϵ4 allele frequencies for all groups that are wholly consistent with our earlier values.[3]) Equally surprisingly, Beffert and colleagues make two more deductions that are prefaced by "in contrast to the results of Itzhaki et al". These statements seem to be based on a misreading of our report since their deductions are exactly those that we make in our results and discussion sections, respectively: that HSV-1 alone is not an independent risk factor for AD and that other apoE-ϵ4 allele carriers are not more susceptible to HSV-1 infection than non-carriers.

Thus Beffert and colleagues' data and deductions add useful support to our findings and conclusions, just as their previous findings (of which we were unaware), in which they detected HSV-1 in a high proportion of elderly normal and AD brains,[4] broadly substantiated our earlier study on that topic.[5] We fully agree with their comment about the need for investigation of larger numbers, although we emphasise that the search for virus at low levels by PCR requires great care and numerous checks for the absence of artifacts[2,3,5]

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1 Beffert U, Bertrand P, Champagne D, et al. HSV-1 in brain and risk of Alzheimer's disease. *Lancet* 1998; **351:** 1330–31.

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Authors' reply

Sir—Although a trend may be indicated by our initial data linking the combination of HSV-1 and the ϵ4 allele of apolipoprotein E (apoE) to Alzheimer's disease (AD), we concluded that by contrast with Itzhaki and colleagues[1] synergism between both markers was not indicated. Because of the low numbers of controls in our study, we may not have had sufficient statistical power to reject the null hypothesis of Itzhaki and colleagues. To be able to make a further contribution to the question of synergy, we pooled our data with those of Itabashi and co-workers.[2] Despite ethnic differences between the populations it was reasonable to pool the two studies since statistical analysis showed no significant differences between the marker distribution within cases and controls.

We recalculated odds ratios (OR) for the event of having either the ϵ4 allele of apoE or HSV-1, or both, compared with having neither marker (table) and compared the results with those of Itzhaki et al.[1] From these results we can conclude that: (1) HSV-1 infection alone is not a risk factor for AD (OR=0·8, NS); (2) the ϵ4 allele of apoE is a risk factor for AD (OR 6·1; 95% CI 1·6–23); and (3) in combination, apoE ϵ4 and HSV-1 confer no greater risk for AD than apoE ϵ4 alone (6·2; 2·3–17). Itzhaki and colleagues, however, showed a low OR for apoE ϵ4 (1·8) and a very high OR for the combination of apoE ϵ4 and HSV-1 (25). Their results yield a synergy factor of 31 compared with 1·3 from our pooled data.

The reasons for such discrepancies between the two studies are beyond our understanding, but an important point to consider when doing population studies with very small sample sizes is errors due to potential sampling bias. For example, it is now well established that the apoE-ϵ4 allele frequency is increased 2–3-fold within a large AD sample compared with a large control sample. In their study, Itzhaki and co-workers found a 10-fold difference (0·045 *vs* 0·43) of the apoE-ϵ4 allele frequency between their cases and controls, probably because of an unknown sampling bias. Therefore, results from studies with low case numbers might not be reproducible by others but represent important findings for further analysis. Furthermore, we are undertaking a more detailed analysis of these same patients with respect to brain region to establish whether a particular area may be more susceptible to HSV-1 in AD patients with the apoE-ϵ4 genotype.[3]

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ApoE ϵ4/HSV-1	Controls	Alzheimer's disease	Odds ratio	95% CI
−ve/−ve	24 (14)	29 (8)	Reference	. .
−ve/+ve	23 (26)	23 (7)	0·8 (0·5)	ns (ns)
+ve/−ve	3 (2)	22 (2)	6·1* (1·8)	1·6–23 (1·4–2·1)
+ve/+ve	6 (2)	45 (29)	6·2† (25)	2·3–17 (5·5–116)

*p<0·01, †p<0·001 (χ^2 Yates' corrected), NS=not signfiicant. Numbers in parentheses=Itzakhi's results.

