CORRESPONDENCE

Treatment of Gaucher’s disease with OGT 918

Sir—Timothy Cox and colleagues (April 29, p 1481) presented the long-awaited results of the trial of OGT 918 (N-butyldexoyojirimicin) for type-1 Gaucher’s disease. They are to be congratulated for timely reporting and for providing detailed data. However, the results raise important concerns about the safety of the drug and the interpretation of the data can be questioned. Despite an impressive body of preclinical data2 and the finding that leucocyte G_M1 concentrations were reduced, their early results provide little convincing evidence that OGT 918 results in a reduction in the number of storage cells or the amount of storage material within cells. A significant reduction of organomegaly was found, but no significant change in haematological variables. There was a modest reduction of serum chitotriosidase, a marker not specific for Gaucher’s disease, but the effect on serum or tissue glucocerebrosidase concentrations is not reported. There was a striking dissociation between mean reduction of hepaticomegaly and splenomegaly at 12 months, lack of haematological response, and only a 16% reduction in chitotriosidase concentration. When comparable organ responses are achieved by reducing the amount of storage material using mannose-terminated glucocerebrosidase infusions, there is an impressive haematological response and reduction in serum chitotriosidase. This dichotomy comes into focus when the data are stratified according to spleen status, because of the impact of splenectomy on Gaucher’s disease and its treatment. In the three patients who completed the study who had had a splenectomy there is 20% reduction of hepaticomegaly, but no significant change of chitotriosidase at 12 months of treatment. Further, in the 18 patients with intact spleens in whom complete data are available, most hepatic and splenic responses occurred by 6 months and at this timepoint there was only a 5% reduction of chitotriosidase concentration. These discordant effects raise the worrying prospect that the shrinkage of organs is not due to reduction of the number of storage cells or the amount of storage material, but may reflect simply organ atrophy. Massive cell dropout involving the lymphoid system, has been reported in animal studies of OGT 918.1 With respect to lack of haematological response, it is of note that OGT 918 caused marrow toxicity in HIV trials.3 The indirect role of OGT 918 in Gaucher’s disease proposed by the investigators as an explanation for lack of haematological response is somewhat tenuous because very significant regression of organomegaly had already occurred in this trial.

79% of patients developed diarrhoea and two withdrew from the study because of this side-effect; another two developed paraesthesiae. Paraesthesia also occurred in the HIV trial. The protocol does not appear to monitor for any possible effects on cerebral function—brain glycosphingolipids could be altered, especially in the long-term because of their slow turnover.2 One patient withdrew because of pre-existing pulmonary hypertension.

Was there progression of pulmonary hypertension during 4 months of treatment with OGT 918? Because of the number of patients who developed diarrhoea, it is important to know if there was weight loss and how this might have influenced organ volume measurement, as multiples of normal, of patients on OGT 918. There was only a single measurement for baseline parameters, and so assessment of response will be confounded by spontaneous amelioration of signs and symptoms.

Enzyme replacement therapy for type-1 Gaucher’s disease is highly effective and it is extremely safe.4 In the 10-year history of the Comprehensive Gaucher’s Disease Treatment programme, New York, USA, there have been no infusion-related infections and no patient has required a permanent catheter. The programme has strikingly improved the lives of patients and prevented premature deaths. Development of effective and safe oral therapy will immeasurably lessen the burden of the disease on the patients and their families. However, we are concerned that the press release from the pharmaceutical company announces the results of the trial as clear cut evidence of activity that further trials of combination maintenance therapy of OGT 918 or Cerezyme are underway (www.ogs.com accessed July 14, 2000). Such over-enthusiastic announcements have prematurely tantalised the hopes of patients and families affected by Gaucher’s disease. I make a plea that Cox and colleagues apply their rigor to the long-term potential and side-effects of this drug, before combination trials are launched, because they will simply add to the confusion.

P K Mistry

Comprehensive Gaucher Disease Treatment Center, Mount Sinai School of Medicine, New York, NY 10029-6574, USA


Author’s reply

Sir—P K Mistry raised important points but we must first correct a misapprehension: our study indeed showed a significant haematological response with an increase in platelets at 1 year (p=0.014). We also found decreased biosynthesis of the glycolipid substrate G_M1 ganglioside. Moreover, plasma glycosylceramide concentrations, which represent the storage material of Gaucher’s disease, were also decreased. This material, ultimately responsible for the disease, can thus be reduced in patients with glycosphingolipidosis by decreasing the supply of its cognate substrate. Plasma chitotriosidase is a useful marker of Gaucher’s disease activity and is in widespread clinical use for monitoring. It has been well-established that raised activity in Gaucher’s disease is associated with the presence of pathological macrophages. The comment on the specificity of chitotriosidase is irrelevant to our study
since the enzyme activity was greatly increased in all patients in whom it could be measured.

One cannot presume to interpret all the changes observed in our study mechanistically in the context of the results obtained with enzyme replacement therapy: the two modes of action, though potentially complementary, are quite distinct. Our study showed a significant reduction in chitotriosidase activity. Neither plasma chitotriosidase activity nor haematological variables change consistently with the reduction in organ volume when enzyme replacement therapy is introduced. Furthermore, we do not believe it is sound to use a statistical test using a subset of only three patients in our complete cohort, as suggested by P K Mistry.

