CORRESPONDENCE

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Was the LIFE trial independent?

Sir—2 weeks after publication of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study reported by Björn Dahlöf and colleagues (March 23, p 995)[1] and Lars Lindholm and colleagues (March 23, p 1004),[2] I received a personal letter signed by Dahlöf, printed on the letterhead of Göteborg University.

My address was printed on the envelope in Dutch, in a pseudo-handwriting font. The letter was in English and carried the message of the published paper somewhat further. It described how much better losartan is than other treatments for hypertension, based on p values.

The jubilant tone and style of the letter, written in slick copywriter's prose, are not compatible with the statements in the report that it was an investigator-initiated study, supported by an unrestricted grant.[1] These statements gave readers the impression that the trial was a balanced study, free from commercial influences. An avalanche of published critical correspondence in the June 22 issue cast doubt on the study's validity. Since the description of the trial as being truly independent is at odds with the letter that I and many colleagues received, an independent investigation into the conflicts of interest of the investigators and into the analysis of the trial results is called for. Since the letter bore a letterhead of Göteborg University, this University might also wonder whether it condones the use of its name for this type of letter.

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1 Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 995–1003.

2 Lindholm LH, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 1004–10.

Sir—Björn Dahlöf, in the LIFE study,[1] mentions no conflict of interest. Yet, on April 12, 2002, I received a perfectly designed letter with a beautiful Swedish stamp from Dahlöf "to share exciting news" and remind me of the results of the LIFE study. On the letter, which bore the Göteborg University header, there was no sign of pharmaceutical industry influence whatsoever. Through a couple of telephone calls, I learned that other cardiologists received the same letter. I wonder whether Dahlöf mailed every cardiologist in Europe or even the entire globe.

What is the interest for a scientist who saw his report published in a leading medical journal to do such a mailing? Can he maintain his independent label and be viewed as having no conflict of interest in future studies?

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1 Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 995–1003.

Author's reply

Sir—I confirm that the LIFE study was an investigator-initiated study, supported by an unrestricted grant from Merck, run by an independent steering committee, in which Merck was represented only by a non-voting member, and that the analyses were validated outside of the company.

The study was reported in *The Lancet* entirely on its scientific merits. There is no undisclosed conflict of interest between Merck or any steering committee member. I supplied comprehensive conflict of interest statements from all in the steering committee.

The letter in question was not intended for mass distribution and a copy was sent by Merck without proper identification of them as sender and without consent from me. No compensation for this action was given to Göteborg University or me, but we have both received formal apologies from Merck for their mistake.

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Ageing of the liver sieve and pseudocapillarisation

Sir—David Le Couteur and colleagues (May 4, p 1612)[1] put forward their hypothesis on hepatic pseudocapillarisation and atherosclerosis in ageing. They suggest pseudocapillarisation and the concomitant decline in porosity of liver sinusoids in relation to age explains the reduction in clearance of chylomicron remnants seen in older people.

The first report of ageing liver sinusoidal endothelial cells (LSECs) was given by De Leeuw and colleagues,[2] who showed that rat LSECs exhibited a constant ultrastructural morphology in all age-groups studied. They noted no loss of integrity of the endothelial lining, which suggests preserved filtration capacity until late age. The discrepancies between De Leeuw and colleagues' and Le Couteur and colleagues' observations might be related to observations made by others that the diameter and number of fenestrae vary from species to species, but also between individuals and species, and within a single individual under the influence of various physiological and pharmacological circumstances.[3] Therefore, testing the hypothesis will not be as simple as Le Couter and colleagues state because species, strain, sex, and husbandry conditions would all have to be taken into account when comparing animals and human beings. For example, the fenestral number differs greatly between adolescent baboons and human beings (1·5–1·9 *vs* 15–25 fenestrae/μm^2).

The term pseudocapillarisation, coined by Le Couteur and colleagues,[4] is defined as defenestration with reduced porosity of the sinusoidal endothelium, thickening of the endothelium, infrequent development of a basal lamina, and minor collagen deposits in the space of Disse. One of

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Mannose-binding lectin genotype as a risk factor for invasive pneumococcal infection

Sir—Suchismita Roy and colleagues (May 4, p 1569)[1] report that homozygous carriers of mannose-binding lectin (MBL) variant alleles may have an increased risk of acquiring invasive pneumococcal infections.

We have previously noted the same phenomenon in patients with systemic lupus erythematosus.[2] However, when we investigated a possible association between MBL genotypes and invasive pneumococcal disease in randomly included adult Danish patients, we identified no significant association compared with background controls for heterozygous (dominant) or homozygous (recessive) carriers of MBL variant alleles.[3] Nevertheless, there was a non-significant increased risk (nine [6·4%] of 140 *vs* seven [2·8%] of 250, p=0·083).

