CORRESPONDENCE

Treatment of Gaucher's disease with OGT 918

Sir—Timothy Cox and colleagues (April 29, p 1481)[1] presented the long-awaited results of the trial of OGT 918 (*N*-butyledeoxynojirimicin) 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 data[2] and the finding that leucocyte G_{M1} concentrations were reduced, these 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 glucocerebroside concentrations is not reported. There was a striking dissociation between mean reduction of hepatomegaly 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 hepatomegaly, 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.[3] With respect to lack of haematological response, it is of note that OGT 918 caused marrow toxicity in HIV trials.[4] 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. Paraesthesiae also occurred in the HIV trial. The protocol does not appear to monitor for any possible effects on cerebral function—brain glycosphinglipids 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.[5] 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

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1 Cox T, Lachmann R, Hollack C, Aerts J, et al. Novel oral treatment of Gaucher's disease with N-butyledeoxynojirimicin (OGT 918) to decrease substrate biosynthesis. *Lancet* 2000; **355:** 148–85.

2 Platt FM, Butters TD. New therapeutic prospects for the glycosingolipid lycosomal storage diseases. *Biochem Pharmacol* 1998; **56:** 421–30.

3 Platt FM, Neises GR, Reinkensmeier G, et al. Prevention of lycosomal storage in Tay-Sachs mice treated with N-butyledeoxynojirimicin. *Science* 1997; **276:** 428–31.

4 Fischl MA, et al. The safety and efficacy of combination N-butyl-deoxynojirimicin (SC-48334) and zidovudine in patients with HIV-1 infection and 200-500 CD4 cells/mm³. *J Acquir Immune Defic Syndr Hum Retrovirol* 1994; **7:** 139–47.

5 Grabowski GA, Leslie N, Wenstrup R. Enzyme therapy for Gaucher disease: the first 5 years. *Blood Rev* 1998; **12:** 115–33.

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 one year (p=0·014). We also found decreased biosynthesis of the glycolipid substrate G_{M1}, ganglioside. Moreover, plasma glucosylceramide 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.

When P K 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 state that the latter studies involved much higher doses of OGT 918 with 10-fold greater plasma concentrations—lymphoid depletion noted in these studies was not observed in the liver. Long-term safety studies of OGT 918 in the rat showed a small increase in liver weight; in a 1-year primate toxicology study there were no significant histological changes in the liver and spleen. The number of circulating lymphocytes has been assessed routinely in all patients participating in the trial and remain clinically unchanged. Weight loss was not a major concern and the mean bodyweight reduction during the study was 6·4%, making no adjustment for a large weight reduction in one individual who was overweight at baseline and adhered to a strict diet during the trial. No significant correlation was observed between change in liver or spleen organ volume and bodyweight change. Lymphoid tissue is, of course, a minor component of the liver and the significant reduction in liver volume related to OGT 918 cannot be explained by a direct effect on this tissue. This fact, together with the observation that changes in liver size are probably the best quantitative index of clinical response,[1] only serves to emphasise the importance of the liver volume changes that we observed.

Diarrhoea usually occurred when therapy started and we included patients with mild intermittent diarrhoea. For most participants diarrhoea did not present insuperable difficulties. None of the patients developed pulmonary hypertension during the trial and none of the three patients with pre-existing pulmonary hypertension deteriorated. Parasthesiae were noted in earlier clinical trials when OGT 918 was given at higher doses to HIV patients. Although this was not statistically significant and there were no effects on cerebral function, we remain vigilant.

We acknowledge that enzyme replacement therapy is a safe and effective treatment for Gaucher's disease but an oral therapy would indeed lessen the burden of the disease. We are encouraged that our study with oral OGT 918 met the predefined efficacy endpoint in Gaucher's disease. Infants and children with the disease have required permanent intravenous cannulae for administration of the enzyme and the astronomical costs of enzyme replacement therapy preclude its use in many parts of the world.

I thank my co-workers for their input to this reply.

Timothy Cox

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1 Beutler E, Demina A, Laubscher K, et al. The clinical course of treated and untreated Gaucher disease: a study of 45 patients. *Blood Cells Mole Dis* 1995; **21:** 86–108.

