

# CORRESPONDENCE

## GM food debate

Sir—Stanley Ewen and Arpad Pusztai (Oct 16, p 1353)<sup>1</sup> raise intriguing questions about the potential of *Galanthus nivalis* agglutinin (GNA) to cause morphological alterations in the intestinal tract and suggest that the lectin's effects may be exacerbated in genetically modified potatoes. However, the ways in which Ewen and Pusztai assess the enteropathic properties of GNA mean that their findings must be interpreted with extreme caution.

The indices of crypt length and jejunal intraepithelial lymphocyte (IEL) count have been used to study intestinal immunopathology for 20 years or more<sup>2,3</sup> but several aspects of Ewen and Pusztai's methodology warrant attention. First, the study relies entirely on image analysis of formalin-fixed, paraffin-embedded sections, which are notoriously subject to shrinkage, distortion, and other fixation artifacts. These problems can be partly overcome by careful choice of well-oriented villus-crypt units combined with exhaustive measurement techniques, but Ewen and Pusztai do not indicate whether they did this. Errors created by measuring crypts in different planes of section on the sample could account for the high variation reported. The fact that the crypt lengths reported (60–90 µm in the jejunum) are much smaller than those normally found in the rat<sup>4</sup> reinforces the view that the measurements may not have been accurate. More sensitive methods for processing and measuring intestinal tissues include non-formalin-based fixatives, microdissection, and direct morphometry of crypt and villus lengths.<sup>2-4</sup> The enterocyte mitotic rate is probably the most sensitive index of intestinal pathology,<sup>2</sup> and this can be measured easily by metaphase arrest or incorporation of bromodeoxyuridine.

Ewen and Pusztai use IEL counts to support their hypothesis that genetically modified potatoes cause jejunal lesions. They state that "IEL are known to increase when non-specific intestinal damage occurs", but an increase in IEL count is specifically a feature of enteropathies associated with activated T lymphocytes.<sup>3</sup> Thus an increased IEL count in animals receiving lectins could be compelling evidence for these materials inducing immunologically mediated damage to the gut. However,

Ewen and Pusztai have not shown this conclusively. They do not seem to have counted IELs by a well-established method in which IEL are counted per 100 enterocyte nuclei or as an absolute number per length, volume or area of mucosa. That the technique they used is not ideal is underlined by the numbers of IEL they report, which are in the region of 7–11 per 48 villi. To reconcile these estimates, given that a single column of villus enterocytes in the rat jejunum contains 200–300 enterocytes and the density of IEL in the normal small intestine is 10–20 per 100 epithelial cells, is difficult. The low protein content of some of the diets, referred to by other commentators as a possible source of error,<sup>5</sup> could account for some deviation of IEL numbers from normal but not for such a gross change. However, it is feasible that such a diet might have made the rats more susceptible to the intestinal infections known to cause the kind of changes in IEL and crypts<sup>5</sup> noted here.

The speculation that the lectin caused jejunal crypt hyperplasia via a direct stimulatory effect on crypt cells cannot be substantiated by the data. Hyperplasia implies increased mitotic activity, which was not measured. Also, the time course for these changes is not described, and no parameters of villus pathology are provided. In the absence of this information, it is impossible to say whether the changes in crypt morphology are primary effects of the lectin or secondary to villus damage.

Interactions between lectins, intestinal epithelial cells, and the local immune apparatus is an important and poorly understood area. Appropriate methods for studying the enteropathic effects of lectins are available and are comparatively simple and inexpensive. Application of these techniques may help elucidate the issues raised by this provocative study.

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- 1 Ewen SWB, Pusztai A. Effects of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. *Lancet* 1999; **354**: 1353.
- 2 Mowat AM, Ferguson A. Intraepithelial lymphocyte count and crypt hyperplasia measure the mucosal component of the graft-versus-host reaction in mouse small intestine. *Gastroenterology* 1982; **83**: 417–23.

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- 5 Kuiper HA, Noteborn HPJM, Peijnenburg AACM. Adequacy of methods for testing the safety of genetically modified foods. *Lancet* 1999; **354**: 1354.

Sir—While much of the debate has focused on the nature of the diets studied by Stanley Ewen and Arpad Pusztai<sup>1</sup> and possible differences between them, one central question is the effects of these on cell proliferation in the gut. Ewen and Pusztai talk about "proliferative effects" when they have not measured intestinal cell proliferation but merely crypt depth. Crypt depth might reflect hypoplasia and hyperplasia but this has yet to be shown. Various methods can be used to measure intestinal epithelial cell proliferation, such as the numbers of dividing cells in optimally sectioned crypts, but for definitive conclusions we need measurements related to the rate of crypt or gland cell production;<sup>2</sup> the size of the epithelial population also needs to be assessed appropriately. Perhaps the best way of doing this is to use metaphase arrest and the microdissection method,<sup>3</sup> in which not only the rate of crypt cell production but also good measurements of crypt and villus size can be captured simultaneously.

Another point is that many such studies can be confounded by concomitant changes in the denominator,<sup>4,5</sup> and the data on intraepithelial lymphocytes, with sectioned villus as the denominator, could be subject to the same criticism.

We hope these comments will help to ensure that if these studies are repeated (as they should be), robust, rapid, and reliable methods for assessment of cell proliferation are used.

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- 1 Ewen SWB, Pusztai A. Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. *Lancet* 1999; **354**: 1353–54.

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- 5 Goodlad RA. Defective denominators, or will people never learn. *Gastroenterology* 1995; **108**: 1963.

Sir—Stanley Ewen and Arpad Pusztai's research letter<sup>1</sup> describing measurements of intraepithelial lymphocyte counts and mucosal thickness in rats in a short-term feeding experiment of potatoes transgenic for snowdrop lectin is unacceptable for the following reasons.

(1) For the intraepithelial lymphocyte counts, one essential group—rats fed with potatoes spiked with *Galanthus nivalis* lectin (GNA)—was omitted on the grounds that the authors claim to know that “dietary GNA or other lectins do not induce lymphocyte infiltration”. This omission is improper and those data should have been provided.

(2) No control data are provided for rats fed on a normal laboratory diet so it is not possible to say what values are normal. The authors simply assume that anything found in group fed GM potatoes is abnormal.

(3) Were the assays done blind on coded samples?

(4) I am unclear as to what disease these markers are a surrogate. Intraepithelial lymphocyte counts are greatly increased in coeliac disease but in normal gut, a modest increase in their number is not known to me to be a marker for any pathological process. Also, what significance attaches to minor changes in mucosal thickness? If there is any evidence for pathological processes associated with these surrogate markers. Ewen and Pusztai should have cited it.

(5) In the statistical analysis there is no correction for “data dredging”. The two measurements reported were not the test of a pre-existing hypothesis. They have been selected from an unstated number of comparisons. The probabilities need to be adjusted for the number of different comparisons made. This will almost certainly make them non-significant and the experiments therefore need to be repeated on a new group of rats.

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#### Authors' reply

Sir—In their Oct 16 commentary Harry A Kuiper and colleagues discuss methods for testing the safety of GM foods. Our research letter only addressed the biological effects of GNA-GM potato diets on the morphology of the rat gut. However, since the safety testing issue has been raised we would like to respond.

According to the Rowett Institute's audit report the parent and transgenic lines we used were “substantially equivalent”. At least for protein content this was confirmed in the alternative report put on the internet by the Rowett (not by Pusztai, as stated by Kuiper et al). All experimental diets were isoproteic and isocaloric and supplemented with vitamins and minerals for optimal growth, and the food intake of all rats was the same. Although 6% protein is suboptimal, the diet was not protein-free, as it was in the paper cited by Kuiper et al. Since the rats were growing, to use emotional terms such as “starvation” is misleading. Furthermore, starvation reduces gut size and crypt length, precisely the opposite what we found. Since trypsin and chymotrypsin inhibitors have no effect on gut morphology, reference to them is irrelevant. The potato lectin is antimutagenic<sup>2</sup> so its effect should be a reduction in crypt cell proliferation rate and crypt size, not an increase. Moreover, GNA was selected for GM insertion because its effect on the gut is minimal so differences in lectin content, as an explanation for the biological effects reported, are also irrelevant.