W H P Mistry refers to a lack of haematological response he fails to point out that not all patients were cytopenic at baseline. Of the nine anaemic patients at the start of the trial, the mean increase in haemoglobin over 12 months was greater than 0·5 g/dL. For platelets there was a small but consistent increase over the study period with an overall trend to significant improvement. We have no evidence for marrow toxicity and in quoting the reports from trials in patients with HIV we should point out that these trials used doses of OGT 918 that were up to ten times greater than those used in Gaucher’s disease.

P K Mistry’s main concern about the trial is that the significant decreases in organ volume measurements that occur with OGT 918 were not associated with a therapeutic effect on Gaucher’s disease. He suggests that a shrinkage phenomenon caused by lymphoid atrophy or simple weight loss may be responsible. We do not accept the suggestion that there is a striking dissociation between the changes in spleen and the changes in liver volumes—reduced volume was significantly correlated for these variables at 6 months and 12 months, respectively. In comparing the trial data with animal studies Mistry omitted to introduce. Furthermore, we do not believe the latter studies involved non-communicable diseases are an important threat to the health of adults in Africa. Worldwide, cerebrovascular disease is second only to ischaemic heart disease as a cause of death (3·8 million in 1990), and most of these deaths (3 million) are in less-developed countries.

In sub-Saharan Africa detection, prevention, and treatment of hypertension should now be regarded as a high priority. It is estimated that if the 10–20 million people who are believed to have hypertension in sub-Saharan Africa were treated, about 250 000 deaths would be prevented annually. In Africa, the reduction in population attributable risk when blood pressure is lowered is 13 times greater than in the USA. However, in places where this is poor health-care provision, where the detection of hypertension is still haphazard and unreliable, population-wide strategies to reduce blood pressure could have an important impact on the number of strokes in the community.

There is good evidence that a reduction in salt intake reduces blood pressure and that black people are more sensitive than white people in this regard. In the western world, notwithstanding this good evidence, it is very difficult to implement successful salt-reduction strategies in the population, since most of the salt ingested is in processed food. So, any process, adverse effects are highlighted and so was the fact that this was the first trial. The statement in the press release “clear-cut evidence of activity of OGT 918” is true. A further randomised, combination/maintenance study is ongoing. This study was carefully designed and received approval by the required ethical and regulatory authorities. Such clinical studies are the correct way to fully assess the efficacy and safety of OGT 918, and will provide physicians treating patients with Gaucher’s disease with the answers and choices they deserve. As Mistry himself states: “development of effective and safe oral therapy will immeasurably lessen the burden of the disease on the patients and their families.”

Michael Kranda
CEO, Oxford GlycoSciences plc, Abingdon Science Park, Oxford, OX14 3YS, UK.

Prevention of hypertension and stroke in Africa

Sir—Walker and colleagues (May 13, p 1684) report rates of stroke mortality in both urban and rural Tanzania that are higher than those of England and Wales, and they suggest that untreated hypertension is an important factor. Non-communicable diseases are an important threat to the health of adults in Africa. Worldwide, cerebrovascular disease is second only to ischaemic heart disease as a cause of death (3·8 million in 1990), and most of these deaths (3 million) are in less-developed countries.

In sub-Saharan Africa detection, prevention, and treatment of hypertension should now be regarded as a high priority. It is estimated that if the 10–20 million people who are believed to have hypertension in sub-Saharan Africa were treated, about 250 000 deaths would be prevented annually. In Africa, the reduction in population attributable risk when blood pressure is lowered is 13 times greater than in the USA. However, in places where this is poor health-care provision, where the detection of hypertension is still haphazard and unreliable, population-wide strategies to reduce blood pressure could have an important impact on the number of strokes in the community.

There is good evidence that a reduction in salt intake reduces blood pressure and that black people are more sensitive than white people in this regard. In the western world, notwithstanding this good evidence, it is very difficult to implement successful salt-reduction strategies in the population, since most of the salt ingested is in processed food. So, any
intervention would involve the participation of the food industry. In contrast, in populations whose intake of processed food is negligible—such as are found in sub-Saharan Africa—salt reduction strategies should be relatively easy to implement and have a good chance of success.

In a recent study in the Teaching Hospital in Kumasi, the second largest city in Ghana, we found that stroke, heart failure, and renal diseases accounted for 23% of acute medical admissions and 29% of deaths.1 In Ghana, food is mainly unprocessed and any salt in the diet comes from the frequent consumption of highly salted fish and meat, the addition of salt during cooking and at the table, and the use of monosodium-glutamate-based flavouring cubes. It is clear that in this population it should be possible to reduce salt intake effectively. In 1999, we did a pilot study as to the feasibility of such a strategy as part of a much larger community-based programme (now supported by The Wellcome Trust). 20 participants (all farmers; eight men, 12 women), mean age 49-2 (range 21–68) years were selected randomly from households in the village of Odoyefe, in the Ejisu-Juabeng District of the Ashanti Region of Ghana.

