

# CORRESPONDENCE

e-mail submissions to [correspondence@lancet.com](mailto:correspondence@lancet.com)

## The statin wars

Sir—In your Oct 25 Editorial (p 1341)<sup>1</sup> you mention the importance of a large-scale outcome trial with a statin in patients with chronic heart failure.

We agree with this view. Although there are reasons to believe that a statin might be of benefit in patients with both coronary and non-coronary causes of heart failure, there are also potentially detrimental effects of statins in this syndrome. Although recognised myocardial infarction is uncommon in heart failure, coronary occlusion can underlie death from progressive pump failure as well as sudden death.<sup>2</sup> Alternatively, statins might be beneficial because of their anti-inflammatory and anticytokine actions, effects on autonomic function and endothelial function, and anti-remodelling action.<sup>3</sup>

Conversely, by decreasing the production of coenzyme Q<sub>10</sub>, statins can further impair muscle function in heart failure.<sup>3</sup> Similarly, by reducing already low cholesterol concentrations in patients with heart failure, statins can impair the postulated protective role that lipoproteins have in detoxifying endotoxins entering the circulation from the gut.<sup>4</sup> The fact that lower cholesterol concentrations are associated with a worse prognosis in heart failure is of concern.<sup>3,5</sup>

Existing statin trials have generally excluded patients with heart failure. The resulting uncertainty about the role of these drugs in heart failure is reflected in current guidelines and clinical practice.<sup>3</sup> Consequently, we and other academic colleagues have for some years advocated a clinical outcome study with a statin in heart failure. At least one study is now underway. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) will enrol about 4950 patients with chronic symptomatic systolic heart failure due to coronary artery disease, in New York Heart Association (NYHA) class III or IV and with a left-ventricular ejection fraction (LVEF)  $\leq 0.40$  or NYHA class II with a LVEF  $\leq 0.35$ . Patients are being randomly assigned to double-blind rosuvastatin 10 mg once daily or matching placebo. CORONA is an endpoint-driven trial that is expected to last 52 months. The primary outcome is the composite endpoint of cardiovascular death or non-fatal myocardial infarction or non-fatal stroke.

We have attended meetings sponsored by AstraZeneca, and received research funding, honoraria, and travel expenses from that company, and from other large cardiovascular pharmaceutical companies.

Peter Dunselman, \*Åke Hjalmarson, John Kjekshus, John McMurray, Finn Waagstein, for the Executive Committee of the CORONA trial

Amphia Hospital, Breda, Netherlands (PD); \*Sahlgrenska University Hospital, S-41345 Göteborg, Sweden (AH, FW); Rikshospitalet, University of Oslo, Oslo 0027, Norway (JK); and Western Infirmary, Glasgow G11 6NT, UK (JM)  
(e-mail: [ake.hjalmarson@hjl.gu.se](mailto:ake.hjalmarson@hjl.gu.se))

- 1 The Lancet. The statin wars: why AstraZeneca must retreat. *Lancet* 2003; **362**: 1341.
- 2 Uretsky BG, Thygesen K, Armstrong PW, et al. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. *Circulation* 2000; **102**: 611–16.
- 3 Krum H, McMurray JJV. Statins and chronic heart failure: do we need a large-scale outcome trial? *J Am Coll Cardiol* 2002; **39**: 1567–73.
- 4 Rauchhaus M, Coats AJ, Anker SD. The endotoxins-lipoprotein hypothesis. *Lancet* 2000; **356**: 930–33.
- 5 Horwich TB, Hamilton MA, MacLellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increased mortality in advanced heart failure. *J Card Fail* 2002; **8**: 216–24.

Sir—*The Lancet*<sup>1</sup> and Tom McKillop<sup>2</sup> both make valid points in their argument over the marketing of Crestor (rosuvastatin) since its recent launch. You are right to raise the issue of safety with statins. This is particularly pertinent to new statins, such as rosuvastatin, which do not yet have the tens of millions of patient-years of exposure and safety data that older medicines of the same class have been able to accumulate. McKillop is also correct in stating that outcome data are rarely available for a new medicine at the time of launch and have never been available for statins and anti-hypertensives at this early stage.

The relation between dose and safety of rosuvastatin is worthy of consideration. AstraZeneca initially applied for a licence for rosuvastatin at a dose range of 10–80 mg. This range is identical to that of Pfizer's atorvastatin. Sales and marketing staff would then have been able to claim dose-for-dose superiority of effect over atorvastatin across its dose range, since rosuvastatin is more potent than atorvastatin.

However, the success of such a strategy relies on a clear understanding of the side-effect profile of the molecule. An 80 mg dose of rosuvastatin clearly has an unacceptable side-effect profile. This issue was highlighted when the US regulatory authorities examined the New Drug Approval data, resulting in the Food and Drug Administration eventually granting a licence for rosuvastatin only at a dose range of 5–40 mg. Interestingly, the regulatory authorities of three European countries withdrew from the mutual recognition procedure to grant a licence for rosuvastatin. Finally, WellPoint Health Networks Inc—the USA's second-largest private health insurer—has said it will not reimburse patients prescribed rosuvastatin because of concerns over the safety and benefits of the drug.

I would suggest that, with increased experience of use by clinicians, the effective dose range of rosuvastatin could fall even further, thus providing a greater safety margin. It might well be, for example, that a dose of 2.5 mg might be clinically adequate for many patients. Indeed, as little as 1 mg of rosuvastatin provides over half the beneficial effect of an 80 mg dose.<sup>3</sup> This would have major pricing and cost implications, and I can already hear the tablet splitters hard at work!