Kuiper et al refer to “no consistency” in the changes. Is there any reason why changes in the different gut compartments should be the same? The ingestion of potatoes may indeed be associated with several adaptive changes, including caecal hypertrophy, but all the rats were given essentially the same potato diet containing the same starch component. Our study was about the effects of GM potatoes on gut morphology, not on their toxicology. The number of rats used (six per treatment group) was more than sufficient and most peer-reviewed, published papers on the biological and nutritional effects of similar diets (including over 40 from our laboratory) use three to four animals per group. Our controls were also

sufficient. For both raw and cooked GM potatoes we used as controls both parent potato and parent potato supplemented with purified GNA, at the level expressed in GM potatoes. With this experimental design we could discriminate between the effects of the transgene product, the transformation, or the cooking and the interactions between these effects. The use of standard rodent diet of undefined composition as a control would have been inappropriate, and the effects of high-protein and low-protein diets would not have been comparable. We agree with Kuiper et al that attention should be paid to bioavailability and toxic effects. Kuiper et al cite their study done with a recombinant form of *Bacillus thuringiensis* toxin and not with toxin isolated from the GM-tomato. They themselves point out that since the stability, survival in the gut, and toxicity of a recombinant protein usually differ from those of the plant-gene product, the two forms can not be used for comparisons. Biotech companies, in their submissions to regulatory authorities, also rely on toxicity studies with *E coli* recombinants. We, by contrast, have been comparing the gene product from the GM plant with that of the non-transformed original.<sup>3</sup>

Indeed it would have been desirable for testing methods recommended by FAO/WHO and so on to have been used for GM food crops currently approved. Unfortunately, no such tests were required, carried out, or their results published. It is therefore surprising for Kuiper et al to state that “the data so far indicate GM-crops . . . that have been introduced into the environment do not differ from traditionally grown crops except for the inserted traits”. Several traits having nothing to do with the transgene save the insertion have been found to differ in GM lines. The Monsanto analyses of glyphosate-resistant soya showed that the GM-line contained about 28% more Kunitz trypsin inhibitor, a known antinutrient and allergen.<sup>4</sup> GM-soya contained significantly less phyto-oestrogens than the parent lines.<sup>5</sup> Why is it that current GM crops need not be examined as thoroughly as the next generation?

We agree that “particular attention must be given to the detection and characterisation of unintended effects of genetic modification” but how will unknown toxins or allergens be found without first biologically testing the GM crop for toxicity? Writing of the sequence to be followed in future safety testing procedures, Kuiper et al say

"depending on the outcome . . . further toxicological and nutritional studies may be needed". The admission by people close to the decision-making committees of the European Union that the biological testing of GM food is needed appears to be an acknowledgment that previous safety testing could not have been rigorous enough.

Allan Mowat comments on the tissue fixation. This has long been a contentious topic. There may not be an ideal fixative but it is mischievous to suggest that the fixative upon which the whole of human histopathology relies could be responsible for different crypt-length measurements. The histology was part of a large series of synchronous physiological measurements on the same animal, demanding rapid tissue handling. Our animals were young (about 85 g) and, at that stage of development, the gut can easily be dissected from the mesentery to provide an unwashed, undistended histological sample at a constant distance from the pylorus. Orientation and plane-of-section problems were minimised by "splinting" tissue samples on card during standardised fixation. The jejunal crypt length of our 85 g rats has not varied and the data reported are similar to those obtained from 5000 jejunal crypts over the past 10 years. Rat intestinal crypt length depends on diet, animal supplier, and housing conditions, all of which are standardised in our rat colony, and the chemical composition of the potato diet was subjected to the exhaustive chemical analysis.

Intraepithelial lymphocytes (IEL) are thought to provide a surveillance function for damaged or virally infected cells, and any increase in the IEL population need not be limited to hypersensitivity reactions. Our young animals could not have been exposed to GNA previously, and any difference between groups is likely to be due to luminal factors in the diet. Moreover, IEL numbers are unaffected by lectin treatment.<sup>1</sup> The only difference in the diets is the presence of unidentified factors caused by genetic modification. Epithelial cell damage induced by the genetic modification cannot be excluded, and we would have studied it if our experiments had not been aborted. IELs averaged 7–11 per villus based on 48 villi counted, and we believe that our estimate is a useful indicator of unspecified immunological events of comparative value between groups. The suggestion that the low-protein content of the diet caused intestinal infection can be rejected; parasites were not evident in the

unwashed histological preparations and the lamina propria did not contain excess eosinophils.

Hyperplasia refers specifically to an increased cell number, frequently, but not necessarily, accompanied by increased mitotic activity although increased crypt mitotic activity is indeed present in our GM-potato fed animals. If, after 10 days of ingestion of GM potatoes villus pathology had been evident we would have described the damage. We reject the notion that potato or GNA lectin could have produced the changes that caused us concern.

Peter Lachmann's points (1) and (2) are addressed in our reply to Mowat. To point (3) the answer is yes, the measurements were done double-blind. With regard to point (4), Lachmann does not understand that the significant changes in mucosal indices represent another nail in the coffin of "substantial equivalence" on which the GM regulatory system is based. The differences in gut metabolic responses demonstrate that GM potatoes were not "metabolically equivalent", and this is important whether the changes are pathological or not. Increased epithelial cell proliferation in the colon is not regarded desirable and the high energy cost of small-intestinal hyperplasia may compromise growth and development.

In his point (5) Lachmann asserts that we had no prior hypothesis. Because the experimental design was obvious from the introductory part of our letter, to save space, a part of our sentence was omitted. Here it is: "It was thought that comparison of the histological parameters of the gut of rats fed potato diets containing either GM potatoes, or non-GM potatoes with or without being supplemented with GNA should give a clear indication whether GNA gene insertion had affected the nutritional and physiological impact of potatoes on the mammalian gut". Our table 1 clearly gives the statistical methods used and the number of comparisons. These methods were approved by independent statisticians. Lachmann says that the experiments need to be repeated. We would be happy to oblige. If our experiments are so poor why have they not been repeated in the past 16 months? It was not we who stopped the work on testing GM potatoes expressing GNA or other lectins or even potatoes transformed with the empty vector, which are now available. If Lachmann represents the view of the Academy of Medical Sciences on GM-food safety he should use his influence to

make funds available for the continuation of this work in the UK.

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- 3 Pusztai A, Grant G, Bardocz S, Alonso R, Chrispeels MJ, Schroeder HE, Tabe LM, Higgins TJV. Expression of the insecticidal bean alpha-amylase inhibitor transgene has minimal detrimental effect on the nutritional value of peas fed to rats at 30% of the diet. *J Nutr* 1999; **129**: 1597–603.
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Sir—Brian Fenton and colleagues' research letter (Oct 16, p 1354)<sup>1</sup> on the insecticidal *Galanthus nivalis* lectin (GNA) makes several questionable assertions. They state that the "distribution, abundance, and micro-heterogeneity" of structures recognised by GNA are "largely unknown". They then provide results which they claim "show that human white blood cells have many proteins that strongly bind to GNA". Several previous studies have reported examination of GNA binding to human proteins and tissues (including breast, Peyer's patches, kidney, brain, photoreceptors, plasma proteins, placenta, gallbladder, and several human-derived cell lines). Moreover, the binding of GNA to proteins from human white blood cells has been already been reported by Benallal et al.<sup>2</sup> The conclusions of the new work cannot be considered novel.

