

# CORRESPONDENCE

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## 25 years of coronary angioplasty: almost a fairy tale

Sir—On Friday Sept 16, 1977, Andreas Grüntzig personally wheeled his age-mate of 38 years (author DB) into the catheterisation laboratory in Zurich, Switzerland, and was about to make medical history.<sup>1</sup>

In view of a discrete stenosis of the left anterior descending coronary artery, Grüntzig had informed the patient about the option of coronary angioplasty, as patient number one. Having shared a room with someone recuperating from bypass surgery, the patient was intrigued by the possibility of avoiding sternotomy, and so gave his consent.

The surgeon, Marco Turina, provided what was henceforth called surgical standby during the intervention, which took place in a calm atmosphere. People came and went, the cardiac surgeons' faces difficult to read. Only to the eyes of friends was Grüntzig tenser than usual. He inserted the balloon catheter into the stenosis with ease that surprised even himself. The conscious patient tolerated the balloon inflation well, and the angiogram showed a good result, as it did at 1 month, 10 years, and 23 years.

The story would be less of a fairy tale were there no bad people in it. Grüntzig outshone his superiors. Difficult working conditions, retarded promotions, and harsh reprimands for not-so-successful cases were the results. At the end of 1980, he left Zurich for Emory University in Atlanta, GA, USA, where the procedure enjoyed the attention it deserved at last.

Although many subsequently pushed the limits of coronary angioplasty, Grüntzig preserved a humble and realistic attitude towards the potential of the procedure. It took 9 years (1 year after Grüntzig's fatal plane crash) to see the first major improvement in the technique, in the shape of the coronary stent. Another 14 years passed before the next significant breakthrough took place, the drug-eluting stent drastically reducing the risk of restenosis.

The technique has changed in 25 years, and then again it has not. In the beginning, it took gifted and highly experienced operators to place the bulky and poorly steerable balloon in the stenosis. Nowadays, dexterity and

manual training are less important. However, early coronary artery disease or isolated stenoses after coronary artery bypass surgery still constitute the typical indications, since only 10–20% of coronary angioplasty procedures worldwide deal with more than one vessel in a single session.

Coronary angioplasty transformed one of the authors from a seriously ill to a healthy man within minutes, and this for 25 years and counting. The two others enjoyed the transformation of cardiology from an investigational, drug-oriented discipline to a hybrid between internal medicine and surgery. Interventional cardiology grew to become the leading medical subspecialty with the highest number of important interventions, making cardiology a mature and comprehensive specialty efficiently dealing with western societies' worst curse: coronary artery disease. Grüntzig's coronary angioplasty paved the way for other non-surgical interventions such as electrophysiology, carotid angioplasty, and gastrointestinal catheter procedures. Had he only lived to take credit for it.

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1 Grüntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978; **1**: 263.

## Keeping scientific advice non-partisan

Sir—Since you do not defend your Editorial against the misguided accusations of Pennie Marchetti (Dec 14, p 1971),<sup>1</sup> I feel compelled to react in your defence. Marchetti fails to understand much of the correct reasoning of your Editorial, which in my view is the epitome of scientific and political correctness.

First, excluding people from an advisory panel because of their affiliations might not be correct, but if the large majority of such a panel has affiliations with one group, this is at least suspicious.

Second, I agree with Marchetti's argument that abortion and its relation with breast cancer does not interest most practising physicians. However, removing a web page from a scientific site because of political comments, rather than leaving it and stimulating discussion, also seems wrong.

Concerning W David Hager, the Editorial does not cite his religious beliefs, but rather his lack of publications as a suggestion that scientific merit is not the issue. Time will tell if he will be as impartial as one of his predecessors, C Everett Koop. If mifepristone becomes the subject of discussion, Marchetti will be proven wrong.

Finally, "seizing control" is a common expression for parties winning democratic elections. Marchetti reads intentions where there are none. Furthermore, her explanation of the American government and elections shows her lack of understanding of the principles of democracy. The House and Senate do not govern, they control government. Their election is a matter of "big money", which is supplied in large part by industry. The proportion of people who actually vote in US elections usually approaches 50%. Marchetti's statement that the Republican party is closest to articulating the views shared by most Americans is therefore valid only for the proportion who actually voted. So being "given the privilege of governing by the American people" is a limited translation of the facts.

*The Lancet* did not debase itself and was not political in its Editorial. Rather, Marchetti tries to involve *The Lancet* in the ideological and political circus that governs the USA throughout all of its institutions, including those that are called scientific.

Please keep up these frank and open discussions in *The Lancet*.

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1 Marchetti P. Keeping scientific advice non-partisan. *Lancet* 2002; **360**: 1971.

## Heart Protection Study

Sir—We have concerns about how the Heart Protection Study (HPS; July 6, p 7)<sup>1</sup> results were reported.

