Probing the Complex Genetics of Alcoholism

Recent findings of an "alcoholism gene" haven't held up—but a huge new study funded by NIH may help to nail down the basis of this costly condition

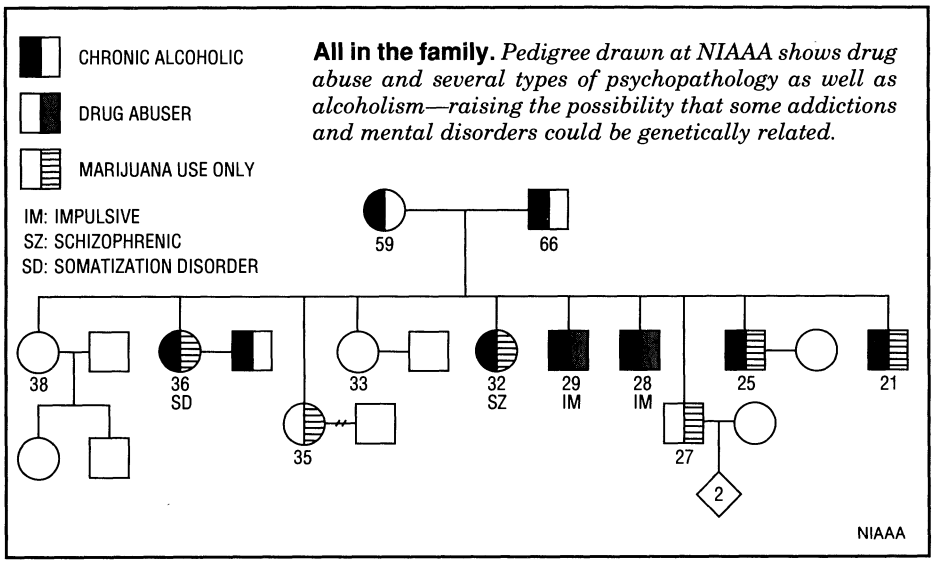
LAST APRIL, RESEARCHERS CAUSED A FLURRY in the media when they announced in the *Journal of the American Medical Association* that they had for the first time identified a gene—an allele of the D2 dopamine receptor—that they believed to be implicated in severe cases of alcoholism. But the first test of the finding, reported last month by researchers at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), has failed to confirm it.*

Frustrating findings are common in the world of alcoholism research, where for the past two decades researchers have been trying, so far without success, to identify biological markers—and more recently, actual genes—signaling a predisposition to alcoholism. Indeed, some scientists are beginning to suspect that there may be no genes for alcoholism per se, but rather for a general susceptibility to compulsive behaviors whose specific expression is shaped by environmental and temperamental factors.

Definitive answers may be on the horizon: The NIAAA, in an attempt to crack the biological riddles of the disease, has launched a massive study—massive for the behavioral sciences anyway—a kind of Manhattan Project on the genetics of alcoholism. Budgeted at $25 million for the first 5 years, it's a multisite, multilevel study including everything from psychological tests to DNA probes that will involve 600 alcoholics and potentially thousands of their family members.

The study will take off from the fragments of knowledge scientists now have about society's most costly disease. For example, it is now widely accepted that a vulnerability to the disorder can be partly inherited. (This certainty is based on results of adoption, twin, and family studies that have been rolling in since the mid-1970s, as well as by success in breeding strains of rats that prefer alcohol over water in their drinks.) Scientists are also now certain that many genes are involved, and that they are different for different groups of individuals.

But the tremendous variability shown in alcoholism has prevented researchers from pinning those genes down more specifically.



All in the family. *Pedigree drawn at NIAAA shows drug abuse and several types of psychopathology as well as alcoholism—raising the possibility that some addictions and mental disorders could be genetically related.*

For many alcoholics, the disease is associated with psychiatric problems: childhood conduct disorder, for example, which is marked by aggression and other antisocial activities, has emerged as one behavioral predictor for alcoholism. But there are also many alcoholics who apparently function normally until they end up in the hospital with cirrhosis. Other mysteries: why alcoholism can set in either early and fast, or gradually develop over decades; and why some alcoholics are binge drinkers, and others "maintenance" drinkers. And the epidemiology is actually changing: the average age of onset has moved from the mid-20's to under 20, and although some alcoholics stick to alcohol, more and more are taking advantage of the availability of illicit drugs.