The study was approved by the local ethics committee and participants gave their informed consent. They underwent initial assessment that included weight and blood pressure measurements, a blood test for creatinine measurements, and two consecutive 24 h urine collections for sodium, potassium, and creatinine determinations. Then for a week they underwent a daily 1.5 h session of vigorous nutrition education, followed by weekly sessions thereafter. After 4 weeks they were assessed again. At the end of the 4 weeks of the study there had been a significant reduction in urinary sodium excretion (both absolute and as sodium/creatinine ratio) indicating a reduction in sodium intake (table). The change in sodium excretion was a fall of about 50% compared with the initial values, despite the initially low urinary sodium. During the same period there was a fall in both systolic and diastolic blood pressure. The mean fall in weight was consistent with the fall in salt intake.

This small open pilot study in one village in rural Ghana shows the feasibility and efficacy of this type of population approach to reducing salt intake, blood pressure and, potentially, the incidence of stroke. There is clearly an urgent need for larger well-conducted community-based studies of salt reduction in sub-Saharan Africa.

3 Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. Lancet 1997; 349: 1269-76.

**Study findings**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline mean (SD)</th>
<th>Intervention mean (SD)</th>
<th>Difference 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodyweight (kg)</td>
<td>58.5 (9.4)</td>
<td>57.7 (9.4)</td>
<td>-0.79 (-0.08 to 1.66)</td>
<td>0.07</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>135.3 (16.5)</td>
<td>128.9 (16.8)</td>
<td>-6.4 (-0.5 to 12.3)</td>
<td>0.035</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>85.8 (8.6)</td>
<td>81.3 (7.5)</td>
<td>4.5 (-0.3 to 9.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>86.7 (14.6)</td>
<td>89.3 (14.0)</td>
<td>-2.6 (-7.0 to 1.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 h)</td>
<td>10.1 (3.2)</td>
<td>9.2 (2.6)</td>
<td>0.9 (0.2 to 1.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Urinary potassium (mmol/24 h)</td>
<td>91.7 (33.8)</td>
<td>82.1 (29.2)</td>
<td>9.6 (-38 to 231)</td>
<td>0.15</td>
</tr>
<tr>
<td>Urinary creatinine (mmol/24 h)</td>
<td>10.1 (3.2)</td>
<td>9.2 (2.6)</td>
<td>0.9 (0.2 to 1.5)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

BP=blood pressure.
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Force on Tobacco Control which is chaired by WHO.

Global generalisations about the relative importance of the communicable and non-communicable disease only go so far, a point that is made in the Gwatkin and Guillot analysis referred to in your editorial. The burden of disease in Eastern Europe, for example, differs greatly from the burden in sub-Saharan Africa. The Bank's work at the country level responds to country conditions and the country context.

You bizarrely suggest that the Bank had a hand in some wrong-minded recent editorials in the Wall Street Journal and the Times of London. You allege that the Bank has converted “tobacco into an issue of individual choice rather than one of collective responsibility for public health”. Yet in 1999, the World Bank published Curbing the epidemic: governments and the economics of tobacco control, which argued strongly that tobacco control is a severe public-health problem for which there are clear justifications for governmental intervention. The Bank urges governments to carry out measures that are highly inimical to international business interests. One indicator of the importance we give to tobacco control is that Curbing the epidemic is being published in 12 languages with help from the US Centers for Disease Control and Prevention, WHO, the Pan-American Health Office, and other partners—an all-time record for any World Bank publication. Mamphela Ramphele, one of the Bank’s Managing Directors, will represent the Bank at the forthcoming World Conference on Tobacco or Health, in Chicago, USA, where the policy recommendations in Curbing the epidemic and some of the analytic work supported by the Bank in countries around the world will be discussed.

Contrary to your unsubstantiated allegations, the World Bank strongly supports the health agenda set out by WHO. You refer to a “deepening rift between the Bank and WHO, the Pan-American Health Office, and other partners—an expression of the importance of good governance, this time at the international level.” The second allegation made is that the WTO is “opposing the health agenda set out by WHO”. I have no idea where you obtained this notion. To start with, it is not the job of the WTO to have a view about the health agenda set out by the WHO. In the WTO, we respect fully the competence of the WHO as the body through which the international community expresses its will in regard to health issues and the WTO has no mechanism for taking a view on such matters. However, to the extent that trade and health do interact, we work closely with the WHO in helping it carry out the mandate that its member governments (which are essentially the same governments as make up the membership of the WTO) have given it. For example, the WTO secretariat participates actively in the WHO/FAO’s Ad Hoc Inter-Agency Task Force on Tobacco Control and co-operates with activity on food safety matters and access to drugs. In fact, the working relations between the two organisations have never been closer.