The issue of pharmaceutical companies launching their products at a dose that turns out to be higher than is necessary is not a new one. Examples from the past include angiotensin-converting-enzyme inhibitors,  $\beta$  blockers, thiazides, and oral contraceptives. Those who forget history are condemned to repeat it. Prescribers of rosuvastatin should consider the dose.

I have worked for, and hold shares in, AstraZeneca. I have undertaken consultancy work for a number of other pharmaceutical companies, and these are listed on my website: <http://www.blenkinsopp.co.uk>.

John Blenkinsopp

Richmond Building, University of Bradford, Bradford BD7 1DP, UK  
(e-mail: [j.blenkinsopp@bradford.ac.uk](mailto:j.blenkinsopp@bradford.ac.uk))

- 1 The Lancet. The statin wars: why AstraZeneca must retreat. *Lancet* 2003; **362**: 1341.
- 2 McKillop T. The statin wars. *Lancet* 2003; **362**: 1498.
- 3 Olsson AG. Statin therapy and reductions in low-density lipoprotein cholesterol: initial clinical data on the potent new statin Rosuvastatin. *Am J Cardiol* 2001; **87**: 33B–36B.

Sir—I was interested in the strength of your polemic on the statin wars.<sup>1</sup> Although clearly the points you raised were important, an article such as this will have a profound effect on prescribing habits. I feel it is therefore essential to declare any conflicts of interest. May I invite you to do so?

I have received hospitality from both AstraZeneca and Pfizer, have sat on a Pfizer Advisory Board in the field of migraine, and received research funding from AstraZeneca.

D P Kernick

St Thomas Health Centre, Exeter EX4 1JH, UK  
(e-mail: su1838@eclipse.co.uk)

1 The Lancet. The statin wars: why AstraZeneca must retreat. *Lancet* 2003; **362**: 1341.

Sir—As a clinician and the Editor of *Atherosclerosis in Primary Care*, I would like to respond to your Editorial<sup>1</sup> on statins, and specifically the attack on AstraZeneca.

Rosuvastatin originated in Japan with another manufacturer. Preliminary data when reassessed by AstraZeneca revealed minor discrepancies (eg, clearance), but nothing striking. As for safety, the product had the same, if not more, patients exposed to it than any other statin at the time of launch. I can say this with confidence because I was involved in the launch of Pfizer's atorvastatin.

Furthermore, I was requested before the approval of cerivastatin by the Therapeutics Product Directorate of Health Canada to give comments or support for the product. At this point I was informed of serious adverse events at the high dose. I was also aware of a press release made by a doctor who touted the drug as being safe "at any dose" when in fact he had not tested these doses nor were there such data in the company database. Despite my objection, this comment was not retracted and I elected not to participate. Although I used the drug in later years, I did so with follow-up and appropriate laboratory work, and never had a serious adverse event. However, some speakers ascended to such a point in their belief of absolute safety, that they proclaimed to primary-care doctors that statins were "so safe" that they did not need frequent laboratory follow-up. Clearly, this was not correct and the product was withdrawn.

Rosuvastatin, by contrast, was tested at high doses from the outset. I commend such foresight because it is essential to know the therapeutic and toxic windows and the amount of overlap within these doses well before product launch. As a result, a maximum dose of 40 mg was recommended on the basis of safety and lack of incremental efficacy at the higher dose. All adverse

events were made available in an open fashion, not unlike the launch of atorvastatin.

Similar to all statins at the time of release, data on the primary endpoint were not available. This is not unusual and is a very accepted practice. Primary endpoint data take many years and large populations to achieve significance. It would be unreasonable with the current patent laws to expect to wait for these data: the drug would be out of patent protection before the study was published. AstraZeneca is responsible for fulfilling the requirements of the regulatory bodies, which it has done, and for disclosing all side-effects as it has in the past and must by law in the future. It has made no attempt to hide any safety issue.

My belief is that rosuvastatin is not a bad drug. I agree with your concern about the "marketing machine", but this is a separate issue from the safety of the drug or funding of basic vascular inflammation research. Tom McKillop has an obligation to market his product. Failure to market a product can result in a good product not being used because few know about it. Doctors are just as much a part of the marketing machine if they declare a product safe at any dose. This is especially disconcerting when the pharmaceutical industry runs to these same people for further endorsements and research projects. AstraZeneca in this particular case has taken the high road in not doing so.

We, as doctors, have the option to accept or reject marketing practices. We can define ethical practice standards and personally follow them. If we want more data, we can wait and prescribe when we feel comfortable with the data (if ever). Marketing is not just an AstraZeneca issue, and personal attacks on an individual or a product is not the solution.

I am not an AstraZeneca employee, nor have I been paid by AstraZeneca to submit this option.

