

CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Sponsorship, authorship, and accountability

Sir—We agree with the views of Frank Davidoff and colleagues, expressed in their Sept 15 commentary,¹ that all research must be done and reported objectively, dispassionately, and with the highest degree of scientific accuracy and integrity.

Rather than as stated, however, the perception of head-to-head competition between contract research organisations (CROs) and academic sites is mistaken and does not portray accurately the roles, objectives, and operations of CROs in the clinical research process.

CROs work on a sponsor's behalf in a highly regulated environment to implement and manage a clinical trial according to the study protocol. They provide research services, including consultation in study design, facilitation of recruitment of investigators and study participants, assurance of participants' protection, and data integrity and analysis to keep the quality of the research to a maximum, and, in particular, guidance through the complex regulatory environment. CROs do not sponsor clinical trials, do not own trial data, do not provide routine care for participants, and do not participate in agreements on publication rights and responsibilities, which are negotiated between sponsors and investigators. The CRO's contractual obligation is to ensure integrity of data and adherence to FDA and international regulations, not specific results. This improves, not erodes, the quality and standards of clinical trials.

Today, most clinical research in the USA is done by physicians in group practices, who are directly involved in office-based care of patients. The research environment is strengthened, not jeopardised, by the increase in the numbers of clinical researchers and the expansion of research settings. The increased participation of physicians in private practice broadens the participant populations from which to draw, creating a vital population of primary-care patients to complement the tertiary-care populations typical of academic medical centres. At the same time, according to the survey referenced by Davidoff and colleagues, major

medical centres are consistently reporting double-digit growth in US National Institutes of Health and industry-sponsored clinical grant revenue.

Academic and community-based investigators participate in clinical investigations managed by CROs, and many of them participate in development of study protocols. In CRO-managed studies, the investigator is neither a CRO employee nor customer but an integral partner in the research process. The breadth of the research spectrum encourages these organisations to seek the best and the brightest physician scientists across all clinical disciplines.

We maintain that CROs contribute to high-standard clinical research by working in collaboration with, not competing against, clinical investigators based at academic medical centres and community-based clinics.

The views of the following CROs are reflected in the letter: Covance Inc, ICON Clinical Research, Inveresk Research Group, Kendle International Inc, PAREXEL International Corporation, PPD Development, and Quintiles Transnational Corporation.

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1 Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. *Lancet* 2001; **358**: 854–56.

Sir—In your commentary, Frank Davidoff and colleagues,¹ as editors of general medical journals, criticise pharmaceutical companies for tying investigators to contracts on publication of research findings. It is timely to reiterate the Faculty of Pharmaceutical Medicine's policy on this topic.²

The guidelines state that “studies are performed to increase knowledge in some way, and this knowledge should be shared with the wider world. Study findings should be communicated, whatever the outcome, for the benefit of the community at large. Communications on clinical studies must be a correct representation of all the findings so allowing others, in their

turn, to give well balanced advice to patients and their families.”

Pharmaceutical physicians, irrespective of their employers, who might be in industry, government, academia, or elsewhere, acknowledge the validity of this guidance, but it is essential that all those involved in research outside the discipline of pharmaceutical medicine acknowledge it as well, and that such acknowledgment is universally adopted.

Recognition that nothing is of greater importance than the health and wellbeing of each study participant is imperative, but each of the many players must spontaneously declare potential conflicts of interest that might affect the making of balanced unbiased judgments of what is best for those participants. Prepublication safeguards are already in place, but they must be transparent. They include an independent review of the science, methods, motivations, processes, safety, and effectiveness of proposed interventions, together with approval of an appropriately constituted institutional review board or ethics committee. Publication, though, is essential to enable the results of research to be disseminated. Its value will be the greater if it is unfettered and unbiased. We endorse the spirit of the editorials.

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1 Davidoff F, DeAngelis CS, Drazen JM et al. Sponsorship, authorship, and accountability. *Lancet* 2001; **358**: 854–56.

2 Ethical Issues Committee, Faculty of Pharmaceutical Medicine. Guiding principles: ethics and pharmaceutical medicine. *Int J Pharm Med* 2000; **14**: 163–71.

Sir—I find Frank Davidoff and colleagues' commentary¹ poorly researched and factually inaccurate in several details. It is at best misleading, and at worst could harm the UK-based clinical research community, which is already under severe threat from other quarters.

I cannot comment on the publication policy of any individual sponsor, but in my association with some 30 different

sponsors over the past 17 years, I have not come across one that has forbidden investigators from publishing the results of a study in which they have been involved, they have simply asked for between 30 and 60 days' notice for precisely the reasons mentioned by Davidoff and colleagues—safeguarding of patent protection.

For recruitment of patients, I believe that the organisations to which Davidoff and colleagues refer are in fact site-management organisations (SMOs) and not CROs. The two have quite distinct and exclusive duties, mainly distinguished by recruitment duties: CROs do not recruit patients whereas SMOs do. A CRO's duties extend to the organisation, management, coordination, and reporting of clinical trials, hence more or less to act in place of a sponsor's own clinical research department. In this context they might be asked to oversee an SMO's activities, much as they would be expected to oversee an individual investigator's (academic or hospital-based) unit. CROs are rarely directly involved with, or responsible for, recruitment of patients. SMOs were set up to streamline recruitment, but I am not qualified to comment further on their internal working procedures.

Finally, the studies in which SMOs take part are subject to the same stringent regulations and procedures as all other clinical studies, including governmental (eg, CTX certificate) and local (eg, approved by ethics committees) checks and approvals, in which the patients' interest and safety is always paramount.

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- 1 Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. *Lancet* 2001; **358**: 854–56.

Sir—Frank Davidoff and colleagues¹ discuss the issues of sponsorship, authorship, and accountability. The effect of the pharmaceutical industry on reporting or suppressing results in clinical trials is of concern,² but only a few studies show a systematic reporting bias.^{3–5} We analysed objectively whether bias could be detected in studies funded directly by a specific pharmaceutical company when comparing its product with that of a direct competitor.

Many trials have compared topical glucocorticosteroids (budesonide *vs* beclomethasone or fluticasone) in asthma and allergic rhinitis; the first drug is made by one manufacturer, the other two are made by a rival

company. In a MEDLINE search we identified original trials published between 1966 and 2001 containing the terms “budesonide+beclomethasone”, “budesonide+fluticasone”, “beclomethasone+fluticasone”, or “budesonide+beclomethasone+fluticasone”. We excluded review articles, and labelled the sponsoring companies A or B. Two observers, unaware of the funding, analysed the MEDLINE abstract conclusions and designated whether they favoured the products of company A or B, or whether they were at least as effective, which implies that, although no difference had been reported, one product was at least as good as, or even better than the other. If the conclusion did not favour either product, the result was recorded as no difference. After classification, a third independent observer identified trial sponsorship if: the study was funded by a pharmaceutical company; an author was a company employee; the correspondence address used a company address; or the company provided statistical analysis. The provision of study drugs alone did not constitute sponsorship.