Odds ratios for controls and Alzheimer's disease according to HSV-1 status

Hyperthyroidism-associated chorea

Sir—The case report by Tadasu Nakaoka and colleagues (May 2, p 1326)[1] emphasises the possible relation between Graves' disease and chorea, suggesting a pathogenetic role for thyrotoxicosis. We report another unusual cause of chorea—antiphospholipid-antibodies-related chorea.

Beside Sydenham and Huntington's diseases, chorea may occur in the course of systemic lupus erythematosus (SLE),[2] and the disorder has been strongly associated in this setting with the presence of antiphospholipid antibodies.[2] The mechanism of SLE-related chorea is not clear, though it might involve a direct, non-vascular mediated, interaction of antiphospholipid antibodies with brain cells.[2] Cervera and colleagues extensive review[2] in 50 patients with chorea and antiphospholipid syndrome showed that its spectrum extended beyond definite SLE (58% of cases) to primary antiphospholipid syndrome devoid of any SLE feature (30% of cases). The incidence of autoimmune hyperthyroidism is increased in both disorders.[3,4] Thus, besides the well known induction of movement disorders by hyperthyroidism,[1] a previously unrecognised pathogenetic role for antiphospholipid antibodies is a possibility in at least some patients with hyperthyroidism-related chorea.

The usual improvement of chorea during treatment of hyperthyroidism does not strongly refute our hypothesis, given that antiphospholipid-antibody-related chorea is self-limited, and resolves within several weeks or months under various regimens.[2] Among published cases of hyperthyroidism-associated chorea, only one woman was found to have associated features consistent with a possible antiphospholipid syndrome—eg, cerebral infarct and seizures.[5] Most of these cases were, however, reported in the 1970s and 1980s so did not include measurement of antiphospholipid antibodies, and few provided long-term data.

We postulate that: young women who present with Graves' disease and chorea should be tested for antinuclear anti-dsDNA antibodies and also for antiphospholipid antibodies; factors associated with antiphospholipid-antibody-related chorea, such as recent onset of oestrogen-containing pill or pregnancy,[2] should be systematically looked for; and that in patients positive for antiphospholipid antibodies, long-term follow-up is mandatory.

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1 Nagaoka T, Matsushita S, Nagai Y, Kobayashi I. A woman who trembled, then had chorea. *Lancet* 1998; **351:** 1326.
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5 Fischbeck KH, Layzer RB. Paroxysmal choreoathetosis associated with thyrotoxicosis. *Ann Neurol* 1979; **6:** 453–54.

Sir—Tadasu Nagaoka and co-workers[1] present an interesting case of the left-sided hemichorea due to thyrotoxicosis caused by chronic thyroiditis. They report the disappearance of the chorea when thyroid function returned to normal and postulate that thyrotoxicosis caused specific effects on the neutotransmitter system in the brain and altered dopamine metabolism in corpus striatum, eventually inducing chorea. Although we agree with the researchers that some kind of dysfunction must have existed in the corpus striatum, we believe that it was important that the chorea was unilateral compared with a previous thyrotoxic bilateral tremor in this patient.

Most cases of chorea are bilateral, and only a few are unilateral.[2] Although little is known about the pathophysiology of thyrotoxic chorea, its features seem to be indistinguishable from those of Sydenham's chorea.[3] Although pathological changes in Sydenham's chorea are also still obscure, an examination of the brain during acute illness has shown non-specific neuronal swelling and degeneration, arteritis, and petechial haemorrhages in the region including the striatum.[4] Exact localisation responsible for chorea has not been confirmed, although it is probably the basal ganglia, cerebral cortex, or both. Some reports suggest that hemichorea is caused by some asymmetric focal lesion in these parts of the brain.[5] Because of the apparent focalisation in the patient in Nagaoka's report, perhaps some kind of, although minimum underlying organic change may have existed in the asymmetric focal portion that would predispose the portion to induce thyrotoxic hemichorea.