Fenton et al also argue that their results are relevant to the debate on genetically modified (GM) food, stating there needs to be "a greater understanding of the interactions of plant lectins and human glycoproteins before they can be safely incorporated into the food chain". However, plant lectins are already incorporated into the human diet. Not only are lectins naturally present in potatoes, lentils, beans, peas, tomatoes, and other crop plants but also many of these lectins bind to human glycoproteins. The first plant lectins were identified over a 100 years ago, and their binding to human cells, and

the potential toxicity of some of them, has long been known. Denaturation by cooking or digestion by enzymes in the gut can even allow consumption of lectins that might otherwise be harmful.

The interaction of lectins with glycoproteins in the digestive tract, and elsewhere in the body, has been extensively studied for decades. Although GNA is not incorporated into any of the GM food currently approved for human consumption in the UK, the need for testing of any food containing GNA is clearly apparent from past studies. The results of Fenton et al reveal nothing that was not already known and provide no new reasons to question the possible use of GNA in transgenic crops.

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- 1 Fenton B, Stanley K, Fenton S, Bolton-Smith C. Differential binding of insecticidal lectin GNA to human blood cells. *Lancet* 1999; **354**: 1354-55.
- 2 Benallal M, Zotter H, Anner RM, et al. *Maackia amurensis* agglutinin discriminates between normal and chronic leukemic human lymphocytes. *Biochem Biophys Res Comm* 1995; **209**: 921-29.

Sir—Brian Fenton and colleagues<sup>1</sup> report that the lectin *Galanthus nivalis* (snowdrop) agglutinin (GNA) can bind glycoconjugates from human leucocytes, and they claim that the work “highlights the need for a much greater understanding of the interactions between plant lectins and human glycoproteins before they can be safely incorporated into the food chain”. Binding of GNA to human leucocytes has been known for a decade, and plant lectins are already common components of foodstuffs.

Shortly after GNA was first isolated, we showed that it was weakly mitogenic for human mononuclear leucocytes,<sup>2</sup> an activity that required binding to cell surfaces. Moreover, GNA acts synergistically with a submitogenic concentration of the tumour promoter, tetradecanoylphorbol-13-acetate,<sup>2</sup> as Fenton et al conjecture it might.

However, all this in itself is unremarkable. Plant lectins are present in active form in a wide variety of “healthy” foods.<sup>3</sup> Lectins in general are resistant to the digestive process, and a small proportion of any ingested lectin may be transported into the circulation. Undoubtedly, some ingested lectins (eg, pokeweed mitogen) could be very harmful; equally, others, like the tomato lectin, seem to be harmless.<sup>4</sup>

GNA is not normally a dietary lectin for man so caution should be exercised before permitting its presence in foods. However, the data indicate that the

GNA gene product itself is non-toxic; the point about the contentious work of Ewen and Pusztai<sup>5</sup> is that some other component of the construct used to transfect the GNA gene may be responsible for unexplained (and potentially harmful) consequences.

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- 1 Fenton B, Stanley K, Fenton S, Bolton-Smith C. Differential binding of the insecticidal lectin GNA to human blood cells. *Lancet* 1999; **354**: 1354-55.
- 2 Kilpatrick DC, Peumans WJ, Van Damme EJM. Mitogenic activity of monocot lectins. In: Koucourek J, ed. *Lectins: biology, biochemistry, clinical chemistry*, vol VII. St Louis: Sigma, 1990: 259-62.
- 3 Kilpatrick DC. Immunological aspects of the potential role of dietary carbohydrates and lectins in human health. *Eur J Nutr* 1999; **38**: 107-17.
- 4 Kilpatrick DC, Pusztai A, Grant G, Graham C, Ewen SWB. Tomato lectin resists digestion in the mammalian alimentary canal and binds to intestinal villi without deleterious effects. *FEBS Lett* 1985; **185**: 299-305.
- 5 Ewen SWB, Pusztai A. Effects of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. *Lancet* 1999; **354**: 1353-54.

Authors' reply

Sir—Sean Munro's first comments are misleading, for he quotes out of context. The distribution, abundance, and microheterogeneity of terminal  $\alpha$ -1-3-mannose residues on human membrane-bound receptor proteins is largely unknown, whilst GNA (*Galanthus nivalis* agglutinin) binding to some plasma (secretory) proteins, such as  $\alpha_2$ -macroglobulin, is well documented. Benallal et al<sup>1</sup> identified a 95 kDa leucocyte membrane protein which also bound GNA, and this probably corresponds to one of the molecules identified in our study. However, we have identified additional GNA binding proteins that also seem to vary between individuals—the importance of which is unknown.

Both Munro and D C Kilpatrick cite the natural abundance of lectins in commonly consumed foods, and the known toxicity of some and apparently harmless nature of others. This variable toxicity emphasises the need for caution before lectins, which are not normally consumed, are incorporated into human-food plants. Snowdrop has never formed part of the human diet. GNA is a mannose binding lectin (MBL) and other MBLs are already in our diet, such as those from onion and leek. However, in these plants, their concentration (0.5-10  $\mu$ g/g) is 100 times less than in

non-edible plants (daffodil and snowdrop; 2-4 mg/g)<sup>2</sup> and that required to control insects with GNA. The other dietary plant lectins that Munro mentions have differing specificities and are more digestible (after one hour only 30% of pea or bean lectin survives digestion whereas GNA is still 90% intact<sup>3</sup>). Daily and seasonal variation in human diets will result in differential intensity and duration of exposure to natural food plant lectins. By contrast, GNA could be incorporated into all main crop plants, resulting in chronic exposure from cooked and uncooked foods.

Kilpatrick rightly advocates caution, and cites his work<sup>4</sup> on which our own comments were based. This reference was omitted at the editing stage. Such recognition of the reported mitogenicity of GNA is not universal.<sup>5</sup> Kilpatrick further highlights the importance of synergy. This synergy could occur between GNA and other dietary lectins or tumour promoters in man and could provide one explanation of Ewen and Pusztai's observations—GM potatoes are likely to contain other changes as a consequence of tissue culture (an intrinsic part of the GM process). If change occurred in an endogenous mitogen it could act synergistically with the GNA gene product to produce the hyperplasia observed in the specific treatment group. A second possible explanation of their results is that the single isoform of GNA used in the transgenic potatoes is more highly mitogenic than the mixture of isoforms purified directly from snowdrops.<sup>2</sup> These alternative explanations do not implicate the genetic manipulation process itself.

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- 1 Benallal M, Zotter H, Anner RM, Lacotte D, Moosmayer M, Anner BM. *Maackia amurensis* agglutinin discriminates between normal and chronic leukemic human lymphocytes. *Biochem Biophys Res Comm* 1995; **209**: 921-29.
- 2 Van Damme EJM, Goldstein IJ, Peumans WJ. A comparative study of Mannose binding lectins. *Phytochem* 1991; **30**: 509-14.
- 3 Bardocz S, Ewen SWB, Grant G, Pusztai A. Lectins as growth factors for the small intestine and gut. In: Pusztai A, Bardocz S, eds. *Lectins: biomedical perspectives*. 1995; 103-16.
- 4 Kilpatrick DC, Peumans WJ, VanDamme EJM. Mitogenic activity of monocot lectins. In: *Lectins: biology, biochemistry, clinical biochemistry*. St Louis: Sigma Chemical, 1990; 7: 259-62.
- 5 Stoger E, Williams S, Christou P, Down RE, Gatehouse JA. Expression of the insecticidal lectin from snowdrop (*Galanthus nivalis*

Sir—Your decision to publish the research of Stanley Ewen and Arpad Pusztai<sup>1</sup> breaks unfortunate new ground for a scientific journal. Put simply, *The Lancet* has placed politics and tabloid sensationalism above its responsibility to report and assess new science. Most peer-reviewed journals are respected, and read, for the integrity of the research they publish and their dependability in weeding out irresponsible work.