Mike Moore
World Trade Organization, 1211 Geneva 21, Switzerland

Sir—In your June 3 editorial and with reference to a report by Gwatkin and colleagues you question the appropriateness of putting communicable diseases on the top of the global health agenda. It seems that The Lancet fears that focusing on infectious diseases among the global poor will divert attention from the fight against the tobacco industry and the harmful effects of free trade of harmful commodities. In support of this view, the editorial quotes a statement in a letter to The Lancet by the cardiologist K S Reddy that the calculation by Gwatkin and colleagues “subverts the efforts of less-developed countries to address important policy issues related to global determinants of non-communicable diseases”. The editorial further argues that “the World Bank is now buttressing a beleaguered World Trade Organisation, and that both institutions are opposing the health agenda set out by WHO”. It is important that the health profession and others stand up against the tobacco industry and the harmful health effect of free trade, in particular of
arms, illegal drugs, and narcotics. Further, it is very commendable that influential medical journals like The Lancet contribute to the disclosure of the agendas of organisations that will not contribute to stop such trade. However, I do not understand why your editorial indicates that an advocacy for increased effort against infectious and other poverty-related diseases should be in conflict with a stand against trade of harmful commodities and other important threats to health.

It is a well documented fact that infectious diseases represent the greatest disease burden for the poor of the world, and that we in the more-developed world have the most cost-effective interventions. As shown among others by Gwatkin and colleagues, the effect of intervention among the poor will also be largest if more resources are made available for the “unfinished agenda” of prevention and treatment of these diseases. This is also the policy of WHO, as expressed in the World Health Report 1999: “First and foremost, there is a need to reduce the burden of excess mortality and morbidity suffered by the poor . . . it will mean focusing more on interventions that we know can achieve the greatest health gain possible within prevailing resource limits”. The report goes on to mention that renewed attention is necessary for diseases like tuberculosis, malaria, HIV/AIDS, and immunisation programmes, in addition to the diseases of mothers and children.

A well accepted ethical criterion for resource allocation in the health sector is first to attend to those with the greatest needs. On the global scale, it is clear that those with the largest deficiencies in terms of access to prevention and care are the poor, and that their greatest and most immediate threats to health come from infectious diseases. I hope The Lancet will not obfuscate this fact by indicating that those who present arguments to this effect serve to create “a manipulated dichotomy in global health policy.”

Gunnar Kvåle

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Space flight related anorexia

Sir—Laurence Vico and colleagues (May 6, p 1607) observed effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. They interpreted their results to be the adaptive effect related solely to the microgravity environment of space. Correlation of bone loss with diet and leptin (adipocyte food intake hormone) was not done. However, it is a critical hormone to measure, because it is now known that leptin has a global influence on bone metabolism, particularly calcium loss from bone. If leptin concentrations were found to be raised, this would significantly contribute to the bone demineralisation that occurs in space, because leptin stimulates osteoblast activity directly and influences calcium homeostasis via a central mechanism, and also contributes to space flight related anorexia. Also, an alteration in leptin concentrations can be induced by a continuous light environment, as in space flights.

We are studying central and peripheral mechanisms responsible for space flight related anorexia. Daily food intake (FI) is a product of meal size (MZ) and meal number (MN)—i.e., FI=MN×MZ. Evidence indicates that normally meal number and size are independently and reciprocally regulated in the hypothalamus. Daily or circadian rhythms are seen in feeding behaviour. Circadian rhythms in food intake are disrupted by hypothalamic lesions, gonadectomy, and the complete absence of a dark period within 24 h. The temporal organisation and rhythmicity of feeding may be associated with the diurnal fluctuations of various neurotransmitters and hormones (eg, adrenaline, noradrenaline, dopamine, serotonin, GABA, and certain peptides such as cytokines, glucose, insulin, glucagon, oestrogen (growth hormone and corticosteroids). Disruption in the normal circadian rhythm, such as by increasing the light period, induced metabolic, hormonal, and neurochemical changes, which influence behavioural outcomes including food intake.

Food consumption during spaceflight is reduced to 70% of the recommended and required intake. We propose that this reduction is a result of decreased food intake and increased energy expenditure. Using a rat water meter, with 24-h continuous light exposure for 7 days, we measured food intake and meal number and size and examined the changes in dopamine: serotonin ratio in hypothalamic related to food intake. We also measured plasma cortisol, leptin, insulin oestradiol, testosterone, and tumour necrosis factor α (TNFα). Controls continued in the 12 h light-dark cycle. After 1 week rats were killed and blood and brain samples were collected. Tissue from lateral and medial hypothalamus, along with suprachiasmatic nucleus and cortex were homogenised and high performance liquid chromatography was done to measure dopamine and serotonin. Data showed that during the 12 h light–dark period both groups had similar intakes, but during continuous light, food intake decreased significantly via a decrease in meal number. Dopamine and serotonin concentrations in the ventromedial nucleus (VMN) and lateral hypothalamic area increased. Plasma cortisol and leptin increased, while a decrease was seen in insulin, TNF-α, oestradiol, and testosterone.

These data suggest continuous light stimuli via direct effect on the suprachiasmatic nucleus and indirect effect on the VMN induces endocrine and neurochemical changes in these rats. The observed changes in food intake, hypothalamic monoamines, and peripheral hormones suggest that besides microgravity, continuous light environment in space shuttles contributes to observed anorexia, and its metabolic sequelae including bone loss.