Peter Wozniak

Unit 102, 101B Holiday Inn Drive, Cambridge, Ontario, Canada N3C 1Z3  
(e-mail: cfmc@golden.net)

1 The Lancet. The statin wars: why AstraZeneca must retreat. *Lancet* 2003; **362**: 1341.

Sir—We congratulate you on your strong editorial statement of Oct 25.<sup>1</sup> Such comments by widely read, high-status journals are an antidote to the billions of dollars spent marketing new "me too" drugs. New drugs often have no advantage over existing products,<sup>2</sup> and can turn out to be less safe,<sup>3</sup> with unexpected and under-recognised adverse effects, such as cognitive impairment from statins.<sup>4</sup> The debate about rosuvastatin raises questions about

commercial environments and regulatory systems that reward companies for developing "me too" drugs at the expense of needed pharmaceutical innovation and for promoting drugs on the basis of surrogate endpoints. Surrogate endpoints have turned out to be misleading for many drugs including flecainide, mibefradil, and hormone replacement therapy.<sup>5</sup>

Increased corporate responsibility can be complemented by prescribers developing skills for assessment of drug promotion. Coincidentally, the inaugural edition of Healthy Skepticism's AdWatch (<http://www.healthyskepticism.org/adwatch.asp>) also focuses on an AstraZeneca product—the proton-pump inhibitor esomeprazole (Nexium). As with rosuvastatin, the promotion of esomeprazole is aimed at a better share of a crowded market, in this case by making comparisons with unreasonably low doses of other proton-pump inhibitors.

JJ and PM are chair and director, respectively, of Healthy Skepticism. JJ, PM, and DM have attended meetings sponsored by AstraZeneca; DM has received an honorarium for chairing a meeting.

\*Jon Jureidini, Peter Mansfield, David Menkes

\*Department of Psychological Medicine, Women's and Children's Hospital, North Adelaide 5006, South Australia, Australia; Department of Psychological Medicine, University of Wales Academic Unit, Wrexham LL13 7YP, UK (DM); and Healthy Skepticism, 34 Methodist Street, Willunga, South Australia 5172 (PM)  
(e-mail: jureidini@wch.sa.gov.au)

- 1 The Lancet. The statin wars: why AstraZeneca must retreat. *Lancet* 2003; **362**: 1341.
- 2 Anon. A review of new drugs and indications in 2002: financial speculation or better patient care? *Prescribe Int* 2003; **12**: 74–77.
- 3 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002; **287**: 2215–20.
- 4 Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med* 2000; **108**: 538–46.
- 5 Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996; **125**: 605–13.

Sir—We offer an abridged response to your Oct 25 Editorial<sup>1</sup> because we believe the assertions that rosuvastatin (Crestor) is somehow an "inadequately investigated" medicine and "has an inferior evidence base supporting its safe use", compared with currently marketed cholesterol-lowering medications, are false and misleading. Readers who require additional information should view our full-length reply available at <http://image.thelancet.com/extras/03cor10176web.pdf>. The key facts, as they relate to the Editorial, are outlined below.

The clinical development programme for rosuvastatin is the largest ever for a statin preapproval, and included more than 12 500 rosuvastatin-treated patients with a broad range of dyslipidaemias (eg, primary hypercholesterolaemia, heterozygous and homozygous familial hypercholesterolaemia, mixed dyslipidaemia, isolated hypertriglyceridaemia) and comorbidities (eg, renal impairment, hypertension, cardiovascular disease, diabetes).<sup>2</sup>

Worldwide regulatory authorities have carefully reviewed the extensive efficacy and safety database from this programme. On the basis of these data supporting the efficacy and safety profiles of rosuvastatin, 36 countries have approved the regulatory applications for rosuvastatin.

LDL cholesterol is the appropriate endpoint for measuring the effectiveness of lipid-lowering medications, according to international regulatory authorities and cholesterol management guidelines.<sup>3,4</sup> This principle forms the basis of clinical decision-making in managing patients with lipid disorders.

All trials in the rosuvastatin clinical programme were done in compliance with Good Clinical Practice requirements and were designed, analysed, and reported to the highest scientific and medical standards.

The trials in the GALAXY Programme have been designed with the help of numerous international thought leaders, representing many medical disciplines, to address specific unanswered questions regarding the use of statin therapy, including an ongoing large-scale clinical outcomes trial in patients with congestive heart failure (CORONA Trial).

The STELLAR Trial,<sup>5</sup> which examines the comparative dose efficacy of rosuvastatin versus comparator statins, was the largest trial of its kind to date and should aid doctors in making informed therapeutic choices in the treatment of dyslipidaemia.

You specifically mention the safety of the 80-mg dose of rosuvastatin. In 2001, after a thorough benefit-risk evaluation, AstraZeneca chose to suspend further development of this dose and voluntarily withdrew it from consideration in the regulatory approval process; however, you fail to mention that other statins have been studied at doses higher than the approved dose range for clinical use.

The efficacy and safety data from the entire clinical programme show a favourable benefit-risk profile for rosuvastatin across its dose range.<sup>2</sup>

Finally, your contention that there are “no reliable data about efficacy and safety” for rosuvastatin is completely inaccurate. In his article assessing the

benefit-risk profile of rosuvastatin,<sup>2</sup> Bryan Brewer Jr, of the National Heart, Lung, and Blood Institute concludes: “the extensive data on the lipoprotein-modifying effects, goal achievement, pharmacologic characteristics, and safety and tolerability of the 10- to 40-mg doses of rosuvastatin indicate that this new statin will be a useful therapeutic agent for the treatment of patients at risk for the development of cardiovascular disease.”

Your subjective Editorial trivialises years of exhaustive research by AstraZeneca as well as the efforts of hundreds of respected lipid researchers, regulators, clinical trialists, and their patients. Despite an increased awareness of lipid disorders as they relate to cardiovascular disease, underdiagnosis and undertreatment of these disorders remain a serious medical problem worldwide. Rosuvastatin has profound effects on lowering LDL cholesterol concentrations, and should be viewed as a welcome alternative to existing therapies.