Sir—As a public company Oxford GlycoSciences is obliged to disseminate material information on investigational drugs. The press release of April 28, 2000, coincided with the public dissemination of the clinical data in *The Lancet* and was factually correct, complete, and balanced. Comments on the drug are taken directly from the paper, which completed the peer-review 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."

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Prevention of hypertension and stroke in Africa

Sir—Walker and colleagues (May 13, p 1684)[1] 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.[2] Worldwide, cerebrovascular disease is second only to ischaemic heart disease as a cause of death (4·38 million in 1990), and most of these deaths (3 million) are in less-developed countries.[3]

In sub-Saharan Africa detection, prevention, and treatment of hypertension should now be regarded as a high priority.[4] 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

Variables	Baseline mean (SD)	Intervention mean (SD)	Difference 95% CI	p
Bodyweight (kg)	58·5 (9·4)	57·7 (9·4)	0·79 (−0·08 to 1·66)	0·07
Systolic BP (mm Hg)	135·3 (16·5)	128·9 (16·8)	6·4 (0·5 to 12·3)	0·035
Diastolic BP (mm Hg)	85·8 (8·6)	81·3 (7·5)	4·5 (−0·3 to 9·3)	0·06
Serum creatinine (μmol/L)	86·7 (11·4)	89·3 (14·0)	−2·6 (−7·0 to 1·7)	0·22
Urinary sodium (mmol/24 h)	99·4 (49·4)	55·3 (30·0)	44·1 (22·3 to 65·9)	<0·001
Urinary potassium (mmol/24 h)	91·7 (33·8)	82·1 (29·2)	9·6 (−3·8 to 23·0)	0·15
Urinary creatinine (mmol/24 h)	10·1 (3·2)	9·2 (2·6)	0·9 (0·2 to 1·5)	0·009
Urinary sodium:creatinine	10·1 (5·1)	6·2 (3·6)	3·9 (1·9 to 5·9)	0·001

BP=blood pressure.

Study findings

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.[5] 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 attended 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.

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1 Walker RW, McLarty DG, Kitange HM, et al. Stroke mortality in urban and rural Tanzania. *Lancet* 2000; **355:** 1684–87.
2 Cooper RS, Osotimehin B, Kaufman JS, Forrester T. Disease burden in sub-Saharan Africa: what should we conclude in the absence of data? *Lancet* 1998; **351:** 208–10.
3 Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. *Lancet* 1997; **349:** 1269–76.
4 Cooper RS, Rotimi C, Kaufman JS, Muna WFT, Mensah G. Hyertension treatment and control in sub-Saharan Africa: the epidemiological basis for policy. *BMJ* 1998; **312:** 614–17.
5 Plange-Rhule J, Phillips R, Acheampong JW, Saggar-Malik AK, Cappuccio FP, Eastwood JB. Hypertension and renal failure in Kumasi, Ghana. *J Hum Hypertens* 1999; **13:** 37–40.

Sir—Collating information on non-communicable diseases (NCDs) in sub-Saharan Africa is an enormous task that is achievable only through collaboration. Richard Walker and colleagues[1] have reaffirmed the importance of collaboration of experts from resource-rich nations with those of resource-poor nations through publication of research in peer-reviewed journals.[2] More importantly, this group is now in the early stages of providing much needed data on the extent of cardiovascular disease in sub-Saharan Africa, which to date has remained fragmented and unreliable. The accumulating epidemiological information shows the need for cost-effective strategies for primary and secondary prevention of cardiovascular disease and the growing public-health challenge of non-communicable diseases in sub-Saharan Africa. The current enthusiasm for collaboration is crucial for the development and implementation of health-care policies throughout the sub-Saharan region. This collaboration is especially important when attempting to validate any developed guidelines for treatment or prevention of non-communicable diseases in sub-Saharan Africa. The epidemiology of cardiovascular morbidity will at least provide the starting point for better health-care planning, which could mirror the way communicable diseases have been handled.