Madhu Varma, Tomoi Sato, Lihua Zhang, Michael Meguid

Neuroscience Program, Surgical Metabolism and Nutrition Laboratory, Department of Surgery, University Hospital, SUNY Upstate Medical University, New York, NY 13210, USA (e-mail: meguidm@upstate.edu)

**CORRESPONDENCE**

**Sentinel-node biopsy sampling in breast cancer**

Sir—Restricting axillary node surgery to sentinel-node biopsy sampling is being widely promoted.1 We believe this is wrong because it may decrease both survival and locoregional control. There is growing recognition that suboptimum locoregional treatment and local recurrence are independent factors reducing 5-year and 10-year survival rates and that formal axillary-node clearance is associated with increased survival, even when the primary tumour is small.2 It seems logical to accept that cancer recurring in the breast or remaining undetected and untreated in the axilla is just as likely to metastasise as the primary tumour.

Sentinel-node biopsy sampling carries the small but significant risk of leaving unrecongnised disease in the axilla and we contend that this may result in more breast cancer deaths. Results tabulated by Rogers and colleagues include published false negative rates of more than 10%.3 In other words, one in ten women who had a negative sentinel node had non-sentinel lymph-node metastases that would not have been found if axillary node clearance had not been done. Breast cancer is common and it follows that many women will have residual cancer left in their axilla after isolated sentinel lymph excision. These women will not receive optimum local treatment and, of possible greater importance, because their axillary metastases remain unrecongnised, appropriate adjuvant chemotherapy may be denied.

Data from Veronesi and colleagues provides a compelling argument in favour of a full level-three axillary-node clearance. He showed that in 5% of cases the only positive nodes were in the small but significant risk of leaving unrecognised disease in the axilla and whom chemotherapy would not normally be advocated if node negative.

Survival figures for breast cancer are improving. This is probably the result of earlier diagnosis, favourable modulation of an already systemic disease, and better organisation of cancer services with a multidisciplinary team approach. It would be tragic to jeopardise these precious achievements by the irresponsible adoption of inadequately tested change. Certainly it would be a great advantage to avoid the significant morbidity of axillary clearance, but we believe that most women prefer acceptance of these occasional consequences until alternative prognostic indicators and therapeutic strategies are confirmed as equally effective by proper trials.

*Peter Jones, Sue Jones, Steve Humphreys, John Schofield, David Pickering*

Departments of *Surgery, Cellular Pathology,* and *Oncology,* Maidstone Hospital, Maidstone and *unbridge Wells NHS Trust,* Maidstone ME16 9QO, UK


**Systolic blood pressure and mortality**

Sir—It is a curious fact that simply fitting a statistical model to data can give the impression that the assumptions of the model are supported by the data. Sidney Port and colleagues1 reassess the sentinel node story. In a linear-logistic model previously been used to relate all-cause mortality to systolic blood pressure: this model assumes that the odds ratio for death for a 10 mm Hg increase in systolic blood pressure is the same at all levels of systolic blood pressure below the 70th centile, so for example, a positive association around the 60th centile could be obscured by an absence of association below the 50th centile.

A more convincing description of the association between risk and systolic blood pressure in the range 140–160 mm Hg probably requires more flexible methods of statistical analysis,2 which avoid assumptions about the form of the association and are not driven by results for people with systolic blood pressures outside this range.

*Ian White*

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(e-mail: ian.white@lshtm.ac.uk)


Sir—Sidney Port and colleagues1 report very important findings, and it is logical to presume that lowering systolic blood pressures with antihypertensive drugs may not increase survival in a large proportion of people with systolic blood pressures higher than 140 mm Hg. Nevertheless, in his commentary, Michael Alderman2 says that “the current consensus that pharmacological treatment be initiated in people with systolic pressures greater than 140 mm Hg . . . need not be altered”. This definite conclusion was obtained from analysing the data of the Systolic Hypertension in the Elderly Program (SHEP).3 However, although SHEP showed that lowering systolic blood pressures could decrease stroke and total
number of cardiovascular events, it failed to prove reduction in total mortality. Since survival is a harder endpoint than stroke or cardiovascular events in studying hypertension, and since Port and colleagues used survival as an endpoint, it is possible to say that their results are concordant with those of SHEP. Therefore, the definite conclusion of Alderman is an overstatement.

Makoto Kondo
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Sir—Sidney Port and colleagues1 remodel the Framingham data and suggest that only those in the 80th percentile for systolic blood pressure have an increased mortality risk. They report the implications for clinicians following the recommendation to treat all patients whose blood pressure exceeds 140 mm Hg. However, this recommendation is not commonly followed in the UK. Joint British Recommendations are that patients should be treated if their estimated risk of developing a cardiovascular event within 5 years exceeds 15%, or their systolic blood pressure exceeds 160 mm Hg.2 So what are the implications of these findings for UK clinicians?

National data were obtained on the age-specific distribution of systolic blood pressure, smoking,3 diabetes,4 and Newcastle heart project data on total cholesterol to HDL cholesterol ratios.5 Using an assumption of independence, these data were used to model the distribution of risk factors in the population of England and Wales. All data were entered into an Excel spreadsheet and the cardiovascular risk of each age, sex, and risk-factor combination was calculated using the Framingham risk equation (Anderson KA, et al. Circulation 1991; 83: 356–62). From this it is possible to estimate the percentage of men and women in each age band, who would be offered treatment under the Joint British Recommendations. If the model presented by Port and colleagues is followed, everyone above the 80th percentile would be treated (table).