Although Nagaoka and colleagues mention that magnetic-resonance imaging of the brain showed no abnormalities, a more precise technique, such as perfusion-weighted, diffusion-weighted, or FLAIR imaging, or gadolinium enhancement, as well as T1-weighted, T2-weighted, or proton-density-weighted imaging, might have revealed an organic lesion, especially when the chorea persisted.

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LRP gene and late-onset Alzheimer's disease

Sir—Jean-Charles Lambert and colleagues (June 13, p 1787)[1] report an association of the C/T polymorphism in exon 3 of the low-density lipoprotein receptor-related protein (LRP) in Alzheimer's disease. Such a study is warranted in Alzheimer's disease, given the well-established role of apolipoprotein E (Apo E) in the biology of dementia and the status of LRP as the main receptor for both Apo E and for the amyloid precursor protein in the brain. We genotyped a series of clinically and neuropathologically verified cases of sporadic late-onset Alzheimer's disease and age-matched controls for the LRP C polymorphism and but were unable to confirm this association.

We used standard and neuropathological criteria for the diagnosis of Alzheimer's disease. There were 133 cases (onset at older than 65 years of age, age range at death 67–98 years, mean age 82 [SD 6·2] years) and 70 controls (age range at death 68–104; mean age 81·8 [6·9] years). Genomic DNA was isolated from frozen brain tissue obtained at necropsy. LRP genotyping was done with the primers of Kang and colleagues[2] (LRP forward: 5'TGCCCTCAGGTCCACAGA3'; LRP reverse: 5'AAGTCCTTACCT TACCTCGGCAG3'). We used the following 20 μL reaction mix: 50 pmol forward and reverse primers, 1 U *Taq* polymerase (Pharmacia, UK), 1×manufacturer's buffer, 200 μmol each deoxynucleotide, and 100 ng of DNA. Samples were amplified at 94°C for 1 min 30 s followed by 35 cycles of annealing at 60°C for 30 s, extension at 72°C for 60 s, and denaturation at 94°C for 30 s. Samples were incubated at 37°C with 8 U of *Fok* I endonuclease (New England Bio-Labs, UK) in the manufacturer's buffer. After digestion, the PCR products were electrophoresed through a composite 3% Nu Sieve/1% standard agarose (Flowgen, UK) gel, and the bands made visible by ethidium bromide fluorescence. Digestion of the PCR product (157 bp) with *Fok* I results in the production of two bands if the rare T allele is present. Assessment of the APOE genotype was done by previously described methods.[3] We compared the frequency of the C variant and C variant homozygosity in cases and controls by χ^2 test.

There was no increase in the LRP C allele frequency in the cases compared with controls (frequency 0·84 *vs* 0·85, p=0·69). We found no change in the allele frequency for LRP C after stratification for the effect of the APOE-ε4 allele (data not shown).

Our findings do not support those of Lambert and colleagues of an association of the LRP C allele with Alzheimer's disease. Our data are, however, consistent with those of Clatworthy and colleagues[4] who reported no association between late-onset Alzheimer's disease and a repeat polymorphism in LRP. No polymorphisms in LRP have been identified so far that alter the coding sequence of the protein.[2] Since the LRP exon 3 polymorphism is silent and does not produce an aminoacid change in the protein or alter a splice/acceptor junction, it is possible that this polymorphism is not functionally related to Alzheimer's, but that an Alzheimer's disease locus is nearby. A locus about 10 cM away has been associated with late-onset Alzheimer's disease.[5] In our population, the LRP polymorphism may be in equilibrium with a chromosome 12 AD locus, whereas in the population described by Lambert the LRP C allele is in linkage disequilibrium. Polymorphisms other than the LRP exon might account for the chromosome 12/AD association.