We need to know the prevalence of risk factors such as hypertension. Passive publications are futile unless there is active use of the information accrued to implement change.[3] Long-term mortality would be much lower and longevity much greater if cardiovascular risk factors are lowered.[4] The onus still remains with the local health practitioner to extrapolate and adapt this information cost-effectively, because the scientific basis for formulation of policy is now more evident. The policies subsequently implemented will at least minimise the impact of the impending double jeopardy from non-communicable diseases, and infectious illnesses within the next 20 years. While it is correct that the top priorities for resources in sub-Saharan Africa are infection and malnutrition, it is negligent to completely ignore the increasing numbers in the population with poor cardiovascular health. The meagre resources available must benefit the whole population. Unfortunately, what we see is a small group of powerful people using the scarce resources to troop around sub-Saharan Africa or more-developed countries to access better health care and cures for preventable complictions of hypertension or diabetes. These people should give more support to the local health practitioners involved in international collaboration, as any success gained is beneficial to all. Research into non-communicable diseases, particularly cardiovascular disease in tropical Africa, should be seen as vital rather than a luxury.[5]

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1 Walker R, McLarty D, Kitange H, et al. Stroke mortality in urban and rural Tanzania. *Lancet* 2000; **355:** 1684–87.
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non-communicable diseases in sub-Saharan Africa: the essential NCD health intervention project. *Public Health* 1999; **113:** 141–46.
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Parity and breast cancer in *BRCA1/BRCA2* carriers

Sir—E J Meijers-Heijboer and colleagues (June 10, p 2015)[1] describe factors that predict a woman's decision to undergo genetic testing for breast cancer susceptibility. The investigators found that parenthood was a strong predictor of testing in unaffected women. This implies that the parity of the sampled population is not representative of parity in the underlying population; this finding has important implications for epidemiological studies. Women with breast cancer may seek testing for other reasons—ie, parity may not influence their decision. We would then observe mean parity to be greater in the unaffected women than in the affected women in the sampled (tested) population. Parity would, therefore, seem protective against breast cancer. In the study by Meijers-Heijboer and colleagues, 24% of the tested population were nulliparous, compared with 40% of women who declined testing. In a case-control study based on this sample, a spurious risk ratio of 1·5 for the risk of breast cancer associated with nulliparity would be observed. We have reported that nulliparity is protective against breast cancer in young women who are *BRCA1* and *BRCA2* carriers.[2] It is important to be aware of the implications of potential ascertainment biases due to self-selection for genetic testing, when interpreting epidemiological studies of gene carriers.

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1 Meijers-Heijboer EJ, Verhoog LC, Brekelmans CTM, et al. Presymptomatic DNA testing and prophylactic surgery in families with a *BRCA1* or *BRCA2* mutation. *Lancet* 2000; **355:** 2015–20.
2 Jernstrom H, Lerman C, Ghadirian P, et al. Pregnancy and the risk of early onset breast cancer in carriers of *BRCA1* and *BRCA2* mutations. *Lancet* 1999; **354:** 1846–50.

Thyroid FNA and benign thyroid disease

Sir—We fully accept the point made by Armando Bartolazzi in his May 13 commentary[1] that the predictive value of thyroid fine-needle aspiration (FNA) for thyroid cancer is poor. There are several reasons for this situation. The accurate distinction of adenoma or well differentiated follicular carcinoma from hyperplastic nodules is not possible on FNA cytology, and the separation of follicular adenomas from hyperplastic or adenomatoid thyroid nodules is also not easy on cytology. Although it should be possible to separate papillary carcinomas from benign or adenomatous lesions on cytology, this is often impossible because the nuclear features of papillary carcinoma may be seen focally in adenomatoid nodules or atypical adenomas, and bizarre nuclei may be seen after carbimazole therapy or after radioiodine therapy. The follicular variant of papillary carcinoma is also particularly difficult to diagnose with confidence on FNA cytology because atypical nuclei present in smears may not be entirely suggestive of papillary carcinoma on FNA cytology, and may show some features, particularly if colloid is present, more suggestive of a hyperplastic nodule or follicular adenoma.

A specific marker of carcinoma that could be applied to the distinction of carcinomas of the thyroid from follicular adenomas would be of great use, similarly a marker that could be used to separate papillary carcinoma from non-malignant papillary hyperplasia would also add greatly to the cytopathologist's armamentarium.