The model proposed by Port and colleagues has considerable implications for UK practice. It would reduce the proportion of the population needing treatment according to different treatment criteria and if those above the 80th percentile are treated.

<table>
<thead>
<tr>
<th>Age band (years)</th>
<th>Joint British Recommendations</th>
<th>Above the 80th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54</td>
<td>Men: 12% Women: 8%</td>
<td>Men: 20% Women: 20%</td>
</tr>
<tr>
<td>55–64</td>
<td>Men: 27% Women: 31%</td>
<td>Men: 20% Women: 20%</td>
</tr>
<tr>
<td>65–74</td>
<td>Men: 57% Women: 53%</td>
<td>Men: 20% Women: 20%</td>
</tr>
</tbody>
</table>

Proportion of the population needing treatment according to different treatment criteria and if those above the 80th percentile are treated.

Sir—We disagree with Ian White that our conclusions concerning the age-sex dependent threshold for hypertension and the behaviour below that threshold are unjustified. A model’s purpose is to produce a theoretical explanation for relations. Data then confirm or deny the validity of the model. Our model postulates a threshold at the 70th percentile and flat risk to the left of that point. Statistically, these assumptions are confirmed by the fact that the model provides an excellent explanation of the data. But, our results do not prove the assumptions are true; no such proof is possible.

To confirm the flatness to the left of the 70th percentile, one can proceed in two ways—significance tests or estimates and CIs of the log odds ratio. Both were calculated. The former was reported and the latter are available in the statistical section of the paper. Both methods show that the log odds ratio is very small, and far from being significantly different from zero.

We cannot concur with Kondo’s suggestion that the difference between hard and soft endpoints can reconcile our conclusions with Michael Alderman’s counterargument based on SHEP.2 In fact, we believe Alderman misinterpreted the results of that trial. As we understand it, his statement implies that it was those reduced to the lowest pressures that gained the maximum benefit. But that is not a valid conclusion from SHEP. All we know from SHEP is that starting with pressures of 160–212 mm Hg there was a mean difference or 12 mm Hg (155 mm Hg vs 143 mm Hg) between the control and the treatment groups and a reduction in the risk of certain outcomes. But there is no way of knowing or inferring which individuals got the benefit or contributed to the difference in the means. Was it those who had pressure reduced from 160 mm Hg to 140 mm Hg or from 180 mm Hg to 160 mm Hg that gained the benefit? There is no way of telling. Although our model implies that no benefit would be achieved in reductions from 160 mm Hg, it does imply that substantial benefit would be gained for the reductions from above 140 mm Hg. In essence, SHEP results are compatible with both models and cannot discriminate between them.

We also find difficulty with Alderman’s declaration that numerous other studies support linearity. Essentially, in all these studies linear logistic models are used, as in the Framingham study. In light of our findings on Framingham, which before our investigation would certainly have been counted as supporting linearity, scientific protocol would dictate that we must now consider the purported linearity in these studies as dubious. At this point, we do not know if the alleged linearity is an accurate reflection of the data or simply an artefact of the linear model. We certainly agree with Marshall that other studies should be carefully scrutinised to see which model they support.

Although, as Marshall points out, our results indicate that a paradigm shift may be in order, we caution that our results apply to people aged 45–74 years from a population analogous to that of white, urban, middle class Americans. Extrapolations (always dangerous) to other age groups or significantly different populations must be viewed with caution.

Sid Port
Department of Mathematics, University of California, Los Angeles, CA 90025, USA (e-mail: sport@ucla.edu)
1 Alderman MH. Measure and meaning of blood pressure. Lancet 2000; $38$: 159.
Evidence-based illiteracy or illiterate evidence

Sir—We entirely agree with Michael O’Donnell (Feb 5, p 489)1 that medical literature is gradually becoming an oxymoron. However, we have some points of contention with his article. He notes that many biomedical articles originate from illiterate and non-scientific people. We can agree with that. Illiteracy hardly generates good medicine or good science. He seems to forget, however, that more than half of the English-language articles published in biomedical literature are written by people whose first language is not English and that the percentage of readers whose first language is not English must approach 90%. English, in becoming the international language of science, belongs no longer just to the English (and Americans), but has become the property of the entire scientific community. This broad application will inevitably affect the linguistic evolution of English. Let us stress that most of the words that Michael O’Donnell does not like (eg, initial, utilise, transmit, majority of) have a French or Latin origin, and are extensively used in many Latin-based languages. The French origin of a large part of the English language is part of English history and is not something to be ashamed of. As a man of letters, Michael O’Donnell must be familiar with Walter Scott’s Ivanhoe, where Scott humourously be familiar with Walter Scott’s Ivanhoe, where Scott humourously

2 Scott W. Ivanhoe, 1819.

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something to be ashamed of. As a man of letters, Michael O’Donnell must be familiar with Walter Scott’s Ivanhoe, where Scott humourously be familiar with Walter Scott’s Ivanhoe, where Scott humourously

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for anyone. In the case of medical doctors, being literate should compliment, and not replace, scientific qualities and medical knowledge. Illiteracy and poor science are closely connected and should therefore be corrected together. Good writers are almost without exception enthusiastic readers, and non-medical literature should form a cultural basis for all physicians and researchers. It not only helps us understand the human condition, for a good writer can describe in a few pages what several scientific texts could not do justice, but observations and comments from the literature provide a superb source of research ideas. Is not medicine after all the natural alliance of the humanities and the sciences?

