It is certainly far too early to recommend, as they do, that physicians use the results to provide a "clearer definition of risk." To make matters worse, the results would not in practice "strengthen physician counseling against smoking" because 97% of patients would be told that they were not in the highest genetic risk group and so, human nature being what it is, would feel reassured and tend to continue to smoke.

DAVID CURTIS
Joint Academic Department of Psychological Medicine
London Hospital Medical College
3rd Floor, Alexandra Wing
Turner Street, London E1, UK

Wang and Wilcken reply — Association studies have their advantages and pitfalls, but in addressing population genetic questions no statistical model has been proven faultless[3]. Nonetheless, association studies have often been useful in identifying genes or DNA variants relevant to genetic susceptibility to disease. Examples are the apoE and angiotensin converting enzyme genes, shown to be involved in the pathogenesis of coronary artery disease (CAD)[4,5]

The polymorphism we studied is one of a few polymorphic markers reported within the endothelial constitutive nitric oxide synthase gene (ecNOS). It is located at intron 4 but is not the fourth ecNOS polymorphism to be tested in relation to coronary risk, as suggested by Curtis. As far was we are aware, it is the first. A requisite for a valid association study is to have a homogenous population. The population we studied was of European origin and classified as Caucasian. All these patients had ischemic heart disease symptoms, these constituting the indication for coronary angiography. It is established that cigarette smoking reduces production of the protective nitric oxide (NO) in the vascular wall. Thus confining the analysis to smokers was an attempt to make the patient population more homogenous in relation to NO, rather than to "maximize the significance" as suggested and we aimed in this way to minimize confounding effects that could not be achieved simply by using a logistic regression model.

We grouped patients with 1, 2 or 3 stenosed major coronary arteries (>50% luminal obstruction) as a single group of patients with severe symptomatic ischemic heart disease. There are many ways of measuring CAD severity. All quantify somewhat different aspects of CAD severity and with different sensitivities. Our approach, grouping patients with disease in 1, 2 or 3 vessels together, was chosen to assess how and to what extent the tested genetic variant could predict severe disease. Segregation into those with angiographically normal coronary arteries and/or mild disease and those with severe disease in 1, 2 or 3 vessels had already been undertaken in this same patient population for studies with different end points[6].

We agree that the polymorphic marker we tested is not a functional one. It is more likely to be in linkage disequilibrium with a flanking region mediating functional changes. However, lack of a significant association between the ecNOS4a/b heterozygotes and CAD in our study does not necessarily indicate either a recessive or a dominant effect for the ecNOS4a allele. It could just reflect the degree of the association between the ecNOS and severe CAD in which the association may not be as strong, or the sample size may not be sufficiently large to show excess risk statistically for heterozygotes. It is nevertheless an arguable point.

Curtis's final comment is very relevant. Smoking increases cardiovascular risk for all, but to a widely varying extent — a fact only too evident to the practicing cardiologist. Genetic predisposition to disease is an important issue. If our findings are confirmed one can easily conceive of circumstances in which some people may wish to learn of any additional risk. But this is a matter for individual decision.

We are of course in complete agreement with the comment that our results require replication. Furthermore, their validity would be underscored if a locus mediating relevant functional changes is shown to be in linkage disequilibrium with the marker we tested. This is a current issue for us. It is perhaps worth mentioning that our preliminary results do indicate that there is a point mutation at the promoter region of the gene that may be responsible.

XING L. WANG &
DAVID E.L. WILCKEN
Department of Cardiovascular Medicine
Clinical Sciences Building
The Prince Henry Hospital
Little Bay, NSW 2036, Australia

1. Wang, X.L. *et al.* A smoking-dependent risk of coronary artery disease associated with a polymorphism of endothelial nitric oxide synthase gene. *Nature Med.* **2**, 41–45 (1996).
2. Lander, E. & Kruglyak, L. Genetic dissection of complex traits — guidelines for interpreting and reporting linkage results. *Nature Genet.* **11**, 241–247 (1995).
3. Lander, E.S. & Schork, N.J. Genetic dissection of complex traits. *Science* **265**, 2037–2046 (1994).
4. Davignon, J., Greeg, R.E. & Sing, C.F. Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis* **8**, 1–21 (1988).
5. Cambien, F. *et al.* Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature* **359**, 641–644 (1992).
6. Wang, X.L., Tam, C., McCredie, R.M. & Wilcken, D.E.L. Determinants of severity of coronary artery disease in Australian men and women. *Circulation* **89**, 1974–1981 (1994).

Anorexia nervosa — more than an eating disorder

To the editor — In the January issue of *Nature Medicine*, Cecilia Bergh and Per Södersten reduce the diagnostic criteria of anorexia nervosa to self-starvation[1]. Although their article appropriately recognizes the preeminence of reward in the early stages of anorexia nervosa, it is overly simplistic. The psychopathology of this condition is readily recognizable[2] and distinguishes anorexics from other individuals such as hunger strikers who engage in severe self-starvation. Patients in whom glucocorticoids are elevated, for example, in Cushing's syndrome, are not necessarily euphoric, in fact depression and emotional lability are more often observed. By contrast the bright cheerfulness of the patient with anorexia nervosa has been noted since the earliest descriptions of the syndrome. Yet depression is never far away, and eating disorders are associated with a range of conditions resulting from abnormal reward-seeking behaviors that might be seen to arise when hunger is not satisfied by food ingestion. These include substance abuse, obsessive compulsive disorder and kleptomania[3]. The relationship of anorexia nervosa to puberty implies that neuronal plasticity might be adversely and lastingly