What kinds of genes can account for even a part of this variability? Are the functions they mediate metabolic or behavioral? The principal investigator of the NIAAA study,† neuroscientist Henri Begleiter of the State University of New York's Health Science Center at Brooklyn, says he has come to the conclusion that no genes specific to alcoholism exist. Noting that it is getting harder and harder to find a "pure" alcoholic, he suspects that the disorder results from an underlying "behavioral disregulation that is not specific to alcoholism...a set of biological factors which are heavily influenced by environmental events and can lead to very different adverse outcomes." These outcomes include problems that look like addictions, such as gambling and eating disorders, as well as other compulsions and disorders of impulse control.

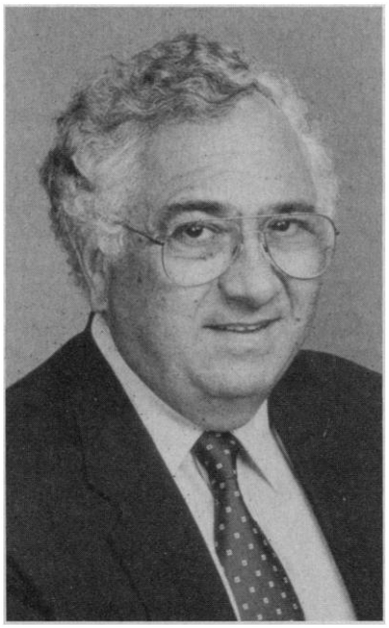
There is no evidence to contradict this idea, says Begleiter: For example, low levels of platelet monoamine oxidase (MAO) have long been suspected to be related to alcoholism, but now it seems they may correspond better to compulsive disorders in general. Furthermore, although he has identified anomalies in the brain waves of young sons of alcoholics, Begleiter doesn't think the phenomenon is specific to alcoholics, pointing to the fact that similar results have been found with cocaine abusers.

Psychologist Victor Hesselbrock of the University of Connecticut, one study investigator who agrees with Begleiter, says he thinks a number of scientists are "privately" leaning to the same view. But other researchers, while open to the idea of a generalized susceptibility, continue to place em-

*The study, "Allelic Association of Human Dopamine D2 Receptor Gene in Alcoholism," was reported in the 18 April 1990 *JAMA* by a team headed by Kenneth Blum of the University of Texas Health Science Center and Ernest Noble of the University of California at Los Angeles. The NIAAA study, "Population and Pedigree Studies Reveal a Lack of Association Between the Dopamine D2 Receptor Gene and Alcoholism," by Annabel M. Bolos et al, appeared in the 26 December 1990 *JAMA*. Two other research teams, at Washington University and McGill University, are also testing the Blum-Noble finding with family studies of alcoholics.

†Principal investigators at the six sites in the National Collaborative Studies on the Genetics of Alcoholism are neuroscientist Bernice Porjesz at SUNY; psychiatric geneticist Theodore Reich at Washington University in St. Louis; psychologist Victor Hesselbrock at the University of Connecticut; psychiatrist Marc Schuckit of the University of California at San Diego; neuroscientist Floyd Bloom of Scripps Clinic and Research Foundation; geneticist Michael Conneally and psychiatrist John Nurnberger at Indiana University, and psychiatrist Raymond Crowe, University of Iowa.

phasis on the possibility that there are genes specific to alcoholism. Kenneth Blum of the University of Texas Health Science Center, for example, believes there may be genes for "compulsive disease" (he and his colleagues suspect their dopamine gene is one), but also "subgenes"—what biologists call modifier genes—that dictate susceptibilities to particular substances. The NIAAA study's co-principal investigator Theodore Reich, psychiatric geneticist at Washington University, is even more emphatic: He contradicts study leader Begleiter by saying, "I am convinced there is a pharmacogenetics of alcoholism." He predicts, "We'll begin to see the [reemergence] of primary alcoholics" as the crack epidemic wanes.



General direction. *Henri Begleiter, principal investigator of the NIAAA study, believes no specific genes for alcoholism exist.*

Psychiatrist Marc Schuckit of the University of California at San Diego is also in this camp, based on his research with high-risk sons of alcoholics. Many subjects, he says, experience a "decreased intensity" of response to alcohol, suggesting that people drink too much because they are getting "less feedback." Since a recent study using Valium with the same subjects failed to show these decreased responses, Schuckit believes they are specific to alcohol.