Gunnar O Olsson, \*James W Blasetto, Brian S Bryzinski, Richard J Caplan, Alex Gold

AstraZeneca, Mölndal, Sweden (GOO);  
\*AstraZeneca, 1800 Concord Pike, D3B-525,  
Wilmington, DE 19803, USA (JWB, BSB, RJC, AG)  
(e-mail: james.blasetto@astrazeneca.com)

- 1 The Lancet. The statin wars: why AstraZeneca must retreat. *Lancet* 2003; **362**: 1341.
- 2 Brewer HB Jr. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol* 2003; **92** (suppl 4B): 23K–29K.
- 3 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–97.
- 4 Wood D, De Backer G, Faergeman O, Graham I, Mancina G, Pyörälä K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J* 1998; **19**: 1434–503.
- 5 Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; **92**: 152–60.

#### Editor's reply

In response to D P Kernick: I receive no personal funding from any pharmaceutical company; I do not hold equity interests or stocks in the pharmaceutical sector; I do not sit on industry advisory boards; and I do not undertake consultancy work for any organisations outside *The Lancet*.

The journal publishes advertising from various commercial (including

pharmaceutical) concerns, and receives income from reprint sales. If a company withdrew its advertising or stopped buying reprints from *The Lancet*—for example, if we published a piece critical of their marketing practices—the journal's revenue could fall. A drop in *The Lancet's* income could conceivably diminish my personal remuneration.

The business climate for most modern medical journals, whether in the for-profit or non-profit sector, is strongly pro-pharmaceutical industry. The industry is an important and much-valued customer for medical publishers. In this environment, I know that it can be difficult for editors to raise questions about the ethics and marketing tactics of pharmaceutical companies, not only in what we write and publish but also in applying strict advertising guidelines. *The Lancet's* editors have long had, and continue to have, complete editorial independence over decisions concerning content.

Richard Horton

*The Lancet*, 32 Jamestown Road, London  
NW1 7BY, UK  
(e-mail: editorial@lancet.com)

## Mercury pollution in India

Sir—The News piece by Dinesh C Sharma on mercury pollution in India (Sept 27, p 1050)<sup>1</sup> is an attempt at sensationalism.

The statement on kidney failure and nervous breakdown among workers of the closed factory attributed to R K Singh, who was a member of the Indian People's Tribunal (IPT), is not based on any scientific evidence. It is based on a public hearing at which some motivated ex-employees gave statements mentioning that they had present or previous health problems. In fact, in the final report,<sup>2</sup> the IPT has put in a disclaimer to disown responsibility for statements made by any person or groups.

The IPT panel had no occupational health expert, and Singh—a senior programme officer with the Wildlife Trust of India—holds a doctorate in wildlife sciences and not in any field of medicine or indeed occupational health.

Hindustan Lever has been following a well established scientific protocol for the occupational health surveillance of its employees. Employees at the thermometer factory underwent monthly biological monitoring (mercury in urine tested through atomic absorption spectroscopy) as well as a comprehensive annual clinical examination. The factory regulated its environment to comply with the national regulation of a threshold limit value of mercury of

0.05 mg/m<sup>3</sup>. Individual and group analysis of biological monitoring over the past 15 years has not revealed any cause for concern, and group means are well below the WHO recommended group mean for mercury in urine of 50 µg/L.<sup>3</sup> Subsequent to the closure of the factory (which, incidentally, was of our own volition to institute an internal audit), we advertised in the local press inviting all ex-employees who were worried about their health to seek assessment by a team of doctors. Only 55 turned up for the assessment, and none of them had any ill health attributable to mercury exposure.

The protocol for epidemiological surveillance for this study, and indeed for the review of the health surveys over the life of the factory (biological monitoring, workplace environmental monitoring, shop-floor health and safety practices, and clinical assessments), have all been independently studied and validated by an expert from the Netherlands Organisation for Applied Science (appointed at the specific request of local non-governmental organisations and Tamil Nadu state government); the country's premier teaching institute—the All India Institute of Medical Sciences; and the country's leading professional body—the Indian Association of Occupational Health.

Over the years, the factory has been subject to statutory inspections and health assessments by the factories inspectorate of the government. This body has not found any mercury-related ill-health among the employees. On the environmental front, comprehensive sampling and analysis by the international firm Dames and Moore of soil, vegetation, lichen, lake water, and fish from Kodaikanal has found no evidence of contamination by organic or inorganic mercury outside the factory.

The report by Toxics Link<sup>4</sup> is erroneous and designed to create a media sensation without any scientific substantiation.

T Rajgopal

Hindustan Lever Limited, 165/166 Backbay Reclamation, Mumbai 400 020, India (e-mail: thirumalai.rajgopal@unilever.com)

## Ethics of research involving vulnerable populations

Sir—Ram Weiss and colleagues (Sept 20, p 951)<sup>1</sup> report the results of clinical research involving obese children with and without impaired glucose tolerance. The research involved a vulnerable population and did not offer the participants the prospect of direct health-related benefits.