76 original research articles were identified and six were excluded because of funding by both drug companies (two), unavailable abstracts (three), or between-observer disagreement (one). Significant bias was shown in favour of the product of the sponsoring company ($p < 0.001$, table), which persisted if studies funded by company A or company B were individually compared with those not funded by either company ($p = 0.02$ for company A, and $p = 0.0002$ for company B). Outcomes in favour of own products did not differ significantly between studies funded by company A and company B ($p = 0.27$).

Studies were significantly biased towards reporting the funding company's own product favourably—only one favoured the rival company. The trials not funded by specific companies showed a greater variety of conclusions. Many reviews have analysed comparisons of budesonide and beclomethasone, and most conclude that there is approximate dose equivalence. Budesonide and fluticasone have greater hepatic clearance than beclomethasone, with possibly fewer systemic effects, but these advantages

Funding source	Company favoured by conclusion		
	A (n=32)	B (n=18)	Neither (n=20)
A	23	1	6
B	0	14	4
Neither	9	3	10

Favouring of sponsored drug in conclusion

have not been studied independently. In the interests of objectivity, funds for comparative trials could be administered by an independent research body, rather than one of the protagonists.

P Thomas has received research funding from the NHMRC Australia, Asthma NSW, Postgraduate Medical Council of NSW, and charitable foundations (Viertel and Ramaciotti Foundations). D Yates was an Astra Draco Research Fellow, has received research funding from NHMRC, the Dust Diseases Board of NSW, Asthma NSW, the Rebecca L Cooper Medical Research Foundation, and the Cooperative Research Centre for Asthma. K-S Tan has previously received funding from the Cambridge Commonwealth Trust and Gonville and Caius College, Cambridge.

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- Davidoff F, De Angelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. *Lancet* 2001; **358**: 854–56.
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Sir—The commentary by Frank Davidoff and colleagues¹ is an important step in ensuring appropriate publication of the results of clinical trials in the future. There is no doubt that the revised publication ethics section described would greatly aid researchers in potential conflicts with pharmaceutical industry sponsors.

That being said, although the section on project support deals at length with the potential for sponsors' interference, it makes little mention of researchers' ethical obligations to the sponsor. As the article makes clear, research costs money. Sponsorship is required, therefore, if research is to proceed as an academic exercise, or to answer specific questions and address specific situations.

There may be less than scrupulous sponsors; there is certainly the scope for less than scrupulous researchers, driven by ambition, or the holy grail of further work; journals themselves, in theory, could not be entirely innocent, driven by considerations of reputation and circulation. These groups, separately or together, have the potential to go forward to compromise the sponsors'

position, or breach sponsors' ethical obligations.

In my own specialty of occupational medicine, the researchers' obligations are clearly to the workers who participate, and the sponsor (commonly the employer) has an important role in ensuring that these obligations are met. In the end, the final sanction is the requirement for the sponsors' permission to publish. I for one would be loathe to advise sponsorship of further occupational health research if that sanction were no longer available because it was deemed to be unethical by the medical media.

The system of publication ethics may well need to be revisited to face the modern situation. The new system, however, must not be based on the presumption of guilt of the sponsor and innocence of the researcher, but should seek to ensure that all parties involved in the process have clearly defined ethical responsibilities to which to adhere if the work is to achieve publication.

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- 1 Davidoff F, DeAngelis CD, Drazen J, et al. Sponsorship, authorship, and accountability. *Lancet* 2001; **358**: 854–56.

Biological response modifiers in rheumatoid arthritis

Sir—D Lee and M Weinblatt (Sept 15, p 903)¹ outline the theory behind use of the biological response modifiers etanercept and infliximab in treatment of rheumatoid arthritis (RA), and describe the enthusiasm generated by their availability.

In the midst of this enthusiasm, there are practical considerations for use of these drugs' in everyday practice. Because of the high costs, the British Society for Rheumatology has developed eligibility guidelines,² the application of which, together with insufficient funding, restricts use of these drugs in the UK to patients with severe RA. A cardinal feature of severe RA is functional limitation of the hands. Reduced motor performance and coordination are well described and could be due to several factors, including pain, swelling, stiffness, permanent deformities, and muscle wasting.^{3,4}

Etanercept is delivered subcutaneously twice weekly, whereas infliximab is used intravenously at less

frequent intervals. Other biological response modifiers likely to reach the market soon (eg, interleukin-1-receptor antagonists) are also delivered subcutaneously even more frequently. The subcutaneous route allows self administration, which, in addition to empowerment of patients, can have advantages for use of health-care resource.

To facilitate self-administration, etanercept is provided with a mixing station, and instructions in written and video formats, describing fifteen consecutive steps that need to be carefully followed by the patient.

We have noticed that, in addition to further education and training by health professionals, these manoeuvres require substantial manual dexterity, which several patients do not possess. Even after extensive training, they encounter difficulties mainly with inserting and withdrawing the needle, turning the needle on the syringe to load it, and with keeping the skin site sterile during the injection process. Moreover, some patients might feel inclined to use a syringe or needle they had dropped on the floor, for example, to avoid wasting such an expensive drug. Use of the mixing station in the educational video provided with etanercept, is demonstrated by a person with normal hands. We understand that no data exist about how the mixing station makes administration of etanercept easier than other methods.

Use of biological response modifiers for RA will increase. We believe there are practical issues that should be addressed by the rheumatological community and commercial companies at an early stage. Patients with RA (or their carers) should be educated extensively and assessed carefully, by use of standard protocols, for their ability to safely administer or self-administer subcutaneous treatment at home. The setting up of a service to deliver such treatments and any health economic models should take this into account.

Finally, any appliances developed to aid preparation and self-administration of injectable drugs for RA should be formally assessed on real patients before wide distribution.

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- 1 Lee D, Weinblatt M. Rheumatoid arthritis. *Lancet* 2001; **358**: 903–11.
2 Report of the Working party of the British Society for Rheumatology. London: British Society for Rheumatology, 2000.

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Patients' motivations for physician-assisted suicide

Sir—James Lavery and colleagues (Aug 4, p 362)¹ add to our knowledge of the thoughts and motivations of certain patients who might choose physician-assisted suicide (PAS); however, certain features of this study warrant critical attention.

We cannot agree that their cohort is an appropriate group to understand why people desire euthanasia or assisted suicide, or that many disabling and debilitating disorders are likely to give rise to similar experience. There are many ways in which the status and medical prognosis of these individuals were particularly and importantly distinguishable from most dying people, and such differences justify caution in generalisation of the findings to most people approaching end of life.