Richard Horton (Oct 16, p 1314)<sup>2</sup> argues that *The Lancet* might have been criticised for suppressing information by not publishing Ewen and Pusztai's work, but I believe he has jeopardised the journal's credibility, especially among readers and contributors in the scientific community. This pandering to popular debate rather than promoting responsible scientific inquiry may appeal to some, but I believe that the editor's poor judgment will strengthen the resolve of other scientific journals to adhere to the publication standards *The Lancet* saw fit to abandon.

I doubt if *The Lancet* would have published Ewen and Pusztai's research if it had implied the safety of biotech foods. But that is fine. Those who work hard to apply biotechnology to agriculture have no interest in flawed data.

Horton is naive if he really believes that "publication of Ewen and Pusztai's findings is not, as some newspapers have reported, a 'vindication' of Pusztai's earlier claims". Anti-technology activists already have seized on *The Lancet's* publication of this work as precisely that. They claim that publication, in itself, is proof the research is valid because that is the standard scientific journals are supposed to apply.

In the USA, biotech crops and foods have been tested more than any other agricultural products in history. We have a regulatory system that applies science-based policies to guard the health of consumers and the environment. That system would have trashed Pusztai's potatoes if they had been submitted for approval. Too bad *The Lancet* failed to exercise such oversight on research submissions.

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- 1 Ewen SWB, Pusztai A. Effects of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. *Lancet* 1999; 354: 1353-54.
- 2 Horton R. Genetically modified foods: "absurd" concern or welcome dialogue? *Lancet* 1999; 354: 1314-15.

Sir—I disagree with Richard Horton's view, expressed at the end of his commentary on the controversy surrounding genetically modified (GM) foods.<sup>1</sup> It seems to be that we as scientists have not been nearly aggressive enough in attacking the scaremongering and sheer nonsense put out by the lay media on a variety of medical and scientific topics. Besides writing about these issues we should be lobbying the Press Complaints Commission and the government to try and ensure that journalists are taken to task and made to publish amendments if they grossly distort the facts in any kind of technical reporting, just as we would expect a retraction and apology for the libelling of an individual. If we do not do this we are in danger of sliding into a sort of mob rule when the media can with impunity whip up such a furore over supposed malpractice that pro-testers burn fields of experimental GM crops.

Consider the damage done to immunisation campaigns by the steady drip of adverse publicity in the media. This public hostility to one of the most effective forms of disease control in the history of medicine (a hostility to which, sadly, *The Lancet* has indirectly contributed) means that there is now a serious possibility of a measles epidemic because of the poor uptake of vaccine.

Let us be proud of the scientific method and of scientific rigour. We must try to stop the slide into alarmism and negativity to innovation. In the Middle Ages superstition led to the burning of witches; if we are not careful it could soon be scientists who are being burned.

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- 1 Horton R. Genetically modified foods: "absurd" concern or welcome dialogue? *Lancet* 1999; 354: 1314-15.

Sir—*The Lancet* criticised the Royal Society last May<sup>1</sup> for its "breathtaking impertinence" in reviewing Arpad Pusztai's work before it had been published. Richard Horton now repeats that criticism.<sup>2</sup> We commented on Pusztai's unpublished work because he himself had commented on it, so extensively that it had become a matter of public interest. Since a one-sided debate was raging on the back of unvalidated experimental data, the Royal Society had a duty to examine such evidence as it could secure from all sources, including Pusztai himself. That is impertinence only if you endorse scientists flouting normal practice and rushing to the press with unvalidated data and invalid conclusions.

In introducing the Ewen and Pusztai research letter<sup>3</sup> Horton helpfully

describes the ambivalence of the referees and emphasises the value of having the data out in the open. He also states that the data are non-generalisable. It is therefore surprising that the journal allowed the paper to appear with two general conclusions in the final paragraph.

In the circumstances, Horton's comments on the "failure to understand the . . . dialogue of accountability" are somewhat ironic.

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- 1 Editorial. Health risks of genetically modified foods. *Lancet* 1999; 353: 1811.
- 2 Horton R. Genetically modified foods: "absurd" concern or welcome dialogue? *Lancet* 1999; 354: 1314-15.
- 3 Ewen SWB, Pusztai A. Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. *Lancet* 1999; 354: 1353-54.

Editor's reply

Stanley Ewen and Arpad Pusztai's research letter was published on grounds of scientific merit, as well as public interest. Four out of six invited reviewers recommended publication after revision on scientific grounds, one argued the public interest case, and one voted against publication. In the face of such clear support, the "irresponsible" action that Carl Feldbaum alludes to would have been to suppress publication. A debate about the science, rather than unsupported claims about that science, has now begun—a useful step forward.

Roger Fisker invites scientists to be more "aggressive". *The Guardian* newspaper has already reported one example of aggression, relating to *The Lancet's* decision to publish Ewen and Pusztai's work.<sup>1</sup> That instance does not speak well of scientists' (in this case, a very senior scientist's) tolerance for open and reasoned debate.

Aaron Klug defends the Royal Society's wish to damn Ewen and Pusztai's work in the absence of both investigators. What he cannot defend is the reckless decision of the Royal Society to abandon the principle of due process in passing judgment on their work. To review and then publish criticism of these researchers' findings without publishing either their original data or their response was, at best, unfair and ill-judged.

Richard Horton

- 1 Flynn L, Gillard MS. Pro-GM food scientist 'threatened editor'. *Guardian* 1999; Nov 1: 1-2.

## Fatal septicaemia after fibroid embolisation

Sir—Arvind Vashisht and colleagues (July 24, p 307)<sup>1</sup> report a death associated with uterine artery embolisation (UAE) for the management of fibroids. We agree that it is very important to report severe sequelae of new procedures. However, we feel that it is important to provide a proper perspective on this and any other reports.

Since the use of UAE as primary therapy in 1991, there have been about 6000 women treated by UAE worldwide. However, two deaths have been reported since this procedure was introduced.<sup>1,2</sup> Careful evaluation of each case should reveal whether the procedure is associated with mortality. However, if we assume that both these deaths were due to the procedure, the mortality risk of UAE would be 1 in 3000.

The mortality risk of hysterectomy is well documented at about 1 in 1000.<sup>3,4</sup> Since nearly all deaths associated with any major elective surgery are due to complications of anaesthesia, a similar mortality risk can be assumed from myomectomy, and possibly even higher because myomectomy is thought of as having a higher overall complication risk than hysterectomy.<sup>5</sup> If the 6000 women who have been treated with UAE to date had been treated with either hysterectomy or myomectomy, about six periprocedural deaths should be expected.

We acknowledge that any procedure, even those believed to be minimally invasive, carries the risk of serious complication or even death. However, it is important to maintain an appropriate perspective about such issues, and to keep in mind the relative risks associated with both the procedure in question and alternative procedures.

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- 1 Vashisht A, Studd J, Carey A, Burn P. Fatal septicaemia after fibroid embolisation. *Lancet* 1999; **354**: 307–08.
- 2 Lanocita R, Frigerio LF, Patelli G, et al. A fatal complication of percutaneous transcatheter embolization for the treatment of fibroids. Presented at the Second International Symposium on Embolization of Uterine Myomata/Society for Minimally Invasive Therapy 11th International Conference, Boston, September 1999.
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Sir—Arvind Vashisht and colleagues<sup>1</sup> report a mortality related to UFE. Our group in Los Angeles has done this procedure in 367 women with menorrhagia associated with uterine fibroids since 1996. Among these women there have been no deaths. Two patients did develop infections after UFE, requiring hysterectomy. We noted in Vashisht and colleagues' report that the patient with a 20-week-sized uterus was embolised with 300  $\mu$ m polyvinyl alcohol (PVA). Some members of our group have used 700  $\mu$ m PVA particles in large uteri (>2500 mL) since the last infection in 1998. We have had no further infections.