There is, however, a different approach to this challenge. In our own hospital and in other centres, FNA cytology is used as a diagnosis of exclusion. If the aspirate shows benign, small, and regular epithelial cells without nuclear and cytological atypia and there is ample colloid present it is classified as benign. Any FNA that does not show both benign epithelial cells and is also colloid in sufficient quantity for a confident benign diagnosis would be regarded as indeterminate (the Portsmouth working formulation for diagnostic criteria for thyroid FNA is given on www.thelancet.com).[2] Our group and others have found that this, (or similar systems of diagnostic categorisation of FNAs of the thyroid), is most helpful for excluding benign disease, in as much as the percentage of malignancies in the benign FNA category (THY2) during the period of a retrospective 2 year audit was zero.[2]

We think that FNA cytology should be used primarily as a means of diagnosing benign thyroid disease rather than as a means of diagnosis of malignant disease. If this simple approach is followed about a third (58 [37%] of 156 in our study) of patients with benign nodules can be excluded from further assessment or treatment, without a significant number of false negative FNAs. Inevitably there will be some false negative cases in a larger series of patients, either due to misdiagnosis or for other reasons (eg, patients with microscopic papillary carcinoma with cells aspirated from co-existent adenoma or colloid nodules or because the aspirate taken is non-representative of the nodule). This fact does not negate the value of this approach to thyroid FNA. The negative predictive value for thyroid neoplasia in our series is as good if not better than that referred to in the article of CD44v6 plus galectin 3.[3]

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1 Bartolazzi A. Improving accuracy of cytology for nodular thyroid lesions. *Lancet* 2000; **355:** 1661–62.
2 Poller DN, Ibrahim AK, Cummings MH, Mikel JJ, Boote D, Perry M. Fine needle aspiration of the thyroid: importance of the indeterminate diagnostic category. *Cancer Cytopath* 2000; **90:** 239–44.
3 Gasbarri A, Martegani MP, Del Prete F, et al. Galectin 3 and CD44v6 isoforms in the preoperative evaluation of thyroid nodules. *J Clin Oncol* 1999; **17:** 3494–502.

Global health policy

Sir—Your June 3 editorial[1] entitled "A manipulated dichotomy in global health policy", caused surprise and dismay. It contains unfounded, incorrect statements, and destructive insinuations.

The World Bank and WHO are both strongly committed to improving health conditions among the poor, and are working closely together to do so. Both institutions have strong programmes to address communicable diseases and non-communicable diseases. For example, WHO and the World Bank are working together to support the global Roll Back Malaria partnership because of the importance of malaria in the burden of disease in many poor countries, especially Africa. There are many other examples of the close working relationship and shared agenda of the Bank and WHO, such as in HIV/AIDS, childhood illnesses, and health-system reform. While the Bank is scaling up efforts against infectious diseases, it is also doing important work on non-communicable diseases, especially those caused by tobacco. The Bank is a strong partner in WHO's Tobacco Free Initiative and a core member of the Inter-Agency United Nations Task

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*,[2] 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 inimicable 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 among international agencies", but in fact the partnership between WHO and the World Bank is stronger than ever before—and especially in tobacco control.

Eduardo A Doryan,
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1 Editorial. A manipulated dichotomy in global health policy. *Lancet* 2000; **355:** 1923.
2 World Bank. Curbing the epidemic: governments and the economics of tobacco control. Herndon: World Bank, 1999.

Sir—In your editorial on global health policy[1] you made two implicit or explicit observations about the World Trade Organization (WTO) both of which reveal gross misunderstandings about the WTO and the international trade rules that it establishes. The first is to suggest that the WTO, through its mandate to promote open markets, is encouraging "the exchange of harmful commodities—firearms, landmines, psychoactive substances, unsafe pharmaceuticals, contaminated food, and hazardous waste", apparently on the basis that the WTO's position on free markets requires all these matters be left to "individual choice rather than one of collective responsibility for public health". You go on to say that "free trade has health consequences, and these should be faced, not shouted down". The notion, being presented, therefore, is that the WTO equates with a total absence of government intervention.

This is completely false. No country would accept international trade rules which restrict its ability to regulate the marketing and importation of the products which the editorial mentions. The WTO's rules make it extremely clear that WTO member countries have an absolute right to ban or restrict the sale and importation of goods when doing so is necessary to protect public health at the level that they choose. This has never been called into doubt and all the products which are mentioned would typically be subject to such restrictions in most if not all WTO members. To take another example, most WTO members restrict the sale of alcohol in some measure, whether on health, public-order, or public mortality grounds. This causes no problem vis-á-vis WTO rules, if the restrictions apply equally to domestically-produced and imported alcohol.