Under such circumstances, clinical research is subject to heightened ethical scrutiny. For example, in the USA, such research may be approved by a local research ethics committee only if the following determinations are made: (1) the risk represents a minor increase over minimal [as defined in the applicable federal regulations] risk; (2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (3) the intervention or procedure is likely to yield generalisable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition; and (4) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.<sup>2</sup> If the local committee believes these requirements are not met, the proposed research must be referred to the Secretary of the Department of Health and Human Services for review by a panel of appointed experts, with an opportunity for public review and commentary.<sup>3</sup>

Weiss and colleagues' clinical research involved a range of invasive interventions (eg, euglycaemic, hyperinsulinaemic, and hyperglycaemic clamps) that were used in a similar research protocol that was temporarily suspended by the US Office for Human Research Protections.<sup>4</sup> Weiss and colleagues do not describe how they determined or ensured that the nature and potential harms of these interventions were commensurate with those implied by the first two requirements enumerated above.

The *Lancet* recently published an essay by Miller and Rosenstein<sup>5</sup> in which the authors recommended a policy of extensive reporting of pertinent ethical issues to promote public accountability for clinical research. The research at issue here is deserving of more comprehensive

reporting. I urge the journal's editors and reviewers to follow Miller and Rosenstein's recommendations when assessing manuscripts for publication.

Howard Mann

University Of Utah School of Medicine, Salt Lake City, UT 84132, USA (e-mail: howard.mann@hsc.utah.edu)

- 1 Weiss R, Dufour S, Taksali SE, et al. Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. *Lancet* 2003; **362**: 951–57.
- 2 Department of Health and Human Services. Code of Federal Regulations: title 45, public welfare—part 46, protection of human subjects, 406. <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> (accessed Sept 25, 2003).
- 3 Department of Health and Human Services. Code of Federal Regulations: title 45, public welfare—part 46, protection of human subjects, 407. <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> (accessed Sept 25, 2003).
- 4 Carome MA. Letter to Michael M. Gottesman. Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1000. Population differences in the insulin sensitivity, resting energy expenditure, and body weight composition of overweight children and children of overweight parents. Office for Human Research Protections. November 3, 2000. [http://ohrp.osophs.dhhs.gov/detrm\\_letters/nov00a.pdf](http://ohrp.osophs.dhhs.gov/detrm_letters/nov00a.pdf) (accessed Sept 25, 2003).
- 5 Miller FG, Rosenstein DL. Reporting of ethical issues in publications of medical research *Lancet* 2003; **360**: 1326–28.

### Authors' reply

Sir—Our study was scrupulously reviewed by our research ethics committee (the Yale Human Investigation Committee), which applied the criteria outlined in Howard Mann's letter. The Committee recognised that the study involved a vulnerable population and that it did not offer the participants the prospect of direct health-related benefits. The euglycaemic and hyperglycaemic clamp studies were assessed by the Committee as procedures that involved "more than minimal risk"; however, the protocol was unanimously approved by the Committee for the following reasons.

First, the study represented a minor increase over minimal risk and used acceptable procedures for the population. This assessment of risk was based on the fact that the studies were being done in a facility that takes special care to ensure the safety and comfort of the children participating in research. Additionally, all test procedures were to be done by paediatric metabolic research nurses and paediatric clinical investigators with almost 20 years of experience of

- 1 Sharma DC. Concern over mercury pollution in India. *Lancet* 2003; **362**: 1050.
- 2 Indian People's Tribunal on Environment and Human Rights. Report on the alleged environmental pollution and health impacts caused by the Hindustan Lever mercury thermometer factory at Kodaikanal. Mumbai: Indian People's Tribunal on Environment and Human Rights, 2003: 5.
- 3 WHO. Recommended health-based limits in occupational exposure to heavy metals: report of a WHO study group. Technical Report Series 647. Geneva: WHO, 1980.
- 4 Toxics Link homepage. <http://www.toxicslink.org/> (accessed Oct 21, 2003).

these studies in children. We have never had a case of any serious adverse effect in many hundreds of such studies.

Second, the Human Investigation Committee found that these procedures did present experiences to the participants that are commensurate with those inherent in their actual or expected medical situations.

Third, the study was likely to yield generalisable knowledge of vital importance for the understanding of the children's disorder. All the children enrolled in our study were obese and affected by many of the intractable clinical complications of this serious metabolic disorder. The enthusiastic responses we have received after publication of our paper are a testament to the importance of the generalisable knowledge gained from the study.

Fourth, adequate provisions were made for soliciting the assent of children and permission of their parents or guardians. Before obtaining such consent, the principal investigator and the paediatric clinical research nurse described the study in great detail. All potential risks were discussed with the patient and parents, and as much time as needed was provided for questions. The families were also informed that their choice to decline to participate in the study would not adversely affect the care that the child received at Yale.

Mann makes reference to an intramural National Institutes of Health (NIH) study protocol that used similar procedures to those described in our study and which was temporarily suspended by the US Office for Human Research Protections.<sup>1</sup> Although the procedures used in the two studies were similar, the ethical concerns and cause for suspension of the NIH study were quite different. Unlike our Human Investigation Committee, the local research ethics committee for the NIH study inappropriately classified their study as a "minimal risk" study. The NIH study also differed from our study in that it involved lean healthy children.

All the children involved in our study were very obese, and most were severely insulin resistant. Such youngsters are at high risk of hypertension, dyslipidaemia,<sup>2</sup> and pre-type-2 diabetes.<sup>3</sup> As a result, their life expectancy is likely to be lower than average. The over-riding rationale for these studies is that the knowledge gained will allow a more rational approach to the development of treatment strategies directed at preventing or reversing the underlying

pathophysiology of the disorder and its complications.