Post-embolisation syndrome is a well documented disorder that occurs in many parts of the body after embolisation.<sup>2–4</sup> Nonetheless, clinicians must be vigilant for any sign of infection after embolisation. In our practice, we obtain blood cultures as well as computed tomography scans of the pelvis. An abscess is clear on such imaging, and requires surgical treatment.

Morbidity has been lower in our group of patients than in patients undergoing surgical correction.<sup>5</sup> We would hope that with better understanding, mortality such as the case reported could be avoided.

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## Therapy for stroke patients living at home

Sir—The recent randomised trial (RCT) of occupational therapy for stroke patients living at home that M F Walker and colleagues report (July 24, p 278)<sup>1</sup> was the first of its kind to show significant benefits across a range of outcomes. We are undertaking a systematic review for the Cochrane Collaboration on therapy-based rehabilitation services for stroke patients living at home. In our initial descriptive analysis<sup>2</sup> we identified a discrete group of RCTs of therapy-based services (physiotherapy, occupational therapy, multidisciplinary teams), which largely focused on modifying task-oriented behaviour such as walking or dressing. These services are broadly comparable to the intervention that Walker et al outlined.<sup>1</sup> Most trials recruited patients after discharge from hospital and provided several sessions of intervention at home. The specific interventions were subdivided into mixed services (usually provided by a mixture of occupational therapy and physiotherapy staff) and occupational therapy (occupational therapy staff only). The main outcomes of interest were the prevention of a deterioration in function and extended activities of daily living (EADL).

We have identified 11 RCTs (1041 patients) that compared a routine intervention with no routine intervention; all used secure randomisation procedures and blinded outcome assessment at 3–12 months. The EADL scores (or ADL score if EADL not available) were available for 890 (85%) of patients combined as the standardised mean difference (95% CI) with a random effects model. The pooled result for all trials was 0.311 (0.176–0.445,  $p < 0.001$ ) with no significant heterogeneity between trials. The exclusion of Walker and colleagues' data<sup>1</sup> did not significantly alter the conclusion (standardised mean difference 0.229 [0.080–0.378],  $p < 0.005$ ).

This analysis was flawed by the need to convert data recorded as median scores and IQRs into means and SDs. We therefore did a second analysis calculating the odds of death or a poor outcome (either deterioration in ADL or dependency in ADL at final assessment). Data were available for 921 (88%) of patients. Adverse outcome was less common in patients receiving home-based therapy (table). The result for all trials was 0.57 (0.42–0.77,  $p < 0.005$ ) with no significant heterogeneity between trials. The exclusion of Walker and

Trial	Number of patients/total*		Odds ratio (95% CI)
	Therapy	Control	
<b>Mixed service</b>			
Wade (1992)	1/49	3/45	0.33 (0.04–2.39)
Hui (1995)	8/59	12/61	0.65 (0.25–1.68)
Smith (1981)	16/89	14/44	0.46 (0.19–1.08)
Subtotal	25/197	29/150	0.51 (0.28–0.94)
<b>Occupational therapy</b>			
Corr (1995)	31/55	33/55	0.86 (0.41–1.83)
Gilbertson (1998)	33/67	41/71	0.71 (0.37–1.39)
Logan (1997)	6/53	14/58	0.42 (0.16–1.11)
Walker (1996)	0/15	0/15	..
Walker (1999)	25/94	41/91	0.45 (0.25–0.82)
Subtotal	95/284	129/290	0.59 (0.41–0.84)
<b>Total</b>	<b>120/481</b>	<b>158/440</b>	<b>0.57 (0.42–0.77)</b>

\*Patients who developed an adverse outcome, death, deterioration, or dependency.

Full references available from author, on request.

#### Analysis of outcome according to treatment in stroke patients living at home

colleagues' results<sup>1</sup> did not significantly alter the conclusions (odds ratio 0.62 [0.43–0.88],  $p < 0.01$ ). Therefore these promising results<sup>1</sup> are consistent with other small trials of broadly similar interventions.

This study was funded by the UK Stroke Association.

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Sir—Occupational therapy is an essential component in the rehabilitation of disabled older patients, having a wide range of interventions able to assist persons towards independence.<sup>1</sup> M F Walker and colleagues<sup>2</sup> assess the effects of such a programme on the physical and psychosocial wellbeing of patients with stroke who were not admitted to hospital. Compared with individuals in a non-treatment group, patients engaged in occupational therapy had benefits in nearly all the outcome variables considered (eg, physical health, daily functioning, and caregiver strain).

We believe that the contention that occupational therapy is of real value would have been strengthened if Walker et al had provided additional information to ascertain the impact of this type of rehabilitation programme on the use of health services. In as much, whether community occupational therapy programmes are associated with a reduced incidence of accidents (eg, contractures, falls,

pressure ulcers), or with an otherwise reduced risk of hospital or nursing home care remains unclear. Subsequently, the demonstration that the physical benefit of such programmes in-home in patients with stroke, without other specific interventions, translates into a reduction of health-related costs is only presumptive. Complete cost-effectiveness and cost-benefit analyses are critical before wholehearted endorsement of occupational therapy.

Furthermore, one should also be able to establish whether there are specific components of the intervention that may be responsible for the positive effects of this intervention. Although we lack details of the occupational therapy programmes Walker and colleagues use, as well as information about which services were used among patients in control group, a more precise comprehension of the prognostic implication of physical therapy itself (ie, specific exercise programme), as opposed to occupational therapy or any multidisciplinary approach, seems to warrant more research. In that respect, only a multidisciplinary approach and an integration of medical, rehabilitation (occupational and physical therapy), and social services, in a continuum of care, has already proven to decrease the rate of morbidity and improve the quality of life among geriatric disabled patients, including those previously estimated inappropriate for a rehabilitation programme.<sup>3,4</sup>

Nevertheless, Walker and colleagues' findings are relevant to geriatric rehabilitation, which has received very little attention. Evidence suggests that rehabilitation and specific occupational research therapy focused in dependent geriatric patients is rare.<sup>5</sup> With the growing of the elderly population and their associated high rate of disability and comorbidity, there is a greater need for preventive and rehabilitative home

care programmes. We believe that improving the ability of a health care system to respond to the needs of disabled people is one of the greatest challenges of our time.

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## Chinese-herb nephropathy

Sir—Graham Lord and colleagues (Aug 7, p 481)<sup>1</sup> report two cases of nephropathy from ingesting Chinese herbal remedies that were traceable to a derivative of the herb MuTong. The acute toxicity of excessive doses of MuTong has been previously reported in Chinese publications. One woman wanting to promote milk production ate soup containing 70 g MuTong and red beans; she and her father-in-law who also ate the beans developed acute renal failure.<sup>2</sup> Another woman who took a decoction made with 175 g of MuTong also had acute renal failure. None of the patients died. Less fortunate were two men and two women who took decoctions prepared with 50 g, 70 g, 60 g, and 120 g MuTong,<sup>3,4</sup> respectively; they died of renal failure. There is no report on the long-term adverse effects of MuTong, except a case of renal-function impairment in a man who took ten doses of a decoction containing 25 g of MuTong.<sup>5</sup> All these cases were probably caused by GuanMuTong, which is derived from *Aristolochia manshuriensis*.