Since this association was not significant, we took no further notice. However, when we combined data from our and Roy and colleagues' investigations in a meta-analysis, homozygosity for MBL variant alleles contributed to a small but highly significant (p<0·0001) increased risk of invasive pneumococcal disease (table).

This finding might lead to the impression that MBL deficiency may predispose to invasive pneumococcal disease per se. However, a concomitant illness is an independent risk factor for acquiring invasive pneumococcal infection. Even though our patients were randomly included 66% had an identified underlying illness. From our experience in several MBL-related disease-association studies, in adults, the MBL phenotype is mostly exposed in patients with a concomitant disease or disturbance in the immune system.[4] In the general population, the most prominent effect of MBL deficiency in relation to infections seems to be confined to the vulnerable period of infancy at age 6–18 months, when the placental transferred antibodies have disappeared and the child's own immune system is still immature.[5]

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1 Roy S, Knox K, Segal S, et al. *MBL* genotype and risk of invasive pneumococcal disease: a case-control study. *Lancet* 2002; **359:** 1569–73.
2 Garred P, Madsen HO, Halberg P, et al. Mannose-binding lectin polymorphisms and susceptibility to infection in systemic lupus erythematosus. *Arthritis Rheum* 1999; **42:** 2145–52.
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5 Koch A, Melbye M, Sorensen P, et al. Acute respiratory tract infections and mannose-binding lectin insufficiency during early childhood. *JAMA* 2001; **285:** 1316–21.

	Patients		Controls		Odds ratio (95% CI)
	O/O	A/A+A/O	O/O	A/A+A/O	
Study					
Roy*	28	201	18	335	2·6 (1·4–4·8)
Roy†	11	97	36	643	2·0 (1·0–4·1)
Kronborg	9	131	7	243	2·4 (0·9–6·6)
Combined analysis					2·3 (1·5–3·5)

A=normal MBL allele; O=common designation for variant alleles B (codon 54), C (codon 57), D (codon 52). *Initial patient set. †Confirmatory study.

Combined analysis of three MBL association studies

Abnormal heart-rate recovery after exercise

Sir—In his May 4 Commentary,[1] Raymond Gibbons discusses the usefulness of heart-rate recovery after exercise as a predictor of outcome in patients with heart disease.

8 years ago, Imai and colleagues[2] described a series of experiments in which heart rate was measured after exercise testing in healthy people, athletes, and heart-failure patients. They noted that heart-rate recovery is a reflection of vagal reactivation. Combining this observation with the known association of autonomic dysfunction with mortality we postulated that heart-rate recovery could predict death.[3]

Our first report of the testing of this hypothesis was based on a Cleveland Clinic Foundation cohort of adults who were candidates for first-time coronary angiography. Afterwards, several important questions remained. Would heart rate recovery be predictive across a spectrum of risk? Would it work outside the Cleveland Clinic? Does the recovery protocol matter? Would it provide additional information to the Duke treadmill score, left-ventricular function, and angiographic severity of coronary disease?

These questions, have been addressed elsewhere, within[4] and outside[5] the Cleveland Clinic cohorts. Heart-rate recovery predicts risk among asymptomatic patients[4] and patients with established coronary disease.[5] It predicts death independently of the Duke treadmill score,[4] coronary angiographic data,[5] and left-ventricular function, and works in the absence of a cool-down period.[5]

Gibbons argues that, the evidence for heart-rate recovery does not yet support its widespread application. He notes that published reports have involved asymptomatic patients or those who had undergone revascularisation, involved different recovery protocols, and that most reports came from the Cleveland Clinic.

Although exercise testing among asymptomatic patients is controversial, the relevant issue in heart-rate recovery is that it predicts death across a wide spectrum of illness, having been studied in more than 23 000 patients.[4,5] The type of recovery protocol does affect the actual magnitude of heart-rate recovery, but its prognostic usefulness remains strong.[3–5]

Heart-rate recovery has met established criteria for a robust epidemiological association. Its study has been based on an a priori biologically based hypothesis. Its ability to predict death is strong, consistent, and independent. It has been validated within and outside the centre where its prognostic usefulness was first described. Finally, it is available to clinicians at no additional cost.

Given the overwhelming evidence supporting this easily obtained and inexpensive measure, it is time for routine clinical use of heart-rate recovery.