The HPS data seemed to show intention-to-treat relative crude risk reductions (RRRs) for patients with prior coronary heart disease (CHD) that were lower than those seen in similar statin trials, such as 4S,<sup>2</sup> in which patients had higher LDL cholesterol concentrations. For CHD events, the crude RRR was only 21% in HPS compared with the Cox-regressed RRR of 34% for 4S; RRRs for major cardiovascular events were 20% and 26%, respectively. However, such differences were potentially obscured by the HPS Collaborative Group's reporting a one-third RRR after adjusting for control-group non-study statin use and treatment-group statin non-adherence.

Adjustment for non-study statin use in HPS helps comparisons with most other statin trials, ensuring that contamination does not dampen effect size. But any non-blinding could bias effect sizes upwards. HPS's RRRs adjusted for non-study statin use alone for patients with prior CHD were lower than 4S's for CHD events (HPS crude RRR 29%), but were identical for major cardiovascular events (HPS 26%).

By readjusting for statin non-adherence, reporting of HPS violated intention-to-treat principles and hence overstated effectiveness in HPS relative to other trials. The authors of other statin trials reported their intention-to-treat results without adjustment for inevitable (if unmeasured) non-adherence occurring in their treatment groups.

Both the HPS report and the accompanying Commentary<sup>3</sup> implied that patients should start statins at much lower LDL cholesterol concentrations, with substantial reductions in events irrespective of the initial concentration. But before making such conclusive recommendations, consider the varying relations between effectiveness and initial LDL cholesterol across statin trials. These variations include positive gradients (lower RRRs at lower initial LDL cholesterol concentrations) in the 110 000 person-years experienced in the CARE, AFCAPS/TextCAPS, and LIPID trials.

A preliminary meta-regression of statin randomised controlled trials including HPS ([www.pharmac.govt.nz](http://www.pharmac.govt.nz)), with adjustment for non-study statin use, suggests that any past significant gradient between initial LDL cholesterol concentrations and overall statin RRRs for CHD events has disappeared. This

finding needs confirmatory prospective pooling of data from individual patients. Given that absolute risk reduction correlates at least with initial LDL cholesterol concentrations, trial evidence overall to date suggests that we need to treat many more patients with low initial LDL cholesterol concentrations than high, with reduced cost-effectiveness and large opportunity costs.<sup>4</sup>

CHD-specific outcomes described in webfigure2 of HPS deserve wider discussion. The stated planned primary outcome measures<sup>5</sup> related to mortality, but planned secondary outcome measures related separately to total CHD and total stroke events.

Subgroup analysis of CHD events alone showed significant relations between effectiveness and the absence of prior CHD and angiotensin-converting-enzyme (ACE) inhibition (RRR 36% for no prior CHD vs 21% for prior CHD; non-significant 11% for ACE inhibitor use vs 31% for no ACE inhibitor use). There was also a significant relation between RRR and  $\beta$  blockade (38% for  $\beta$  blockade vs 21% for no  $\beta$  blockade). Might these results for CHD events herald a previously unsuspected relative waning of effect with ACE inhibition, or enhancement with  $\beta$  blockade, at least deserving some comment?

RSM is externally contracted to the New Zealand Pharmaceutical Management Agency (PHARMAC)—the government agency responsible for funding community pharmaceuticals. None of the above material necessarily represents the views of either PHARMAC or the Ministry of Health New Zealand. RJM is contracted to the New Zealand Guidelines Group, and has undertaken pharmacoeconomic analyses for many pharmaceutical companies.

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- 1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
- 2 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994; **344**: 1383–89.
- 3 Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 2002; **360**: 2–3.
- 4 Moore W. 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184. <http://bmj.com/cgi/content/full/325/7357/184> (accessed Dec 19, 2002).
- 5 MRC/BHF Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering

therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. *Eur Heart J* 1999; **20**: 725–41.

Sir—The data from HPS<sup>1</sup> contain information which could be relevant to the debate on the clinical relevance of the non-lipidic or pleiotropic effects of statins.

The subgroup of patients in the treatment group with baseline LDL cholesterol concentrations greater than 3.5 mmol/L had an average on-trial plasma LDL cholesterol concentration of 2.7 mmol/L. This value is, probably by chance, exactly the same average as that of the subgroup of patients with baseline LDL cholesterol values less than 3.0 mmol/L in the placebo group.

The incidence of a first major cardiovascular endpoint over the duration of the trial is virtually the same in these two subgroups (22.0% in the treatment group vs 22.2% in the placebo group). Therefore, patients who have the same LDL cholesterol concentrations, due either to simvastatin treatment or enrolled in the placebo group, share an identical risk of subsequent CHD events. This finding speaks against a significant contribution of the non-lipidic effects of statins to the protective action seen with simvastatin in the trial. Therefore, as in a large pravastatin trial,<sup>2</sup> it seems reasonable to conclude that the protective effect of statins can be explained mainly by their action on LDL cholesterol.

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- 1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
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The reports of the Heart Protection Study<sup>1,2</sup> state that a 2×2 factorial design was used to allocate patients to active drug (simvastatin or vitamins) or matching placebos. Investigators who attended the meeting at which changes in drug formulation were announced informed me that medication and placebos were changed part way through the study because the

appearance and smell of active drugs and placebos were found to differ over time. Irrespective of whether this change would have affected outcome, investigators have a responsibility to ensure that research methods are accurately reported.