In more general terms, the WTO rules allow for the fact that governments may need to intervene to deal with market imperfections and further, that where markets are not the most suitable means of meeting social needs, they can be superseded entirely. Far from being incompatible with strong government and appropriate government intervention in markets, the market economy is predicated on such governance—including ensuring the provision of basic services, the protection of property rights, and the rule of law. Although the market is a remarkable mechanism for harnessing the energies of individuals in the social interest, government intervention will always be necessary to structure markets in such a way that they serve this purpose and to prevent actions that would be harmful to others. Indeed, the WTO system of consensus-based multilateral trade rules, aimed, as they are, at ensuring the rule of multilateral law in trade relations, can itself be seen as 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.

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1 Editorial. A manipulated dichotomy in global health policy. *Lancet* 2000; **355:** 1923.

Sir—In your June 3 editorial[1] and with reference to a report by Gwatkin and colleagues[2] 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".[3] 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 tobaco 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 agenda 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".[4] 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."

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Space flight related anorexia

Sir—Laurence Vico and colleagues (May 6, p 1607)[1] described 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,[2] 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)—ie, 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, norepinephrine, 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,[3] hormonal,[4] and neurochemical changes,[5] which influence behavioural outcomes including food intake.

Food consumption during spaceflight is reduced to 70% the required and recommended intake. We propose that this reduction is a result of continuous light environment. Using a rat eater 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 hypothalamus 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 stimulus 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.

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1 Vico L, Collet P, Guignandon A, et al. Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. *Lancet* 2000; **355:** 1607–11.
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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 unrecognised 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%.[1] 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 unrecognised, 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 levels two and three.[3] Therefore an adequate sample or level one clearance may leave undiagnosed cancer in the apex of the axilla. Kissin and colleagues had previously eloquently described how axillary sampling led to an error rate of 24% compared with a level three clearance.[4]

Even in small tumours of under 1 cm in diameter, ipsilateral axillary node metastases will be present in up to 16·7% of patients,[5] therefore these women cannot safely be treated differently. Routine axillary radiotherapy alone would deny access to vital prognostic information, especially important in women with small grade I tumours, for 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.

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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 colleagues[1] reassess the Framingham data,[2] in which a linear-logistic model has 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. Port and colleagues[1] show convincingly that this assumption is false, and they propose a better model in which the odds ratio for a 10 mm Hg increase in systolic blood pressure is larger at systolic blood pressures above the 70th centile.

This new model clearly fits the data better than the linear-logistic model. However, the conclusion of Port and colleagues that "there is an age-dependent and sex-dependent threshold for hypertension" is not justified by the analysis done. It is instead a consequence of their assumption that the threshold lies at the 70th centile of systolic blood pressure for each age and sex group. Alternative models with the threshold at a fixed level of systolic blood pressure, or modelling variation in the threshold with age and sex, were not assessed.

The conclusion that risk is unrelated to systolic blood pressure below the 70th centile is also dubious. The estimated odds ratio in this range and its confidence interval are not reported, so the reader is unable to judge whether the data are consistent with a substantial association. Also, the odds ratio for a 10 mm Hg increase in systolic blood pressure is assumed to be 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,[3,4] which avoid assumptions about the form of the association and are not driven by results for people with systolic blood pressures outside this range.

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1 Port S, Demer L, Jennrich R, Walter D, Garfinkel A. Systolic blood pressure and mortality. *Lancet* 2000; **355:** 175–80.
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Sir—Sidney Port and colleagues[1] 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 Alderman[2] 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.

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1 Port S, Demer L, Jennrich R, et al. Systolic blood pressure and mortality. *Lancet* 2000; **355:** 175–80.
2 Alderman MH. Measures and meaning of blood pressure. *Lancet* 2000; **355:** 159.
3 Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265:** 3255–64.

Sir—Sidney Port and colleagues[1] 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).

Age band (years)	Joint British Recommendations		Above the 80th percentile	
	Men	Women	Men	Women
45–54	12%	8%	20%	20%
55–64	27%	31%	20%	20%
65–74	57%	53%	20%	20%

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

The model proposed by Port and colleagues has considerable implications for UK practice. It would reduce the treatment of older people and significantly increase treatment of younger people. Because of its potential significance, data should be collected to establish which model is the better predictor of cardiovascular mortality.

