microbiological techniques require microvolumes of serum to test antibody levels to several microorganisms. Well designed, robust, large-scale epidemiological studies may opportunistically test simultaneously for the involvement of several microorganisms in atherosclerosis. Genetic susceptibility to atherosclerotic infection may also be relevant. Epidemiological investigators should seize the opportunity to examine the contribution of a new range of possible risk factors for cardiovascular disease.

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the mechanism of any benefit might be. Whether the finding of an apparent beneficial mechanism implies a 
clinical benefit also needs to be explored. One area of interest has been the effect of magnesium on 
complement activation.

Acute myocardial infarction and complement activation

While published data suggest that the presence of circulating immune complex is associated with genetic 
deficiencies in complement and that, as such, presence of complex may be an aetiological factor predisposing 
to acute infarction, most attention has focused on changes in the level of complement and its role during 
the infarct itself. In animal experiments and human sampling studies, Vakeva et al. and others have shown 
that activation of complement, together with expression of membrane regulators of complement (including 
acquired loss of resistance to membrane attack complex (MAC) by the shedding of the protective inhibitor CD59 to MAC), may all constitute mechanisms for clearing tissue injured by ischaemia. Important data also exist, however, to suggest that the inflammatory system is involved in mediating reperfusion-induced tissue damage. Data from animal studies indicate that complement activation always 
accompanies myocardial infarction, and is initiated by deposition of C3 within 2 h of coronary obstruction, 
with loss of protective CD59 from day one onwards. Mathey et al. suggest that in the absence of 
reperfusion, accumulation of the membrane damaging complement complex C5 b-9 occurs late during the 
necrotic tissue phase (after 5–h) whereas, following reperfusion, C5 b-9 accumulates after 30 min of 
myocardial ischaemia, supporting the role for the complement system in causing reperfusion injury. 
Additionally, the use of a monoclonal antibody to C5a in a pig model of ischaemia and reperfusion reduced the size of the infarcted area from 58 to 38%, 
and reduced in vitro superoxide generation, data which again support the belief that complement promotes ischaemic damage during reperfusion.

Streptokinase and complement

The formation of streptokinase–antistreptokinase 
antibodies is likely to be the cause of complement activation seen after infusion of this agent. Frangi et al., for example, have clearly shown a 10-fold increase in C4a, C3a and SC5 b-9 in 20 patients receiving this thrombolytic as compared with levels seen in 20 patients who did not receive streptokinase.

A transient neutropenia, and the production of hypotension in treated patients, may be the clinical consequences of induced leukocyte margination and plugging of cells in the microcirculation produced by complement activation. Similar changes in C4a, C3a and SC5 b-9 were found following streptokinase treatment by Agostini, but interestingly have not been shown in patients treated with tPA.

Magnesium, streptokinase and complement

Whether the effect of complement activation during acute infarction and its potential amplification by streptokinase is of clinical importance is unclear, although evidence suggests that such pathophysiological changes may have adverse clinical consequences. There is certainly scope for studying the effects of streptokinase on complement and observing any clinical benefits derived from limiting the interaction as compared to patients in whom streptokinase-induced complement activation has not been attenuated. Evidence that magnesium protects against anaphylactic shock has led Roth et al. (this issue) to evaluate the effect of high-dose intravenous magnesium on streptokinase-induced complement activation. In a small study, patients treated with streptokinase were given, in addition, either a bolus of MgSO4 (1 g) plus a further 4 g over 24 h, or 1 g MgSO4 (plus 14 g over 24 h or normal saline (n=10, 9 and 10 respectively). C3, C4 and CM-100 were measured at baseline and 
over the next 48 h. According to Roth et al. magnesium appears to attenuate the effect of strepto-
kinese on complement consumption. The discrepancy between the authors' work and that of others quoted 
in this article, where complement activation was demonstrated but changes in actual levels of C3 and C4 
were minor, exposes the difficulty of interpreting the pathophysiological consequences of measuring 
absolute levels. On the one hand we appear to have high levels of complement activation, with no changes in absolute levels and no apparent consumption, whereas on the other it is suggested that there is a significant reduction in complement levels, implying consumption. Such discrepancies, perhaps the consequence of trial size, clearly need to be resolved.

What of magnesium? Does it have a role?

The data from Roth et al. suggest that magnesium attenuates the changes in complement produced by streptokinase treatment. Such findings may not only
explain the beneficial effect shown in animal studies and human trials pre-ISIS-4, but would add weight to the argument that, for this agent to be of benefit in limiting reperfusion injury, it should be present at the time of reperfusion. Reperfusion is even more likely when a thrombolytic is being used. If magnesium is having a protective effect through an action on membrane attack complex (MAC), then given very early it may truly be of extra benefit. Timing may be all. As yet the clinical case for an injury benefit with magnesium is, however, unproven. It is possible that limiting reperfusion injury, the significance of which is unclear, may still be overshadowed by the overall benefit of thrombolytic therapy itself. Alternatively, if early administration of magnesium turns out not to be as valuable clinically as the theory suggests it might be, the more important role for complement may be the clearing of necrotic tissue rather than its potentially adverse effect on effecting reperfusion injury.

Before these published preliminary data — which suggest that streptokinase-induced activation of complement can be attenuated by magnesium — lead to too much excitement, a number of important studies are required. First, the issue of complement levels versus complement activation and complement consumption needs to be resolved. There would also need to be a much larger trial than any yet published indicating the effect of thrombolytic on complement activation and consumption. Such a trial should clearly address the issue of clinical benefit of any effect seen. A trial assessing the additional benefit of early magnesium over and above that from thrombolytic therapy on infarct outcome, complement activation and markers of reperfusion injury is needed for the issues to be resolved. Whether such a trial is justified is a mute point. Perhaps if either the LIMIT-2 group or ISIS-4 group have any frozen blood samples, analysis of complement levels and consumption and correlation with clinical outcome in those patients treated with magnesium, and at what time, would be an initial step.

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References