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- 1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
- 2 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 23–33.

#### Authors' reply

Sir—In “intention-to-treat” analyses of the 4S trial, the 5-year average difference in plasma LDL cholesterol concentration was 1.7 mmol/L, and the reduction in the risk of “major coronary events” (defined as non-fatal myocardial infarction or coronary death) was one third.<sup>1</sup> By contrast, in the intention-to-treat analyses of HPS<sup>2</sup> (and of the other main trials of 5 years of statin versus placebo), the average LDL difference was about 1 mmol/L, and the risks of major coronary events and of “major vascular events” (defined as major coronary event, stroke, or revascularisation) were reduced by about one quarter. When comparing the intention-to-treat analyses of 4S and HPS, however, Scott Metcalfe and colleagues fail to take any account of these differences between the absolute LDL reductions achieved on average during each trial. Moreover, they seem not to have understood that the Conclusion of our report was intended to provide estimates (derived from the intention-to-treat analyses) of the benefits of actual use of 40 mg simvastatin daily among the types of high-risk patient studied in HPS (rather than comparisons with other trials), since such estimates should be of most direct relevance for high-risk patients who remain compliant, for the doctors who are treating them, and for health authorities that require appropriate cost-effectiveness analyses.

Observational studies in different populations indicate that the proportional difference in coronary disease risk associated with a given absolute difference in usual LDL cholesterol concentration is similar throughout the LDL range that has

been studied, without any “threshold” below which a lower concentration is not associated with lower risk.<sup>4</sup> Despite these consistent observations, unduly selective emphasis in a previous trial on a retrospectively defined subgroup of patients with pretreatment LDL below 3.2 mmol/L, which involved few major coronary events (89 [21.7%] pravastatin *vs* 93 [21.1%] placebo),<sup>5</sup> has been used to suggest that there might be a threshold at about this level below which lowering LDL would not reduce risk. By contrast, HPS prospectively planned to assess the effects of lowering LDL substantially among about 7000 participants who presented with LDL below 3.0 mmol/L, and it has shown unequivocally that lowering LDL from below 3 mmol/L to below 2 mmol/L reduces the risk of major vascular events (598 [17.6%] simvastatin-allocated *vs* 756 [22.2%] placebo-allocated,  $p < 0.0001$ ) by about one quarter, which is similar to the proportional risk reduction produced in HPS by a 1 mmol/L reduction among those who started at higher LDL concentrations.<sup>2</sup> It is surprising, therefore, that Metcalfe and colleagues seem to give as much weight in their discussion to the small numbers of events in a retrospectively defined subgroup of the CARE trial (and, indeed, do not even consider the prospectively defined subgroup in that trial) as they do to the very much more robust findings from HPS or from the aggregate of all the randomised trials. Moreover, by contrast with their assertion, the absolute benefits produced by a 1 mmol/L reduction in LDL among the types of high-risk participants studied in HPS were similar, and substantial, both among those with pretreatment LDL below 3.0 mmol/L and among those with higher levels.<sup>2</sup>

The prespecified data analysis plan for HPS states that comparisons of the effects of simvastatin allocation among participants in different subcategories would be based on the large number of major vascular events that were anticipated, supplemented by the results for the smaller number of major coronary events (see <http://www.hpsinfo.org>). Figures 7 and 8 in the main report indicate that, despite analysis of a large number of prespecified subcategories, the proportional reduction in major vascular events was about one quarter in each subcategory of participants studied.<sup>2</sup> Metcalfe and Dawson have chosen instead to emphasise the observed results in particular subcategories for the statistically less

robust outcome of major coronary events, and then mistakenly suggest that there was significant heterogeneity between the proportional risk reductions observed among those with or without prior coronary disease. By contrast, there were similar highly significant reductions in major coronary events (webfigure 1 with main report), as well as in major vascular events (figure 7), among people in each of these prior disease categories.<sup>2</sup> With appropriate allowance for multiple comparisons (as prespecified), there was not significant heterogeneity between the effects observed on major coronary events among participants subdivided with respect to ACE inhibitor or  $\beta$ -blocker use at study entry (webfigure 2), and this lack of significant heterogeneity is supported by the more robust findings for major vascular events (figure 8). Hence, HPS does not provide any good evidence that the proportional effects of simvastatin on coronary or other major vascular events differ materially in the presence or absence of ACE inhibitors or  $\beta$  blockers (or of any other treatments being used) from the substantial risk reductions observed overall.<sup>2</sup>

We can confirm for Peter Wilmshurst that the colour of the vitamin and placebo capsules was changed from red to dark brown early in HPS in order to ensure that some slight discolouration during long-term storage would not lead to unblinding of the treatment allocation. Finally, we agree with Andrea Poli and Alberico Catapano that the results of HPS and the other major statin trials are entirely consistent with the observed reductions in the risk of vascular events being largely or wholly a consequence of the reduction in LDL cholesterol concentration.

P Sleight has received honoraria from the pharmaceutical industry for participating in scientific meetings, but the other authors have not.

