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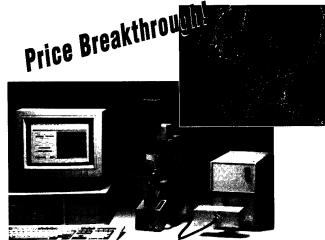
# The D<sub>2</sub> Receptor Gene

Kenneth Blum and Ernest P. Noble (Letters, 2 Sept., p. 1346) incorrectly imply that we have demonstrated (Articles, 17 June, p. 1715) that the gene encoding the dopamine D<sub>2</sub> receptor locus (Drd2) influences several responses to alcohol, morphine, and cocaine in the mouse. We would like to clarify our interpretation of the data we presented (in our original figure 2) and reiterate our intent in creating the composite figure representing genetic influences on drug responses.

The method of quantitative trait locus (QTL) gene mapping allows identification of the tentative chromosomal positions of the genes influencing traits showing multigenic inheritance (1). We applied the QTL method to data from our own and others' laboratories to seek patterns of association that might suggest hypotheses regarding commonality of genetic control of multiple drug responses. We indeed reported preliminary evidence suggesting that several drugrelated behaviors are tentatively associated with marker loci in a region of mouse chromosome 9 near the gene Drd2 (2). However, we are rather less sanguine than Blum and Noble appear to be about the interpretation of this pattern of results. As we tried to make clear, the composite map we presented was designed to stimulate hypothesis generation, not to serve as a springboard for jumping to conclusions.

We briefly reiterate here the important reasons for not assuming that this pattern of association shows that the Drd2 gene is the QTL mapped in each case (our original note 76). First, the associations presented in the figure represent tentative assignments of genetic association and need to be verified in a segregating F<sub>2</sub> or backcross population [our original notes 69 and 74; see also (3)]. While we expect that the majority of the provisional QTLs will be confirmed by further, rigorous tests with F<sub>2</sub> or backcross populations, only two QTLs for responses in the Drd2 region have thus far been tested and verified. Contiguity of multiple verified QTLs in a relatively small region of chromosome 9 could reflect several causes (our original note 76). Each trait could be influenced by a different gene. Some (or all) could be affected by the same gene, or a gene cluster. Finally, all could be affected by





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### LETTERS

the same single gene. Any of these genes could be, but is not necessarily, the Drd2 gene. We agree with Blum and Noble that a single gene can influence a complex trait (ascertaining the location of such genes is the point of QTL mapping), but it is specious to insinuate that David Goldman or any other geneticist would disagree. All of the drug responses that we found to be associated with markers in the region near Drd2 also were associated with markers in several other regions of other chromosomes. The enthusiasm of Blum and Noble notwithstanding, dopamine remains an important neurotransmitter in determining some drug responses, and the D<sub>2</sub> receptor may also have a role. Much more work will be necessary to test these hypotheses in available genetic animal models. The QTL method is one among many approaches discussed in our article that should allow the ultimate clarification of any possible role of dopamine D<sub>2</sub> receptor variants in alcoholism.

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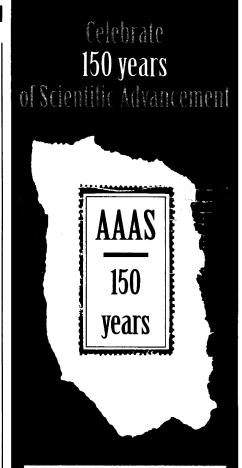
#### References

- E. S. Lander and D. Botstein, Genetics 121, 185 (1989).
- 2. D. L. Smith et al., Mouse Genome 90, 439 (1992).
- 3. J. K. Belknap, Behav. Genet. 22, 677 (1992).

#### **Corrections and Clarifications**

In the article "Genetic dissection of complex traits" by Eric S. Lander and Nicholas J. Schork (30 Sept., p. 2037), on page 2038, in column 2, under "Other transmission mechanisms," the second sentence should have begun, "These include mitochondrial inheritance (in which mitochondria pass solely through the maternal germ line..."

In the response by E. A. Finch and S. M. Goldin (5 Aug., p. 813) to the technical comment "Calcium and inositol 1,4,5-trisphosphate-induced Ca<sup>2+</sup> release" by L. Combettes and P. Champeil (5 Aug., p. 813), in parts B and C of figure 1 (p. 814), the insets referring to Ca concentrations were inadvertantly interchanged. The concentration for figure 1B should have been, "300 nM Ca" and that for figure 1C should have been, "10 nM Ca."



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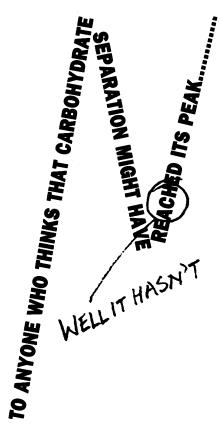
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