CORRESPONDENCE

Organ donation and kidney sales

Sir—Your decision to publicise J Radcliffe-Richards and colleagues' (June 27, p 1950)[1] case for allowing kidney sales reveals the unwillingness of sectors of medical opinion to accept the verdict of the professional associations, parliaments, and governments quoted in the paper. The investigators assume that the provision of transplantation for patients on dialysis justifies everything, that ethics are a variable concept which depends on fashion, and that objectors to anything would eventually suffer from outrage fatigue.

I have previously recounted how, in commercial kidney transplantation in India, not only the recipients did poorly, but the donors never received more than 10% of the funds required from the recipients, hardly a way of escaping their poverty.[2] The need for an ethical cadaveric and living-related-only kidney-transplant programme in that part of the Middle East was evident then, and with others I was instrumental in commencing it. Today this programme has flourished in the hands of Saudi doctors with 222 transplantations having taken place by the end of 1997, with excellent results in terms of graft and patients' survival. All the patients and relatives understood the benefits of ethical donation and stopped travelling to buy organs.

We should strive to increase rates of transplantation in a way similar to that reported by Xavier Bosch in his June 20 news item (p 1868)[3] about Spanish transplantation. He suggested that one of the reasons for its success was the transparency and accountability of the organisation responsible.

The arguments of Radcliffe-Richards and co-workers are based on the assumption that poverty is impossible to deal with and that the owner of surplus non-vital organs could sell them to escape poverty, and should not be denied such a possibility. With this type of tunnel vision of mankind and humanity, one would be expected to conclude that by establishing a commercial transplantation service in the famine areas of Sudan, the whole kidney transplant waiting lists of the developed world would disappear within a few weeks and that payment of donors could be done cheaply since donors would be desperate enough for any agreement, which would be life-saving anyway.

Arguments in favour of the sale of kidneys distort facts that usually fail to fool people that have deep feelings of repugnance about paying desperate people to undergo a painful procedure, lose an organ, and take risks associated with surgery. The lessons of the defeat of fascism in Nazi Germany have not been learnt when the exploitation of large numbers of people judged sub-human at the time, was condoned by the same sections of the medical establishment who saw only the so-called scientific value of such experimentation.[4] The implication of Radcliffe-Richards and colleagues' proposal is that some human beings are intrinsically more medically worthy than others. Imagine the outrage and anger if, with similar arguments, we justify child labour, child prostitution, or many other activities that occur in the context of an economically unequal world. Logic is not the basis for acceptable behaviour, and judging by their proposals I am happy that legislation is not in the hands of doctors who, after all, are no more ethical than anyone else. We should not take for granted that our responsibilities as doctors are limited to looking after our individual patients. We are accountable for our actions at large and there is such a thing as crimes against humanity.

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1 Radcliffe-Richards J, Daar AS, Guttman RD, et al, for the International Forum for Transplant Ethics. The case for allowing kidney sales. *Lancet* 1998; **351:** 1950–52.
2 Mohamed AS, Velasco N. Kidneys for sale. *Lancet* 1990; **336:** 1384.
3 Bosch X. Spain celebrates leading the world in organ donation. *Lancet* 1998; **351:** 1868.
4 Seidelman WE. Nuremberg lamentation: for the forgotten victims of medical science. *BMJ* 1996; **313:** 1463–67.

Sir—The report by J Radcliffe-Richards and colleagues for the International Forum for Transplant Ethics[1] is refreshing. The carefully worded document asks for a careful, unpartial re-evaluation of the prohibition to accept the sale of kidneys for transplantation under carefully controlled conditions.

My colleagues and I have previously reported our medical experience with Palestinian Arab children who travelled from the area of the Palestinian authority to Iraq for a commercial renal transplant, as more than 100 adult Palestinians had done before them.[2,3] All the children were on dialysis in the Israeli part of Jerusalem. We cooperated by providing a covering letter on their departure and by accepting them for follow-up immediately on their return to our public hospital. The patients lived in an area beyond the jurisdiction of Israel and obviously this holds true for the hospital where the transplants were performed. The donors were adult, consenting, healthy, young men eager to sell their kidneys.

The first journal to which we submitted our results, refused to accept the article because of its ethical implications. We were accused of facilitating the sale of kidneys, a practice which certainly should not be publicised for fear of inducing others to follow a similar path. A second try in a prominent nephrology journal was more successful; the same text was accepted with only a few clarifications.

My support for the report by Radcliffe-Richards and co-workers does not mean that I have no mixed feelings about commercial transactions with regard to organ transplantation. Nor do I think that it will be easy to regulate the practical features of the sale of kidneys, particularly when dealing with developing countries. The proposal by these researchers will no doubt rekindle discussion among the various medical, legal, and religious forces in Israel, as we seek to find ways to expand the local kidney donor pool. Reconsideration of the legal supervised sale of kidneys received a certain impetus after the unexpected endorsement (in principle) by the chief rabbinate.

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1 Radcliffe-Richards J, Daar AS, Guttman RD, et al, for the International Forum for Transplant Ethics. The case for allowing kidney sales. *Lancet* 1998; **351:** 1950–52.

2 Frishberg Y, Feinstein S, Drukker A. Living, unrelated (commercial) renal transplantation in children; and ethical dilemma. *J Am Soc Nephrol* 1998; **9:** 1100–03.

3 Friedlaender M. Living unrelated renal tansplantation: principles and practice. In: Andreuci VE, Fine LG, eds. International Year Book of Nephrology. Oxford UK: Oxford University Press, 1996, pp 153–59.

Sir—As a medical journalist and, more importantly, after, respectively, 9 and 12 years' experience as a renal dialysis and transplant patient, I agree with J Radcliffe-Richards and co-workers[1] that both society in general and the medical profession in particular should keep an open mind in the search for solutions to the shortage of donor kidneys. For example, this report has inspired interest at some UK units in the use of organs from living, unrelated (and unpaid) donors such as spouses or friends.