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Sir—Salim Yusuf's Commentary on the Heart Protection Study<sup>1</sup> states that “practically all patients with vascular disease in Western countries will benefit from statins” and this headline was echoed in many of that day's newspapers.<sup>2</sup>

But are we being seduced too much by population rather than individual statistics, and by relative rather than absolute risk reduction? Even if we ignore the two-thirds of patients deemed ineligible to enter the Heart Protection Study, the results show that a patient starting treatment with a statin has no statistical chance of benefit for the first year on treatment. After the first year, 1% of patients will benefit for each year that they take their tablets. At the end of 5 years of continuous treatment, 5.4% will have derived benefit, and 94.6% will not. The 5.4% benefit cannot be said to constitute “practically all patients”.

The view of the patient is seldom considered or sought. Many will take any number of tablets to prevent vascular disease, but increasing numbers are wary of drug treatment. A 1% per year chance of benefit may be below the threshold that most patients view as acceptable from a preventive drug strategy.<sup>3</sup> The 35 000 simvastatin tablets needed to be taken to prevent one vascular event and the 97 000 needed to delay one death will be viewed favourably by the pharmaceutical companies, but less so by the patient.

It would be a shame if the results from the rigorous and disciplined Heart Protection Study were to be marred by what many may see as inappropriate spin.

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- 1 Yusuf Y. Two decades of progress in preventing vascular disease. *Lancet* 2002; **360**: 2–3.
- 2 McDonald C. Heart drug could save 10 000 lives every year. *Times Newspapers*, July 5, 2002: 13.
- 3 Trewby PN, Reddy AV, Trewby CS,

Ashton VJ, Brennan G, Inglis J. Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs. *Clin Med* (in press).

Author's reply

Sir—In an ideal world, we would prefer to use preventive approaches only in individuals who would actually develop any given disorder. However, this is simply not possible for almost all clinical conditions. For example, we have to immunise a large number of children to prevent a range of childhood ailments; or all passengers in a car should be encouraged to use their seatbelts at all times, although only a tiny proportion of individuals would be injured in a traffic accident in a single journey. These examples indicate that the need to use preventive strategies in relatively large numbers of people to obtain its benefits in a few individuals is a ubiquitous phenomenon. In this context, the actual numbers of people that need to be treated with a statin to prevent an event over 5 years (5.4 per 100) is relatively small. Therefore the use of statins in the types of patients included in the Heart Protection Study is an excellent “buy”.

Peter Trewby calculates the 5-year benefits. First, the absolute reduction of 5.4% in major vascular events should be interpreted as being substantial, and not small. Second, these calculations do not take into account the fact that many patients receive symptomatic benefits—eg, prevention of angina or hospital admissions for unstable angina. Third, because of the use of open-label statins in the control group of the Heart Protection Study, and the less than perfect compliance in the active group, among patients who actually took a statin, the benefit is about 1.5 times the numbers indicated by Trewby. Fourth, preventive strategies are meant to be used lifelong in high-risk individuals. Therefore over a 20-year period, treatment of 100 high-risk individuals with a combination of preventive strategies for 20-years will lead to the avoidance of major vascular events in about a third to a half of them.

These absolute benefits are substantial, and the appropriate and widespread use of statins and other preventive strategies in high-risk individuals has the potential to have large benefits at individual and societal levels.

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## Cogan's syndrome as an autoimmune disease

Sir—With their finding that the isolated 12-residue Cogan's peptide is homologous to four autoantigens—laminin, connexin 26, the collagen disease-associated Ssa/Ro, and the receptor-like phosphatase DEP-1/CD148—and one viral protein, Claudio Lunardi and colleagues (Sept 21, p 915)<sup>1</sup> have advanced greatly identification of the eye, inner ear, nervous system and endothelium autoantigens of Cogan's syndrome.

Connexin 26 belongs to a family of gap-junction proteins, and thus it is important for cell-to-cell adhesion and for allowing aminoacids, electrolytes, and other small molecules to pass between adjacent cells. Laminins have a role in cell attachment through binding to various extracellular matrix components and cell-surface receptors, including integrins. Viral homology is relevant because infections of the upper respiratory tract typically precede onset of Cogan's syndrome. Hence, molecular mimicry between autoantigens and exogenous antigens could be one pathogenetic mechanism of this disorder.<sup>1</sup> However, details on the computer-assisted search for homology were not provided by Lunardi and colleagues.<sup>1</sup>

Because of our interest in molecular mimicry,<sup>2,3</sup> we wished to expand the computer-assisted search done by Lunardi. We entered Cogan's peptide to search the SWISSPROT and SPTREMBL databases with PATTINPROT.<sup>4</sup> We recorded no matches in the 100% to 68% range of aminoacid identity. We detected homologies (<http://image.thelancet.com/extras/02cor11113webfigure.pdf>) in the 58% (or seven of 12 identities) to 67% (or eight of 12) range, which is greater than the 33% (four of 12) to 58% (seven of 12) range reported by Lunardi and colleagues.<sup>1</sup>

The homologies we recorded included laminin and laminin (another cell-adhesion molecule) and kinesin and calcineurin. Autoantibodies against these molecules are seen in autoimmune diseases of the skin or collagen. Microtubule-associated kinesins are contained in the cilia and flagella of eukaryotic and prokaryotic cells. Kinesin-2 is needed for transport pathways in motile and non-motile cilia and flagella; in these organisms it is essential for sensory functions in ciliated neurons such as the otic neuro-epithelium. An immune response against ciliated or flagellated micro-organisms can thus become an autoimmune response against ciliated

human cells—eg, inner-ear hair cells—because of molecular mimicry between exogenous and endogenous kinesins.