There are some patented Chinese medicines that contain GuanMuTong. Seven of them, for example, are registered in the People's Republic of China Pharmacopoeia, Anyang Jingzhi plaster, Dahuang Qingwei Pills, Daochi pills, Fenqing Wulin pills, Fuke Fenqing

pills, Longdan Xiegan pills, and Xiao'er Jindan tablets. Priority should be given to review of the long-term safety of these products, and GuanMuTong should be excluded from further use. Other sources of MuTong, for example ChuanMuTong from *Clematis armata* and *C. montana*, which do not contain aristolochic acids, could be used instead.

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Sir—Graham Lord and colleagues<sup>1</sup> report two cases of nephropathy from ingesting a Chinese herbal remedy containing aristolochic acid<sup>1</sup> calls to attention a similar series of cases recently reported from Belgium. Ten similar cases of nephropathy were reported in Japan in 1995, of which five could be attributed to a herbal medicine imported from China by a company in Osaka. After a warning was published,<sup>2</sup> the suspected product was recalled. Toxicity occurred in this case because *Aristolochia manshuriensis* had been substituted in the Chinese product for *Akebia quinata Decaisne*, a herb with diuretic properties that is included in the Japanese Pharmacopoeia. We have confirmed the presence of aristolochic acid in *Aristolochia manshuriensis* and other plants of the genus *Aristolochia* (Aristolochiaceae), and *Asarum* (Aristolochiaceae), but not in authentic samples of *Akebia quinata Decaisne*.<sup>3</sup> *Aristolochia manshuriensis* and other plants of the genus *Aristolochia* are not contained in the Japanese Pharmacopoeia and the Japanese Herbal Medicine Codex, the basic compendia used by the manufacturers of traditional Japanese herbal medicines (kampo) in Japan.

Incidents of this kind highlight the importance of developing and enforcing appropriate quality assurance procedures for herbal medicines. Japan's experience with traditional Japanese herbal medicines has shown that high standards of quality and consistency are possible for oriental medicines with more than one ingredient, which

typically contain crude herbs from various sources. The Japanese Ministry of Health and Welfare has mandated Good Manufacturing Practices for kampo that are similar to those applied to other pharmaceutical products. In addition, the Japan Kampo Manufacturers Association, an industry group, has imposed on its members even higher standards than these. Today, more than 75% of Japanese physicians prescribe traditional herbal medicines to their patients.

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## Diagnosis of *Helicobacter pylori* infection by HpSA test

Sir—We thank Michele Caselli and colleagues, Mario Plebani and Daniela Basso, and Athanasios Archimandritis and colleagues (Oct 2, p 1209)<sup>1</sup> for their comments on our paper.<sup>2</sup> There seems to be agreement that the HpSA test is highly accurate in untreated patients. However, its value as a test of successful bacterial eradication is debated.

Caselli and colleagues cite a study by Makristatius and colleagues (their ref 3), who report a specificity of 68.3% for HpSA in the post-treatment assessment of *Helicobacter pylori* status in 55 patients tested 4 weeks after treatment. Surprisingly, PCR had an even lower specificity (48.8%). The investigators found 21 and 13 positive results for PCR and HpSA, respectively, in 41 patients successfully treated, as assessed by histology and culture. These findings cast doubt on the validity of the histology and culture results obtained. The second report (Caselli and colleagues' ref 4) contained insufficient information about the post-treatment assessment of *H pylori* status. However, a recent study by Trevisani and colleagues (their ref 5) achieved a sensitivity and specificity of 93% and 82%, respectively, in 116 patients after treatment. They obtained 12 false-positive results by HpSA, but used a fixed cut-off point. In our experience, the wash step is crucial and may

produce a high background. Most of the false-positive cases in their study were borderline. A key point in our study is that we recognised a grey zone of 0.140-0.159. Remarkably, in Trevisani and colleagues' study the sensitivity and the specificity of the <sup>13</sup>C breath test was 100%.

When new commercially available tests are assessed, their evaluation must be rigorous. We undertook a multicentre study, involving dedicated centres. In 501 patients, the sensitivity and the specificity of urea breath test were assessed independently in each centre giving values of 95.3% and 97.7%, respectively, with 13 false-positive and five false-negative results. HpSA was also assessed independently.

We have recently presented our completed post-therapy follow-up study<sup>3</sup> of the ten European centres involved in our first study. We were able to confirm a sensitivity and a specificity for HpSA of 93.8% and 96.9%, and for the urea breath test of 90.6% and 99.2%, respectively. These values were assessed against endoscopy-based tests for *H pylori* status. In 162 re-endoscoped patients, 4 weeks after stopping treatment, there were four false-positive, one indeterminate and two false-negative results for HpSA, and one false-positive and three false-negative results for urea breath test.<sup>3</sup> Our findings are supported by two studies. The first from Germany reports a sensitivity and specificity of 91.3% and 94.6%, respectively, in 115 patients assessed 4 weeks after treatment.<sup>4</sup> The second (in children with a mean age of 7 years) reports 100% and 97.2% respectively.<sup>5</sup>

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## Swimming in cold water

Sir—Michael Tipton and colleagues (Aug 21, p 626)<sup>1</sup> report that immersion deaths in cold water are associated with deterioration in swimming performance rather than severe hypothermia. Although hypothermia is an important cause of swimming failure and immersion, the investigators clearly indicate that therapeutic strategies should focus on near-drowning symptoms rather than hypothermia-related symptoms. They mention some of the physiological features of muscle function under cold water, but do not fully discuss metabolic/enzymatic function alterations.

Cold exposure elicits substantial alterations both in metabolic and physiological aspects. Free radical formation is increased during cold stress.<sup>2</sup> Further, cold stress elicits shivering and muscle movement to maintain body temperature, and this action increases production of reactive oxygen species. Lower body temperature during cold water immersion may inhibit enzyme activity. Thus, metabolism of glutathione, which is important in protecting various cells against oxidative stress and plays a part in cellular protein and immune function, may be impaired during cold water immersion. The ratio of oxidised glutathione to glutathione is increased after short-term whole body cold exposure in human beings and mice.<sup>2,3</sup> However, winter swimmers have a higher concentration of glutathione and a greater activities of glutathione peroxidase and catalase than do healthy controls.<sup>4</sup> These findings indicate that glutathione metabolism and function might be impaired during acute cold water immersion but can be preserved during chronic or repeat immersion.

Although cold stress is known to have several physical consequences in human beings, the role of excess production of reactive oxygen species, which impair muscle and diaphragm function,<sup>5</sup> on the deterioration of swimming performance in acute cold water immersion should be further elucidated.

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## Meningococcal vaccine and herd immunity

Sir—Jane Bradbury reported (July 24 p 310)<sup>1</sup> on the UK Secretary of State for Health's announcement on a new meningitis C vaccine to be launched in the UK this autumn. Because stocks are not sufficient, the vaccine will be initially targeted only at certain population groups. In our experience, partial vaccination can induce a herd immunity that is quite effective for unvaccinated individuals.

The island of Crete has a population of 540 000 inhabitants, 115 000 of whom are children aged less than 14 years. In 1998, an increase in meningococcal cases was noted, with a local incidence of 4.3 reported cases/100 000 population, compared with the average incidence of 2.1 in Greece for the same year.<sup>2</sup> Four children and young adults were reported to have died from meningococcal disease.

Routine immunisation is recommended only for military recruits in Greece. However, in September, 1998, a polysaccharide vaccine (Vaccine Meningococcique, Merieux A+C) became commercially available, and parents in Crete gradually agreed to immunisation of their children at their own expense. This immunisation does not allow an exact calculation of the child population coverage. At the start of 1999, a survey of 735 children in the prefecture of Heraklion (49% of the total population of the island) showed that 31% of 2–6-year-old and 52% of school aged children (7–14 years) had received the vaccine.<sup>3</sup>

A sharp decrease of meningococcal morbidity was recorded after this partial vaccination programme. By contrast with the 6 months from September, 1998, to February, 1999, during which seven cases were reported in unvaccinated children resident in Heraklion (two being classified as C, one as B, and four unclassified), not one case occurred in the 6 months from March to August, 1999.

