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

the questions they pose in the current hypothesis concerns the nature of factors involved in age-associated defenestration, for which we might contribute to an answer.

When we assessed the method of isolation, purification, and culture of LSECs,[5] we noted that the yield of cells was significantly higher in older (12 months) than in younger (3 months) rats ($49{\cdot}2\times10^6$ [SD 4·5] *vs* $23{\cdot}9\times10^6$ [3·7] LSECs/liver). Further analysis showed that the mean frequency of fenestrae is 3·4 fenestrae/μm^2 (SD 0·2) in older rats and 3·2 fenestrae/μm^2 (0·1) in younger rats, which is a non-significant difference ($p>0{\cdot}05$, n=5). There was also no difference in fenestrae diameter. These data indicate that there is no significant difference in the porosity of cultured LSECs obtained from rats of the same strain and of different ages. Moreover, cultivation of LSECs under standardised conditions excludes possible environmental factors, affecting fenestrae dynamics.

Taking these findings together with the possible explanation for the observed defenestration in older rats suggested by Le Couteur and colleagues, it is indeed reasonable to consider that the sinusoidal endothelial lining in vivo is exposed to various gut-derived toxins, xenobiotics, and vascular mediators that have an effect on fenestrae. The question remains whether these factors work in harmony to keep the porosity of the hepatic endothelium in balance, and whether this equilibrium is disturbed in older animals and human beings.

Elucidating the pathways of pseudocapillarisation is an important challenge and will hopefully result in an additional alternative treatment of postprandial hyperlipidaemia in ageing people.

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1 Le Couteur DG, Fraser R, Cogger VC, McLean AJ. Hepatic pseudocapillarisation and atherosclerosis in ageing. *Lancet* 2002; **359:** 1612–15.
2 De Leeuw AM, Brouwer A, Knook DL. Sinusoidal endothelial cells of the liver: fine structure and function in relation to age. *J Electron Microsc Tech* 1990; **14:** 218–36.
3 Braet F, Luo D, Spector I, Vermijlen D, Wisse E. Endothelial and pit cells. In: Arias I, Boyer JL, Fausto N, Jakoby WB, Schachter DA, Schafritz DA, eds. The liver: biology and pathobiology, 4th edn. New York: Raven Press; 2001: 437–53.
4 Le Couteur DG, Cogger VC, Markus AM, et al. Pseudocapillarization and associated energy limitation in the aged rat liver. *Hepatology* 2001; **33:** 537–43.
5 Braet F, De Zanger R, Sasaoki T, et al. Assessment of a method of isolation, purification and cultivation of rat liver sinusoidal endothelial cells. *Lab Invest* 1994; **70:** 944–52.

Uptake of flexible sigmoidoscopy screening

Sir—The UK Flexible Sigmoidoscopy Screening Trial Investigators (April 13, p 1291)[1] state in their summary that the screening regimen is acceptable; in their discussion they state they expect that, if they were able to invite the whole population, and appropriate media support were used, uptake would approach the high rates achieved in breast and cervix screening programmes in the UK. However, we question whether this assertion can be justified from the uptake data presented.

The investigators report that the trial used a two-stage recruitment procedure whereby eligible participants were enrolled only if they responded positively to a questionnaire asking whether they would be likely to accept the offer of screening. 55% of questioned people responded positively, and 71% of those invited for screening (all of whom had replied positively) actually attended. Therefore, as the researchers state, the population coverage achieved was equivalent to 39%.

We accept their point that the two-stage recruitment limited the population uptake rate, because the individuals who did not express an interest in screening (45% of those contacted) were not invited. However, it is reasonable to assume that, although a proportion of the individuals who did not respond positively to the questionnaire would have attended if invited, it would probably be lower than the 71% attendance among those who responded positively. On a whole-population basis, therefore, the uptake rate would probably be higher than 39% but somewhat lower than 71%.

The values the investigators present suggest that it would be optimistic to expect uptake rates for single flexible sigmoidoscopy screening to approach the current uptake rate of about 75% for the breast-screening programme[2] or coverage rate of 83% for cervical screening in England.[3]

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1 UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002; **359:** 1291–300.
2 Department of National Statistics. Statistical bulletin: breast screening programme, England, 2000–01. London: Department of Health, 2002.
3 Department of National Statistics. Statistical bulletin: cervical screening programme, England, 2000–01. London: Department of Health, 2001.

Sir—The baseline findings of the UK Flexible Sigmoidoscopy Screening Trial Investigators[1] are important.

This intervention affords an opportunity to address on a national basis the high incidence and mortality attributable to colorectal cancer in the UK. In this large-scale study, the prevalence of distal neoplasia was high (12%). With use of defined criteria for risk, 5% of participants were referred for colonoscopy. The acceptability by participants, feasibility, and safety of the procedure across a wide variety of centres suggests that consideration should be given by public-health authorities to prepare for widespread implementation in anticipation of the availability of data on incidence and mortality in 2005.

Such advance preparation would involve public and professional education, including the training of endoscopists. This opportunity to substantially reduce morbidity and mortality from colorectal cancer in the UK should not be missed.

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1 UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002; **359:** 1291–300.

Authors' reply

Sir—We agree our assertion that uptake rates with a single flexible sigmoidoscopy (FS) screen could approach those achieved in the breast-cancer and cervical-cancer screening programmes cannot be justified from the data presented. Rather it was based on our view that (1) the limitations of our trial protocol (two-stage recruitment, no publicity, no reminder) meant that our attendance rate represented a lower limit for population screening, and as such was surprisingly high; (2) if only one flexible sigmoidoscopy screen is required, timing is not crucial; and (3) our survey of non-attenders' reactions to flexible sigmoidoscopy screening