

refusing pilot studies) and said that the major benefit would be "that we will have far more data about what we are doing—about what we can get for our money and about how much things cost."<sup>1</sup> Is it naive of me to point out that all this could have been achieved without the need for a potentially catastrophic "second founding of the health service," as he describes it?

I note too that he did not answer the question about the possibility of a large hospital going under, presumably because he believes it to be more than a possibility. When a previous health minister (Mr Roger Freeman) spoke at a BMA meeting here I asked him what would be the position if the x ray department in a neighbouring hospital charged less for its various examinations than mine and local fundholding general practitioners sent all their patients there. Would I need to sack any redundant radiographers? "That's what market forces are all about," was the reply. In my view that is not what a national health service is all about.

MYER GOLDMAN

Fazakerley Hospital,  
Liverpool L9 7AL

1 Smith R. NHS profile: William Waldegrave: thinking on the new NHS. *BMJ* 1991;302:636-40. (16 March.)

## Vitamins and IQ

SIR,—Editorials on 9 March in both the *BMJ*<sup>1</sup> and the *Lancet*<sup>2</sup> have reviewed important doubts about the recent claim<sup>3</sup> that vitamin supplements have been shown to improve IQ. That claim derived chiefly from a study that was published only in a relatively obscure journal edited by one of the study's authors, but the claim was widely publicised by the BBC in its *QED* programme on 27 February, which concluded, to an audience of millions, that "the experts have given their verdict, and they are confident the link between diet and intelligence is now proved." The next day BBC Books published *Improve your Child's IQ and Behaviour*,<sup>4</sup> a monograph (by the principal investigator of the study) that forcefully restated the claimed benefits and said that the best vitamin supplements for improving IQ were Vitachieve, a brand launched on the same day as the book and with financial links to the sponsors of the study.

Because of this wide publicity it is important to note that, purely from the viewpoint of clinical trial methodology, the published report does not provide reliable evidence of any real effects of such supplementation on IQ. The methodological problem is that so many p values could have been generated that even if vitamins are wholly ineffective it would not be particularly surprising for a few fairly extreme p values to be unearthed—indeed, it would be mildly surprising if they could not be. The trial was a placebo controlled comparison of 0%, 50%, 100%, and 200% of a set of vitamin and mineral supplements for 13 weeks among 615 children with an unstated degree of compliance.

At least six main outcomes were studied—MAT (matrix analogies test), EPQ (Eysenck personality questionnaire), RMT (Raven's matrices test), WISC-R verbal (Wechsler intelligence scale for children, revised), WISC-R non-verbal, and CTBS (comprehensive test of 13 basic skills). Subanalyses of these six were also considered. The follow up was 90-93% complete for MAT, EPQ, and RM, 67% complete for WISC-R, and 48% complete for CTBS.

At least five treatment comparisons were available of different strengths of vitamin supplementation (0 v 50, 0 v 100, 0 v 200, 0 v any, and the trend 0 v 50 v 100 v 200), and only one of these (0 v 100) indicated any conventionally significant difference.

Hence, the number of hypotheses implicitly available for statistical analysis must have been at

least 30 (6×5), but in fact it was probably far more. The most heavily emphasised result is that for "non-verbal intelligence" (WISC-R non-verbal): the mean changes for the 0%, 50%, 100%, and 200% groups are 8.9, 10.1, 12.6, and 10.4 respectively—and, although 0 v 50% is "not significant" and 0 v 200% is "not significant," the main claim in the paper and in the *QED* programme is that 0 v 100% is "significant" (p=0.01—that is, about 2½ standard deviations). Given the number of hypotheses implicitly examined, however, it should not be particularly surprising to get one at about 2½ standard deviations just by the play of chance.

The particular analysis can itself be run two ways—for all children, or for those who took most of their pills, again doubling the number of hypotheses implicitly examined. If those who did not take their pills are excluded the difference rises to p=0.002, but again this is not remarkably significant, given the number of hypotheses implicitly tested. For example, the one other place where a p value of 0.002 arises is said to be for the changes in arithmetic ability—but the *worst* change in arithmetic ability is for those who got 200% vitamins. Neither an increase of non-verbal IQ by 100% vitamins nor a decrease of arithmetic IQ by any other dose of vitamins is, however, established by such p values.

The central problem in the interpretation of any such analyses is to assess the extent to which, in the absence of any real therapeutic effect, nominal p values could have been inflated by choosing to emphasise the most extreme of a large number of p values that might have been emphasised had they looked remarkable (and some even more extreme p values may be generated when future analyses of the blood samples taken before randomisation allow subgroups to be defined in dozens of different ways by deficiencies of various degrees in several different markers of nutrition). Yet the authors simply do not consider this question.

