The dangers of xenotransplantation

To the editor — In the September issue of *Nature Medicine*, Fritz Bach and colleagues contributed to the recent spate of enthusiasm for xenotransplants as a source of organs[1]. Throughout this episode, there has, however, been little discussion of the dangers posed by the possible activation of endogenous retroviruses[2]. Such viruses are widely distributed in mammalian species including pigs and baboons, potential donors for these procedures. Since they are inherited in the germ line in the form of proviral DNA, they are impossible to remove using the usual methods for deriving pathogen-free animals. Many endogenous retroviruses cannot replicate in their native hosts but will grow to high titres on heterologous cells, a phenomenon known as xenotropism. For example, human tumour cells grown in nude mice are often found to release C-type particles, the result of mouse xenotropic virus infection[3]. One might therefore expect that xenotropic virus originating from the transplanted tissue could replicate in the cells of the (probably immunosuppressed) recipient. Indeed, transplanting an organ carrying endogenous xenotropic provirus is equivalent to injecting a patient with live C-type virus. Even the slightest trace of such a virus renders vector preparations absolutely unsafe for gene therapy trials; to casually ignore its virtual certain presence in transplant trials makes little sense.

The pathogenicity of these viruses has not been studied. However, since growth of related viruses in immunosuppressed hosts can lead to tumour development[4], this prospect is somewhat alarming. We suggest that strenuous efforts be made to identify or breed virus-negative donors and that all protocols for xenotransplants include specific steps to monitor human recipients for possible infection by retrovirus of donor origin.

JONATHAN P. STOYE
National Institute for Medical Research
The Ridgeway, Mill Hill
London NW7 1AA, UK

JOHN M. COFFIN
Tufts University School of Medicine
136 Harrison Avenue
Boston, Massachusetts 02111, USA

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The cystic fibrosis heterozygote advantage

To the editor — In the July issue of *Nature Medicine*, Schroeder and colleagues report a potentially important relationship between heterozygosity of the ΔF508 mutation of the cystic fibrosis transmembrane regulator (*CFTR*) and protection against asthma, in an American population[1]. The authors suggest that this association might explain the long sought-after and presumed heterozygote advantage accounting for the high incidence of cystic fibrosis and may also shed light on the causal mechanism of asthma. Subsequent data reported by Mennie and colleagues[2], in the October issue, seem to suggest that the association does not exist in a British population, and underscore the importance of first exploring this observed association in other populations. However, even if this association were to be confirmed in other data sets, I believe that the authors' proposal that protection against asthma may explain the high frequency of ΔF508 alleles in the population must be rejected.

Respiratory diseases are the single largest cause of death in childhood, accounting for an estimated 4.3 million deaths globally in young children in 1990, and there is evidence that a similar picture existed in Europe at the beginning of the twentieth century[3]. However, the great majority of these deaths are accounted for by respiratory infections and in particular, bacterial pneumonia. In contrast, asthma accounts for a very small proportion of these deaths and the prevalence of asthma is significantly lower in developing than in industrialized countries[4]. It has been suggested that the recent fall in the importance of respiratory infections as a cause of mortality is causally linked to a rise in the incidence and mortality from asthma. Published epidemiological data[5] and underlying immunological mechanisms that would account for this have been proposed[6]. If true, this would explain the above findings in developing countries and would imply that asthma was a less important cause of mortality historically than it is at the present time.

It can be estimated that, if we assume the existence of a Hardy–Weinberg equilibrium, the heterozygous state would have to have a fitness of approximately 1.03 in order to sustain the current population allele frequencies for *CFTR* mutations. If this operates through an effect on viability rather than fertility[7], then this level clearly cannot be achieved with the low levels of mortality from asthma globally that are now found and are likely to have been present historically.

We will have to look elsewhere for an explanation for the high population frequency of the *CFTR* mutations. The two most fruitful lines of enquiry may be to test the hypothesis that ΔF508 blunts the response to bacterial toxin-mediated diarrhoea (as Schroeder suggests) or to look for evidence of preferential transmission of *CFTR* mutations in appropriate pedigrees.

HARRY CAMPBELL
Department of Public Health Sciences
University of Edinburgh Medical School
Teviot Place
Edinburgh EH8 9AG, UK

Schroeder and Swift reply — Campbell argues against our hypothesis that protection against childhood asthma is the heterozygote advantage that accounts for the high prevalence of ΔF508 and states that asthma *per se* accounts for only a very