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2 Scott W. Ivanhoe, 1819.


Authors’ reply

Sir—If journals want to reverse their priorities and put the needs of their readers above those of their authors, they will need to use language that readers, rather than authors, prefer. The list I have was not of “words that Michael O’Donnell does not like”—indeed I am rather fond of some of them—but of words and phrases that readability studies1 suggest make prose less likely to be read, especially when dispensed as liberally as they are in scientific papers.

I suspect, however, that most readability studies were done on readers whose first language was English or American—they certainly pay little attention to cultural differences—so maybe we should repeat them on the international readership defined by Joseph Watine and Johannes Borgstein. Though I warn these correspondents that they will not necessarily be pleased with the results; these studies rarely bring comfort to authors.

Vocabulary, however, is only one component of the language evolved by those who write to be published rather than to be read. And English as a second language confers no immunity to the other aberrations I described. The paper that used up five pages before concluding that “the null hypothesis that both treatments will show equal results cannot be confirmed or rejected because of the small number of participants”2, came from an institute in The Netherlands. And it was an Italian physician who invited European colleagues to a meeting that he claimed would offer “an in-depth overview of the state of the art in HHD”.3 I confess to having failed abjectly as a writer by allowing at least two readers to conclude I was promoting an interest in what it means to be an individual as an alternative to evidence-based medicine. I would like any doctor looking after me to be well versed in both.

To use the example given, the evidence database will indicate the most effective treatment for colorectal liver metastases but the doctors, particularly the family doctors, looking after individuals with such a disease must also help their patients cope with what I described as the “feelings of regret, betrayal, fear, loneliness, and all the other perplexing emotions than can turn the same disease into a different illness in different individuals”. For the moment, I suggest, the most helpful database they can draw on is The Arts. And, as the American physician Faith Fitzgerald has pointed out, the rewards for consulting this database are not confined to patients. “The point is not, of course, that knowledge of literature, history, music, art, or other non-medical scientific subjects makes one a better diagnostician (although this may be true) or a better therapist (although this is almost certainly true), but that the possession by the doctor of a background necessary to explore these areas with patients vastly enriches the relationship.”

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3 Circular distributed at European Heart House, Nice, France. March, 1996.

Life after sanctions: the fate of Iraq

Sir—Mohamed Ali and Iqbal Shah (May 27, p 1851)1 present shocking evidence on the effects of the United Nations (UN) sanctions on Iraq on infant and child health and mortality during the past 8 years. The editorial2 places the blame for this monstrous deterioration of the past 8 years on the Iraqi leadership and especially Saddam Hussein. By the same logic, then who is responsible for the undisputed advances in Iraqi society that were seen during the 20 years running up to the Gulf conflict if not the same government now so sanctimoniously blamed for its huge leap backward? In those years health care reached most of the urban and rural population, safe drinking water was universally available, and there was a good quality of education.

The editor does not see fit to explore an alternative hypothesis, namely, that the UN, acting for the geopolitical interests of the USA and Britain, is deliberately bringing about the destruction of Iraqi society. There is a misguided theory among liberals that a desperate Iraqi population will rise up and overthrow their dictator. And this goal is taken as the basis of the western world’s good intentions—the deaths of children being an unfortunate collateral effect. But the real lesson of such a massive collective and exemplary punishment on millions of civilians is not lost on the non-western, natural-resource-rich world.

The future of Iraq, whose natural resources once provided so much of its pre-Gulf-conflict advances, may include its breakup into a number of client regimes answerable, not to the international community, but to the ally nations headed by the USA in appeals to the international community, the political dominance of the west,3 and secret violence.4 Now is the time for health professionals to stand as advocates for the oppressed and the forgotten. Otherwise, understandable hostilities against the allied nations by the Iraqi people will be exacerbated and continue to the generations to come.5

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Attraction of mosquitoes to pregnant women

Sir—Steve Lindsay and colleagues (June 3, p 1972)1 observed that pregnant women attracted twice the number of mosquitoes belonging to the *Anopheles gambiae* complex, the predominant vectors of malaria in Africa, than the non-pregnant counterparts. They postulated that physiological and behavioural changes caused by pregnancy are responsible for this increased attraction. Data we have obtained from Manaus (Brazilian Amazon),2 by studying pregnant and non-pregnant malaria women, suggest that the phenomenon observed by Lindsay and colleagues disguises another aspect of malaria transmission to pregnant women. In the study by Lindsay and colleagues no data on the Plasmodium species infecting the mosquitoes was reported, but in Gambia *P falciparum* is responsible for most of the registered cases of malaria. In contrast, in Brazil, the situation is quite different since the ratio of *P falciparum* to *P vivax* in the general population varies from 1:4 to 1:5 (depending on the region). In our study, this ratio increased from 1:5 in non-pregnant to 1:2.6 in pregnant women, indicating a greater susceptibility to *P falciparum* infection or vulnerability to the *P falciparum* malaria during pregnancy.

