have the luxury of a crystal ball for predicting the outcomes of these experiments. What we do have is AIDS as a reference point.

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The Sobering D_2 Story

The article "A cautionary genetic tale: The sobering story of D_2" by Constance Holden (News, 17 June, p. 1696) sends the wrong message to the field and creates embarrassment for scientists who are pioneering at the forefront of research in the genetics of addictive-compulsive disorders.

The article states that "attempts to replicate [our] finding [about the A1 allele of the D_2 receptor gene] have been largely unsuccessful." A meta-analysis (*1*) of nine independent studies of a total of 491 heterogeneous alcoholics (severe and less-severe) and 495 heterogeneous control subjects (assessed and unassessed for alcohol abuse) found a statistical association between the D_2 A1 allele and alcoholism that was highly significant: the value of P was 10^{-7}. When attention was focused on six studies dealing only with a homogenous sample of 158 severe alcoholics, the association was found to be even more striking: the value of P was 10^{-8}.

The article states that "even those whose research appears to confirm it can't come up with a mechanism for the gene's presumed effects. . . ." In fact, the finding of a genetic marker is only the first step in what may be a long and involved process of continuing research. As in the case of Huntington's chorea, a chromosomal marker first discovered in 1983, adequately marks vulnerability to a disease without knowledge of the gene responsible for its expression. The actual gene was discovered 10 years later. The DRD_2 variants appear to adequately mark vulnerability to addictive-compulsive behaviors, but the mechanism for the specific genetic defect may not be discovered for the next decade. The causative factor may even involve closely linked microsatellites at the DRD_2 locus or possibly distant genes that are in linkage disequilibrium with the DRD_2 gene.

The article quotes psychiatric geneticist Elliot Gershon and his colleagues as saying that, in a study of alcoholics and schizophrenics (whose disorder also involves dopamine transmission) examining the gene instead of the marker, they "found several coding variants," but "the frequency was pretty much the same in the subjects and the controls." In fact, we were also coauthors of that report (*2*), and the findings were not unexpected. Gershon was referring to exonal anomalies that might alter the structure of the D_2 receptor and hence its ability to bind to its ligand. Our finding (*3*) suggests an anomaly in the transcriptional process that affects the number of receptors. Gershon's study did not examine anomalies around the 5′ promotor region, introns, and the 3′ untranslated region, all of which have been shown in a number of other disorders to have mutations that alter transcriptional or translational processes.

The article states that [David Goldman's group] "could find no significant difference between alcoholics and nonalcoholics in the frequency of the suspect allele. . . ." In fact, Goldman's sample (*4*) excluded severe alcoholic subjects having medical complications. Moreover, the nonalcoholics were not assessed for the presence or absence of alcohol or drug abuse. In contrast, our sample (*5*) of severe alcoholics had died from alcohol-related pathology. Furthermore, our nonalcoholic control subjects were assessed for the presence of alcohol and drug abuse. Goldman's study, therefore, was not a replication of our first study and has little bearing on it.

Joel Gelertner's group is indirectly quoted as saying that "there is little reason to accept Blum and Noble's conclusion." In fact, in the Gelertner study (*6*), as in Goldman's, any alcoholic subject showing liver enzyme abnormalities, let alone significant medical problems, was excluded. This is a clear indication that Gelertner's group was excluding severe alcoholics. Furthermore, their paper included no assessment of the control subjects. By excluding the severe alcoholic phenotype, the group was studying the more "environmental" rather than the more "genetic" type of alcoholism.

Holden's article refers to preliminary work by Robert Cloninger and says it "appeared to support the A1 connection, at least with regard to severe alcoholism." Holden then says that "when the group expanded its sample, it found . . . that the association between the D_2 receptor and alcoholism faded out." In their first study (*7*), Cloninger's group found that 60% of the severe alcoholics in the sample had the D_2 A1 allele, a prevalence that was significantly higher than the nonalcoholic controls. But careful scrutiny of their follow-up paper (*8*) revealed that the sample of alcoholics in the second study was heterogeneous, including both severe and less severe alcoholics. The inclusion of less severe alcoholics diluted the sample. Moreover, although the group found that the homozy-

gote copies of the D_2 dopamine receptor C1 allele were significantly associated ($P < 0.002$) with their mixed alcoholics compared with those of their nonalcoholics, they did not report this finding in the paper.

The article quotes Goldman as stating that "there aren't too many geneticists who would be sanguine about the authenticity of this association." This statement may be true for geneticists who doubt that a single gene can play a major role in complex behaviors such as alcoholism. However, John C. Crabbe and his colleagues (Articles, 17 June, p. 1715), using the quantitative trait loci (QTC) technique, found clear evidence that several responses to alcohol, morphine, and cocaine map to the middle portion of chromosome 9 in the mouse (the DRD_2 locus), which suggests that the single locus accounts for all of these associations.

There is increasing evidence from at least 14 laboratories in the United States, the United Kingdom, Canada, France, Japan, and most recently Finland and Australia, that behavioral anomalies ranging from alcoholism to drug abuse (*10*) to attention deficit hyperactivity disorder to Tourette's Syndrome to obesity to pathological gambling to nicotine abuse are associated with anomalies in the DRD_2 locus. Recent studies (*10*), subsequently confirmed (*11*), have found an association of the D_2A1 allele with components of the evoked potential, including the P300 (a cognitive component), first found by Henri Begleiter's group, to be altered in alcoholics and found by others to be of predictive value for substance-abuse liability in children of alcoholics. We are witnessing the birth of a new paradigm in our understanding of the genetic basis of addictive-compulsive behaviors, and from the total evidence available it should be clear that the DRD_2 gene will continue to play an important role in these behaviors.

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Response: What I conveyed in my article was the majority opinion in the field: that although interest in the D_2 dopamine receptor was strong a couple of years ago, the findings as a whole have been too ambiguous to be encouraging. It does not appear at this point that we know enough to pass final judgment on the idea.

Blum and Noble cite a meta-analysis, as if to suggest that there could be no question that their results are being confirmed by other studies. But Gelernter and his colleagues published another meta-analysis last year in the *Journal of the American Medical Association* (7 April 1993, p. 1673) in which they concluded that ethnic differences in the occurrence of D_2 and sampling error were more likely explanations than was alcoholism for differences in the prevalence of the suspect D_2 allele.

Much of the division of opinion in the field stems from the fact that different researchers put different constructions on the same data. For example, in the linkage study done at the National Institute of Mental Health (NIMH), P. V. Gejman and other authors, including Gershon, differ with their co-authors Blum and Noble about the significance of the negative finding. Blum and Noble say the result was not surprising, because they believe the genetic difference is likely to be found in some yet unexplored regulatory sequence. The NIMH researchers think that is highly unlikely.

Another disparity concerns Cloninger's work: Blum and Noble strongly imply that Cloninger's expanded sample would have yielded positive results if his alcoholics had been more severely afflicted. Cloninger, however, believes that we simply don't know how to subdivide the subjects in a way that is pertinent to this question. He points out that there is no agreement in the field on the definition of "severe" alcoholism. And the picture is further complicated, he says, by the fact that the D_2 association has been reported in "mild" alcoholics with a history of cigarette smoking but no severe medical problems.

One of the greatest areas of disagreement is over selection of controls. Blum and Noble insist that alcoholics must be removed from control groups. Gelernter and others argue that "purifying" the controls would not substantially alter the outcome.

In short, what Blum and Noble seem to be objecting to is not my article, but the opinions of others in the field who hold very different views about the D_2 hypothesis, views that were accurately reflected in my reporting.—***Constance Holden***