There are, moreover, some other aspects of the discussion in the paper that are unsatisfactory—for example, the authors claim that dietary supplementation improved non-verbal IQ by a minimum of 6 points and an average of 11 points. This is quite wrong: although the three treatment groups, taken together, increased by an average of 11 points, the placebo group increased 9 points, so the difference is only 2 points and, especially when due allowance is made for multiple significance testing, is not significant. Nearby, they say "it is clear" that the 100% supplement is better than the 50% or the 200% supplement (and then start erecting theories to explain why). Again, this is quite wrong: there is no significant heterogeneity between the values of 10.1, 12.6, and 10.4 for the 50%, 100%, and 200% groups.

In summary, detailed scrutiny of the report of the trial strongly reinforces the general doubts expressed in the *BMJ* and *Lancet* editorials. The question of whether some form of dietary change or nutritional supplement can improve the intelligence of a substantial proportion of the children in Britain is important, but it has not been reliably answered—and if it is to be reliably answered this should be done by specialists not only in nutrition and in personality testing but also in the proper design and interpretation of clinical trials.

RICHARD PETO

Clinical Trial Service Unit,  
University of Oxford,  
Radcliffe Infirmary,  
Oxford OX2 6BR

- 1 Whitehead RG. Vitamins, minerals, schoolchildren and IQ—more questions than answers (still). *BMJ* 1991;302:548. (9 March.)
- 2 Anonymous. Brains and vitamins [Editorial]. *Lancet* 1991;337:587-8.
- 3 Schoenthaler SJ, Amos SP, Eysenck HJ, Peritz E, Yudkin J. Controlled trial of vitamin-mineral supplementation: effects on intelligence and performance. *Person Individ Diff* 1991;12:351-62.
- 4 Schoenthaler S. *Improve your child's IQ and behaviour*. London: BBC Books, 1991.

## Invasive pulmonary aspergillosis in non-immunocompromised patients

SIR,—Dr Jonathan L Hovenden and colleagues draw attention to locally invasive pulmonary aspergillosis in ill patients and speculate on the aetiology and diagnosis of this condition.<sup>1</sup> They do not refer to two previous reports in your columns of this normally fatal disease<sup>2,3</sup>; in one of these my colleagues and I discussed criteria for diagnosis<sup>3</sup> that are less invasive than those suggested by Dr Hovenden and colleagues.

Aspergillus diseases always seem to occasion surprise in clinicians coming across them. They need not. The organism is a soil saprophyte, the spores of which get into the air from the dead leaves on which they flourish, mainly in the winter months.<sup>4</sup> They intend humans (and animals)—they are a major pulmonary pathogen in birds—no harm, but have unfortunately developed sophisticated antiprotozoal defences in their natural habitat which equip them well to survive in the lung by resisting macrophage attack.<sup>5</sup> In the normally fit human the lung's defences usually win. In people with asthma certain characteristics of the bronchial exudate tip the balance towards aspergillar survival, which explains why bronchopulmonary allergic aspergillosis occurs,<sup>6</sup> while leucocyte depletion, influenza, and a variety of other conditions make locally invasive disease much more probable. Immunosuppression may allow disseminated disease.

The key to diagnosis is examination of the sputum for hyphae. These are almost never present as a consequence of direct inhalation from the air, whereas sputum culture may be incidentally positive because of the natural elimination of inhaled spores.<sup>7</sup> However, profuse or repeated culture of aspergillus species from sputum should always be taken as an indication of likely pulmonary disease, in the presence of consolidation and fever.<sup>3</sup>

Aspergillus species are the only important pathogenic lung fungi in the United Kingdom.<sup>8</sup> Their effects are common enough for physicians to bear them in mind in any patient ill with pneumonia. They may be diagnosed and treated successfully if sputum is cultured on appropriate media and examined under a microscope.

A SEATON

Department of Environmental and Occupational Medicine,  
University of Aberdeen,  
Aberdeen AB9 2ZD

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SIR,—Having recently completed a retrospective study of invasive aspergillosis detected by necropsy, I was interested to read about the experiences of Dr Jonathan L Hovenden and colleagues.<sup>1</sup> My own series of 32 cases (out of 2315 consecutive necropsies carried out in one hospital over 10 years) included three patients who did not fall into conventionally defined "high risk"