It is unfortunate—and surprising given their wish to avoid emotional reactions to the sale of kidneys—that Radcliffe-Richards and co-workers base their argument partly on the unreferenced and emotive statement that "dialysis is a wretched experience for most patients". How do the researchers draw this conclusion? Does it apply to all forms of dialysis wherever performed? Do they have access to evidence-based information that they fail to reference? Or have they fallen into the common trap of judging quality of life, not from the point of view of those who experience the illness or disability, but from that of the physically fit?

In the UK alone, thousands of patients on dialysis hold down demanding jobs, enjoy family life, and travel abroad. Both haemo- and continuous ambulatory peritoneal dialysis demand self-discipline and commitment from patients and families. It is also undeniable that, as in transplantation, the side-effects and long-term sequelae of dialysis are causes for concern. However, I do not believe that I was alone in finding that most of the difficulties I experienced as a dialysis patient arose from the ignorance, lack of understanding, and prejudice of the general public, employers, and some members of the medical profession.

Few—and certainly not I—would deny that successful transplantation is the treatment of choice for renal failure. But not all transplants are successful and not all patients are suitable for transplantation. By their unconsidered statement, Radcliffe-Richards and colleagues undermine the case for kidney sales and do a disservice to renal dialysis patients.

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1 Radcliffe-Richards J, Daar AS, Guttman RD, et al, for the International Forum for Transplant Ethics. The case for allowing kidney sales. *Lancet* 1998; **351:** 1950–52.

Sir—I applaud the efforts of J Radcliffe-Richards and his colleagues[1] to revisit the case for allowing kidney sales. I believe that they perform a great service for patients with end-stage renal disease and for society at large.

However, their arguments would have been equally effective if they had not described dialysis as a "wretched experience for most patients". That statement suggests that they have never looked after dialysis patients, otherwise they would not have said this. My point is not to argue whether or not dialysis is a wretched experience (unsuccessful transplantation could be an equally wretched experience for some patients), but to point out that transplantation and dialysis are complementary programmes that help patients with end-stage renal disease to lead lives of the best possible quality.

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1 Radcliffe-Richards J, Daar AS, Guttman RD, et al, for the International Forum for Transplant Ethics. The case for allowing kidney sales. *Lancet* 1998; **351:** 1950–52.

Sir—J Radcliffe-Richards and colleagues[1] favour kidney sales by living vendors as a way to increase the number of organs available for transplantation. The decline in number of cadaveric renal transplants is multifactorial. One reason is the reluctance of relatives of brain-dead patients who could be potential donors. Time and again one is faced with relatives' refusal to allow retrieval of cadaveric organs. Rather than making a case for accepting the sale of kidneys by live vendors, perhaps a case should first be made for remunerating those who allow cadaveric organs of brain-dead relatives to be used for transplantation.

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1 Radcliffe-Richards J, Daar AS, Guttman RD, et al, for the International Forum for Transplant Ethics. The case for allowing kidney sales. *Lancet* 1998; **351:** 1950–52.

Sir—I Kennedy and colleagues (May 30, p 1650)[1] reconsider the ban on the sale of human kidneys, to meet the growing disparity between the waiting lists and the availability of organs. They attribute the foundation upon which these judgments are based to a visceral instinct, not capable of clear of consistent articulation.

There should be no illusion that the question they open is an immediate and pressing one worldwide: a candid admission by the General Secretary of the Indian Medical Organisation, indicated that commercial transplantation is widespread in at least two states in India;[2] César Chelala's March 7 news item (p 735)[3] describes a successful FBI operation to sting Chinese trade in prisoner's kidneys in New York;[2] and most troubling of all, kidneys are advertised for sale on the internet, even from states where commerce in transplants is forbidden.

Without any controversy, a principal and venerable medical imperative is *primum non nocere*, first of all to do no harm. Yet, paradoxically, transplant donation does require the doing of harm to a healthy person, thus transforming him or her into a patient. Under the exceptional circumstances implicit in a living related or unrelated (spouse or friend) transplant, the donor is regarded as the most important of patients. The main issue is not free consent, it is proper medical practice.

There is sacred and important trust between the donor and the doctors handling the transplant, a trust that will be inexorably undermined by the introduction of such direct commercial interest in the commissioning of harm. Unlike any other private medical practice, the donors are paid by the doctors for substantial potentially life-threatening harm done to them by the doctor for no reason other than their own financial gain. Will not this violation of trust for commercial interest do irreparable harm to the profession as a whole? This practice is as much a deviation from ordinary medical practice as the supervision of torture in prison or the administration of a fatal injection. A risk-benefit analysis analogous with unpaid donation is, therefore, inappropriate. Do the potential benefits of a cash windfall for the vendor justify any act? It is a shame if the only lessons drawn from Nuremberg are restricted to questions of personal autonomy.[4]

The immediate practical consequences of such a policy would be disastrous for our patients, both recipients and those on the waiting list, for paid donors and for public confidence in the medical profession. How is it possible to introduce a central regulatory purchase authority for kidney sales, when the commodity is regarded as priceless? I Kennedy and co-workers are naive to suggest that "all purchasing could be done by a central organisation responsible for fair distribution". How is the absence of coercion to be tested? The sale of kidneys is most likely in the poorest countries, the very countries where safeguards to ensure that consent is free and informed are weakest. Reopening this debate provides impetus to the burgeoning trade in organs in some developing countries. Technical quality is not a key ethical issue, but poor results, a high rate of infection in recipients, graft loss, and allegations of criminal involvement, including man-theft and murder, have all been reported from such trade.[5] These factors alone render the report by Kennedy and colleagues irresponsible, even before any serious consideration of its enquiries.

Kennedy and co-workers seek to open a box that would make even Pandora blush. Resolute confirmation of the original judgments is needed to safeguard our professional ethics, with careful consideration of policing in new potential areas of abuse.