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1 Lambert JC, Wavrant-De Vrieze F, Amouyel P, Chartier Harlin M-C. Association at LRP locus with sporadic late-onset Alzheimer's disease. *Lancet* 1998; **351:** 1787–88.
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Pulmonary hypertension in type 1 Gaucher's disease

Sir—Deborah Elstein and co-workers (May 23, p 1544)[1] report a 7% (9 of 134) rate of pulmonary hypertension among type 1 Gaucher's disease, and raise the issue of whether enzyme-replacement therapy (ERT) can induce or worsen this disorder. Some case reports suggested such a causal relation, in the frequent absence of baseline pulmonary pressures before ERT.[2–4] Elstein and colleagues, however, show a moderate increase in doppler-detected pulmonary pressures in one patient treated with alglucerase, confirmed after reintroduction of imiglucerase.

We report a 68-year-old woman with Gaucher's disease who developed important pulmonary hypertension during ERT. Type 1 Gaucher's disease was diagnosed at age 4 years and she had splenectomy at age 12. She remained symptom-free for Gaucher disease until 1992; at that time, she had severe asthenia, bone pain, and hepatomegaly. Alglucerase was started in October, 1994, 80 IU/kg twice a month, which led to a substantial decrease in bone pain and reduction of hepatomegaly. In April, 1996, a transthoracic echocardiogram showed trivial mitral regurgitation and normal systolic pulmonary pressure (28 mm Hg). In November, 1996, imiglucerase 45 IU/kg twice monthly was introduced. From May, 1997, she developed progressive dyspnoea and had shortness of breath during usual exercise. Chest radiography, computed-tomography scan, and pulmonary scintigrams were normal. Doppler echocardiography showed preserved left-ventricular function and estimated systolic pulmonary pressure of 54 mm Hg. Right heart catheterisation confirmed increased pulmonary pressures (67/28, 40 mm Hg) with normal pulmonary-capillary-wedge pressure (13 mm Hg) and cardiac output (3·2 L min^{-1} m^{-2}). ERT was discontinued. 1 year later, the outcome was uneventful.

Pathophysiological mechanisms involved in the development of precapillary pulmonary hypertension include perivascular infiltration by Gaucher's cells with vascular obliteration and plugging of the capillaries with Gaucher cells.[3,5] Whether pulmonary hypertension can be reversed, stabilised, or worsened by ERT is not clear.[1–4] Decrease in ERT dose, as in our case, and switch from alglucerase to imiglucrase, should also be taken into account.

We do agree with Elstein's recommendation of routine doppler-echocardiography in all patients with Gaucher's disease as part of the initial examination, repeated after 6 months of ERT, and then once a year, especally in patients at high risk of developing pulmonary hypertension.

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HIV-1 in injecting-drug users and heterosexuals

Sir—Of the 126 countries worldwide with injecting-drug users, 98 report HIV-1 among the population of injecting-drug users. Since the publication of C Y Ou and colleagues' 1993 report,[1] a general assumption is that HIV-1 epidemic among injecting-drug users was caused by infection with subtype B. Their finding of a preponderance of subtype B among the injectors and subtype E among the female sex workers led many health professionals to believe that the epidemics of HIV-1 among injecting-drug users and heterosexuals were independent. The finding that subtype B HIV-1 did not readily infect Langhans cells supported the hypothesis that the epidemic in injecting-drug users was not likely to spread easily to the heterosexual population.[2]

There are two concerns about this assumption; first, heterosexual transmission of subtype B does occur;[3] and second, most injecting-drug users in Thailand, Vietnam, China, and Manipur (India) are no longer infected with subtype B. The only subtype reported in injecting-drug users in Vietnam is subtype E, and an increasingly high proportion of injecting drug users in Thailand are now infected with subtype E rather than subtype B.[4,5] In Manipur, we found that most injecting-drug users were infected with subtype C, and reports suggest that this subtype C is also common among injectors in Yunnan. Both subtypes C and E are readily transmitted by heterosexual contact, so an epidemic in injecting-drug users does pose a threat to the mainstream population, most of whom are heterosexual. Intensive intervention strategies to stop the HIV-1 epidemic should start as soon as HIV-1 infection is first identified among injecting-drug users in a country.