The absence of an ideal meningococcal vaccine is undoubtedly a considerable gap in protection. However, until such a vaccine is developed, the limited immunisation of certain population groups with the available vaccines not only protects the vaccinees, but could provide sufficient herd immunity and protect the community.

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## Oral rehydration and hyponatraemia

Sir—N H Alam and colleagues' (July 24, p 296)<sup>1</sup> report of hyponatraemia in adult cholera patients treated with low osmolarity oral rehydration solutions (ORS) indicates a hazard associated with ORS containing sodium concentrations far below those in cholera diarrhoea. The WHO ORS solution was compared with an ORS formulation, which in previous, chiefly non-cholera studies, was reported to lower gross stool losses. The low osmolarity solution had not only lower osmolarity, but also decreased glucose and sodium, which may have affected the outcome. No reduction in gross stool losses was seen, but the data confirmed the rapid development of hyponatraemia in adult cholera patients receiving low salt ORS.<sup>2</sup>

Cholera therapy should aim to replace deficits by achieving positive net balance of water and electrolytes, and then to maintain balance. Treatment may be given by intravenous or oral routes; the latter route should use appropriate concentrations of glucose, as a substrate for sodium absorption, and of electrolytes. For best therapy, intake of water and salts should match losses. Additionally, for oral therapy, substrate/sodium ratio should be within the best range for increase of sodium and water absorption.

Hyponatraemia is a potentially dangerous complication of inadequate

sodium replacement.<sup>3</sup> Large sodium deficits, identifiable only in studies that include sodium balance measurements, occur before serum sodium starts to drop. The WHO ORS formula was itself a compromise, including a sodium concentration that can be given to cholera and non-cholera diarrhoea patients, and adults and children. Convenience as a single formula was offset by negative sodium balance<sup>4</sup> and by the need, in adult cholera patients, to drink greater volumes. That some patients in both groups developed hyponatraemia is not surprising; the lower sodium concentration in ORS, compared with that in cholera stools, leads to greater sodium deficit accruing during therapy. The proportion of patients who develop hyponatraemia depends on sodium reserves at the start of treatment and the rate of negative sodium balance during treatment, neither of which were measured in Alam and colleagues' study. Patients with multiple diarrhoea attacks each year, who receive ORS with sodium content too low to correct deficits or to maintain sodium balance, will end up with more salt deficits and, in series large enough to detect them, increased complications.

Hyponatraemic patients are also prone to potassium deficits, as the kidneys retain sodium and excrete more potassium.<sup>5</sup>

Alam and colleagues' conclusion that the results warrant use of this formula as a single formula for all patients is not supported by the data, which indicate that in adult cholera patients this formula increases risk of complications with no advantage in gross stool reduction. For these reasons the use of such a solution for all types of diarrhoea patients should not be recommended.

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- 1 Alam NH, Majumder RN, Fuchs GJ, CHOICE study group. Efficacy and safety of oral rehydration solution with reduced osmolarity in adults with cholera: a randomised double-blind clinical trial. *Lancet* 1999; **354**: 296-99.
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#### Author's reply

Sir—We agree with Richard Cash and colleagues' initial comments. Hyponatraemia is indeed a potentially dangerous complication of cholera patients when treated with low sodium ORS. However, there is great concern about the risk of hypernatraemia when solutions with high sodium concentration are given to well nourished children with non-cholera diarrhoea, especially rotavirus diarrhoea.<sup>1,2</sup> Keeping in mind both these concerns, our study was done with ORS with a sodium content slightly lower than that of standard WHO ORS.

Cash and colleagues refer to the study<sup>3</sup> that showed negative sodium balance in adult cholera patients when treated with low sodium ORS. However, the patients were not given any food until diarrhoea ceased. In our study, all patients were offered food (containing salts) immediately after initial rehydration with intravenous fluid (Na<sup>+</sup> 133 mmol/L, K<sup>+</sup> 13 mmol/L, Cl<sup>-</sup> 98 mmol/L, acetate equivalent to 48 mmol/L bicarbonate). Therefore, the patients in our study were not thought of as having important negative sodium balance before and after the start of ORS. Although sodium balance was not assessed, patients with hyponatraemia were evaluated carefully and any clinical symptoms attributable to hyponatraemia were noted. Symptom-free hyponatraemia might suggest insignificant rate of negative sodium balance of these patients.

We disagree that patients with multiple diarrhoea attacks each year who receive ORS with low sodium concentrations will end up with more salt deficits. Patients are unlikely to have several attacks of cholera each year. Sodium deficiency is an unlikely event unless patients with diarrhoea are also deprived of nutritional care during the acute and convalescent phases of illness. The recommendations for use of this formula in all causes of diarrhoea irrespective of age will depend on the evaluation of its benefits and risks by the expert committee on ORS formulations.

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#### A rare and bloodless situation

Sir—I recently came across an interesting and rare situation while working overseas for the medical aid organisation Médecins Sans Frontières. One day, just before anaesthetising an otherwise healthy young woman for a laparotomy, I was told by one of the other surgeons that my surgeon was a Jehovah's Witness, who would not allow blood to be given to his patients. I was stunned by this restriction.

The extent of surgery was not clear from the onset. Routine haemoglobin estimations were not done in this hospital before surgery and blood was difficult to obtain. I was not unduly worried, but the warning could not be ignored. Since I was the only anaesthetist in the hospital and I was a guest in the country, I decided to postpone surgery to discuss the situation with the senior surgeon. The problem was well known to his colleagues but efforts to come to a solution seemed to have failed in the past. I then discussed the situation further with my surgeon.

His argument consisted mainly that the patient and her family were aware of the fact that he was a Jehovah's Witness and that she had agreed not to be given blood. He said that as the consultant surgeon he decided that she would not be given blood. I countered that as the consultant anaesthetist I would give blood whenever I felt it necessary without reference to the surgeon. He smiled at me and said that he respected my point of view, and added that in that case he would have to leave theatre for the duration of the blood transfusion. This amused me greatly. I decided not to delay any further and I anaesthetised the patient without difficulty and the operation proceeded without blood loss.

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## Screening of schoolchildren for tuberculosis

Sir—Tuberculosis is cause for concern, particularly because there has been an increase in the number of disease notifications in the past few years. Surveillance and screening are seen as the most effective methods in the control and prevention of this disease.<sup>1</sup>

The British Thoracic Society recommends that all immigrants or other entrants from Asia, Africa, South and Central America, and other countries where tuberculosis is common (an incidence of 40/100 000 population) who plan to stay longer than 6 months should be screened,<sup>2</sup> either at the port of entry or the district of intended stay. Screening is also advised for children. However, there is no guidance on exclusion and screening of children who have spent substantial time (eg, 12 months or more) in countries with high prevalence of tuberculosis but who are normally resident in the UK. In Walsall, there is not enough justification to continue to screen children who belong to this category, and the policy was changed some years ago. To ascertain the policies of other districts, we sent questionnaires to consultants of communicable disease control in 180 districts in England and Wales in May, 1999, on their screening policy.

35 (19%) of 180 districts replied. Three districts had no policy for screening children on return from countries with high prevalence of tuberculosis because they had few or no people of ethnic origin. 32 districts that had a policy allowed children who were returning after a short stay ( $\leq 6$  months) to join school immediately without screening. In 30 districts, children returning after a visit of 12 months or longer would be allowed to join immediately without screening. Only two districts screened children on return after a visit of 12 months or longer to areas of high tuberculosis prevalence (40/100 000), before they were allowed to join school.