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Magnetic-resonance imaging and prediction of recovery from post-traumatic vegetative state

Sir—I welcome the research published by Andreas Kampf and colleagues (June 13, p 1763),[1] but as Keith Andrews implies in his accompanying commentary,[2] the title of the paper is optimistic. The overlap between the outcome groups renders the margin of error too large for use of these findings in treatment decisions. What can be seen in these data is a significant trend but not a clear-cut relation between findings on cerebral magnetic-resonance imaging (MRI) and prediction of outcome in post-traumatic vegetative state. Furthermore, such a finding is predictable given current knowledge about the normal variations that can be seen between individuals in the relation between brain structures and behaviour, and which would be further complicated by the effects of recovery processes after injury, such as plasticity. Barbara Wilson[3] summarised the situation well when she stated: "Although imaging techniques may help us to understand the recovery process, it is hard to argue that they help in planning rehabilitation".

Given the limitations of imaging for prognostic purposes, are there other sources of information that could aid treatment decisions? Vegetative state has always been defined by behavioural rather than pathological criteria, so behavioural data seem a good place to start. Preliminary studies that I have carried out with colleagues[4,5] showed quantitative and qualitative behavioural differences between patients who emerge from vegetative state and those who remain in this condition. One of the differences found (with data from momentary behaviour sampling) was that patients who later emerged showed a characteristic pattern of behaviour after an environmental event, unlike those patients who remained in vegetative state.[4] I have also analysed data collected by Gill-Thwaites and found that patients who later emerged from vegetative state could be differentiated from those who did not by the magnitude of changes in scores between behavioural assessments carried out every 2 months.[5] The assessment protocol used assessed degree of functioning within vegetative state by systematic application of discrete stimuli to each of the senses in turn. The findings from these two studies need replication and some of the measures require refinement; the results, however, indicate the prognostic value of behaviourally based assessment since behavioural features that are unique to patients who later emerge from vegetative state can be identified.

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1 Kampf A, Schmutzhard E, Franz G, et al. Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. *Lancet* 1998; **351:** 1763–67.
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Fenoterol and asthma mortality

Sir—Richard Beasley and colleagues (May 9, p 1406)[1] reiterate their original view, that there was a causal link between the high-dose preparation of fenoterol and the epidemic of asthma deaths in New Zealand in the 1970s and further suggest that a smaller increase in asthma mortality in Japan may also be due to fenoterol use. Beasley and co-workers do not cite or mention the substantial body of scientific evidence that does not support their view.

Beasley and colleagues discuss two kinds of evidence: national trends in drug sales and asthma mortality, and epidemiological studies of patients prescribed fenoterol. With regard to the former, in New Zealand, asthma mortality started to fall in 1979 when fenoterol sales were still increasing and 11 years before restrictions for reimbursement of fenoterol curbed the sales. The use of β-agonists as a class doubled, whereas asthma mortality declined by 40%.[2] Moreover, sales of fenoterol in Austria, Belgium, and Germany were similar to those in New Zealand near the peak of the epidemic, but asthma mortality in these countries remained low.[2] Thus, there is no visible relation between fenoterol sales and asthma mortality. The cause of the asthma epidemic in New Zealand remains unknown, whilst its decline has been attributed to substantial increases in use of medium-dose and high-dose inhaled steroids, and other improvements in asthma care.[3]

The 1990–96 survey by the Committee on Asthma Death of the Japanese Society of Pediatric Allergy and Clinical Immunology in patients aged up to 26 years examined 123 asthma deaths, seven of which were judged to be due to overdose of fenoterol. These data cannot be interpreted without knowing the number of cases that would have been expected to use fenoterol in the absence of any causal relation. To get this figure would require a carefully designed control group, which is unavailable. In lieu of a control group, Beasley and colleagues substitute data in overall market share that disregards age, asthma severity, and other important factors. Understandably, such shortcuts do not yield valid scientific answers.

According to the judgment on each individual case of the survey by the Subcommittee on Adverse Drug Reactions of the Japanese Ministry of Health and Welfare, a causal relation between excessive use of the drugs involved and asthma death was not established, however, the Ministry and Nippon Boehringer Ingelheim agreed to issue a warning about overdosing of and over-reliance on fenoterol.

There have been other formal epidemiological studies of the risk of fenoterol. The difficult challenge confronting these studies is that fenoterol has been prescribed preferentially to patients with severe asthma.[4] Due to the prescribing pattern, fenoterol will be over-represented among patients who die from asthma. Researchers who have adjusted appropriately for asthma severity have shown that high rates of deaths from asthma among fenoterol patients are due to underlying severe asthma, and do not point to any adverse effect of fenoterol.[5]

Asthma mortality results from an elusive combination of factors, many still to be identified. Taken as a whole, neither the epidemiological data on mortality trends nor the analytical studies support Beasley and colleagues' belief that an asthma therapy is responsible for increases in asthma mortality.

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1 Beasley R, Nishima S, Pearce N, Crane J. β-agonist therapy and asthma mortality in Japan. *Lancet* 1998; **351:** 1406–07.
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Authors' reply

Sir—Gerhard Kremer and Bernd Disse correctly point out that the ideal way to assess whether fenoterol increases the risk of death is to undertake a case-control study. There have been four such case-control studies, all of which showed a significantly higher death rate in patients prescribed fenoterol than in those prescribed other β-agonists.[1] There is limited evidence of selective prescribing of fenoterol in the populations studied in New Zealand,[2] or in Canada,[3] and detailed analyses indicate that the association between fenoterol and deaths from asthma was not due to confounding by severity of asthma.[2] A formal case-control study in Japan would be of interest, although the available data on asthma mortality and fenoterol market share in Japan[4] accord with the findings of the case-control studies in New Zealand and Canada.

Trend data are more difficult to interpret because many factors affect mortality time trends. However, it is noteworthy that the Japanese data are consistent with the time-trend data from New Zealand.[5] The New Zealand epidemic started when fenoterol was introduced in 1976, and despite a slight decrease in the death rate after publicity about the epidemic and the dangers of overuse of β-agonists in 1981, the New Zealand death rate remained the highest in the world for more than 10 years, during which time fenoterol maintained a consistent market share. After the publication of our initial case-control study, the death rate immediately fell by 50% and remained low in 1990. On the other hand, the time-trend data are inconsistent with the hypothesis of a role of a class effect of β-agonists in the epidemic. There was no association between total sales of β-agonists and the start of the epidemic, and total sales of β-agonists actually increased slightly in 1989–90 when the epidemic came to an end. The time-trend data are also inconsistent with the hypothesis that the epidemic may have occurred because of under-prescribing of inhaled corticosteroids, or that the abrupt end to the epidemic occurred because of increased prescribing of inhaled corticosteroids.[5]

In addition to this epidemiological evidence, clinical studies have shown that fenoterol has greater acute and chronic adverse effects than other β-agonist drugs.[1] Thus, the Japanese data are consistent with an increasing body of evidence that the use of the high-dose (200 μg/puff) preparation of fenoterol increases the risk of death in asthma.