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Argyria after short-contact acupuncture

Sir—K Hanada and colleagues (March 28, p 960)[1] describe systemic argyria in a man after the long-term use of silver-coated sugar particles to stop smoking. Recently we have observed localised argyria after acupuncture with silver needles. Localised argyria due to acupuncture has been reported in Japan,[2,3] but no such cases have been published from other parts of the world.

A 39-year-old woman presented with one well circumscribed, blue-black macule in the skin of her left ear. The macule was 2 mm in diameter, had a smooth unaltered surface, and was situated at the site where the crura anthelices unite to form the anthelix. A dermatologist suggested the diagnosis of a blue nevus and excised the lesion by punch biopsy to rule out melanoma.

Conventional histological examination of the biopsy specimen revealed a dense, brown-black fusiform particle, about 75 μm in length, in the connective tissue near the outer surface of the auricular cartilage. This particle was encapsuled by dense collagen fibres. In the surrounding dermis, numerous brown-black granules, mainly situated around blood vessels, nerve fibres, and sebaceous glands, were found. Polarised light revealed these granules to be refractile.

The chemical nature of the granules was analysed by a laser microprobe mass analyser which excites microvolumes of a sample to an ionised state by a focused laser beam; the ions produced are detected by a time-to-flight mass spectrometer. In an unstained paraffin section, a representative area, showing brown-black granules in the haematoxylin-eosin stain, was brought into focus of the laser beam and irradiated, and revealed that silver was present in the tissue section.

Previous reports from Japan describe localised argyria which developed 1–14 years after silver acupuncture needles had been implanted. In all these cases, the needles had been left in continuous contact with the tissues until localised argyria was noted. 20 years ago, our patient had undergone five sessions of short-contact acupuncture in her ears because of lumbalgia. 10 years later, she noticed the blue-black macule in her left ear. Her acupuncture sessions had lasted not longer than 30 min each. Thus, the needles had been in contact with the tissue for not longer than 3 h, which would certainly be too short a time to induce localised argyria by the acupuncture needles themselves. However, the blue-black macule was located at exactly the site of acupuncture, and the patient did not wear silver jewellery at that site.

We believe that during the short sessions of ear acupuncture, a small particle of a silver needle might accidently have been deposited. This small silver particle then, over the years, could have led to the development of localised cutaneous argyria presenting as a blue-black macule in the skin of the left ear of the patient. With the increasing popularity of acupuncture, this disorder might be observed more often.

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Reappraisal of Malthus

Sir—The 200th anniversary of *An Essay on the Principle of Population, as it affects the Future Improvement of Society* seems to have provoked a reappraisal of Thomas Malthus, including R V Short's June 6 commentary,[1] without shedding much light on the historical implications of his particular contribution to political economy. A recent review in the *Archives of Disease in Childhood*, for example, portrays him as the avuncular founder of modern family planning, despite his strongly stated objections to contraception. Malthus was only one of many clerics who were preoccupied with the population question. For Karl Marx, his distinction lay simply in that as a Fellow of Cambridge he was required to take a vow of celibacy, unlike the other clergy "who have . . . taken 'Be fruitful and multiply' as their special Biblical mission . . . that they contribute to the increase of population

to a really unbecoming extent, whilst they preach at the same time to the labourers the 'principle of population'".[2]

As for bringing Darwin inspiration, Malthus did not suppose that the struggle for existence within a population would ever lead to improvement. In this sense, Darwin's principle of the survival of the fittest is clearly anti-Malthusian, even if its conception did require the theoretical detour via Malthus. Engel's stated view was that: "The whole Darwinian theory of the struggle for existence is simply the transference from society to organic nature of Hobbes' theory of *bellum omnium contra omnes* [a war of all against all] and the bourgeois economic theory of competition, as well as the Malthusian theory of population".[3] Once this feat had been accomplished, it was easy to transfer the theories back again from natural history to the history of society and maintain that these assertions had been proved as eternal natural laws of society.

With the constant threat of revolution and repeated rounds of violence and repression in England from 1789 to the European uprisings of 1848, it is no wonder that Malthusian doctrine was promoted by the ruling elite as a necessary antidote to such dangerous eighteenth-century ideologists as Condorcet who argued that man had the potential for continuous improvement.