Many (probably most) participants in the study were far from terminally ill—the median CD4-cell counts were 139 and 230 cells/ μ L. Only about 50% had been admitted to hospital, and only 41% had had an AIDS-defining symptom. They, like many patients with HIV/AIDS, were not facing death, but rather years of treatment, with fair to good functional status and with realistic hope that treatment will improve, perhaps sufficiently to cure.

Although patients with HIV/AIDS are frequently stigmatised by and alienated from society and family, people dying of cancer, cardiac, or neurological disease generally have more attention, respect, and empathy from these sources.

Lavery and colleagues report that nearly all participants had witnessed the worsening or death of several friends with AIDS. Such events are not typical for other illnesses. Therefore, the finding of loss of community was very real, but might be quite specific to HIV/AIDS patients.

The reported findings are based on expressions of future intent about a hypothetical (not to mention illegal) situation that might never become viable in Canada. Such intentions are qualitatively different from voluntary

requests for PAS by patients with terminal disease in the Netherlands or Oregon, USA. It seems reasonable also to question reliability over time. Preferences given in advance frequently do not conform to those given when crisis is at hand. Only about 60% of actual treatment decisions made by older veterans are compatible with the preferences they had expressed before becoming ill.² In addition, PAS has been used in fewer than 1% of cancer deaths in Oregon, despite around 66% of Oregon's voters being in favour of legalisation of the practice.³

There seem to be certain ethical issues beyond those pointed out by Lavery and colleagues. Discussions on PAS as an option seem to have been introduced by the investigators rather than by the participants, which might not reflect usual practice. In addition, given the non-terminal status of most of the participants, we wonder whether Lavery and colleagues are proposing that PAS should be available at any point during an illness, not just when death is imminent, a suggestion that would raise serious further concerns.

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- 1 Lavery W, Boyle I, Dickens BM, Maclean H, Singer PA. Origins of the desire for euthanasia and assisted suicide in people with HIV-1 or AIDS: a qualitative study. *Lancet* 2001; **358**: 362–67.
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Authors' reply

Sir—Gerson Lesser and Debbie Peters point out that many of our participants were not facing death but rather years of realistic hope of treatment improvement. Researchers and practitioners in end-of-life care understand that there are hazards associated with defining end of life too narrowly. We believe that our findings support this caution by demonstrating that deliberation about euthanasia or PAS is not restricted to patients facing death who are devoid of hope.

Lesser and Peters also question the generalisability of our findings. In the report we explained, in some detail, the design restrictions we faced because of the illegal nature of euthanasia and

PAS in Canada and the limits to generalisability that these restrictions entail. But challenging our findings with new data is exactly how we see our model contributing to furthering understanding of these complex social phenomena.

Finally, we are deeply puzzled by Lesser and Peters' concern that we might be proposing that euthanasia and PAS should be available at any point during an illness, not just when death is imminent. We make no proposal of any kind about the availability of euthanasia and PAS. Rather, the purpose of our study was to further our understanding of the origins of the desire for these options. We believe we have done so by illustrating the connection between disintegration and loss of community and the perception of the loss of self.

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Splenic tuberculosis and HIV-1 infection

Sir—Despite notable advances in diagnosis and treatment, tuberculosis continues to be a major health hazard. Incidence of HIV-1 infection is reaching pandemic proportions, and tuberculosis has resurged even in more-developed countries.¹

We saw a man aged 23 years who presented with acute abdominal pain of 6 h duration. He denied a history of trauma. On clinical examination he was pale and hypotensive. He had abdominal tenderness and generalised abdominal distension. Paracentesis revealed free-flowing blood. An emergency exploratory laparotomy revealed a haemoperitoneum. The spleen was enlarged and there was a large laceration on the posterolateral surface. Histopathology revealed multiple necrotic masses with caseating granulomas on microscopy. Acid-fast bacilli were seen. HIV-1 ELISA was positive. Postoperatively, we administered multidrug tuberculosis chemotherapy for 9 months. At 1 year after surgery the patient was symptom free.

Tuberculosis is a systemic disease with varied manifestations. Extrapulmonary tuberculosis accounts for almost 15% of all cases of tuberculosis. The most common site of extrapulmonary tuberculosis is the abdomen, where the intestines are

generally involved, mainly in the ileocaecal region and the lymph nodes. Splenic tuberculosis is very rare. This form is normally seen as a part of miliary tuberculosis and is rarely the isolated presenting feature.

Incidence of tuberculosis has risen, mainly because of increased incidence of HIV-1 infection.¹ Presenting symptoms are usually vague and include fever, weight loss, and non-specific abdominal pain. The patient may or may not have a history of pulmonary tuberculosis. For disseminated miliary tuberculosis, clinical findings include generalised lymphadenopathy and pulmonary tuberculosis on respiratory examination. Abdominal examination may reveal hepatosplenomegaly, lymphadenopathy, and ascites.

Splenic rupture is frequently caused by trauma. Spontaneous splenic rupture by itself is unusual, but has been described in diseased spleens such as in chronic malaria and infectious mononucleosis. Splenic tuberculosis presenting with rupture is extremely rare—only two cases have been reported. The first was a patient with sarcoidosis who had been treated with steroids and who developed disseminated tuberculosis. The disease was complicated by splenic rupture and a reactive haemophagocytic syndrome; the patient subsequently died.² The other patient presented with recurrent gastric haemorrhage due to a ruptured splenic haemangioma and associated splenic tuberculosis.³

Splenic rupture in most cases necessitates laparotomy with splenectomy. Conservative surgery is not possible in diseased spleens because of the friable tissues and the risk of recurrence. Furthermore, splenectomy generally provides the diagnosis in a diseased spleen.

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Invasive and medical therapy for coronary artery disease

Sir—The trial of invasive versus medical therapy (TIME) Investigators' report (Sept 22, p 951)¹ and the accompanying Sept 22 commentary by Wilbert Aronow² do not properly emphasise the most important endpoints of the study.

The TIME investigators erroneously conclude that patients aged 75 years or older with angina benefit more from revascularisation than from optimum medical treatment. Aronow echoes this conclusion.

The data actually show that deaths were more than twice as frequent (13 vs 6) in the invasive group than in the optimum medical group. Death plus non-fatal myocardial infarction was also more common in the invasive group (25 vs 23).

The combined endpoint of major adverse cardiac events equated death, non-fatal myocardial infarction, and hospital admissions. Such disparate events should not have been combined and then used to suggest that objective measures of outcome were better (or at least equivalent) in the invasive group than in the optimum medical group. The combined endpoint also resulted in a substantially underpowered study for mortality, since a doubling of mortality was not significantly different.