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1 Pearce NE, Beasley R, Crane J, Burgess C. Epidemiology of asthma mortality. In: Busse W, Holgate S, eds. Asthma and rhinitis. Oxford: Blackwell Scientific, 1995: 58–69.
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5 Pearce N, Beasley R, Crane J, Burgess C, Jackson R. End of the New Zealand asthma mortality epidemic. *Lancet* 1995; **345:** 41–44.

Sir—Richard Beasley and colleagues[1] present what seems to be a cogent hypothesis to support an association between the use of fenoterol and asthma mortality in Japan and New Zealand. However, a more detailed analysis of risk factors has shown that the positive association between fenoterol and severe life-threatening asthma may be explained by preferential prescribing to patients with more severe disease.[2]

In a study of 257 patient with acute severe asthma, dose-titration with fenoterol (≤3200 μg), or salbutamol (≤1600 μg) given via a spacer showed no evidence of any clinically relevant cardiac arrhythmias, despite the fact that the two-fold higher dose of fenoterol exhibited greater systemic β_2-mediated effects.[3] None of the patients showed evidence of pronounced prolongation of the QT_c interval. Although fenoterol exhibits a higher degree of intrinsic efficacy at systemic β_2-adrenoceptors than salbutamol,[4,5] such differences are of small magnitude and unlikely to be of any clinical relevance.

Although it is tempting to implicate the use of fenoterol with asthma mortality, this hypothesis is not substantiated by data from carefully controlled pharmacodynamic or pharmacoepidemiological studies. Doctors should follow accepted asthma-management guidelines in that excessive use of β_2-agonists including fenoterol should point to inadequate suppression of the underlying inflammatory process and the need to optimise the dose of inhaled corticosteroid therapy.

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1 Beasley R, Nishima S, Pearce N, Crane J. β-agonist therapy and asthma mortality in Japan. *Lancet* 1998; **351:** 1406–07.
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Natriuretic peptides and contractile reserve in dilated cardiomyopathy

Sir—Natriuretic peptides are secreted in response to increased intracardic volume and pressure. The measurement of these peptides in biochemical assessment of left-ventricular dysfunction has been reported.[1,2] With regard to the report by the Metoprolol in Dilated Cardiomyopathy Trial Study Group (April 18, p 1180),[3] we wondered if the investigators had the opportunity to measure natriuretic peptides in the patients in relation to treatment with β-blockers, since these peptides could have prognostic value in dilated cardiomyopathy.

Raised plasma concentrations of atrial natriuretic peptides (ANP) and B-type natriuretic peptide (BNP) have been reported in patients with left-ventricular dysfunction after myocardial infarction[4] and in people with symptomless left-ventricular systolic dysfunction.[1,2] Previous studies focused on the role of these peptides in detection of underlying cardiac impairment, whether symptomatic or symptomless. However, there is no consensus about the relation between plasma concentrations of these peptides and the severity of left-ventricular dysfunction.[4] Moreover, the role of the peptides in dilated cardiomyopathy is unknown. Low-dose dobutamine infusion has been reported to be useful in assessment of functional inprovement in regions with rest asynergy in patients with previous myocardial infarction. We tested whether plasma concentrations of BNP and ANP can be used as biochemical indicators in the assessment of contractile reserve of dysfunctional myocardium in dilated cardiomyopathy.

22 patients with dilated cardiomyopathy (age 54 [SD 14] years; 17 men and five women; left-ventricular ejection fraction 34 [7]%) had low-dose dobutamine infusion (5 μg kg^{-1} min^{-1} and 10 μg kg^{-1} min^{-1}) during cardiac catheterisation. Plasma concentrations of BNP, ANP, and norepinephrine were analysed in relation to haemodynamic indices. With low-dose dobutamine infusion, cardiac indices increased significantly: 32 (22)% increase at 5 μg kg^{-1} min^{-1}, and 69 (26)% increase at 10 μg kg^{-1} min^{-1}. Plasma concentrations of BNP, ANP, and norepinephrine were slightly raised at rest: BNP 91 (93) pg/mL, ANP 39 (31) pg/mL, and norepinephrine 302 (229) pg/mL. The raised BNP and ANP concentrations negatively correlated to percentage increase of cardiac indices by dobutamine infusion at 10 μg kg^{-1} min^{-1}: (BNP r=–0·55, p<0·01; ANP r=–0·48, p<0·05), but did not correlate to the degree of impaired ejection fraction at rest. Plasma concentrations of norepinephrine did not correlate with haemodynamic indices.

BNP and ANP correlated negatively to the response of the left ventricle to low-dose dobutamine infusion, although a raised BNP concentration seems to be more accurate than a raised ANP concentration in assessment of contractile reserve in dilated cardiomyopathy. Ejection fraction at rest is important in the definition of left-ventricular dysfunction, but is probably unreliable for assessment of reversibility of left-ventricular dysfunction and the cardiovascular system as a whole in relation to compensatory mechanisms. The ability of the heart to respond to dobutamine infusion may partly reflect good functional reserve of the cardiovascular system in patients with dilated cardiomyopathy. These results have clinical importance in the management of patients with dilated cardiomyopathy, since diminished contractile reserve may predict adverse clinical outcome in these patients.[5]

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1 Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997; **350:** 1347–51.
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Authors' reply

Sir—Treatment with β-blockers improves cardiac function in many patients with congestive heart failure. Our long-term Metoprolol in Dilated Cardiomyopathy (MDC) trial was the first large placebo-controlled trial of a β-blocker in heart failure.[1]

Some patients show a poor response to β-blocker therapy, whereas others may display a dramatic improvement. Several attempts have been made to identify predictors of a favourable response. Although some factors have been associated with subsequent improvement, the correlations have been only slight. A high heart rate at baseline and an increase in plasma noradrenaline are associated with a beneficial response to β-blockers.[2,3] The possibility that a dobutamine stress test might identify possible responders has been suggested but not proven.