The 1834 New Poor Law Act shows how the population question influenced government in ways of real consequence to the poorer strata of society. This legislation did away with outdoor relief for the destitute, who were forced to compete in the labour market or face the workhouse. William Cobbett denounced the Act as a "Malthusian bill designed to force the poor to emigrate, to work for lower wages, to live on a coarser sort of food". Thomas Wakley presented petitions from general practitioners to the House of Commons, pointing out the "ruinous and cruel consequences to the poor who are farmed out to the lowest bidder".[4] When first introducing the Bill to the House of Lords, the Lord Chancellor "condemned, in terms of unreserved severity, hospitals for foundlings, hospitals for ordinary diseases, hospitals for infants, and almshouses for succouring the aged and decrepit".[5] *The Lancet* at that time was less sanguine about Malthusian solutions to the population question and allied itself with the many who envisaged society progressing through cooperation, education, emancipation, technological advance, and democratic participation. The huge rise in world population, rather than proving Malthus' writings to be prophetic, have shown their fallibility.

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Sir—Perhaps the time has come to recognise Malthus as a false prophet, and to honour his long-neglected predecessor Condorcet. Malthus' fame has come to rest on ideas that were not his own, as he himself admitted.[1] However, it was not for these ideas that he was vilified for the rest of his life and beyond, but for his solution, which R V Short curiously omits in his commentary,[2] perhaps because it would sit uncomfortably in the editorial pages of *The Lancet*.

In his depiction of mankind's potential, Condorcet believed that population might exceed the means of subsistence.[3] However, he foresaw that this threat could be prevented by universal education, sexual equality, and the progress of reason and science, which would enable the birth rate to fall. Malthus's essay was written as a reaction to Condorcet's visionary manifesto. Ridiculing his (dead) opponent from behind a cloak of anonymity, Malthus proposed that the only way to limit population growth was to abolish the poor laws, which encouraged the lower classes to breed irresponsiblity.[4] (He recommended deferred marriage only after the storm of criticism.) Such controversy, perhaps coupled with the accessibility of language, ensured that it was he and not his French source who came to the attention of Darwin, Wallace, Marx and others in nineteenth-century England.

Malthus's observations on the principle of population were second-hand, and few today would openly repeat his original contribution, his ideas for population control. By contrast, Condorcet predicted the conditions that would lead to demographic transition and a fall in birth rates to offer some hope for our survival. His view is much more of our time; surely Condorcet is the prophet who should be honoured at last.

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DEPARTMENT OF ERROR

Low plasma concentrations of interleukin 10 in severe malarial anaemia compared with cerebral and uncomplicated malaria—Tables 2 and 3 were omitted from this article by Jørgen AL Kurtzhals and colleagues (June 13, p 1768). The tables follow:

Cause of exclusion	Number of patients excluded
Haemoglobin 50–59 g/L or 91–110 g/L	217
Convulsions in patients without cerebral malaria	199
Temperature <37·5ºC	156
Positive sickling test	71
Parasitaemia <1 parasite/WBC	60
Coma score of 4	45
Respiratory distress in patients without cerebral malaria	35
Coma score of 0–3 for <60 min	24
Other*	14

WBC=white blood cell.
*Includes cerebrospinal-fluid analysis suggestive of meningitis or encephalitis, history of epilepsia, and concomitant diseases.

Table 2: **Causes of exclusion in 1996**

Group	Slope of regression line, B (95% CI)	Correlation *r*	p
All patients and controls (n=209)	1·41 (1·24–1·58)	0·77	<0·001
Severe anaemia (n=27)	0·53 (0·13–0·93)	0·49	0·02
Uncomplicated malaria (n=52)	1·04 (0·67–1·41)	0·63	<0·001
Cerebral malaria (n=74)	1·18 (0·91–1·45)	0·71	<0·001

Table 3: **Linear regression analyses between log(TNF), independent variable, and log(IL–10), dependent variable**