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4 Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* 2000; **284:** 1392–98.
5 Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: validation and methodologic issues. *J Am Coll Cardiol* 2001; **38:** 1980–87.

HIV/AIDS data in South Africa

Sir—We were disappointed to read the letter by Christian Fiala and colleagues (May 18, p 1782)[1] who criticise your journal for endorsing our report[2] when they seem not to have understood its argument.

They claim that the report uses extrapolations and projections based on the Bangui and other unreliable registrations. It does no such thing. Had they understood the report they would have seen that we used data from the national vital registration to show a change in the age pattern of deaths, with a substantial increase in the mortality of young adults. Apart from the difficulties in correctly ascertaining the underlying cause of death, we could not attempt any classification of the causes of death because these data are not yet available for years later than 1996.

We made reference to a model simply to explore the plausibility of the hypothesis that HIV/AIDS was the cause of this change in pattern. The consistency between the model and the data together with observations from other data sources lead to the conclusion that HIV/AIDS must largely account for the observed increase. The change in pattern of deaths is clear in the raw data before adjustment for extent of under-reporting of deaths, as has been confirmed by official South African mortality statistics for 1997–2000.[3] In that statistics report's introduction, it states that: "Using the electronic population register maintained by the Department of Home Affairs, it is possible to obtain rapid provisional estimates of the number of deaths among South Africans . . . Over the period 1997–2000 . . . the age profile of deaths changed nationally with more deaths occurring in the young adult ages."

We can only conclude that such an unsubstantiated attempt to discredit our work represents the last kicks of a dying horse now that the AIDS dissident cause has been abandoned by the South African government. It is typical of the orchestrated campaign of misinformation that has, unfortunately, characterised the discourse around HIV/AIDS in South Africa. This approach has seriously undermined the response required from the government and has sadly cost many lives. We are heartened by new announcements from the South Africa government[4] that create a climate for tackling the epidemic in earnest.

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2 Dorrington R, Buorne D, Bradshaw D, Laubscher R, Timæus IM. The impact of HIV/AIDS on adult mortality in South Africa: technical report. http://www.mrc.ac.za/bod/bod.htm (accessed July 16, 2002).
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4 Cabinet statement on HIV/AIDS, 17 April 2002. http://www.gov.za/speeches/cabinetaids02.htm (accessed July 16, 2002).

International humanitarian aid: paradigm lost

Sir—Your June 22 Editorial[1] was a voice of reason among the traditional warring protagonists in the global humanitarian aid theatre. However, you place your spotlight wrongly—the hurdles to help the poor in Angola are not spats between Médecins Sans Frontières (MSF) and the Office for the Coordination of Humanitarian Affairs (OCHA).

The accusations from MSF of delayed response of the UN and criminal neglect of the Angolan government could be levied at any emergency in any country and are superficial. However, UN-OCHA, should not hide behind lack of resources and have no right to point at the disarray of other organisations.

Sparring between civil society groups and the establishment are in the very nature of their respective positions. More important is that the international aid community lacks a realistic development paradigm for resource-rich countries in chronic conflict such as Angola.

Angola has been at war for more than three decades. It is one of the world's poorest countries, despite its mineral riches. It is set to produce 2·5 million barrels of oil per day by 2015 and currently supplies 7% of US daily imports. Money paid to the government by oil companies for the right to explore untapped oil reserves provide nearly US$1 billion, but much of that is used to finance the war effort. In the past decade, more than $4 billion worth of diamonds have been sold, despite UN Security Council sanctions. 1·0–1·2 million worth of diamonds are estimated to leave the country every day. In 1998, the annual output was $5–600 million, mostly bought by international firms through illicit and untaxed channels.

Greater partnership between non-governmental organisations and OCHA would help the Angolans, but that is not the barrier to helping the civilians. The hurdles lie in the inability of the international community to control their need for Angola's diamonds, petrol, and other natural resources. Angola tops UNICEF's child risk measure for death, malnutrition, abuse, and inadequate development. Rather than fund humanitarian programmes and rebuild the infrastructure, the Angolan authorities undertake mutually satisfying lucrative deals with diamond dealers, oil companies, and financial institutions.

There is no current acceptable assistance model to help Angola, and there will not be one if the international aid community ignores the reasons behind the need. Short-term emergency relief has been continually provided since 1975. No donor country is willing to research a model of development for the 29 countries in chronic conflict. We should not strengthen the alibi for inaction by focusing on squabbles between non-governmental organisations and UN bodies.

House cleaning for OCHA, as you suggest, is an excellent idea. To coordinate non-governmental organisations, however, it needs

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