We also noted homology with integrins, calcineurin, receptor-like protein kinase, large tegument proteins, two bacterial proteins (selenocysteine-specific elongation factor and avirulence protein). Integrins and calcineurin are abundantly expressed in inner-ear cells, cochlear and vestibular nerve, cornea, retina, optic nerve, and endothelium. In the inner ear, integrins regulate hair-cell differentiation and cilia maturation, and transduce mechanosensation. Receptor-like protein kinase is homologous to a viral movement protein and several allergens. Large tegument proteins are expressed in viruses, and one model to explain herpes virus stromal keratitis is cross-reactivity of these and other viral proteins with corneal autoantigens.<sup>5</sup> We noted homology with proteins expressed in bacteria and avirulence protein, which is implicated in bacterial pathogenesis.

Finally, other homologous proteins we recorded are six small-molecule transporters in eukaryotes and prokaryotes—eg, sodium proline symporter, lactose-proton symporter, and the galactoside transport ATP binding protein MGLA—and cecropins. MGLA is homologous to surface-presentation antigens of enteropathogens, including spirochaetes. Homology with cecropins, which are natural peptide effectors of innate immunity against pathogens, could result in formation of neutralising autoantibodies that would facilitate infections.

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## Low back pain and psychiatric disorders

Sir—Michele C Battié and colleagues (Nov 2, p 1369)<sup>1</sup> deal with the influences of occupational driving on lumbar disc degeneration. Low back pain is the most common specific complaint leading to consultation with primary-care physicians.<sup>2</sup> Accordingly, the number of causes is huge, and ranges from disc herniation and vertebral fracture to musculoskeletal conditions and psychogenic syndromes.

The outcome of any treatment of low back pain strongly depends on psychiatric cofactors. Levy and colleagues<sup>3</sup> reported a poorer functional outcome and health-related quality of life after surgery of lumbar disc herniation when a positive response on screening for depression was given. Polatin and colleagues<sup>4</sup> assessed 200 patients with chronic low back pain, of whom 77% met lifetime diagnostic criteria for psychiatric illness, and 59% showed current symptoms. Furthermore, psychosocial risk factors—so-called pain-prone factors—are partly responsible for lengthening the duration of pain syndromes, and associations with life events and lack of coping strategies can also be found.

We analysed the medical records of 245 consecutive inpatients with low back pain at our department between January, 2001, and November, 2002. The median age was 54 years, and the male-to-female ratio was 123/122. We did computed tomography or magnetic resonance imaging for all patients, 161 (65%) of whom showed structural damage with disc herniation. 106 of these patients had radicular neurological deficits, including paresis, hypaesthesia, and loss of reflexes.

We also screened our patients for psychiatric disorders, and found that the overall incidence was 38% (93 of 245). Further analysis showed that patients with neither disc herniation nor clinical evidence of radicular deficits had a higher incidence of psychiatric disorders (47 of 76 patients, 62%) than patients with these problems (17 of 106 patients, 16%). Further analysis for specific psychiatric disorders was not done, but depression and anxiety disorders were seen most frequently.

As a result of these findings, we began to assess patients with low back pain for psychiatric illnesses using a standardised questionnaire<sup>5</sup> followed by a structured psychiatric interview for depression, anxiety, and alcohol abuse according to the 10th revision of the International Classification of Diseases. Although this assessment is still in progress, we have so far discovered that

the fewer structural and neurological deficits we find, the more psychiatric symptoms are present, and vice versa.

Clinicians, primary-care physicians, and specialists should pay more attention to the psychiatric status of their patients with low back pain, especially if they have no clear structural damage or clinical deficit.

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## HLA in French patients with variant Creutzfeldt-Jakob disease

Sir—The prion protein gene (*PRNP*) seems to have a major role in susceptibility to variant Creutzfeldt-Jakob disease (vCJD), but other still uncharacterised genes might also be involved.

The accumulation of abnormal prion protein (PrP)—the hallmark of prion diseases—in the lymphoreticular system of patients with vCJD has formed the basis of a study on the association between HLA alleles and vCJD. This initial study<sup>1</sup> of 50 UK patients revealed that the HLA class II type DQ7 was significantly less common among individuals with vCJD than among controls (12% *vs* 35%), suggesting that HLA-DQ7 has a protective effect against vCJD.