Hiroaki Kitaoka and colleagues suggest that high concentrations of the natriuretic peptides ANP and BNP are associated with left-ventricular contractile reserve in patients with dilated cardiomyopathy, as assessed by dobutamine stimulation. They question whether the concentration of natriuretic peptide might identify responders to β-blocker therapy. When we began the MDC study, little was known about natriuretic peptides, and no such data are available from that study or from any other β-blocker trial, as far as we know. Although the question proposed by Kitaoka and co-workers is straightforward, the complexity of neurohormones and their relation might be an obstacle to finding an answer.

Natriuretic peptides are affected by atrial distension, left-ventricular filling, renal function, and renin-angiotensin activation. Furthermore, all neurohormones are inter-related, and natriuretic peptides are increased secondary to sympathetic or inotropic stimulation. Although high concentrations of neurohormones predict a poor prognosis in congestive heart failure, the effects of different therapies on neurohormones do not generally correlate with the effects on mortality. Moreover, whereas the improvement in cardiac function and a reduction in filling pressures would result in lower concentrations of natriuretic peptides, several studies have shown that β_1-selective and non-selective β-blockers might increase the concentration of natriuretic peptides.[4] Natriuretic and vasodilating properties of the atrial peptides could be responsible for some of the positive effects of β-blockers. A proposed mode of action is that β-blockade induces a down-regulation of the natriuretic peptide-C clearance receptor, leading to increased peptide plasma concentrations.[5]

In this context, it should be emphasised that although most neurohormones exert negative long-term effects on heart failure pathophysiology, the effects of atrial peptide are beneficial in counterbalancing other neuro-hormones. Nevertheless, natriuretic peptides are probably better predictors of long-term prognosis than other neurohormones in congestive heart failure. A study on the ability of these peptides to predict β-blocker effects would be of value.

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Insulin-like growth factor-I and risk of breast cancer

Sir—Susan Hankinson and colleagues' (May 9, p 1393)[1] finding of a positive relation between the concentration of circulating insulin-like growth factor (IGF)-I and risk of breast cancer in premenopausal women is of interest with respect to hormone-replacement therapy in postmenopausal women. In fact, oestrogen and IGF-I have synergistic effects on cell proliferation[2] and IGF-I is necessary for maximum oestrogen-receptor activation in cell lines in breast cancer.[3]

Circulating concentrations of IGF-I are affected differently by the various types of hormone-replacement treatments.[4] The use of oral oestrogens causes about a 25% decrease of circulating IGF-I concentrations through metabolic and hepatocellular actions (enhanced by the first liver passage), whereas transdermal oestradiol has on average no such effect.[4,5] Oestrogen-mediated reduction of IGF-I is opposed by androgenic progestagens such as norethisterone, but not by progestagens such as dydrogesterone that have no androgenic action.[4]

The finding that the effect of oestrogen-replacement therapy is largely dependent on basal IGF-I values is noteworthy, and may help to interpret Hankinson and colleagues' findings. IGF-I reduction associated with oral oestrogen use is pronounced in most women with high basal values, but is not seen in women with low basal values (figure, unpublished results). Transdermal oestradiol, at the usual dose of 0·05 mg per day, seems to produce a bimodal effect: if basal IGF-I is low, an increase during treatment is seen; conversely, if the basal value is high, IGF-I tends to fall.[5] Overall, different oestrogen preparations can reduce the wide variations of basal IGF-I.

Hankinson and colleagues showed no correlation between IGF-I and breast-cancer risk in postmenopausal women, even after exclusion of the 165 breast-cancer cases (54% of postmenopausal patients) and of a similar number of controls who were on hormone-replacement therapy. Nevertheless, breast cancers appearing during hormonal therapy might more frequently be endocrine sensitive and responsive to the stimulus of both oestrogens and IGF-I. A rise in basal IGF-I in individuals harbouring such disease would be hidden by oestrogen-replacement treatment. Can Hankinson and co-workers give details on menopausal age and IGF-I values in cases and controls on hormone-replacement therapy, and in postmenopausal women and controls not on hormone therapy?

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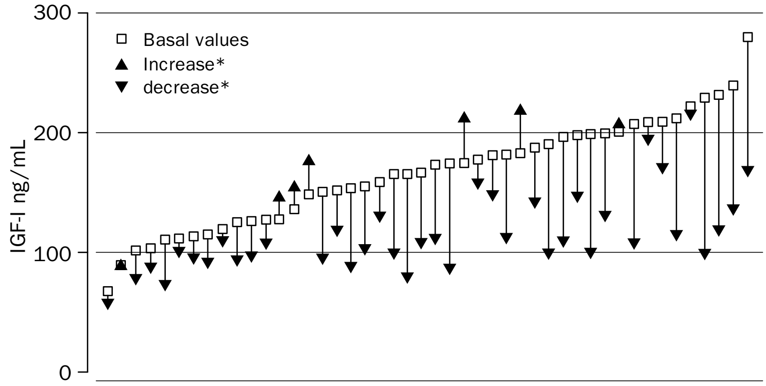

Serum IGF-I concentrations in 46 postmenopausal women

Basal values and those after 6 months* on oral conjugated equine oestrogens (0·625 mg per day) are shown.

factor I modifications induced by oral HRT in menopause. *Gynecol Endocrinol* 1995; **9:** 67–74.
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Sir—Susan Hankinson and colleagues[1] describe an increased risk for breast cancer in premenopausal women with raised serum IGF-I concentrations. This increased risk was not shown in postmenopausal women. Raised circulating insulin and IGFBP-3 values are present in premenopausal women[2] and can be explained by an underlying syndrome of insulin resistance. IGF-I is secreted in a circadian fashion, introducing variability in single-point measurements, which were used in Hankinson's study. The total serum concentration of IGF-I, as well as in growth hormone and IGFBP-3, depend on body mass, age, and time of menstrual cycle.[3,4] Hankinson and colleagues adjusted their analysis for body-mass index but not for age and time of menstrual cycle. It would be of interest to know how the risk ratio for breast cancer would change if adjusted for these indices. Women younger than age 35 with a higher normal range of IGF-I seem to have more aggressive breast carcinoma.[5] Is the risk of breast cancer in premenopausal women also increased when the age-adjusted standard-deviation scores of IGF-I (SDS IGF-I) are used in the regression analysis?