To explain this observation, one could consider that, independently of the attraction they have for malaria carrying mosquitoes, pregnant women would be more susceptible to *P falciparum* infection or more vulnerable to the disease caused by this species because of hormonal, metabolic, or mechanical (increased expression of adherence factors in placenta enhancing the conditions for *P falciparum* development)3,4 changes. Alternatively, mosquitoes infected by *P falciparum* could be more attracted to pregnant women than non-infected anopheles mosquitoes. In this case one would have to admit that both pregnancy and *P falciparum* infection would lead to physiological and behavioural changes (in women and mosquitoes respectively), and that the increased frequency of *P falciparum* malaria among pregnant women in our study would result from these two distinct but complementary factors. In light of our results, the increased attraction of malaria vector mosquitoes to pregnant women observed in African anopheles by Lindsay and colleagues could give rise to two additional conclusions: that the phenomenon could be found in very different transmission situations, such as those in South America; and that it could reflect a specific attraction to *P falciparum* carrying mosquitoes (and result in increased transmission of *P falciparum* malaria) to pregnant women, which is relevant for strategies aimed at protecting this high-risk group against malaria.

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Tailored treatment for heart failure

Sir—In their June 10 commentary1 Ronnie Wilhelmi and Karl Swedberg proposed the idea of tailoring therapy for heart failure.2 They say that some patients may not benefit from angiotensin-converting enzyme (ACE) inhibitor therapy, and that in some cases treatment may cause harm. This concept raises important issues. In clinical practice physicians usually decrease the dose, or discontinue ACE inhibitor therapy, when patients have symptoms or signs that are suggestive of side-effects. These patients do not benefit from morbidity and mortality reduction from ACE inhibitor shown in clinical trials. Many national and international cardiology societies are advocating guidelines to promote evidence-based medicine, in the hope that treatments found to be beneficial in clinical trials be put into practice so that morbidity and mortality can be reduced. The investigators state “it is sometimes difficult to combine several drugs at their optimum dose because of side-effects, it may not be advisable to always combine all drugs with proven efficacy in heart failure.” They propose that plasma renin activity measurements of angiotensin II, aldosterone, and gene polymorphism may be useful in the tailoring of therapy to an individual patient. The use of surrogate endpoints in heart failure trials is misleading. For example, exercise capacity in patients with heart failure was improved with milrinone.3 But in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial a 53% increase in mortality was observed in patients with heart failure in New York Heart Association (NYHA) class IV receiving milrinone.4 No single treatment will have beneficial effects on all the mechanisms involved in heart failure. Instead of trying to identify patients who will or will not benefit most from therapy using surrogate endpoints, treatment for heart failure should be based on data from sound clinical trials that show clear reductions in morbidity and mortality. Many studies have shown that ACE inhibitor therapy is already underprescribed in heart failure.5 We are concerned that promoting the use of ACE inhibitor therapy on the basis of surrogate markers will further reduce the proportion of patients who receive this beneficial treatment.

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A surgical amputation in 2nd century Rome

Sir—The upper midshift portion of an adult left femur showing signs of surgical amputation has recently been found at the necropolis of Isola Sacra, the 2nd–3rd century AD graveyard of Portus, Rome’s seaport. This specimen, from an ossuary collection containing over 2000 individuals from single and collective interments, provides an example of the practice of, and survival after, surgical amputation in Imperial Rome times, and represents the only unequivocal available case in classical Roman paleopathological samples (according to the bibliographic record on human paleopathology edited at the San Diego Museum of Man, USA).

Celsius (1st century BC) reported that surgical amputation of limbs was done.1 By the 2nd century AD, amputation with control of bleeding was used in cases of tumours, trauma, and deformities.2 Typically, a tissue flap was used to cover the amputation.3

The specimen from Isola Sacra shows signs of months, and perhaps years, of survival: typical amputation-related bone remodelling and chronic osteomyelitis.4 The distal extremity (figure A) shows part of the original cut surface with cut mark striations and the bony cap that often forms after amputation. The femur shaft (figure B, C) shows post-amputation reactions and remodelling—ie, periostitis, diffuse appositional bone, porosity, spicules, osteophytes, focal discolouration, and small cloacae. These signs suggest amputation osteomyelitis.5 Although osteomyelitis could have preceded amputation, pyogenic osteomyelitis after amputation seems more likely, considering non-aseptic Roman surgery.

Re-examination of the ossuary material from the same collective burial provided other bones which probably belong to the same individual. They have the same colour, texture, and condition as the femur, and show osteomyelitis-associated porosity and appositional bone (osteomyelitis was often multifocal and pre-antibiotic times).5 Among these bones, the right metatarsals show medial shaft torsion, perhaps a result of remodelling caused by gait changes following contralateral amputation.

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1 Albutt TC. Greek medicine in Rome. New York: Benjamin Blom, Inc, 1921.