Many districts have no policy and expect the children to attend school immediately, which seems to be independent of ethnic origin. Of the districts that responded, the proportion of children who were black or of other ethnic origins varied from 0 to 17%. A study on screening of immigrants reported a yield of active cases of 0.65%.<sup>3</sup> Studies on the effect of imported cases of tuberculosis on the increase in tuberculosis notification have indicated that socioeconomic factors play a major part with a small contribution from immigration, particularly from endemic areas.<sup>4</sup>

A balance needs to be struck between the concern over public health and safety, and the protection of individual rights and civil liberties.<sup>5</sup> A way forward would be to institute specialised medical consultation before departure and investigate children who have symptoms of tuberculosis on their return.

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## Japanese doctors' attitudes to complementary medicine

Sir—Complementary and alternative medicine has become more important in view of dissatisfaction with modern western medicine (conventional medicine) or with medical economics.<sup>1</sup> Most studies on attitudes to complementary medicine have been done in European and North American countries.<sup>1–5</sup>

Several Asian countries have their own specific medical systems. In Japan, Chinese herbal medicine (kampo), which was originally introduced in the 5th to 6th century, has been greatly modified by Japanese practitioners over a long time. The exclusion of kampo from authorised medical education by the government about 100 years ago has meant that modern western medicine is the conventional form practised in Japan at present.

We surveyed Japanese doctors' attitudes to complementary medicine by distributing questionnaires to 540 randomly selected doctors of the 3774 doctors of the Kyoto Prefecture Medical

Association in Japan. Replies were received from 364 doctors, a response rate of 67%.

Some form of complementary medicine was practised by 267 of the respondents (73%), the most common being kampo (70% of the respondents; table). Surprisingly, almost all doctors practising complementary medicine were kampo practitioners (96%). In addition, 200 (55%) doctors were consulted by their patients about kampo, and 44 doctors (12%) referred their patients to kampo specialists. Thus, kampo was most frequently practised by doctors themselves.

Acupuncture, electroacupuncture, and moxibustion were practised by electroacupuncturists and specialists in moxibustion rather than by doctors.

A few doctors (8%) practised other forms of alternative medicine including chiropractic, aromatherapy, homoeopathy, health spa therapy, ayurveda, hypnosis, flower therapy, thalassotherapy, herb therapy, qigong, yoga, dietary therapy, imagery, meditation, art therapy, and prayer. This result is very different from that of doctors in European and North American countries.<sup>2</sup>

Therefore, we examined whether Japanese doctors recognise kampo as a form of complementary medicine or if they regard kampo as mainstream medicine. Replies were received from 335 of 364 doctors (a response rate of 92%) who returned responses to the previous questionnaires. About 25% of doctors did not regard kampo as complementary medicine. This attitude of Japanese doctors to complementary medicine CAM may reflect the philosophical, historical, and cultural background particular to Japan.

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	Yes (%)	No (%)	Total (%)
Practising some form of CAM	267 (73)	97 (27)	364 (100)
Chinese herbal medicine (kampo)			
Practising	251 (70)	106 (30)	357 (100)
Consulting	200 (55)	161 (44)	361 (100)
Referring	44 (12)	318 (88)	362 (100)
Acupuncture, electroacupuncture, moxibustion			
Practising	38 (10)	324 (89)	362 (100)
Consulting	156 (43)	206 (57)	362 (100)
Referring	79 (22)	284 (78)	363 (100)
Other alternative therapies—practising	28 (8)	326 (92)	354 (100)

CAM=complementary and alternative medicine.

Doctors' attitudes to CAM in Kyoto, Japan

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## Disability in developing countries

Sir—Benedicte Ingstad (Aug 28, p 757)<sup>1</sup> exposes the distorted picture of disabled people's lives that may arise if health officials alone are consulted about burdens of disability. This view dovetails nicely with Ustun and colleagues<sup>2</sup> attempt to ground the estimation of international burden of disease, through the involvement of people with disabilities and their carers. The views of such people are considered, highlighting the impact of local situations on their overall burden.

What is the appropriate way to incorporate both international and local descriptions of burden in a national health plan? The international disability adjusted life year (DALY) index draws attention to the importance of disability in calculation of disease burdens, and this emphasis on disability should be incorporated by national planners. But DALY calculations assume that each disability carries the same burden in every situation,<sup>3</sup> and recognise that such an inert measure needs to incorporate local issues before they can be applied to a national health programme. Not only the frequency of different diseases, but also the resources available for health care, and the socioeconomic condition of people with disabilities will determine the burden each condition places on the country.

The challenge is to remain true to individuals' experiences and place them in a comparative and objective national context. How do we grasp the relevance of a social context in a way that is useful to burden calculations? What weight do we give to different information sources? Although we may or may not need the DALY, "an international standard of disability analogous . . . to a kilogram for weight",<sup>4</sup> there is no doubt that a standardised measuring device analogous to a weighing scale is required for use at national level.

If individuals with a disability or their carers are invited to make their case to health planners, there will be direct competition between interest groups, with the most articulate or manipulative claiming the resources. Alternatively, if only experts are allowed to judge, the real situation may be misrepresented. A possible solution is to involve key informants from various sectors: people with disabilities and their carers, public health and clinical experts, social workers, and policy makers.<sup>2</sup> We need clear criteria on how the burden of conditions should be assessed. The availability of compensation and health care resources for people with different conditions should be clarified to inform the participants. The epidemiological considerations in DALY calculations should be incorporated. The resultant ranking of burdens should be more relevant to the country's health needs than the present unbalanced health policies for people with disabilities.

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Box 273, Banjul, The Gambia

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## Register of randomised trials

Sir—In their Oct 2 commentary<sup>1</sup> Richard Horton and Richard Smith recommend a register of randomised clinical trials. This register could help achieve not only the objectives they set forth, but might also reduce the risk of abuse to which we drew attention 2 years ago<sup>2,3</sup> in the description of the premature closure of a clinical trial that involved volunteers, by its industrial sponsors for purely commercial reasons. The event provoked surprisingly little reaction in the clinical research community. Were we wrong to protest, or have we become so dependent on industrial sponsors that we do not wish to offend them?

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## An old case of pathological laughing and crying

Sir—In addition to being of intrinsic and historical interest, knowledge of the antiquity of a disease can potentially be useful in the generation and testing of hypotheses about the cause of the disease. Indeed, the cause of a disease has to be at least as old as the disease itself. Here we present one of the oldest cases of pathological laughing and crying, taken from the casebook of the famous barber-surgeon Ambroise Paré (1510-90).<sup>1,2</sup>

"An honoured gentleman brought his wife to this city to get the advice of Messrs. le Grand. Duret, and myself [physicians], to find why she wept and laughed without reason, and no one could cure her. We treated her with many remedies but could accomplish little; finally he took her away in the same state she had come."

The patient in this description had a long history of unexplained laughing and crying. The differential diagnosis for pathological laughing and crying includes pseudobulbar palsy, gelastic epilepsy, and psychiatric illness.<sup>3</sup> In this patient, no paresis or neurological events were noted, making pseudobulbar palsy unlikely, but this diagnosis cannot be ruled out. With the presence of both laughing and crying, gelastic seizures can probably be excluded. Meissner<sup>4</sup> discusses episodes "which occur in the form of convulsions, or as emotional outbursts or moods that appear to be entirely unmotivated, or as screaming, laughing or crying spells". Psychiatric disease is probably the most likely explanation for this type of episode. Despite some advances, this condition remains difficult to treat.

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## DEPARTMENT OF ERROR

*Leg lengthening*—In this commentary by Richard Gross (Nov 6, 1999, p 1574), an extraneous passage appeared with each of the bullet points. The first two lines and the first word of the third line of each bullet point should be ignored.