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Authors' reply

Sir—The data presented by Carlo Campagnoli and colleagues are very interesting. We had noted that in women who had not used postmenopausal hormones within 3 months of their blood collection (thus their IGF-I concentrations would reflect basal values), there was no significant relation between plasma IGF-I and breast cancer.[1] To assess this issue further, we evaluated the IGF-I/breast cancer relation in women who had never used postmenopausal hormones (76 cases and 189 controls). The relation was not positive, as was seen in premenopausal women, although the number of cases and controls in this analysis was small and the confidence limits were wide. Among cases and controls who were current hormone users, the mean age at menopause was 48 (cases) and 49 years (controls), the median duration of hormone use was 6 and 5 years, and the median IGF-I concentrations were 131 ng/mL and 137 ng/mL, respectively. Among previous hormone users, the mean age at menopause was 49 years for each group, the median duration of hormone use was 1·3 years and 1·8 years, and the median IGF-I concentrations were 155 ng/mL and 165 ng/mL, respectively. Among those who never previously used postmenopausal hormones, the mean age at menopause was 51 years for each group and median IGF-I values were 169 ng/mL and 161 ng/mL, respectively.

In our report, the matching factors (age, month, time of day of blood collection, and fasting status) were controlled in all analyses. As pointed out by Strohm and colleagues, we were not able to control for phase of menstrual cycle. However, most previous studies[2–5] have shown little variation in IGF-I or IGFBP-3 during the menstrual cycle, thus having untimed samples is unlikely to be a substantial limitation of the study. We did an analysis of age-specific IGF-I *Z* scores (in a model controlling for the matching factors plus IGFBP-3) in premenopausal women younger than 50 years. Relative risks remained significant (eg, top to bottom tertile contrast relative risk 5·1 [95% CI 1·7–15·5]).

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Sir—Susan Hankinson and colleagues'[1] report of a positive relation between circulating insulin-like growth factor (IFG)-I and risk of breast cancer, also reviewed by Jeff Holly in his commentary,[2] raises important issues about growth-hormone administration.

Concerns have been expressed over the potential for growth hormone to promote cancer, especially in adult hypopituitarism, since doses used previously may have been higher than true replacement.[3] In our experience, the use of locally validated age-standardised reference ranges[4] for plasma IGF-I has helped to show that doses of growth hormone previously recommended for adult growth-hormone deficiency may have been above the optimum.[5] In adult-onset growth-hormone deficiency, we used these reference ranges to achieve optimum continuing growth-hormone replacement for individual patients on long-term therapy.

Further long-term studies of the association between age-standardised IGF-I concentrations and the risks of cancer are needed. However, as indicated by Holly,[2] the fact that the binding protein, IGFBP-3, increases when growth-hormone is given to growth-hormone deficient adults[5] may be relevant if risk relates to free IGF-I.

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1 Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth-factor-I and risk of breast cancer. *Lancet* 1998; **351:** 1393–96.
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Sir—Plasma-free and albumin-bound concentrations of androgen and oestrogen are the biologically active fraction of circulating sex-steroids. Plasma sex-hormone-binding globulin (SHBG) is important in the regulation of plasma-free and albumin-bound androgen and oestrogen concentrations. Gann and colleagues[1] reported that high concentrations of circulating testosterone and low levels of SHBG—both within the normal ranges—were associated with increased risks of prostate cancer. In a group of patients, a positive association was found between circulating total insulin-like growth factor (IGF)-I concentrations and the subsequent relative risk of prostate cancers.[2]

Susan Hankinson and co-workers[3] also report a strong association between circulating total IGF-I concentrations and the relative risk of breast cancer in premenopausal women. Since the relative risk of prostate and breast cancer associated with total steroid concentrations has previously been reported to be substantially lower than that observed for total IGF-I concentrations and prostate and breast cancer in the studies by Chan and colleagues[2] and Hankinson and colleagues,[3] respectively, Jeff Holly suggests in his May 9 commentary[4] that circulating total IGF-I concentrations do not merely reflect sex-steroid status. We believe that Holly's conclusion might not be correct or based on evidence.

Breast and prostate are sex-steroid dependent tissues. We found an age-independent inverse relation between total IGF-I and SHBG concentrations in both sexes.[5] We also found a positive relation between total concentrations of IGF-I, IGFBP-3, or both and free-androgen index (an index of free testosterone) in men and a positive relation between total IGF-I and free oestradol index (an index of free oestradol) in women.[5] However, free IGF-I concentrations were not associated with free steroid indices in both sexes.[5] Free IGF-I concentrations probably reflect the bioavailable IGF-I better than total IGF-I concentrations. Total IGF-I offers only a crude estimate of biologically active IGF-I because of the wide variations between individuals in circulating IGF binding proteins. Free IGF-I probably has greater physiological and clinical relevance than total IGF-I.

Circulating concentrations of free sex hormone and total IGF-I are significantly inter-related. The associations observed between total IGF-I concentrations and breast and prostate cancers could reflect overall sex-steroid activity, although the value of measuring total IGF-I concentrations to estimate the biologically active moiety of IGF-I is not known.

