hypertension in animal models, ACE polymorphisms have been linked to the regulation of blood pressure[8,9]. In the current study, and in sib-pair linkage studies of the ACE gene in human essential hypertension[10], no relationship was found between ACE and increased blood pressure. So the increased risk for myocardial infarction in patients with the deletion polymorphism does not seem to be related to the level of systolic or diastolic blood pressure as typically measured in the brachial artery. However, given that the ACE gene can be expressed in the aorta, the relationship of ACE genotype to other haemodynamic determinants of cardiovascular disease such as aortic stiffness, aortic root pressure and pulse pressure may be worth looking at[11,12]. The importance of the renin–angiotensin system in the genetic control of blood pressure has been underscored by recent linkage and association studies suggesting that molecular variants of the angiotensinogen gene contribute to the inheritance of essential hypertension[13].

Third, the results of Cambien *et al.* derive further interest from the observation that, in hypertensive patients, increased levels of plasma renin activity are also associated with increased risk for heart attack, particularly in patients with a relatively low risk profile for cardiovascular disease[14]. It had previously been found that the plasma level of ACE in subjects homozygous for the deletion polymorphism was twice that in subjects without the deletion polymorphism[15]. Although measurements of circulating ACE or plasma renin activity are not reported by Cambien *et al.*, it is conceivable that a measurement profile that includes both plasma renin activity and ACE levels might be particularly useful for identifying individuals at increased risk for heart attack. Measurements of kinin levels or of angiotensin II, perhaps the ultimate villain in this story, could also prove to be of interest.

However, it is difficult to obtain reliable measurements of plasma angiotensin II, kinins, ACE or renin activity in the clinical setting and, unlike genomic DNA sequence, these biochemical variables may change in response to cardiovascular disease and to changes in diet. Furthermore, measurements of circulating levels of these substances may not reflect their activities at the tissue level. Although still a matter of considerable controversy[16], some investigators believe that the tissue renin–angiotensin and kallikrein–kinin systems may be of special functional significance. Given observations that the ACE insertion/deletion polymorphism may be a determinant of ACE levels in lymphocytes[17], it is tempting to speculate that the ACE genotype also determines ACE activity in cardiovascular tissues. So the use of DNA-typing techniques to determine a risk profile for cardiovascular disease has both practical and theoretical appeal.

Finally, the current work is more than the usual association study in which a small group of disease patients is compared to a control group with totally unknown genetic background. Cambien *et al.* looked at fairly large sample sizes and the relationship of ACE genotype to heart attack seems to hold across four different populations. Given possible questions about the strength of the statistical findings in the separate populations and the potential clinical implications of the results, however, it is essential that the findings should be independently replicated. Accordingly, the authors have been prudent in offering a concluding note of caution to their discussion.

Assuming that others do confirm that the ACE deletion polymorphism is associated with increased risk for heart attack, this will not prove that the ACE polymorphism itself is a culprit. Such positive association studies could be reflecting an effect of some other DNA sequence variant as much as 500 kilobase pairs away from the ACE insertion/deletion site[18]. For now, however, a molecular variant in the ACE gene seems to be the most likely suspect. In any case, Cambien *et al.* have dealt a very exciting hand to those interested in the molecular genetics of cardiovascular disease. □

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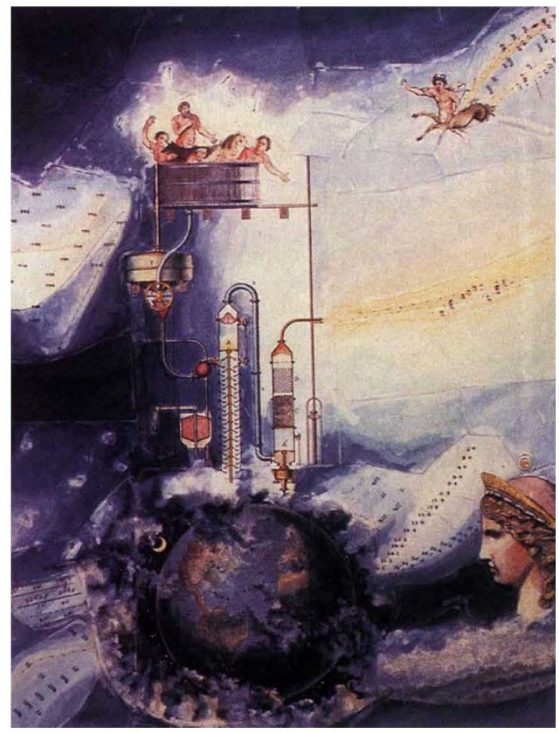
## Chemical communications



**CHEMISTRY, especially its history, fuses with art and literature in the "Chemistry Imagined" exhibition currently running at the National Academy of Sciences, Washington DC. The picture reproduced here, *Greek Air*, is a characteristically surreal collage by Vivian Torrence in which drawings from old books are combined to illustrate particular propositions. The main theme though is that of collaboration — not only in collage as an art form and as a hallmark of much of contemporary scientific research, but because the exhibition is a joint endeavour between Torrence and Roald Hoffmann. Hoffmann, Nobel laureate in 1981 for his work on understanding the course of chemical reactions, provides prose and poetry to elaborate on and complement the pictures; among other titles of the collage–text pairs are *The Periodic Table*, *Electron Transfer*, *Air of Revolution* and *The Philosopher's Stone* (alchemy has its place). The exhibition runs in Washington until 6 January next year. T.L.**