The TIME investigators should be applauded for undertaking a relevant trial in the increasing population of elderly people. However, they should have acknowledged the trade-off of potentially increased death rates for improved quality of life, and should have expressed this in their summary, lest casual readers be misled.

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1 The TIME Investigators. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. *Lancet* 2001; **358**: 951–57.

2 Aronow W. Approach to symptomatic coronary disease in the elderly: TIME to change? *Lancet* 2001; **358**: 945–46.

Sir—In their otherwise informative paper, the TIME investigators¹ enrolled 305 patients older than 75 years with chronic angina despite use of two or more antianginal drugs. Their data show that 79% of patients had disease in two or three coronary vessels, 14% had left main disease, and around half were hyperlipidaemic, had survived a previous acute myocardial infarction, or

were hypertensive. Despite the fact that all patients were under medical care, only 22–25% received lipid-lowering drugs, 50% received calcium antagonists, and 23–35% received angiotensin-converting-enzyme inhibiting drugs. At 6 months' follow-up, 27% required assistance in completing quality-of-life forms, and 19% of forms were not completed.

There was no mortality benefit in the short-term follow-up and the significant improvement in event-free survival was entirely related to a reduction in hospital admission for ischaemic symptoms. The death rate was twice as high in the invasive group, although not significantly so, because of the small number of events. Figure 2 in the study shows that time to death or non-fatal myocardial infarction was similar in both groups.

The investigators use the term optimum medical therapy, yet no evidence is included to show that this was achieved. Optimum medical therapy would represent the achievement of ideal lipid values including a goal LDL-cholesterol lower than 100 mg/dL, a blood pressure of 130/80 mm Hg, and the discontinuation of the 31–37% of those who were currently smoking. Each of these goals is attainable in most optimally treated patients.

The study clearly included many patients who required invasive treatment, certainly the 14% with left main disease and many of the 60% with triple-vessel disease have much to gain from invasive treatment. On the other hand the 7% of patients with no vessel disease and the 14% with single-vessel disease might have done equally well with truly optimum medical care, with no notable mortality or non-fatal myocardial infarction cost. Studies such as AVERT² were referenced by the TIME investigators, in which the well known finding that there was a reduction in ischaemic events with lipid-lowering treatment, as was seen in the MIRACL³ study, was not discussed.

That many of these otherwise well described patients did not receive optimal medical management is unfortunate.

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1 The TIME Investigators. Trial on invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. *Lancet* 2001; **358**: 951–57.

2 Pitt B, Waters D, Brown U, Eisenberg D, for AVERT Investigators. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary disease. *N Engl J Med* 1999; **341**: 70.

3 Schwartz GG, Olsson AG, Ezekowitz MD, et al, for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes—the MIRACL study—a randomized controlled trial. *JAMA* 2001; **285**: 1711–18.

Authors' reply

Sir—George Everett misunderstands the primary endpoint of our study, which was not death or death and non-fatal myocardial infarction, but quality of life measured by established instruments and by event-free survival. We could show a significant improvement in quality of life in both treatment groups, but the benefit was significantly greater after revascularisation. These results were substantiated by significantly fewer major adverse cardiac events after revascularisation—mainly admission for refractory symptoms. There were more deaths in the invasive group, as Everett and others have noted, which was not significant.

We did emphasise that TIME was not intended nor powered as a mortality trial. One reason to withhold revascularisation to elderly patients is the increased risk, of such procedures in this population. The TIME data confirmed this risk, but showed that it is lower than expected. Intervention-related mortality was far lower (2.5%) than noted in other registries¹ and comparable to the mortality of the 1999 Swiss population aged 65–79 and 80 years or older (2.3% and 11.5%, respectively).² Therefore, 6-month mortality of 8.4% in the invasive group was low given that about half the cardiac deaths occurred in patients unwilling or unsuitable for revascularisation. Certainly, long-term follow-up of the TIME study is necessary to assess a possible long-term survival benefit balancing the early intervention hazard as noted in other high risk-patient subsets.

David Nash considers the treatment of our medically managed patients not optimum, mainly for lipid-lowering drugs. He submits that patients aged 75 years or older would benefit similarly to younger patients from such treatment. This suggestion is not based on available evidence since studies such as CARE³ or 4S⁴ excluded patients older than 75 years. Similarly, the MIRACL study, cited by Nash, but which was published after TIME was finished, included much younger patients (mean 65 years) and showed a benefit of lipid-lowering treatment mainly for recurrent symptomatic ischaemia requiring readmission to hospital.

Many patients in our study were withdrawn from statins during follow-up

by their treating physicians for reasons of adherence, cost, or both. This reflects a discrepancy between care in and out of hospital, which is a known phenomenon, especially in studies of elderly patients. The same holds true for blood pressure control and the Hypertension Optimal Treatment (HOT) study,⁵ which included patients with a mean age of 61.5 years. Baseline blood pressure of our patients was similar to the values achieved in the most aggressively treated patients in HOT.

We agree with Nash that patients with no or one-vessel disease are generally at lower risk than patients with multivessel disease, despite similar symptoms. Patients with no vessel disease may, however, benefit from this diagnosis because unnecessary anti-ischaemic multidrug (optimum) treatment can be stopped. Alternatively, a quarter of patients in the invasive group were not revascularised, which could also be misinterpreted as not optimum, but revascularisation was not appropriate, not possible, or refused.

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- 1 Batchelor WB, Anstrom KJ, Muhlbaier LH, et al. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7472 octogenarians. *J Am Coll Cardiol* 2000; **36**: 723–30.
- 2 Swiss Statistical Yearbook, 2000: Bundesamt für Statistik BFS, Zurich: Verlag Neue Züricher Zeitung, 1999.
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Sir—I cannot agree with the TIME investigators' results¹ nor the accompanying conclusion of Wilbert Aronow² that, on the basis of the data, older patients (>75 years) with chronic angina should routinely be offered angiography with a view to revascularisation.

The apparent benefit in the invasive group is entirely due to the lower rates of admission for acute coronary syndrome, which, to the patient, hardly compares as an adverse event to death or acute myocardial infarction. As the

TIME investigators acknowledge, death is more than twice as frequent in the invasive group than in the medical treatment group, and, although this difference does not reach conventional significance, it might be too high a price to pay for fewer admissions for acute coronary syndromes.

I believe that the sensible interpretation is that patients older than 75 years with stable angina who wish to improve their quality of life should consider revascularisation, understanding that risk of death is probably greatly increased in the first month. Those who are comfortable with their severity of symptoms can safely pursue medical treatment, reserving revascularisation for unstable or deteriorating angina. Longer-term follow-up of these patients may reveal late benefits in the group who have undergone successful revascularisation, but until such data are available the trial does not support a change in clinical practice.