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1 Port D, Demer L, Jennrich R, Walter D, Garfinkel A. Systolic blood pressure and mortality. *Lancet* 2000; **355:** 175–80.
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Author's reply

Sir—We disagree with Ian White that our conclusions concerning the age-sex dependent threshold for hyprtension 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 details. 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[1] 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.

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1 Alderman MH. Measure and meaning of blood pressure. *Lancet* 2000; **355:** 159.
2 Cooperative Research. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final report of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **275:** 1557–62.

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 compares some English-French words with their English-Saxon equivalents.[2] Michael O'Donnell should understand that it is natural for French or Spanish writers (and many other Latin writers) to preferentially use the English-Latin words rather than English-Saxon words. In our experience, most English people correctly understand us when we do so. And it is easier for us to understand this type of English.

Michael O'Donnell also implies that evidence-based medicine equals illiterate medicine or inhuman medicine (a medicine which is not able to listen to the patients' secrets of the heart), which is perhaps not entirely fair to this useful discipline[3]. For example, evidence-based medicine clearly indicates that a patient with colorectal liver metastases is much more in need of an excellent medicosurgical team[4] than of a physician listening to the secrets of his heart; unless, of course, this patient wants to have his life expectancy significantly shortened.

Being literate is obviously a good thing, not only for medical doctors, but 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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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 studies[1] 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 IHD".[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."[4]

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1 Albert T. The A-Z of medical writing. London: BMJ Books, 2000.
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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 editorial[2] 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 sactimoniously 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 regimens answerable, not to the citizens, but only to the western powers and huge petroleum interests that have systematically brought about its destruction. The future generation of Iraqi citizens will not be permitted to experience the distribution of their natural and national wealth for the rebuilding of a civilised and healthy society.

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1 Ali MM, Shah IH. Sanctions and childhood mortality in Iraq. *Lancet* 2000; **355:** 1851–57.
2 Editorial. Iraq's children. *Lancet* 2000; **355:** 1837.

Sir—The paper by Mohamed Ali and Iqbal Shah[1] gave clear evidence of the detrimental effects of economic sanctions on children's health in Iraq. Their results imply that children's lives would be saved if the UN embargo were lifted, or at least eased for food and medicines. At this very moment children of Iraq are suffering from ordinary preventable and treatable diseases. In the paper by Ali and Shah and in the editorial[2] there are strong appeals to the international community, the allied nations headed by the USA in particular, for lifting the UN embargo. I believe that *The Lancet* and these two investigators take a strong stance against Saddam Hussein's dictatorship, 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 malarious 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 collegues 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 commentary[1] Ronnie Willheimer and Karl Swedberg proposed the idea of tailoring therapy for heart failure.[1] 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. 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.[2] 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.[3–5] 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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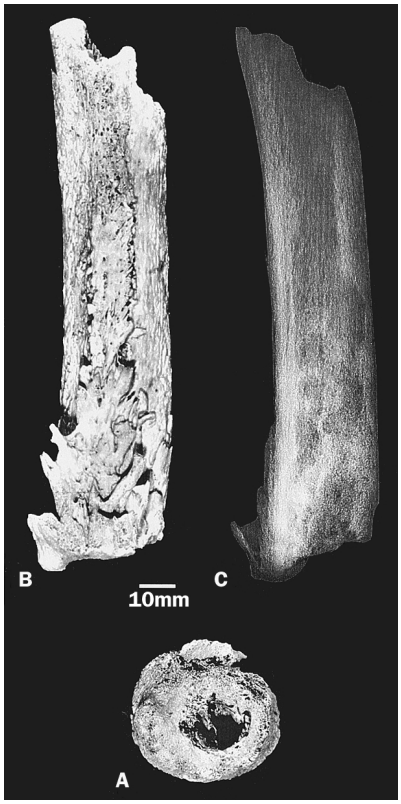
A surgical amputation in 2nd century Rome

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 internments, provides an example of the practice of, and survival after, surgical amputation in Imperial Roman times, and represents the only unequivocal available case in classical Rome paleopathological samples (according to the bibliographic record on human paleopathology edited at the San Diego Museum of Man, USA). Celsus (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]



Views of adult left femur
A: distal end of left femoral shaft, showing original cut surface, traces of the cut marks, and bony cap; B: lateral view of the specimen, showing extensive bone reaction and remodelling; C: radiograph of the specimen.

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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