The genetic picture is enormously complicated by the fact that mental disorders, particularly anxiety, depression, manic depression, and personality disorders are seen in close to half of alcoholics, according to the National Institute of Mental Health's epidemiologic Catchment Area Study. But which conditions precede alcoholic drinking, and the circumstances under which they lead to alcoholism, are not understood. Possible genetic linkages with alcoholism cannot be ruled out in some cases—most notably with antisocial personality disorder, which by definition begins in adolescence and which often includes criminal activity and substance abuse.

Schuckit, for one, says most alcoholics do not have mental disorders and that the search for a genetic predisposition should focus on this group. But other researchers disagree, in large part because so many alcoholics have antisocial personality characteristics—about one-quarter, according to the NIAAA (only 1.5% of the general population qualifies for the diagnosis). Many scientists, therefore, view the disorder as part and parcel of the puzzle of alcoholism.

Enter the NIAAA collaborative study which was started a year ago in hopes of fitting together all the disparate pieces. Principal investigator Begleiter characterizes it as part of a "new era of research on the genetics of predisposition" that is "much more complex, challenging, and interesting" than the search for "typical Mendelian disorders."

Indeed, the study involves an elaborate design in which state-of-the-art behavioral and biological assessments will be applied to an unprecedentedly large population. All six sites will follow the same research protocols, and technical people have been trained to carry out all tests in an identical manner. The first phase has involved the development of several new assessment instruments, including a 71-page diagnostic questionnaire covering drinking and drug habits, medical history, and psychiatric problems. These, along with tests of cognitive and motor skills, electrophysiological measurements, and biochemical assays, will be administered to the 600 alcoholics and their immediate families as well as to members of 200 control families where no addictions (as far as can be ascertained) exist. One-third of the subjects will be women, who have hitherto received short shrift in genetics studies. Says Reich: "We'll be trying to put together the whole phenotype" of alcoholism.

The next phase will involve segregation analysis to model potential mechanisms of inheritance and to characterize the effect of genes suspected to be involved in alcoholism and other familial disorders. Finally, there will be formal linkage studies, involving dozens of members each from between 100 and 200 families of alcoholics, for an in-depth look at candidate genes and their association with diagnoses and with possible biological markers. These include blood platelet enzymes such as adenylate cyclase and monoamine oxidase, neurotransmitters, and brain waves. Perhaps the most promising candidate as marker at the moment, according to several investigators, is a decrement in a certain brain wave, called the P3 wave, that Begleiter has identified in studies of young sons of alcoholics. The anomaly, which is linked to the processing of significant sensory stimuli, is also evident in alcoholics.

Ultimately, the study will result in the creation of a tissue bank of blood cells from alcoholics and family members that will "capture the full range of variation" in alcoholism, says Reich. That will enable the products of the study to be used for many years, to be available for the rapid testing of new hypotheses as they come along. Psychiatrist Robert Cloninger of Washington University says the study design "has a lot of information." For example, "If we find a linkage in St. Louis, we can tell Indiana and New York to check it." So, although baseline data will be collected for prospective research, "We'll be able to replicate within the study without doing follow-up."

The field of behavioral genetics, says NIAAA director Enoch Gordis, "is ripe for this attack" because of advances in computerized pedigree analysis and biotechnology. Cloninger points out that such a study wouldn't have flown 10 years ago because not enough of the human genome had been explored; but now, he says, "There are markers spanning 95% of the human genome. If there are major susceptibility genes, the probability of finding them approaches one." Whether that will happen in 5 years depends on luck, but "it really is a matter of time."

In any case, investigators say the study will help researchers agree on a typology for alcoholics that will sort out which cases are strongly genetically influenced. It may lead to new pharmacological treatments, and to the development of tests combining biological and psychological indicators to predict individuals at risk for alcoholism and other addictions. Another likely outcome, says Cloninger, will be closer coordination between what have been the separate domains of alcoholism and drug abuse research.

Begleiter says he will be "overjoyed" if, as he suspects, it turns out that all addictions stem from "the same biological core of anomalies." In that case, he says, the study "will tell us a hell of a lot more than just about alcoholism." It would imply the same research model could be extended to "many other disorders," and would justify a much broader application of the basic model of alcoholism treatment. Indeed, it could mean nothing less than a major reconceptualization of the disease.

■ CONSTANCE HOLDEN