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Metformin in non-alcoholic steatohepatitis

Sir—Marchesini and colleagues (Sept 15, p 893)¹ report that patients with non-alcoholic steatohepatitis (NASH) who were given metformin for 4 months had significantly reduced mean transaminase concentrations compared with controls.

Lactic acid increased significantly by 30% in the treated group, but remained within the normal range in all but one patient. The researchers conclude that the lactic acidosis does not occur in patients with normal hepatic synthetic function. However, we want to highlight the risk of lactic acidosis and liver damage during the course of metformin-treatment in NASH.

Treatment of NASH with a drug that increases insulin action such as metformin is rational and theoretically correct. In fact, X syndrome, treated also with metformin, and NASH are both characterised by insulin resistance. NASH is associated with reduced ATP synthesis and mitochondrial injury in the hepatocytes. Lactic acidosis and liver function impairment, related to the

mitochondrial toxic effects of antiretroviral drugs, are frequently seen in HIV-infected patients with lipodystrophy, which is characterised by dislipidaemia, body-fat maldistribution, and insulin resistance. Notably, Saint-Marc and colleagues² successfully treated 14 HIV-infected patients who had lipodystrophy with metformin during the course of antiretroviral therapy with HIV protease inhibitors. However, a case of liver damage induced by HIV nucleoside analogues with transient lactic acidosis has been described in a patient with diabetes who was taking gliclazide and metformin.³ Those workers suggest that even mild hyperlactacidaemia can be associated with liver damage.

Although lactic acidosis is not associated with correct use of metformin because of its short half-life and minimal interaction with liver metabolism, cases of hepatotoxic reaction and acute hepatitis have been described.⁴ In a retrospective cohort study, Emslie-Smith and colleagues⁵ reported a prevalence of metformin contraindications in 24.5% of treated patients, with 2.8% developing chronic liver disease, and one patient developing lactic acidosis in a total of 4600 patient-years. Although rare, this serious complication can be kept to a minimum by strict adherence to prescribing guidelines and contraindications, especially renal impairment.

In patients with NASH, serum alanine aminotransferase concentrations fall substantially with the sole dietary regimen. Thus, we emphasise the importance of reducing risk factors with specific nutritional protocols before using drugs such as metformin. Patients suitable for biguanide treatment must be selected carefully because lactic acidosis seems to be more common in people with pre-existing hepatic disease. Therefore, serum lactate concentrations need to be closely monitored in patients receiving metformin. Early measurement of drug plasma concentrations seems to be the best criterion for assessing involvement of the drug if lactic acidosis does occur.

The risk of lactic acid accumulation should be assessed in patients with liver dysfunction, renal insufficiency, and hypoxia, so we agree with Marchesini and colleagues that randomised controlled studies are required.

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Unreliable immunoassays, patients' safety, and clinical research

Sir—In selection of kit methods in laboratory medicine, the importance of reagent quality and method performance, and quality and availability of technical information and aftersales support must be taken into account when deciding to introduce new analytical methods.¹

Rotmensch and Cole² reported the medical consequences of poor immunoassays of polypeptide hormones and tumour markers. For serum thyrotropin, several diagnostic reagents used to be affected by heterophilic antibodies that falsely raised values.³ Most, but not all,⁴ manufacturers have succeeded in producing reagents, and as a result, this complication has mostly been eliminated.

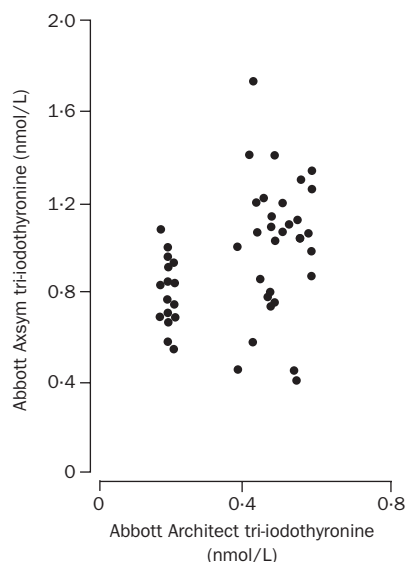
Interference by serum globulins, such as heterophilic antibodies and antibodies to ligand, is common in both competitive and non-competitive immunoassay, and with high and low-molecular-weight components in the Swedish nationwide external assurance programme in endocrinology. In Sweden, serum samples from about 20 patients are distributed every year to about 35 laboratories because of conflicting or unexpected laboratory findings, especially thyroid-related values. Within 1–2 weeks, several serum or plasma components are measured by various methods, providing a basis for better laboratory diagnosis and an overview of the susceptibility to analytical interference of immunoassay methods.

The availability of this programme, however, does not preclude the necessity to assess analytical methods in a professional way before introducing them into the clinical routine. A new immunoanalyser (Abbott Architect) was taken into use, despite the manufacturer being severely criticised by the US Food and Drug Administration. We soon noted

unexpectedly low values for serum 3,5,3'-tri-iodothyronine (T3) for several patients. In the first case, a tri-iodothyronine value of less than 0.38 nmol/L differed from other laboratory values. Reassay with Abbott Architect after precipitation of globulins with 12.5% polyethyleneglycol 6000 gave a value of 1.5 nmol/L, which suggests that globulins, or globulin-bound material, might be a cause of falsely low values. The addition of normal mouse serum to neutralise heterophilic antibodies, however, had no effect. Several cases of seemingly falsely low values were reported from the thyroid unit at the Department of Medicine.

The figure shows a comparison of the values lower than the stated normal reference interval (0.60–2.1 nmol/L) obtained by this new analyser with the values obtained by another method from the same manufacturer (ordinate, stated reference interval 0.70–2.1 nmol/L). With the exception of a few samples, the methods gave grossly discordant results. For Architect values lower than 0.38 nmol/L the AxSym mean was 0.80 nmol/L (range 0.55–1.08). For Architect values ranging 0.38–0.59 nmol/L (mean 0.49), the AxSym mean was 0.99 nmol/L (range 0.41–1.74). In our laboratory, the assay is accredited according to the European standard EN 45 001 as controlled by the Swedish Board for Accreditation and Conformity Assessment.

It is a sad fact that some diagnostic



Relation between values for serum tri-iodothyronine concentration measured by two immunoassay methods

Abbott Architect values <0.60 nmol/L reassayed with Abbott AxSym. Values <0.38 nmol/L obtained with Abbott Architect are reported as 0.38 nmol/L.

laboratories, and some of their customers, pay too little attention to the quality of diagnostic methods. The importance of the role by regulatory bodies and high professional competence in them as well as ability to react when issues are identified, cannot be overemphasised. However, the users of diagnostic reagents, and of the measurement data obtained with them, must recognise their responsibility to provide laboratory data that do not violate patients' safety and the quality of clinical research.