\*Sonia Caprio, Ram Weiss, William Tamborlane

Department of Pediatrics, Yale University School of Medicine, PO Box 208064, New Haven, CT 06520, USA (e-mail: sonia.caprio@yale.edu)

- 1 Department of Health and Human Services. Code of federal regulations: title 45, public welfare—part 46, protection of human subjects; 406. <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm> (accessed Nov 4, 2003).
- 2 Dietz HW. Health consequences of obesity in youth: childhood predictors of adult obesity. *Pediatrics* 1998; **101**: 518–23.
- 3 Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002; **346**: 802–10.

### Factors that precipitate development of diabetic foot ulcers in rural India

Sir—William Jeffcoate and Keith Harding's Review (May 3, p 1545)<sup>1</sup> on diabetic foot ulcers provides a useful summary of the condition. In India, patients with diabetic neuropathy who live in rural areas are more prone to foot ulcers than those who live in urban areas for various reasons.

First, individuals in rural areas often sleep in huts, farm houses, or outdoors on the farm, where rodents are common; rodent bites to the feet of patients with diabetes can lead to chronic ulcers. The second common predisposing factor is barefoot walking, which can result in damage to the feet by sticks and thorns. This problem is especially common in farmers. Finally, walking on hot coals without any protection is often undertaken in rural India as part of a religious ritual. The resultant burns, especially on the feet of patients with diabetes, can lead to chronic ulcers.

In 1995, WHO estimated<sup>2</sup> that there were 19.4 million people with diabetes in India, and that the number would probably rise to 57.2 million by 2025. Foot problems such as ulceration, infection, gangrene, and amputations are quite common in Indian patients with diabetes. Such injuries result in frequent and long-term admission to hospital, and are a great cause of morbidity and mortality. The economic and emotional consequences for the family of the patient can be enormous. However, with proper care, many of these injuries can be prevented. Most of the foot problems associated with diabetes in India are

neuropathic and infective, rather than vascular in origin as in developed countries.

M A Aleem

Department of Medicine KAPV Government Medical College and ABC Hospital, Trichy-620 018, Tamil Nadu, India (e-mail: drmaaleem@hotmail.com)

- 1 Jeffcoate WJ, Harding KG. Diabetic foot ulcers. *Lancet* 2003; **361**: 1545–51.
- 2 King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998; **21**: 1414–31.

### Effect of multidrug resistance on global tuberculosis control

Sir—In their Seminar on tuberculosis, Thomas Frieden and colleagues (Sept 13, p 887),<sup>1</sup> note that to tackle the current epidemic affecting many resource-poor settings, emphasis needs to be placed on effective global control of the disease. It is important to add discussion on the extent to which high rates of drug-resistant forms of tuberculosis, now emerging in many resource-poor regions of the world, are jeopardising pre-existing tuberculosis control measures. If we are to have any hope of stemming the global pandemic, emphasis needs to be placed on the freeing up of resources globally to address drug resistance, and to bring treatment options to infected patients.

In our experience in Uzbekistan, drug-resistant forms of the disease have a major effect on our ability to run an effective DOTS programme,<sup>2</sup> as noted in other parts of the former Soviet Union. In areas where the pool of patients with multidrug-resistant tuberculosis comprises more than a quarter of all smear-positive patients, a DOTS programme alone is unlikely to succeed in reaching the WHO target of 85% in terms of treatment success. Frieden and colleagues note that DOTS programmes in the Russian Federation are only reaching a 68% cure rate. Failure to reach this target will not result in the necessary decline in tuberculosis incidence, thus prolonging epidemics.<sup>3</sup>

In this context, to treat multidrug-resistant tuberculosis effectively, and hence have any hope of stemming the ongoing tuberculosis epidemic, resources need to be made available to ensure that patients with multidrug-resistant disease are detected and provided with alternative treatment regimens. Unfortunately, routine drug susceptibility testing, specialist laboratory services, complicated drug

regimens, and treatment centres are not likely to be an affordable option for the resource-poor countries with the bulk of multidrug-resistant tuberculosis in the foreseeable future. Owing to the lack of laboratory infrastructure in Uzbekistan, and central Asia as a whole, Médecins Sans Frontières had to fly out all sputum samples to a laboratory in Germany just to gauge the extent of the problem in this region. The difficulties and costs involved in doing such a survey might well mask the extent of the drug-resistance problem globally.

In response to the high level of multidrug-resistant tuberculosis in Uzbekistan, Médecins Sans Frontières is now implementing a pilot DOTS-Plus programme under the auspices of WHO's Green Light Committee. This pilot programme aims to demonstrate the feasibility of DOTS-Plus in this setting, given adequate resources and technical support. The pilot programme will treat an initial cohort of 100 patients over 3 years. The pilot programme includes the establishment of a specialist laboratory capable of drug susceptibility testing and a large investment in training of local staff.

However, the DOTS-Plus pilot programme will cover only about 100 patients of the 800 who would be diagnosed with multidrug-resistant tuberculosis every year if drug susceptibility testing was available for all presenting tuberculosis patients. Pilot programmes are therefore just a start. The scale of the problem in the rest of Uzbekistan, and the rest of the former Soviet Union, can only be imagined.

In such settings, in which the presence of multidrug-resistant tuberculosis is a major barrier to tuberculosis control, and in which local resources do not permit the provision of essential services such as adequate laboratory and treatment facilities, international resources must be mobilised to offer these patients a treatment option where a treatment option exists.