An association between a disease and HLA class II alleles is usually regarded as a strong indicator of an antigen-specific T-cell-mediated pathogenesis. However, vCJD is known to be mediated via a T-cell-independent mechanism,<sup>2</sup> so its

	HLA-A	HLA-B	HLA-DRB1	HLA-DQB1	TNFA (–308G/A)
<b>Patient</b>					
A	02/-	44/56	03/08	02/0402	GA (high)
B	03/24	07/51	01/15	0501/0602	GG (low)
C	02/03	40/51	04/13	0302,07/0609	GG (low)
D	23/32	18/39	11/16	<b>0301,09,10</b> /0502	GG (low)
E	11/24	27/40	12/16	<b>0301,09,10</b> /0502	GG (low)
F	23/24	35/44	12/15	<b>0301,09,10</b> /0602	GG (low)

DQB1\*0301, 09, 10 correspond to DQ7 specificity. In last column, "high" and "low" refer to TNF $\alpha$  production phenotype.

#### HLA-A, HLA-B, HLA-DRB1, HLA-DQB1, and TNFA typing in French vCJD patients

pathogenesis requires an alternative explanation. Besides their established role as antigen-presenting elements, the HLA class II molecules are also important signalling receptors leading to activation or cell death.<sup>3</sup> Additionally, differential signalling through HLA class II isotypes or alleles has been shown.<sup>4</sup> Differential signalling via the DQ7 molecule could therefore have a key role in protection against vCJD.

To study further the implication of the HLA system in vCJD susceptibility, we determined the HLA class I and II alleles in the six French individuals diagnosed with vCJD to date. HLA-A, HLA-B, HLA-DRB1, and HLA-DQB1 typing was done with the PCR-SSO reverse dot blot technique (Innogenetics, Zwijndrecht, Belgium). Three of the six patients were identified as DQB1\*0301, 09, 10 (table). This proportion was slightly higher than the phenotype frequency of DQ7 seen in 314 controls (37%).

The strong linkage disequilibrium seen in the HLA region (haplotype effect) prompted us to investigate the TNFA gene, which is in close proximity to DQB1. Tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) is an essential cytokine in the maturation of follicular dendritic cells in which the abnormal form of PrP accumulates.<sup>2</sup> Polymorphism (in particular at position –308 of the promoter of TNFA) correlates with a low versus high TNF $\alpha$  producer phenotype. Five out of the six French cases of vCJD had a GG phenotype (72% in controls) and were therefore poor producers of TNF $\alpha$  (table).

In conclusion, within the limits of data based on a necessarily small number of patients, we found no major departure from the expected frequencies of the HLA class II, including HLA-DQ7, or TNF $\alpha$  alleles, in French vCJD patients. Notably, by contrast with a previous report,<sup>1</sup> DQ7 was not under-represented in these patients and was in agreement with the data presented by Pepys and colleagues (see p 487),<sup>5</sup> who did not find significant deviation

of the frequency of the HLA types in UK vCJD.

We thank P Loiseau for helpful contribution.

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#### More on the LIFE study

Sir—Two correspondents (Oct 12, p 1171)<sup>1,2</sup> have questioned the actions of the lead author of the LIFE study,<sup>3</sup> Björn Dahlöf, after he distributed a letter on the letterhead of Göteborg University, recommending the drug losartan. A similar letter was sent to Scandinavian doctors and caused a discussion in *Läkartidningen* last year. The university then considered taking legal action for the misuse of its letterhead.

Both then and in *The Lancet*,<sup>4</sup> Dahlöf claims that his name had been used by Merck without authorisation and that the company has apologised. The wording of the Swedish letter to physicians does not, however, use language that is usual when addressing only one or a few colleagues, which was the purpose of the letter according to Dahlöf. The actions of Dahlöf in this respect have been questioned by many

Swedish colleagues who know of his close ties to Merck. These ties are also evident from the fact that the company had access to his personal letter on the university letterhead.

As a former professor of medicine, and dean of its medical faculty, I have been in contact with the administration of Göteborg University, which is still considering what kind of disciplinary action it can take. Dahlöf is not employed by the university but by the city of Göteborg. His connection to the university is as honorary assistant professor.

In his defence,<sup>4</sup> Dahlöf states that he "supplied comprehensive conflict of interest statements from all in the steering committee". He must, then, have disclosed that he has been receiving research grants from Merck and furthermore has published a book on hypertension paid for by Merck. This statement does not appear in connection with the article in *The Lancet*. Is the journal to blame for this statement's omission? In a follow-up article to the LIFE study, published in *JAMA*, Dahlöf again mentions no conflicts of interests. What kind of statement did *JAMA* receive?

The recent decision by the large medical journals to request a declaration of conflict of interest from the authors of submitted articles will only work when all authors submit a true statement and the journal publishes it.

L Werkö was Executive Vice President of AB Astra 1975–85.

Lars Werkö

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- 4 Dahlöf B. Was the LIFE trial independent? *Lancet* 2002; **360**: 1171.

Sir—In his reply asserting the independence of the LIFE trial,<sup>1</sup> Björn Dahlöf states that "the analyses were validated outside of the company". However, the Methods section of the original publication<sup>2</sup> specified that "Study data are in a Merck database", and the section on committees reads: "Data analysis: Steve Snapinn (Merck Research Laboratories, West Point, PA, USA)". The trial was described as supported by an "unrestricted grant", but would such data-management and analytical arrangements guarantee independence from a sponsor, as claimed by Dahlöf?