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Reply from Abbott

Sir—Abbott was informed by Lindstedt, Frändberg, and others about the issue of the immunoassay. Specifically, Lindstedt reported low values in the tri-iodothyronine assay. Upon receiving these reports, Abbott did an investigation that led to the following conclusion: the low values occurred in the hypothyroid region of the test. As a result of suppressed relative light units in the 0 calibrator, the low end of the calibration curve was suppressed. This information was communicated to our customers and the Food and Drug Administration.

Lindstedt and Frändberg cite an article by Rotmensch and Cole, in which false-positive results in an human chorionic gonadotropin assay are noted. Two points need to be made about that report. First, all immunoassays generate some false-positive results and they are not all due to the presence of heterophilic antibodies. Second, the product labelling specifically follows Food and Drug Administration guidelines on the intended use of the human chorionic

gonadotropin assay and outlines supplemental testing to use when test results do not agree with the clinical presentation.

Heterophilic antibodies were not the cause of the observations made with the Architect tri-iodothyronine assay. In addition, the performance of the this assay in the College of American Pathologists Survey shows that the test performs equivalently to other tri-iodothyronine assays.

Thus, a shift in the low-end calibration of the T3 assay caused the effect recorded by Lindstedt and Frändberg; heterophilic antibody interference was not a cause. Abbott has properly addressed the calibration issue. Present laboratory survey results show that the test performs comparably to other T3 assays.

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Treatment of cervical cancer

Sir—John Green and colleagues (Sept 8, p 781)¹ report that patients with cervical cancer have improved progression-free and overall survival when radiotherapy is combined with chemotherapy. They conclude that evidence favours use of chemotherapy, that the results are potentially generalisable, and they suggest a regimen of cisplatin once a week. Although these conclusions are phrased cautiously, we think there are more reasons for reservation concerning acceptance of combined radiotherapy and cisplatin as the standard treatment for all patients with advanced cervical cancer.

We have previously reviewed the publications that led to the US National Cancer Institute alert in February, 1999.² Those studies leave several important questions unanswered, such as the optimum dose schedule for cisplatin, and the effect of additional cisplatin in less-selected patient groups. Green and colleagues show no evidence of cisplatin being the drug of choice. Furthermore, there is no evidence that patients with International Federation of Gynaecological Oncology stage III and IV benefit from additional chemotherapy.

In only one study are results in advanced cases reported separately; no difference in overall survival was noted. Another question is whether cisplatin would improve the results of state-of-the-art radiotherapy, since in several studies the overall treatment time

	In radiotherapy plus chemotherapy review ¹	In hyperthermia trial ²
Outcome		
Odds ratio for pelvic tumour control	0.61	0.48
Hazard ratio for death	0.71	0.53

Effect of adding chemotherapy or hyperthermia to radiotherapy in patients with uterine cervical cancer

was relatively long. Furthermore, a Canadian study shows no benefit from adding cisplatin to radiotherapy.

A detailed study of the different trials might provide us with a better understanding about the effect of concomitant cisplatin, and about which patient groups may benefit. Indeed, a meta-analysis of individual patient data would be required.

A point of concern about standard application of cisplatin concurrently with radiotherapy is that late toxic effects might increase, as has been seen in experimental and clinical studies, even though cisplatin by itself causes no adverse effects in the organs involved. Workers in all studies of cervical cancer report an increase in acute toxic effects, and animal and human studies have provided evidence for a relation between acute and late intestinal radiation sequelae.

In part of the Netherlands, patients with advanced cervical cancer are treated with combined radiotherapy and hyperthermia, after a randomised study showed substantial benefit from additional hyperthermia to patients, of whom 80% had a stage IIIB or IVa tumour.³

Although the study populations in the various trials are not comparable, the effects of adding either hyperthermia or cisplatin can be compared for odds ratios for pelvic-tumour control and hazard ratios for death, and seem similar (table). In the hyperthermia study, acute or late radiation toxic effects were not increased.

In view of the reasons listed above, we find that, to date, no definite conclusions can be drawn about adding cisplatin to standard, state of the art, radiation treatment for all patients with advanced stage cervical carcinoma, and have decided to continue with combined radiotherapy and hyperthermia in this group of patients.

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Sir—We are concerned about the wider use of some regimens studied by John Green and colleagues¹ in the general population.

We have encountered several difficulties with cisplatin and adjuvant radiotherapy, with four cycles of cisplatin 70 mg/m² and a 96 h infusion of fluorouracil 1000 mg/m². Of four patients, we lost one because of cardiac arrest, and another elderly patient developed severe radiation enteritis. Two young patients tolerated this regimen without severe adverse effects.

SWOG² has reported that patients entering their randomised studies do not mirror the population as a whole, but are selected for age and performance status. For cervical cancer the researchers showed that only 7% of study patients were older than 65 years but represent 24% of cervical-cancer patients in the USA.² In a Dutch cancer registry, 32% of cervical cancer patients were older than 60 years of age which coincided with comorbidity in 45%.³ In Peters and colleagues' study,⁴ the median age of participants was 41 years (range 20–74 years), whereas the median incident age is about 50 years for cervical cancer in the Netherlands. In that study, diarrhoea was absent in 40% of patients in the combination group and in 45% of the radiotherapy-only group. Admissions for adverse effects were not reported, but only 60% of patients completed four cycles.

In our opinion, side-effects of radiation plus chemotherapy are probably under-rated and understated, mainly because of selection of patients. Fluorouracil is a constituent in most combined chemotherapy and radiation studies in cervical cancer. Its attribution to the overall treatment result is unclear, but it adds an extra burden to the small bowel, compromised already by radiotherapy.⁴ Use of a critical dose of 1000 mg/m² fluorouracil daily raises the chance of severe or life-threatening diarrhoea, especially in carriers of

dihydropyrimidine dehydrogenase deficiency. Since the contribution of fluorouracil is unclear and possibly detrimental, and since it demands admission for 96 h continuous infusion, it should be applied with some reserve in standard regimens. Age by itself should be no contraindication for combined treatment per se, since fluorouracil can successfully be used in elderly patients for the adjuvant treatment of colorectal cancer, albeit without radiotherapy and with caution in case of comorbidity.⁵

New studies should be directed to finding more convenient regimens that can be given as outpatient treatments, such as with carboplatin as an alternative for cisplatin.

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Author's reply

Sir—Our report was a systematic review and meta-analysis, in which we sought to objectively summarise all evidence relating to concomitant chemoradiotherapy, rather than relying on the results of individual trials. This approach increases the power to detect an effect, and prevents conclusions being drawn from the results of one or two trials with striking positive or negative results. By selectively quoting from individual studies, Jacoba van der Zee and colleagues and P Willemse and colleagues risk attributing differences in results to factors they believe are important.

