

## LETTERS TO THE EDITOR

### Scope

*Heart* welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

### Presentation

Letters should be:

- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors

They may contain short tables or a small figures. **Please send a copy of your letter on disk.** Full instructions to authors appear in the January 1998 issue of *Heart* (page 106).

### Possible association of a reduction in cardiovascular events with blood donation

SIR,—As Meyers *et al* note, data regarding the iron hypothesis of atherogenesis are inconsistent,<sup>1</sup> and data regarding the closely allied oxidation hypothesis are also conflicting.<sup>2</sup> Thus, I suggest that the beneficial effect of blood donation on cardiovascular disease is caused by a reduction in haematocrit and blood viscosity. Haematocrit was shown to be a risk factor for atherosclerosis in the Framingham study.<sup>3</sup> Haematocrit is also a very powerful determinant of blood viscosity.<sup>4</sup> Increased blood viscosity is thought to accelerate atherogenesis by perpetuating areas of low shear in the vascular tree, prolonging the residence time of atherogenic particles, such as platelets and lipoproteins, on the endothelium.<sup>5</sup> This prolonged residence time would facilitate microthrombus formation and lipoprotein diffusion. A decrease in blood viscosity, as well as reducing residence time, would increase the shear dependent expression of atheroprotective molecules such as nitric oxide and prostacyclin.<sup>6</sup> The decreased expression of these molecules in atherosclerosis is usually ascribed to a putative endothelial dysfunction caused by the cytotoxic effects of oxidised low density lipoprotein (LDL).

LDL increases blood viscosity, presumably by fostering erythrocyte aggregation.<sup>4</sup> Thus, the decrease in blood viscosity associated with blood donation might be most pronounced in individuals with the highest serum LDL. This is consistent with the observation of Meyers *et al*, who noted that the benefit of blood donation was greatest in males with the highest serum LDL.<sup>1</sup>

Atherosclerosis is a non-specific condition affecting nearly everyone in industrialised societies, not simply those with hypercholesterolaemia. In my view, theories of atherogenesis that focus on lipids and do not adequately explain the accelerated atherogenesis associated with other risk factors, such as increased haematocrit, hypertension, hyperfibrinogenemia, and raised plasma viscosity, are unlikely to be correct. Increased blood viscosity is found in association with each of these risk factors.<sup>5</sup> The *Principle of Simplicity* (Ockham's

Razor), which holds that the simplest theory that explains all possible cases is most likely to be correct, suggests to me that a non-specific effector such as blood viscosity must play a more central role in atherogenesis than accumulation of cholesterol in the vessel wall.

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- 1 Meyers DG, Strickland D, Maloley PA, *et al*. Possible association of a reduction in cardiovascular events with blood donation. *Heart* 1997;78:188-93.
- 2 Stehbens WE. Atherosclerosis and degenerative diseases of the heart. In: Stehbens WE, Lie JT, eds. *Vascular pathology*. London: Chapman and Hall Medical, 1995:240-1.
- 3 Gagnon DR, Zhang T-J, Brand FN, *et al*. Hematocrit and the risk of cardiovascular disease—the Framingham study: a 34-year follow-up. *Am Heart J* 1994;127:674-82.
- 4 Sloop GD, Garber DW. The effects of low-density lipoprotein and high-density lipoprotein on blood viscosity correlate with their association with risk of atherosclerosis in humans. *Clin Sci* 1997;92:473-9.
- 5 Sloop GD. A unifying theory of atherogenesis. *Med Hypotheses* 1996;47:321-5.
- 6 Reinhart WH. Shear-dependence of endothelial functions. *Experientia* 1994;50:87-93.

### Reduction in time delays in administering thrombolytic treatment

SIR,—Two recent papers in *Heart* showed that direct admission of patients with acute myocardial infarction to the coronary care unit (CCU) by ambulance staff reduced time delays in administering thrombolytic treatment.<sup>1,2</sup> The approach is novel; however, because it involves training a large number of ambulance personnel in reading ECGs as well as evolving a system for admitting suitable patients directly to CCUs, it will consume resources. Moreover, the position of the CCU within many hospitals may not allow easy access by ambulance.

