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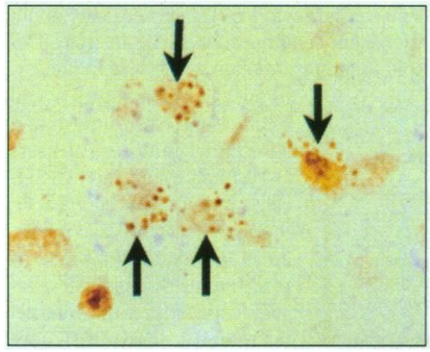
Apoptosis and Alzheimer's Disease

An article by Marcia Barinaga (Special Section, News, 28 Aug., p. 1303) in the recent issue devoted to apoptosis presents the case for apoptotic neuronal death in Alzheimer's disease (AD) based on culture studies and histological analyses. We strongly disagree that this evidence supports widespread apoptosis in AD. Apoptosis requires only 16 to 24 hours for completion and, therefore, in a chronic disease like AD with an average duration of almost 10 years, less than one in about 4000 cells should be undergoing apoptosis at any given time (that is, observation of apoptotic events should be rare) (*1*). Indeed, if all the neurons reported with DNA cleavage were undergoing apoptosis, the brain would rapidly be stripped of neurons. This is certainly not the case in AD.



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Do neurons in a brain from an Alzheimer's patient (dotlike staining pattern) indicate cells undergoing apoptosis?

Perhaps the greatest source of misunderstanding is that the criteria used for apoptosis have relied primarily on DNA fragmentation, where even the laddering pattern of fragmentation is not apoptosis-specific because histones protect DNA from a variety of insults, including those of necrosis and oxidative damage. When the more rigorous standard of nuclear condensation is examined, few neurons show apoptosis in AD. In fact, that we can observe neurons displaying many of the features of apoptosis argues that neurons in AD have mounted an effective defense to apoptotic death rather than that they are succumbing. The presence of a wide array of apoptotic markers is more likely indicative of an avoidance of apoptosis rather than actual completion of apoptosis. That neuronal cell death in AD occurs over a lengthy period suggests distinct mechanisms from the classical apoptotic process.

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Genetics of Alcoholism

We disagree with the interpretations of Ernest P. Noble (Letters, *Science*'s Compass, 28 Aug., p. 1287), of the results of our recent study (*1*). The Collaborative Study on the Genetics of Alcoholism (COGA) tested the hypothesis that the D2 dopamine receptor gene (*DRD2*) TaqI-A polymorphism was associated with alcoholism. We used the transmission disequilibrium test (TDT), a family-based method that compares alleles transmitted by heterozygous parents to their affected offspring with the alleles that could have been (but were not) transmitted (*2*). Because the TDT uses control alleles and does not use control individuals, Noble's discussion of the supposed problem with controls in the COGA study is not relevant to our results.

We tested individuals defined as alcohol-dependent by any of three criteria: those of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), 4th edition (*3*); the *International Classification of Disease*, 10th edition (*4*); and "COGA criteria" [alcohol dependence by DSM-III (revised) criteria (*5*), plus definite alcoholism by Feighner criteria (*6*)]. In no case was there any evidence that the TaqI-A1 allele was associated with alcoholism. Tests of a more informative simple tandem repeat polymorphism (STRP) marker in intron 2 were also negative. In light of the controversy surrounding this hypothesis, we tested the hypothesis in multiple ways; none of these tests provided evidence for either linkage or association of the *DRD2* gene with alcohol dependence.

To avoid missing any potential association, we also examined unaffected individuals in these families and again found no evidence of association (*1*). Noble appears to misinterpret our definition of unaffected in this part of our study. Unaffected individuals had 0, up to 4, or up to 8 of 37 symptoms collected in the interview instrument, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (*7*). These were symptoms, not criterion items for diagnosis. If they had been criterion items, no one with more than three could have been diagnosed as unaffected. As we stated in our paper, none met criteria for diagnosis of either alcohol abuse or dependence. The data for unaffected individuals did not show evidence for association of the *DRD2* gene with alcoholism.

Sib-pair analyses also provided no evidence of linkage (*1, 8*). Noble quotes two studies using sib-pairs (*9, 10*). As discussed in our paper (*1*), the first provided no evidence for linkage with the alcohol dependence syndrome; all of the putative evidence for linkage with heavy drinking came from one large sibship analyzed with no correction for non-independence (*9*). Neither the remaining families nor the replication sample gave any evidence for linkage (*9*). The other study (*10*) notes a nearly significant ($p = 0.06$) result by one technique that could not be replicated by more powerful analyses, including TDT, and therefore represents a negative report, in line with ours. An earlier study by the same group also found no linkage, although reporting a population association (*11*).

In summary, our study used a powerful method of analysis that avoids the major pitfall of previous association studies, the proper matching of controls. It yielded no evidence that the *DRD2* TaqI-A1 allele or an STRP in the same gene is associated with alcoholism.

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