They are right to be concerned about toxic effects, especially late effects, which may be under-reported. This issue is important because of extrapolation to earlier stages of cervical cancer, in which the outlook with

conventional radiotherapy is relatively good, and the contribution of late toxic effects to adverse quality of life is greater. Since these studies extend over several years, there is bound to be a drift in the consensus of what constitutes optimum therapy. Although we attempted a definition of optimum radiotherapy, we suggest that the radiation regimens in the reports by Morris¹ and Pearcey² are closest to what would be judged ideal by most radiation therapists, although no randomised trial supports this conclusion. These regimens should be given in specialist centres by experienced clinicians.

Benefit was greatest in stages IB and IIB. For FIGO stages III and IV, we refute the suggestion that there is no evidence of benefit, since 32% of the 3611 patients were in these categories, and the one study to which van der Zee and colleagues refer³ was underpowered to detect a difference between subgroups, including advanced stages. However, we believe control groups of radiation therapy alone for future studies in these categories remain reasonable.

2750 randomised patients in the review were in studies based on cisplatin. Although many workers using combinations of cisplatin with fluorouracil (and hydroxycarbamide) commented that these drugs added to toxic effects rather than survival, we provide some evidence that new trials should be based on drugs with proven activity in addition to cisplatin, such as paclitaxel,⁴ since chemoradiation clearly benefited distant recurrence rates, which suggests that the systemic cytotoxic effect was important. All the platinum-based trials in the meta-analysis, except one, used cisplatin rather than the analogue carboplatin, and although the effect on progression-free survival was similar for platinum and non-platinum trials, a clearer and larger benefit of platinum was evident for survival. The single-agent activity of carboplatin in cervical cancer is poor, and although the data quoted in favour of hyperthermia look promising, they are based on only 114 patients. The CIs are not given, and the data in the published reference are insufficient to verify the odds and hazard ratios quoted.

We agree that an individual patient meta-analysis of these data might throw some light on these questions, and have now achieved a consensus view from the Gynecological Cancer Intergroup, representing the major clinical trial organisations, to recommend such an analysis.

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Breastfeeding and the second baby

Sir—In their report, Jennifer Ingram and colleagues (Sept 22, p 986)¹ suggest that breastfeeding the second baby is independent of whether or not the first was breastfed.

The mothers included in the study produced significantly more breast milk at 1 week for the second lactation and spent less time feeding their second baby. We believe these results are important for health professionals, who can thus offer reassurance to women who experienced difficulties with their first baby. Ingram and colleagues, do not, however, mention possible external factors that might have conditioned increased milk production.

The very fact that mothers accepted to take part in a study of this kind might have had a positive effect. Some hormones involved in the lactation process are affected by maternal emotional factors alone.² The attitude of health professionals, moreover, may have been different with second children, such as in encouraging earlier breastfeeding and breastfeeding on demand, or in avoiding early integration of other foods—all factors significantly correlated with successful breastfeeding.^{3,4}

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Family planning in Bangladesh

Sir—Mizanur Rahman and colleagues (Sept 29, p 1051)¹ make the case for improved family planning, for example through provision of depot medroxy-progesterone acetate and intrauterine devices, to lower abortion rates in less-developed countries. I do not dispute their results, but the methods they advocate are not representative of family planning in Bangladesh.

Matlab Thana has been the guinea-pig area for every sort of family planning experimentation in the past 20 years; therefore, generalisation of data obtained from there to the whole country does not make sense. Nowhere, not even in China, do family planning workers visit every household every 2 weeks, and offer a very limited array of choices.

In other parts of Bangladesh the choices offered are wider, and include modern natural family planning—the Billings method, which, because of its high efficacy, cannot be dismissed as a traditional method.

The Bangladesh Billings programme of natural family planning² was offered through Caritas, a Catholic agency, but only 34% of the acceptors were Catholic, the rest were Muslims and Hindus.³ 90% were referred by a family planning outreach worker.¹ Most people chose natural family planning for health (75%) and economic (56%) reasons (some respondents offered more than one reasons).² There were no method-related unplanned pregnancies in Bangladesh, whereas user-related unplanned pregnancies were 14.9% at 12 months (life table). Among these unplanned pregnancies, two-thirds were informed choice pregnancies—the rules were understood but not followed—and one-third said they misunderstood the rules. Even when pregnancies were unplanned, they were not aborted.

Rahman and colleagues seem to fear that the rejection of essentially non-voluntary methods of family planning will lead to an increase of abortions. A far better preventive route is to engage both marital partners in the initial choice, rather than to exclude the husbands, as seemed to have been done in the Matlab programme. When people are respected, they respond. Long-acting contraceptives and

intrauterine devices are closer to veterinary than to human medicine. Bangladeshis say as much by rejecting them.

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Algorithm-based management of pneumonia in HIV-1-infected patients

Sir—In his Aug 18 news item, Haroon Ashraf¹ reports on the poor performance of the WHO guidelines for management of respiratory-tract infections in adults in Kenya who are HIV-1-positive.² He raises important questions about the need for further refinement of clinical algorithms and improvement of clinical care in resource-poor settings. The WHO algorithm was clearly inadequate to stratify patients according to severity of the pulmonary disease, rather than because of the inappropriateness of antimicrobials.

The need for validated algorithms is also a challenge in more-developed countries, where incidence of community-acquired pneumonia (CAP) is much higher among people who are HIV-1-positive than in the general population.³

We are undertaking a prospective, multicentre, observational study in patients with HIV-1 and CAP admitted to 40 Italian infectious disease facilities. Severity is classified in accordance with variables investigated in studies on HIV-1-negative⁴ and HIV-1-positive⁵ patients with CAP. We have assigned variable points: age older than 65 years is 20 points; residence in a long-term facility, ten points; neoplasm, 20 points; cirrhosis, 20 points; congestive heart failure, 20 points; acute or chronic renal failure, ten and 20 points, respectively; abnormal mental status, 25 points; respiratory rate more than 25 breaths per min, 15 points; pulse more than 100 beats per min, 15 points; temperature less than 36°C or more than 38°C, 15 points; systolic blood pressure less than 90 mm Hg, 20 points; pleural effusion, ten points; previous pneumonia, 20 points; sodium less than

130 mmol/L, 20 points; haematocrit less than 30%, ten points; neutrophils fewer than $1 \times 10^9/L$, ten points, or fewer than $0.5 \times 10^9/L$, 20 points; CD4 cell count 100–200 cells/mL, ten points, or fewer than 100 cells/mL, 20 points; and Karnofsky performance status score less than 50, 25 points.