The description of the arrangements can be read in the original LIFE publication. But does simply mentioning such arrangements suffice, or should journal editors be given more detail when a sponsorship is qualified as “unrestricted”? I would suggest that most readers believe that true unrestricted independence supposes that the investigators or the investigators’ institution were owners and keepers of the data, and that all data analyses were done by one or more of the authors themselves. In this context, the often-used formal expression “authors had unrestricted access” to data that they do not own and of which they did not do the primary analysis is essentially meaningless since it gives no structural guarantee for a separation of responsibilities and influences. However, the meaning of the term “unrestricted grant” is a problem that *The Lancet* cannot solve by itself, but that should be discussed by the international community of medical journal editors.

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- 1 Dahlöf B. Was the LIFE trial independent? *Lancet* 2002; **360**: 1171.
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#### Response from Merck

Sir—Merck understands the importance of undertaking randomised controlled clinical trials to the highest scientific and ethical standards, and has extensive experience doing so. We have demonstrated this over many years in landmark clinical trials such as 4S,<sup>1</sup> FIT,<sup>2</sup> RENAAL,<sup>3</sup> and, most recently, LIFE<sup>4</sup> and OPTIMAAL.<sup>5</sup> In all of these trials, results were reported promptly in major peer-reviewed journals, irrespective of the outcome.

In every instance, the scientific integrity of these (and all Merck-sponsored) trials is preserved by rigorous study protocol development, prespecified plans for data analysis, and extensive quality assurance and control processes. For outcomes trials such as LIFE, Merck protocols provide for an independent steering committee to be responsible for the scientific conduct of the trial, and a separate data and safety monitoring board for protecting patients’ safety.<sup>4</sup> Merck typically manages data coordination and trial administration on behalf of the steering

committee, as was the case with LIFE. Although the LIFE consolidated trial database resides at Merck, the steering committee has complete and unrestricted access to the data for analysis.

My role in the LIFE trial was to do the statistical analysis based on the prospective, comprehensive plan that was developed with and reviewed and approved by the steering committee before unmasking and study completion. The analyses of the key efficacy endpoints were independently replicated and validated by Hans Wedel, a biostatistician and steering committee member.<sup>4</sup>

Like the other landmark trials cited, the results of LIFE reflect the quality of the study design, data integrity, and investigator independence in analysis and reporting of study results—principles that Merck has long supported.

Steven Snapinn

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- 1 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–89.
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#### Author’s reply

Sir—I have already given the facts related to the unfortunate letter sent out by Merck.<sup>1</sup> The only reasons I can see for Lars Werkö to bring up that discussion again without any new facts is to attack me personally or to question the scientific integrity of the steering committee for no good reason. Some people seem to have used this mistake by Merck as a means to discredit the LIFE study. The study has been reported on its scientific merits, and the

rigour of conduct and reporting fulfils all requirements of the Food and Drug Administration and the guidelines according to the International Conference on Harmonisation/Good Clinical Practice (ICH/GCP).

There is no undisclosed conflict of interest in relation to my participation (or that of the steering committee) in the study, and my relationship to the company was disclosed by me in the conflict of interest statements I sent in for publication in the main paper.<sup>2</sup> On request from *The Lancet*, we formulated a summary of those statements thus: “None of the voting steering committee members or their families have any propriety interest in Merck Co; however, some have received fees for services such as lectures, writing, and research on a smaller scale, not constituting any conflict of interest. KK is a Merck employee and was a non-voting member of the steering committee”. That *The Lancet* chose not to publish the conflict of interest statements or the above comprehensive statement was out of my control.

The point about independent conduct brought up by Jan Vandenbroucke merits a much broader discussion. If we are to mistrust any analyses done by the pharmaceutical industry, the whole drug regulatory process should be changed. Large endpoint studies have been accepted and used for regulatory submissions for many years. These are done according to GCP rules, with independent scientific bodies (steering, endpoint, and safety committees) overlooking the study, and procedures in place to safeguard scientific integrity and quality. The steering committee of the LIFE study have unrestricted and complete access to the database, and analyses have been validated outside of Merck.

The LIFE study was initiated to answer two important scientific questions: does effective blocking of the renin angiotensin system carry benefits beyond lowering of blood pressure in comparison with established therapy? And is left ventricular hypertrophy a valid surrogate endpoint for outcome in hypertension? The first question we have answered with an indisputable “yes”, and the answer to the second will be communicated soon. I have no doubt in my mind that the quality of the data is of the highest scientific standard, that the analyses have been done correctly, and that the evidence will be accepted by the regulatory bodies.

Björn Dahlöf

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- 1 Dahlöf B. Was the LIFE trial independent? *Lancet* 2002; **360**: 1171.
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## ERA in International Health: an experiment worthwhile?