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Multiple-antibiotic-resistant salmonella

Sir—The importance of the increasing incidence of multiple-antibiotic-resistant salmonella is noted by Shelley Rankin and Michael Coyne (June 6, p 1740).[1] We would add that antibiotic resistance in *Salmonella* spp is no longer restricted to older compounds. *Salmonella* spp resistant to second-generation and third-generation cephalosporins and related antibiotics by the production of various extended-spectrum β-lactamases are increasingly common worldwide.*

The reported enzymes include TEM-3 from *Salmonella kedougou* in France and possibly *S enteritidis* in Spain, TEM-25 from *S mbandanka* imported into France from Algeria, and TEM-27 from *S othmarschen* in Spain. There have been two reports of SHV-2 in *S mbandanka, S typhimurium,* and *S wien,* all associated with Tunisia, although the *S mbandanka* strain was isolated after importation into the UK. We have reported an SHV-5-producing strain of *S senftenberg* that caused an outbreak of wound infection in a hospital in India.[2]

Other molecular class A β-lactamases have also been found in salmonella, including CTX-M2 from *S typhimurium* in Argentina. PER-1 β-lactamase, which was previously seen in only *Pseudomonas aeruginosa,* was found in two *S typhimurium* strains in Turkey, one of which caused an outbreak of neonatal meningitis. Two *S typhimurium* strains that produced PER-type enzymes were reported from Argentina, and one that produced an enzyme that may be related to MEN-1 from Russia. An isolate of *S enteritidis* from Saudi Arabia produced a plasmid-encoded molecular class C β-lactamase (DHA-1) that conferred resistance to extended-spectrum cephalosporins and cephamycins. Another group I enzyme, CMY-2, was reported in *S senftenberg* from Algeria. Two unidentified extended-spectrum β-lactamases have also been reported from Algeria and Slovakia.

Extended-spectrum β-lactamase production is usually encoded on transmissible plasmids together with a range of aminoglycoside-modifying enzymes,[3] and, therefore, most of these cephalosporin-resistant salmonellas are also resistant to aminoglycosides. The resistance plasmids have probably been acquired from other multidrug-resistant enterobacteriaceae, especially *Klebsiella pneumoniae,* which are also increasing in incidence worldwide.[4]

We agree with Rankin and Coyn that an effective strategy for the containment of antibiotic resistance in foodborne pathogens is needed, but would add that enteric pathogens can also acquire multiple resistances by conjugation with commensal bacteria in the human bowel. Although most cases of human illness from *Salmonella* spp do not need to be treated with cephalosporins or aminoglycosides, these antibiotics are useful in invasive complications such as bacteraemias and meningitis.

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1 Rankin SC, Coyne MJ. Multiple antibiotic resistance in *Salmonella enterica* serotype enteritidis. *Lancet* 1998; **351:** 1740.
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Drug approval in Japan questioned

Sir—The ministry of Health and Welfare of Japan (MHW) banned four drugs classified as cerebral-metabolism enhancers on May 25. The drugs—idebenon, propentofylline, ideloxazine hydrochloride, and bifemelane hydrochloride—were approved in the late 1980s because they were believed to ease symptoms such as emotional disorders resulting from stroke. However, studies showed that the drugs failed to outperform placebos. Despite the lack of effectiveness, the total sales of the four drugs reached about ¥875 billion (US$6·25 billion) since their approval.

Although their effectiveness had been doubtful,[1] many physicians dispute the MHW's decision; it is hard to explain to their patients why these drugs had been prescribed until the day when then should be stopped. The director of the Japan Medical Association said, "This decision had a great impact on the medical service providers, because it injured badly the mutual trust between doctors and patients". We believe that this kind of tragedy will happen again if the MHW continues to use the current approval system for new drugs.

We have criticised the approval system since 1994 because it lacks the reproducibility. The primary endpoint of Japanese controlled clinical trials (CCTs) is called Zenpan Kaizen Do (the global improvement rating, GIR), which were determined subjectively by physicians. However, the GIR is similar to a clinical global impression of change, and has no structured criteria; it therefore, has limited reproducibility.[2]

Japanese CCTs of the four drugs have used numerous (30–100) endpoints assessed by GIR that were also judged by physicians subjectively. In the statistical analysis, the CCTs used the significance of $p=0·05$ for every endpoint; this analysis is erroneous in the multiple comparison. For instance, we found a CCT of indeloxazine hydrochloride that had only three significant ($p=0·05$) endpoints out of 54. In the Japanese CCTs, so many patients were excluded that most endpoints were assessed in half of the eligible patients.[3] Consequently, we found that significantly different endpoints differed from one study to another; which proves that the Japanese CCTs lacked reproducibility. Moreover, the statements of virtues of the cerebral-metabolism enhancers claimed different effectiveness from the confirmed one in related CCTs; such are not evidence based.

We believe that Japanese unscientific CCTs and the current approval system bear the responsibility for a mountain of ineffective and potentially harmful products in Japan. Many other dubious drugs such as antiallergic drugs[4] or psychotropic drugs[5] have been approved by the MHW on the basis of the same GIR. Without a radical reform of the evaluation system, it is difficult to avoid this kind of scandal.

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Biological warfare

Sir—Richard Wise (May 9, p 1378)[1] is wrong about secondary spread by anthrax in biological warfare. There is no person-to-person spread of anthrax: the only reported case of such spread was when a loofa was shared. in fact, this is one reason why anthrax is a classic choice for such warfare: it only affects the area in which it is used and does not spread back toward the perpertrator. Anthrax can however, mimic landmines, recurring unpredictably in the future from a soil reservoir

Anthrax was developed as a biological weapon by Japan in the 1930s,[2] by the USA and Great Britain in the 1940s, and by other nations since. Yet in the intervening 60 years, only very limited use of it for biological warfare has been documented.[2,3] With respect to the administration of vaccines and other therapies in response to the threat of biological warfare, several points apply.

There has never been a trial of efficacy in man for the current US (or British) anthrax vaccine,[4] and the issue of whether vaccinations (or their combination) contributed to development of Gulf War illnesses has yet to be resolved.[5] In particular troops who were vaccinated in preparation but never deployed to the Gulf, and therefore lacked other Gulf-related exposures, have developed such illnesses. Furthermore, both naturally occurring and recombinant strains of anthrax exist which are antibiotic and vaccine resistant. It is such strains that are likely to be used in a biological attack. If so, the proposed vaccinations and antibiotics are unlikely to have much impact. To further complicate matters, the February, 1998, US Food and Drug Administration inspection report for the Michigan Biologic Products Institute (the sole US vaccine manufacturer) lists 11 pages of quality-control failures for anthrax vaccine production, including reuse of expired vaccine, grossly inadequate testing, and use of lots that failed testing.