It is possible to reduce delays by simpler methods. Transferring patients from the accident and emergency department to the CCU takes time that might explain the delay between the two groups observed in these studies.<sup>1,2</sup> Data from Edinburgh<sup>3</sup> showed that administering thrombolytic treatment in the accident and emergency department significantly reduced delays. Therefore, the simple step of giving thrombolytics in the accident and emergency department might achieve the same results as direct admission to CCU by trained ambulance personnel. A study comparing the delays between thrombolysis provided in the accident and emergency department and thrombolysis provided after direct CCU admission is advisable before the policy of direct admission to CCU by trained ambulance personnel is widely adopted.

There are other factors that may influence the timing of thrombolytic treatment. Our data<sup>1</sup> show that the delay in administering thrombolytics in accident and emergency depended on the method of administration: for infusions (streptokinase or alteplase) it was a mean (SD) of 49.5 (43.82) minutes but for a bolus (anistreplase) it was 16.5 (16.46) minutes. Therefore, greater use of thrombolytic agents that can be given by bolus may be particularly important.

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- 1 Millar-Craig MW, Joy AV, Adamowicz M, *et al*. Reduction in treatment delay by paramedic

- ECG diagnosis of myocardial infarction with direct CCU admission. *Heart* 1997;78:456-61.
- 2 Prasad N, Wright A, Hogg KJ, *et al*. Direct admission to coronary care unit by the ambulance service for patients with suspected myocardial infarction. *Heart* 1997;78:462-4.
- 3 Pell ACH, Miller HC, Robertson CE, *et al*. Effect of "fast track" admission for acute myocardial infarction on delay to thrombolysis. *BMJ* 1992;304:83-7.
- 4 Rao AC, Joseph SP. Reduction of time delay in administering thrombolytic therapy in acute myocardial infarction; anistreplase versus streptokinase or alteplase [abstract]. *Eur Heart J* 1993;14(suppl):72.

### Serum cytokines and cardiovascular risk factors

SIR,—The data on low density lipoprotein (LDL) concentrations in table 2 of the paper by Mendall *et al* appear to be flawed.<sup>1</sup> Assuming that the values given for LDL and high density lipoprotein are expressing the concentration of cholesterol in each lipoprotein fraction, and assuming that the triglyceride median value is close to the geometric mean, then the calculated mean value of LDL cholesterol using the Friedwald equation<sup>2</sup> would be 4.22 mmol/l, not 1.47 mmol/l. The latter concentration is so low as to be in the range seen in subjects with hypobeta-lipoproteinaemia.<sup>3</sup> Thus the lack of any relation between interleukin 6 or tumour necrosis factor  $\alpha$  and LDL cholesterol in this study may have been spurious. If, as suggested by the authors, raised cytokines in the blood are a reflection of the atherosclerotic process, it is possible that they would have shown a relation between cytokines and the concentration of LDL cholesterol (not just with triglyceride) if this had been calculated correctly.

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- 1 Mendall MA, Patel P, Asante M, *et al*. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart* 1997;78:273-7.
- 2 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
- 3 Schonfeld G. The hypobetalipoproteinemias. *Annu Rev Nutr* 1995;15:23-4.

This letter was shown to the authors, who reply as follows:

The LDL cholesterol was indeed miscalculated. The coefficients in table 2 should actually be 0.032 for tumour necrosis factor  $\alpha$  (95% confidence limits  $-0.126$  to  $0.190$ ) and  $0.015$  for interleukin 6 (95% confidence limits  $-0.117$  to  $0.196$ ). Both of these associations are weak and not significant.

We offer two, rather than one, possible explanations for the association of serum cytokine concentrations with evidence of coronary disease and cardiovascular risk factors. The first is that they are an epiphenomenon of the atherosclerotic process, and the second that they, either directly or through an effect on many conventional cardiovascular risk factors, play a role in the pathogenesis of atherosclerosis. It is still possible for the cytokines to be related to the atherosclerotic process without necessarily being associated with LDL cholesterol. LDL cholesterol may be associated with a different aspect of the pathogenesis of atherosclerosis from that indicated by these particular cytokines.