Scores were less than 50, 51–100, and more than 100 for classes 1, 2, and 3, respectively. We gathered data daily during the patient's stay, and at a 30-day follow-up visit after discharge. Antimicrobial treatment was chosen by clinicians in accordance with each institution's recommendation. Main outcomes were death and clinical stability, defined as the normalisation of mental status, ability to feed, cardiac and respiratory rates, and body temperature.

The preliminary results of 364 patients showed that once clinical stability has been reached, only 1.1% (four of 364) of patients worsened thereafter. Second, death rates within 30 days varied significantly: 0%, 3.5%, and 29.3%, respectively, according to severity. Mean times to clinical stabilisation were 5.7, 7.9, and 12.6 days, respectively. In class 1, time to clinical stability was unaltered by choice of treatment (monotherapy *vs* combined therapy, or oral *vs* intravenous).

Our preliminary data suggest that the outcome of CAP in HIV-1-infected patients can be predicted by a simple algorithm, irrespective of causal agents.

We believe that our findings could be useful for countries with limited resources, where more simple severity scores tailored to specific geographical features of HIV-1 infection (ie, wasting syndrome, tuberculosis, diarrhoea) may be helpful to assess patients' need to be admitted, the most cost-effective drugs, and time to discharge.

This work was supported by AIDS projects of Italian Ministry of Health-ISS grant number 50.C.33 and grant number 20.C.10.

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Prescription charges for tuberculosis drugs

Sir—There is a potential cause of non-adherence to tuberculosis treatment that relates to charging patients for prescriptions.

A patient of mine did not keep her follow-up appointment with the tuberculosis clinic. While we tried to contact her, I received a letter from a colleague in a neighbouring hospital stating that the patient had chosen to seek treatment there, and that her care was continuing uneventfully. She chose to move because the other hospital waived prescription charges for tuberculosis medication. Another patient, who also defaulted a review appointment, had sought information on nearby hospitals that do not levy prescription charges for tuberculosis drugs.

After these experiences, I contacted 22 hospitals in London listed in a directory of hospitals dealing with chest diseases¹ to find out their policies for prescription charges for tuberculosis drugs. Seven waive the charges, 15 do not. In one hospital, payment is sought, but patients are not pressed if they say they cannot pay.

In four hospitals that charge, tuberculosis drugs were prescribed for longer than is customary (up to 2 months worth of drugs were dispensed on one prescription) to lessen the expenses incurred by the patient. Decisions to waive prescription charges were made locally at the Trust level or in concert with the local health authority and Centre for Communicable Diseases Control.

Most patients undergoing treatment for tuberculosis in England are eligible for exemption from prescription charges (table). About 15% of the prescriptions for tuberculosis drugs incurred charges in 2000, and about half of these were paid by prepayment certificates that lower costs to the patient by varying amounts, dependent on the time between prescriptions. Although it is unlikely that many patients with tuberculosis do not adhere to treatment because of prescription charges, in a small but

Prescription items	Total	Number charged	Prepayment certificate
Aminosalicylic acid	0
Capreomycin	0
Cycloserine	0.1	0	0
Ethambutol	19.1	2.2	1.8
Ethionamide	0
Isoniazid	11.3	1.5	1.2
Protionamide	0
Pyrazinamide	6.2	0.7	0.5
Rifabutin	1.0	0.1	0.2
Rifampicin	30.8	5.4	1.3
Rifampicin combined preparations	22.1	3.5	1.4
Streptomycin	0.1	0	0
Total	90.8	12.4	6.4

Values are in thousands.

Prescriptions of tuberculosis drugs in England in 2000

important minority, prescription charges are an issue. Some Trusts and health authorities have, therefore, acted locally by waiving these charges or recovering the costs from sources other than the patient.

However, given that tuberculosis control is a national issue of ever increasing importance² and non-adherence to treatment has serious implications for public health, a universal decision not to charge patients seems appropriate. The cost to the exchequer from the abolition of prescription charges levied on tuberculosis drugs (or by absorption into other sources of funding), as derived from the table, must be a small price to pay for ensuring that tuberculosis is dealt with effectively at all levels. Such a measure also renders unnecessary the unseemly need for patients to move from one hospital to another in search of free prescriptions for a disease for which the proper treatment is a matter of importance to us all.

I thank the Statistics Unit at the Department of Health for prescription cost analysis information on tuberculosis drugs, and Deepthi Kumar and R N Davidson for their discussions on the subject. I acknowledge the initiatives taken by various Trusts, health authorities, and other organisations in exempting tuberculosis drugs from prescription charges.

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- 1 Directory of training posts and services in Respiratory Medicine. London: Hawker Publications, 2000.
- 2 Rose AM, Watson JM, Graham C, et al. Tuberculosis at the end of the 20th century in England and Wales: results of national survey. *Thorax* 2001; **56**: 173–79.

Getting science into international aid

Sir—In your Dec 1 editorial¹ you make a remarkably similar assertion to that which appeared in *The Guardian* newspaper the same week²—namely that the Department of International Development, and in particular Secretary of State, Claire Short, was sceptical of the workability of the effort to create a global fund for AIDS, tuberculosis, and malaria.

As the Secretary of State made clear in her response to *The Guardian*, nothing could be further from the truth. The UK announcement of \$200 million support to the fund is a clear statement of that support.

We do however remain actively engaged in ensuring that focus, scope and effectiveness remain paramount.

Rather more disappointing is your faith in a technocratic approach (international technical panels).

Development is a complex process. A global fund such as that for AIDS, tuberculosis, and malaria is but one part of the development effort. Nationally owned and led processes, collectively supported by the international community, must be the way forward. Funds will need to be provided to the most effective responses, and across sectors.

The project approach, as you advocate, is the old way of doing business. Rather, let us look forward to comprehensive strategies, nationally driven, that capture the best of evidence-based policy responses.

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- 1 Editorial. Getting science into international aid. *Lancet* 2001; **358**: 1827.
- 2 McGregor L, Boseley S. The AIDS aid dilemma. *Guardian*. Nov 30, 2001.

DEPARTMENT OF ERROR

Cardiovascular protection and blood pressure reduction—In this meta-analysis by Jan A Staessen and colleagues (Oct 20, p 1305), in the lower section of figure 1, the headings “All ACEIs” and “CCBs and ACEIs” should be transposed. In the last paragraph of the results section, the sign for blood pressure differences of HOPE, PART2, SCAT, and combination of PART2 and SCAT should be “+” not “-”.

Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study—In this Article by C Janson and colleagues (Dec 22/29, p 2103), the fourth sentence of the Findings section of the Summary should have read: “Passive smoking in the workplace was significantly associated with all types of respiratory symptoms and current asthma (odds ratio 1.9 [95% CI 1.25–2.88]).”