It is generally agreed that a strong biological warfare treaty, one that includes full inspections and other verification methods, would not be 100% effective at preventing such warfare. Yet such a treaty would still have great positive effects. The possibility of being inspected without warning would deter many programmes. UN inspections in Iraq have established the usefulness of such strategies at uncovering biological warfare programmes.

We should face the fact that micro-organisms might be created against which our therapeutic arsenal would be impotent. Therefore, maximum efforts should be made in primary prevention such as adding teeth to the Biological Weapons Convention. Yet the USA and some other nations continue to hold out against surprise inspections and full verification in the protocol to the convention that is now being negotiated. Before we get caught up in a frenzy of stockpiling and use of vaccines, antibiotics, and other therapies, a careful evaluation needs to be made of their actual benefits and costs. And strategies for prevention must be moved to the forefront of this debate.

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Health research in the tropics

Sir—In response to Ivan Wolffers and colleagues' (May 30, p 1652)[1] discussion of tropical medicine in the South, we wish to report on the work of the Abidjan Health Project (Project Santé Abidjan, PSA) in Côte d'Ivoire. The PSA aims to improve the supply of health care in Abidjan both qualitatively and quantitatively. From the time of its conception, the PSA has included a research and development component that supports the implementation of the different elements of the project. In the past 5 years, 26 research projects have been completed in various disciplines (epidemiology, socioanthropology, health economics, health sciences), not only in tropical medicine.

The definition of priorities within the framework of the PSA focuses on the orientations specified in the National Health Plan (Plan National de Développement Sanitaire) in collaboration with national partners. The research projects are executed by national research institutions, according to terms of reference defined by the project. These research institutions frequently use local researchers, and occasionally young French researchers working on a masters or doctoral thesis. The remuneration of researchers is contractual and is fixed in relation to experience acquired and employment status. The amount is calculated according to government salaries and varies between US$400 per month for a junior level civil servant to US$1300 for an independent senior level private consultant. The fee scale is identical for local and expatriate researchers.

The implementation of research results is a major goal and is facilitated by a way in which the research component is integrated into the project as a whole. An operating committee is convened whenever necessary to ensure that the results are used to improve the targeting of public-health initiatives. In most cases, the results are used at regional level, but sometimes they are used to elaborate national strategies. The results obtained since 1993 from our research have allowed the implementation of efficient interventions and have also yielded useful correctional elements for regional health policy.

Research results are systematically disseminated during official presentations to regional, and national health decision-makers, and to bilateral and multilateral aid agencies. Research reports are also distributed. Publication in professional journals requires a large effort in the areas of conception and composition, but is one of the objectives of the PSA's research component.

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I'll take the health benefits of exercise without the risks please

Sir—Preferring in middle age to follow a sedentary lifestyle, I am greatly comforted to learn from the study by Goya Wannamethee and colleagues (May 30, p 1603)[1] that if guilt for my complacency gets too much to bear I can invest in regular exercise and secure immediate protection for my health in later years. Their study shows that changing my lifestyle from inactive to one which includes at least occasional light active participation in exercise, will reduce the fully adjusted risk of my all cause mortality to 0·55 (0·36–0·84) relative to the risk of those of my colleagues who remain inactive. My initial feelings of comfort, however, become almost smug when I consider that late investment derived from such slight changes in lifestyle will reduce my risk to below that of other colleagues whose continuous active participation in sports since their now distant youths has been interrupted only by periods of enforced abstinence due to the many injuries they have sustained (relative risk 0·58).

The clear message from this latest contribution from the British Regional Heart Study[1] that exercise is beneficial to health in older men and that small changes away from inactivity are immediately associated with a reduced risk of major chronic diseases, is obviously one to be welcomed. However, the results also support the findings from our earlier study which are more controversial and have been less well received.

We developed a model to assess the costs and benefits of exercise[2] with estimates of the relative risks in exercisers and non-exercisers of the chronic diseases that have been shown to benefit from exercise,[3] and the injury risks and treatment costs of exercise-related morbidity,[4] published in the scientific literature. The main outcome measure was the impact for the health services of direct costs incurred and costs avoided by exercise, in a total exercising population. We found that clear health and economic benefits are achievable by encouraging exercise in older populations, but that the reverse is true for younger adults. This somewhat surprising conclusion (which is similar to the results reported in a study of a Dutch population[5]) rests on the assumption that the costs and benefits of exercise are contiguous. Thus, the health benefits in terms of reducing the risk of the onset of chronic diseases in previously sedentary individuals who take up exercise in middle age are the same as those resulting from lifelong participation in exercise. This assumption is confirmed by the British Regional Heart Study. The added health bonus for delayed exercisers, however, is that they can maximise the health benefits of exercise and minimise the health and direct health-care costs[4] by avoiding exposure to high-risk sports in which younger adults participate.

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1 Goya Wannamethee S, Shaper AG, Walker M. Changes in physical activity, mortality, and incidence of coronary heart disease in older men. *Lancet* 1998; **351:** 1603–08.
2 Nicholl JP, Coleman P, Brazier JE. Health and healthcare costs and benefits of exercise. *PharmacoEconomics* 1994; **5:** 109–22.
3 Fentem PH, Bassey EJ, Turnbull JB. The new case for exercise. London: Sports Council and Health Education Authority, 1988.
4 Nicholl JP, Coleman P, Williams BT. Injuries in sport and exercise: main report. London: Sports Council, 1993.
5 Reijnen J, Velthuijsen JW. Economic aspects of health through sport. Conference Proceedings: sport an economic force in Europe. Lilleshall, UK, November, 1989.

DEPARTMENT OF ERROR

Disclosure of novel autoantigens in human autoimmunity—In this Commentary by Rita Mirakian and colleagues (July 25, p 255) the last sentence of the fourth paragraph should read: "One thing is certain: autoantibodies to intracellular autoantigens are not directly pathogenetic. . . "