\*Helen Cox, Sally Hargreaves, Gabit Ismailov

\*DOTS-Plus Pilot Project, Médecins Sans Frontières, Berkakha Street 109, Nukus, Karakalpakstan, Uzbekistan (HC, GI); Médecins Sans Frontières, London, UK (SH) (e-mail: pi@msf-mdr.uz)

- 1 Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. *Lancet* 2003; **362**: 887–99.
- 2 Cox H, Hargreaves S. To treat or not to treat: implementation of DOTS in Central Asia. *Lancet* 2003; **361**: 714.
- 3 Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide control under the WHO DOTS strategy. *Lancet* 1998; **352**: 1886–91.

## Normative role for medical humanities

Sir—Several recent papers, including a Commentary in this journal,<sup>1</sup> have attempted to set out a vision of the aims of medical humanities in medical education. Leaders in this fledgling speciality have been cautioned against becoming elitist and exclusionary.<sup>2</sup> In this debate, however, one important theoretical contribution seems to have been overlooked.

Medical humanities remain to be thoroughly assessed as a normative tool—ie, a mechanism of critical reflection on the fundamental human virtues and principles of conduct that underpin regulatory systems. So conceived, medical humanities can represent a tangible manifestation of the idealistic norm-creating process that John Rawls in his *Theory of Justice* terms “reflective equilibrium”.<sup>3</sup> Ronald Dworkin calls a similar jurisprudential method “law as interpretation”<sup>4</sup> because it involves the judiciary’s attempting to discern and render coherent the mass of normative principles on which their community has reached apparent consensus.

The criticisms by legal positivists of such normative techniques seem to have dimmed somewhat with the passage of legislation such as the Human Rights Act 1998 (UK) and the New Zealand Bill of Rights Act 1990 (NZ), as well as the recently announced Human Rights Act of the Australian Capital Territory. Such acts encourage the relevant judiciary and legislatures to engage in international normative consensus on a grand scale.

The project to expose the theoretical foundations of medical humanities to jurisprudential, philosophical, and regulation-theory analysis could see it emerge as an important strategy for awakening and supporting the sense of conscience that the foundational ethical codes and central instruments of human rights place at the heart of professional rule development and obedience.<sup>5</sup>

Questions that the Centre for Medical Humanities and Human Rights at the Australian National University plans to research include how best to depict or arouse “conscience” and to map its relation to professional virtue, ethical principle, law, and human rights. Similarly subject to scrutiny will be how and whether we should encourage medical students to accept potential roles as conscience-motivated “whistle-blowers” who risk personal and professional destruction to ensure greater individual safety for patients as well as more transparent and enforce-

able norms of clinical governance. Likewise scrutinised will be medical humanities’ involvement in the rigorous assessment of how best to ensure that modern doctors are prepared, encouraged, and supported to challenge injustice, inhumanity, and human rights violations.

Medical humanities, then, might yet find that among its central roles in medical education is the nurturing of an active professional conscience in graduates. One method of doing this might involve the arousal and encouragement to practical expression of the foundational virtues (eg, justice, fairness, empathy, compassion, and loyalty to the relief of patients’ suffering) that normatively generate and support the efficient use of principles of medical ethics, health law, and human rights. The normative role of conscience, via medical humanities in professional regulation, should become a valued area of interdisciplinary research.

Thomas Alured Faunce

Australian National University Faculties of Medicine and Law, Acton, Canberra, Australian Capital Territory 2000, Australia (e-mail: Thomas.Faunce@anu.edu.au)

- 1 Bolton G. Medicine, the arts, and the humanities. *Lancet* 2003; **362**: 93–94.
- 2 Pattison S. Medical humanities: a vision and some cautionary notes. *J Med Ethics: Med Humanities* 2003; **29**: 33–36.
- 3 Rawls J. A theory of justice. Cambridge, MA: Belknap Press of Harvard University Press, 1999.
- 4 Dworkin R. Law’s empire. Cambridge, MA: Belknap Press of Harvard University, 1986.
- 5 World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Article A.2. <http://www.wma.net/e/policy/b3.htm> (accessed Oct 8, 2003).

## Prevalence of iodine deficiency worldwide

Sir—Vitti and colleagues<sup>1</sup> have reported on iodine deficiency in Europe, and Koutras and colleagues<sup>2</sup> have described the situation in Greece. We present a report on the situation of this deficiency worldwide.

Iodine deficiency is the main preventable cause of brain damage in children and therefore constitutes a public-health concern worldwide. Assessment of the magnitude of iodine deficiency disorders (IDD) and monitoring of the progress made towards its elimination represent the cornerstone of the strategy for IDD control. Over the past few years, WHO has developed a database on IDD, in which data on urinary iodine and goitre from all countries of the world are compiled. On the basis of urinary iodine data collected during

WHO regions*	Population† with urinary iodine <100 µg/L	
	General population	School-age children
Africa	260 325 000 (42.6%)	49 465 000 (42.3%)
Americas	75 081 000 (9.8%)	9 955 000 (10.1%)
Eastern Mediterranean	228 451 000 (54.1%)	40 224 000 (55.4%)
Europe	435 452 000 (56.9%)	42 215 000 (59.9%)
Southeast Asia	624 013 000 (39.8%)	95 628 000 (39.9%)
Western Pacific	365 332 000 (24.0%)	47 056 000 (25.7%)
Total	1 988 654 000 (35.2%)	284 543 000 (36.4%)

\*192 WHO Member States. †Based on population estimates for 2002 (United Nations, Population Division, World Population Prospects: the 2002 revision).