Sir—In July, 1999, *The Lancet* launched its Electronic Research Archive (ERA) in International Health and e-print server (<http://www.thelancet.com/era>),<sup>1</sup> which promised a new era in the dissemination of international health research findings to a wider audience. In 2000, *The Lancet* Publishing Group, a division of Elsevier, joined hands with five other publishing groups for free distribution of electronic versions of their respective journals to some of the poorest nations around the globe.<sup>2</sup> It was a welcome move for many. In 2002, with the launch of Rapid reviews (July 13, p 102),<sup>3</sup> a *Lancet* Commentary reflected on the journal's publication priorities, which include "coverage of global public-health and health-policy research".

ERA provides the international research community with an electronic way to quickly self-archive their original work. One of the main aims of such a website is to provide researchers with a unique opportunity to shadow peer reviewing of the first drafts of their article in the form of comments posted alongside from readers. ERA also seemed to be a way to help bridge the North-South information gap. But since 1999, only 12 articles have been posted; there were no submissions in 2002. My study<sup>4</sup> is the latest one posted since August, 2001. It is surprising and discouraging that only three articles have any comments posted alongside them. A couple of articles have, however, been published elsewhere, including a revised print version in *The Lancet* of Simon Hales and colleagues' empirical model of dengue fever (Sept 14, p 830).<sup>5</sup>

The apparent failure of ERA calls into question the concept of self-archiving and an electronic public library of research in international health. The viability of the ERA experiment, which was born out of a serious commitment to promote research in international health, is a wake-up call that raises important issues for the authors and readers alike.

Is it true that only a few researchers from less-developed nations are aware of the website? Is there a lack of interest on

the part of the publishing group to promote ERA adequately, which may well address the previous issue? Do the studies posted on ERA lack the so-called minimum standard to invite additional comments and, if true, would some form of peer reviewing improve their quality? Would a future print version in the form of an annual review of all the articles submitted be more attractive? Most importantly, do researchers from less-developed nations have free and easy access to such a technology-driven project? Unfortunately, the ERA in International Health still remains an enigma to many and merits sincere attention.

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- 4 Kabir Z. Effect of DTP vaccines on overall mortality in non-BCG vaccinated infants: a population-based study. ERA-International-Health 20010002. <http://www.thelancet.com/era/LLAN.ERA.1126> (accessed Oct 22, 2002).
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## The hazards of whirlpooling

Sir—Whirlpools or jacuzzis are known to be associated with legionellosis<sup>1</sup> and pseudomonas skin infections.<sup>2</sup> The following case illustrates that there might be additional, less common risks in people with predisposing factors.

A 36-year-old man with end-stage renal disease caused by chronic glomerulonephritis followed the advice of his renal physician to do more physical exercise to improve severe hypertension. For the first time in a long while, he went swimming in an indoor pool, and afterwards used the whirlpool facility and found the pressure to be very strong. About 18 h later he was on regulatory haemodialysis (5 h) without conspicuous clinical signs (systolic blood pressure 140–160 mm Hg, pulse rate 72–84 beats per min).

Back home, the patient experienced severe abdominal discomfort about 1 h after dialysis and, having called his nephrologist for advice, returned to the dialysis unit for a physical examination. He presented with moderate left-sided abdominal pain and tenderness.

Notably, the pain radiated to the left flank. Because of accompanying vomiting, high blood pressure, and the impression of a seriously ill patient, the physician decided to transfer him to the accident and emergency department of our hospital, where we found chemical and haematological values to be in the normal range (haemoglobin concentration 134 g/L). An ultrasound examination revealed no abnormalities.

Pain relief with dipyrone and hyoscine was not satisfactory. Temporary improvement was achieved by administration of laxatives and opioid analgesics. After overnight observation with the provisional diagnosis of constipation, the patient reported reappearing abdominal pain and "nervousness". He was tachycardic (128 beats per min), and haemoglobin had dropped to 85 g/L. Contrast-enhanced computed tomography of the abdomen revealed a massive retroperitoneal haematoma surrounding the left kidney, with bleeding into the abdominal cavity. Angiography identified the left kidney as the source of bleeding, which was stopped by catheter embolisation. Afterwards the patient experienced pain relief and remained haemodynamically stable.

We infer that the patient's kidney was mechanically injured by "whirlpooling", resulting in subacute and subclinical bleeding that became symptomatic only when intensified by anticoagulation during haemodialysis.

Therefore we conclude that, under certain conditions such as hypertension or anticoagulation, the use of whirlpools is associated with potential health risks.

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- 1 Jernigan DB, Hofmann J, Cetron MS, et al. Outbreak of Legionnaires' disease among cruise ship passengers exposed to a contaminated whirlpool spa. *Lancet* 1996; **347**: 494–99.
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## DEPARTMENT OF ERROR

Another loss in the privatisation war: *PubScience*—In this Commentary by Michael Jensen (Jan 25, p 274), the second sentence of the fourth paragraph should have started: "Although my employer broadly supports open access to scientific research . . ." The author's address should have been: Upper Marlborough, MD 20772, USA. Also, an acknowledgment was omitted: "This commentary expresses Michael Jensen's personal views and not those of his employer."