seems likely, then, that groups 1*b* and 2*b* consisted of both control transplants and natural offspring. Given the small yield of transplants (three or fewer per litter), it is also likely that a majority of pups identified as control transplants were instead natural offspring, equivalent, except for the surgical stress to the mother, to the untreated controls.

Uncertainty about the composition of the control transplant groups precludes any conclusion about the effects of maternal environment: the increased alcohol consumption of the between-strain transplants could equally well be due to the transplant procedure in general or the surgical stress it entails. In this latter case, *b* groups (stressed) should have differed from *c* groups (unstressed), which they did not. The stress to the mother is, however, confounded with the transplantation procedure (affecting the ova?) in the *b* groups; if the two events oppose each other in their effects, the offspring might not differ from naturally bred ones.

Unfortunately, the confounding of variables does not permit any definite conclusion.

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1 Randall, C. L., and Lester, D., *Nature*, **255**, 147–148 (1975).

Randall and Lester reply—We agree with some of the arguments presented by Joffe, Najman and Nettleton[1], but we take issue with others. The difference in eye pigment between newborn C57BL and DBA pups is obvious at birth: C57BL pups have dark black eyes and DBA pups have lightly pigmented eyes. While differences in coat colour become evident within a few days and could be used, eye pigment allows immediate identification and the early and accurate culling of the litter.

In control transfers (C57BL–C57BL and DBA–DBA), the pups are, obviously, indistinguishable. We could have used mates of the opposite strain to ensure identification of the transferred ova, but this approach has its own inherent problems; we could also have mated females to infertile males of the same strain, but this was not a preferable method: the female is only pseudopregnant, no control uterine horn is provided and the transferred offspring are not intermixed with natural offspring. We thus considered other controls; without prior knowledge of the outcome, we chose the method described in our paper. We do not deny the validity of the arguments against this approach: the possibility certainly exists that natural, rather than experimental offspring, were examined. These other control procedures can, of course, also be used to determine whether transplantation *per se* exerts no effect; should the results not agree, the issue would remain unresolved because of the differences in methods and the introduction of other confounding variables.

Preimplanted mouse embryos are resistant even to the most severe types of chemical and drug intervention, at least in regard to morphological development in a foster mother's uterus[2]. Runner[2] suggests that nucleic information is not integrated until implantation occurs. Rather than attributing the increase in ethanol intake to the transplantation procedure *per se*—because surgery is performed at least 2 d before implantation—it is more likely that the outcome is a result of critical mother–foetal interactions. This issue is unresolved, however, since we do not know whether biochemical changes associated with implantation and pregnancy are similar in natural and transplanted offspring.

Maternal surgical stress does not explain the increase in alcohol intake of transferred young, unless we assume that transplanted ova are differentially sensitive to subtle changes in the maternal milieu or to subsequent postnatal events. In unpublished pilot work, we found anaesthesia alone did not alter phenotypic alcohol intake. Further, natural offspring tested concurrently with transferred pups did not demonstrate an atypical strain effect. For the sake of brevity and because we regarded the data as superfluous, these data were not in our report; obviously, in retrospect, they should have been included.

We can hardly argue that the alcohol consumption of C57BL and DBA mice is not subject to environmental alteration because we have produced such alterations[3]. The issue raised here is, however, the contribution of genetic and maternal variables to the strain extremes, since differences in intake are evident at weaning. We argue that if alcohol selection were determined by maternal rather than by genetic inputs, we should observe selections resembling the phenotypic norm of the foster mother. We noted no such effects in either strain: although alcohol choice increased in DBA mice transferred to C57BL mothers, the offspring never demonstrated C57BL-like high selection of alcohol.

Our report cannot be read to exclude the importance of environmental variables in determining behaviour, although it assuredly emphasises that maternal behaviour is not as important a determinant of alcohol intake as is genetic constitution.

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Molecular structure of NAD

Viswamitra[1] has speculated on the structure of free NAD which he then extrapolates to the NAD conformation when bound to enzymes. Unfortunately, he has neglected to take into account the extensive results which have been obtained during the past five years on the conformation of NAD when bound to lactate dehydrogenase[2], malate dehydrogenase[3], liver alcohol dehydrogenase[4] and glyceraldehyde-3-phosphate dehydrogenase[5]. Suffice it to say here that his speculations are inconsistent with facts and that the only 'fact' he does quote concerning the fit of his proposed NAD model to the low resolution difference map of Adams *et al.*[6] is incorrect.

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Viswamitra replies—The model proposed for NAD[1] was essentially for a free molecule. The reference to the work of Adams *et al.*[2] was to point out that NAD conformations with the adenine and nicotinamide bases far apart had been considered earlier. Although the statement about the possible compatibility of the model with the low resolution electron density maps of Adams *et al.* was unfortunate, it was only made as it was felt that electron density maps at 5-Å resolution, could admit, in general, a certain flexibility where the derivation of the shape of a small substrate molecule is concerned. It is also difficult to rule out conformational states of coenzyme molecules other than those derived from structural studies of bound enzymes as inconsistent with facts. The molecular structures found for ADP in the crystal structure of its rubidium[3] and *tris* salts (M.A.V., Z. Shakked and O. Kennard, to be published) are different from those deduced for the coenzyme from structural studies of bound enzymes[4].

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