### Prevalence of iodine deficiency in general population (all age-groups) and in school-age children (6–12 years) in 2003

1993–2003, the current national, regional, and worldwide prevalence of iodine deficiency has been estimated.

The estimates presented focus on urinary iodine, since it is a more reliable indicator of recent iodine status than clinical goitre.<sup>3</sup> However, clinical goitre prevalence was used to compare the 2003 results with those of the previous decade, for which figures for urinary iodine were not available.

For each country, the most representative estimate of iodine deficiency was selected by use of two criteria: the administrative level for which the sample is representative (eg, national, regional, or local) and the population groups surveyed (eg, school-age children, pregnant women, adults). The database and results of the epidemiological analysis are available at: <http://www3.who.int/whosis/micronutrient/> (accessed Oct 14, 2003).

The results show that data for urinary iodine have been collected for 92% of the world's population. Globally, more than 1.9 billion individuals have inadequate iodine nutrition (defined as urinary iodine excretion <100 µg/L), of whom 285 million are school-aged children (table). The world prevalence of school-aged children with inadequate iodine nutrition is 36.4%. The lowest prevalence is found in the Americas (10.1%) and the Western Pacific (25.7%), whereas the highest prevalence is found in Europe (59.9%). These findings show that iodine deficiency is still a public-health problem in some regions of the world.

Salt iodisation is the recommended strategy for IDD control, since it has been shown to be an effective way of reducing the prevalence of IDD. The lowest prevalence of iodine deficiency is found in the American Region, where the proportion of households consuming iodised salt is the highest in the world (90%), and the highest prevalence of iodine deficiency is in the European Region, where the proportion of households consuming iodised salt is the lowest (27%).<sup>4</sup>

We hope that this information system will be maintained in order to monitor the IDD situation and track progress towards the goal of global IDD elimination adopted by the World Health Assembly in 1990.

\*Bruno de Benoist, Maria Andersson, Bahi Takkouche, Ines Egli

Department of Nutrition for Health and Development, World Health Organization, Avenue Appia 20, CH 1211 Geneva 27, Switzerland (e-mail: debenoistb@who.int)

- Vitti P, Delange F, Pinchera A, Zimmermann M, Dunn JT. Europe is iodine deficient. *Lancet* 2003; **361**: 1226.
- Koutras DA, Alevizaki M, Tsatsoulis A, Vagenakis AG. Greece is iodine sufficient. *Lancet* 2003; **362**: 405–06.
- WHO, UNICEF and ICCIDD. Assessment of the iodine deficiency disorders and monitoring their elimination. Geneva: WHO, 2001: WHO/NHD/01.1. pp 1–107.
- WHO, UNICEF and ICCIDD. Progress towards the elimination of iodine deficiency disorders (IDD). Geneva: WHO, 1999: WHO/NHD/99.4: pp 1–33.

### What's major about adverse cardiac events?

Sir—The major finding of Joachim Schofer and colleagues' E-SIRIUS study (Oct 4, p 1093)<sup>1</sup> is that, although more than 40% of control patients had angiographic restenosis, only 5% had serious clinical events. The so-called major adverse cardiac events that drive the difference between the two study groups include the soft endpoint "need for target lesion revascularisation". The study confirms that, in 2003, you can't stop an interventional cardiologist. To quote Abraham Kaplan: "Give a small boy a hammer and he will find that everything he encounters needs pounding."

Jonathan Silberberg

Stationmaster's Cottage, 92 Scott Street, Newcastle, New South Wales 2300, Australia (e-mail: jsilberb@ozemail.com.au)

- Schofer J, Schlüter M, Gershlick AH, et al, for the E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with

long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003; **362**: 10093–99.

### A conspiracy against the professions

Sir—As an old man, like those who twittered like grasshoppers on the walls of Troy as the battle raged below, I have a privileged spectator's view of what is going on while still being concerned about my duty to the past and future of our (one-time, in my case) profession. One of my own mentors—the otherwise liberal and left-wing-leaning child psychiatrist, Donald Winnicott—warned me when I first qualified that the establishment of a centralised health service would lead inexorably to the loss of professional independence and the bureaucratisation of our practice, as has now happened in the UK under the successive onslaughts of Thatcherism and Blairism.

Now the chief executives reign supreme, like the generals in 1914–18, with no personal experience of service, while those delivering the sophisticated and humane care that the public is told it has a right to expect struggle like Laocoon in coils of red tape and regulations before even getting to grips with the real enemy—ie, human suffering caused by disease. It is a great sadness to learn from one's best pupils that, in the prime of their life, what they look forward to is either retirement or a move sideways into one of those semi-administrative positions that confer more status, pay, and prestige than bedside medicine and clinical research. One is tempted, with regard to politicians and journalists in their relationship with the professions, to borrow the Kleinian concept of envious destruction.

John A Davis

1 Cambridge Road, Great Shelford, Cambridge CB2 5JE, UK

### DEPARTMENT OF ERROR

Zaidi FH, Weir R, Fielder AR. Reporting on the eye and other surgical organ systems. *Lancet* 2003; **361**: 1915–16—In this Correspondence letter (May 31), R Weir's address should be "Institute of Ophthalmology, University College London, London, UK", and A R Fielder's address "Department of Ophthalmology, Imperial College London, London, UK". The correct e-mail address for correspondence is "fhz12@hotmail.com".

Moffett SE, Menon AS, Meites EM, et al. Preparing doctors for bedside computing. *Lancet* 2003; **362**: 86—In this Education and practice piece (July 5), the last author's name should be Henry J Lowe.