The authors observe that mortality from the combined effects of systolic blood pressure and serum cholesterol although higher in men than women, is not supported by any definite cause. We would like to offer the following suggestions. The use of hormone replacement therapy (HRT) in women in the age group 45–55 has become common. It is also well known that this therapy raises high density lipoprotein cholesterol levels and lowers low density lipoprotein cholesterol levels. Therefore, the possibility of exogenous/endogenous oestrogen playing a role in the lower mortality rate observed in women cannot be excluded. Maybe if the authors analysed the number of women on HRT, our suggestion might be substantiated.

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Uric acid concentrations and the mechanisms of cardiovascular disease

We read with interest the article by Yusuf and Bosch[1], which addresses the potential role of uric acid (UA) as a causal factor in cardiovascular disease. The association between raised serum UA concentrations and increased cardiovascular risk is unequivocal, but observational or epidemiological data are unlikely to resolve whether UA is a causal, compensatory, or co-incident factor. We support the authors’ view that basic and experimental studies are now needed to identify potential biological links between UA and mechanisms of atherosclerosis. We also agree that allopurinol may have therapeutic potential in this setting. However, we are not convinced that the proposal of the authors, to use allopurinol to lower serum UA concentrations, will effectively address the mechanistic issues.

Allopurinol causes a modest reduction in serum UA concentration, up to 30%[2], by inhibiting xanthine oxidase (XO), which normally catalyses conversion of hypoxanthine to xanthine, and xanthine to UA, an end product of purine metabolism in man (Fig. 1). However, XO activity also results in formation of hydrogen peroxide (H$_2$O$_2$), a potentially detrimental free radical, which is thought to contribute to vascular dysfunction, for example in patients with hypertension. In Dahl hypertensive rats, endothelial XO activity makes an important contribution to oxidative stress[3]. In humans, hypertensive patients have significantly greater H$_2$O$_2$ production than normotensive individuals, and the consequent increase in oxidative stress raises blood pressure and promotes target organ damage[4]. Inhibition of XO significantly reduces H$_2$O$_2$ production, and ameliorates vascular oxidative stress.

Additionally, allopurinol has antioxidant properties, which are independent of its effects on XO activity[5]. The potential cardiovascular effects of allopurinol could be due to inhibition of XO-mediated free radical generation, or direct antioxidant quenching of free-radical activity, and its use as a urate lowering agent requires cautious interpretation. The potential clinical benefits of allopurinol are threefold, but do not specifically address the question of a biological link between UA and mechanisms of atherosclerosis.

Another approach to lowering serum UA concentrations is administration of the enzyme urate oxidase (UO), which catalyses the further metabolism of UA. UO substantially lowers circulating UA concentrations, by up to 90%[6], and restoration can take several days, depending on the rate of purine metabolism. UO provides an opportunity to study the direct cardiovascular effects of UA lowering, in the absence of effects on XO or H$_2$O$_2$ liberation. Therefore, UO is a more effective and specific means of lowering serum UA concentrations than allopurinol and may, therefore, provide better insight into the relationship between UA and mechanisms of atherosclerosis.

An alternative approach to UA lowering is to study the cardiovascular effects of raising circulating UA concentrations, and the feasibility of systemic UA administration has recently been established[7]. This is an equally valid approach, because acute elevation of established major cardiovascular risk factors has been shown to cause impaired endothelial function in healthy individuals, for example after ingestion of a meal rich in saturated fats[8], or after raising circulating homocysteine concentrations by oral methionine administration[9].

We accept that allopurinol may confer significant cardiovascular benefits, and its therapeutic potential should be explored. However, the short-term approaches we have outlined are more likely to allow a better understanding of the possible mechanisms that link raised serum UA concentrations and increased cardiovascular risk.

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Myocardioocyte loss due to apoptosis

The findings presented by Dispersyn et al. (June 2002 issue) on dedifferentiation and apoptosis of myocardio-
cytes late after AMI were extremely interesting. The presence of both myocytes with metabolic rearrangement ('dedifferentiated' or 'hibernated') and cells committed to programmed death (apoptotic) in this experimental model of post-infarction left ventricular remodelling in sheep suggests that both these mechanisms are possible cellular responses to ischaemia.

However, a major issue is the effective myocardioocyte loss due to apoptosis. The data presented by the authors on myocardial apoptosis substantially confirm results presented earlier in a similar model of multiple AMI in dogs (0-12% of apoptosis in the former and 0-53% in the latter), while they appear strikingly different from our recent data in post-mortem human hearts. We have recently shown that the apoptotic rate is as high as 25% in the infarcted area of the hearts of human subjects who died 12 to 62 days after an AMI. A comparison of the two studies reveals a nearly 200-fold increase in our samples compared to the data by Dispersyn et al. Could these differences be due to selection bias in both studies? Perhaps yes.

We believe that estimates of apoptotic rates may show quite different results in hearts of individuals dying spontaneously compared to animals surviving and being killed. In facts, our results may have been biased by the selection of a population with a significantly poor prognosis (median time to death 23 days), who may have been associated with extremely elevated rates of apoptosis. On the other hand, Dispersyn et al. may have selected individuals who were relatively protected from apoptosis with a more favourable prognosis (the sheep with a 50% reduction in left ventricular ejection fraction were allowed to survive at least 6 weeks after the last embolization).

We think it would be of interest to the readers of this Journal to know whether any of the sheep in the protocol by Dispersyn et al. died before reaching the time they were due to be killed (as reported for the similar protocol in dogs). If this were the case, it would be extremely interesting to obtain data regarding the apoptotic rates in this group of animals, who were characterized by a certainly more unfavourable prognosis.

Most experimental studies in animals are affected by a similar selection bias. Sabbah et al. reported that approximately 30% of their dogs died early after intervention and were therefore excluded from the study. On the other hand, when, in an experimental study conducted on mice, all individuals were followed from time of intervention (surgical constriction of the aorta) until death, these animals, apoptosis-prone due to genetic manipulation, had an apoptotic rate greater than 30% and almost all died of dilated cardiopathy within a few weeks. Furthermore, a human observational study of post-mortem samples showed an apoptotic rate of 11-6% up to 10 days after AMI.

We were unable to understand, moreover, whether coronary embolization in the protocol by Dispersyn et al. resulted in total occlusion of a major coronary artery. In particular, we would like to know if coronary artery angiograms were repeated before they were killed. Patency of the infarct-related artery at the time of death may represent a major determinant for apoptosis late after AMI. We have shown that individuals with an open artery at the time of death have significantly lower apoptotic rates at sites of infarction.

An accurate definition of the factors promoting death or survival should lead to a more complete understanding of the variability observed in experimental animal models and human observational studies. Indeed it is possible that some individuals are relatively protected from apoptosis, surviving longer after AMI and showing only low grade apoptosis and a very low rate of transition from metabolic rearrangements to commitment to death, as in the cases presented by Dispersyn et al.

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