National Institute on Alcohol Abuse and Alcoholism

ALCOHOLISM: AN INHERITED DISEASE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOREWORD

Ever since its creation by Congress in 1970, the National Institute on Alcohol Abuse and Alcoholism has given strong emphasis to research on the causes of alcoholism, including the ancient question of why the disease seems to "run in families."

For many years, research on the causes of alcoholism was almost exclusively the domain of the psychological and social sciences. Explanations for alcoholism were sought, and found, in the personality and social environment of the individual alcoholic, while biological and clinical scientists concentrated on understanding and treating the ravages to the body caused by alcoholism. Both areas of research remain critically important to this day.

It in no way diminishes the value and continuing importance of psychosocial and clinical research on alcoholism, however, to point out that humans are shaped by both environment and heredity, and that this must also be true of alcoholics. Although scientists have long suspected that susceptibility to alcoholism might be influenced by inherited biological factors, systematic research on the question had to await the development of an adequate fund of basic knowledge. Thanks to a wise national policy that regards alcoholism not as moral degeneracy but as a researchable, treatable, and preventable disease, that fund of basic knowledge has grown. As a result, it has become abundantly evident, in just the past few years, that genetically based biological predisposition is an important contributing factor in the development of alcoholism. We now know that both heredity and environment are involved in the making of most alcoholics.

As the following report, *Alcoholism: An Inherited Disease*, makes clear, this is a profoundly important discovery that has put us on the threshold of major advances in the understanding, prevention, and treatment of one of our most serious public health problems.

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PREFACE

The last 15 years have seen increasing efforts to understand the causes of alcoholism, a disease that annually causes death for thousands of our people; personal suffering for many thousands more; and national loss of billions of dollars in medical bills, social service costs, and diminished productivity.

How does this terrible disease start? Why do some people slip easily into alcoholism while others seem to have a resistance to it? Why does alcoholism occur generation after generation in some families and not at all in other families? Why is alcoholism common in some ethnic groups and rare in others? These questions go back to antiquity.

Traditional explanations for these differences in susceptibility often made the alcoholic solely responsible ("weak character," "no will power"), or put the responsibility on parents or cultural background ("bad parental example," "poor upbringing," "inferior people"). With either explanation the tone was moralistic, and the effect, if not the purpose, was often to stigmatize the victim and exalt the explainer.

In recent years these questions have undergone intense scientific scrutiny. It is now becoming very clear that differences in susceptibility to alcoholism and alcohol abuse exist, not for "moral" reasons, but for genetic ones. An impressive amount of evidence gathered over the last 10 years indicates that susceptibility to alcoholism can not only be genetically transmitted, but that genetic factors (in addition to familial environmental factors) are involved in a large proportion of alcoholism cases, and probably in the majority of them.

It is important to emphasize that these genetic factors in susceptibility, which involve subtle biochemical and metabolic differences at the molecular and subcellular levels, are probably not in themselves pathological. They only become manifest when alcohol is consumed, and they are important only because consumption of this substance is a permanent part of our culture. In evolutionary terms they are neutral mutations, meaning that in the natural state they would probably neither enhance nor diminish the ability of individuals to reproduce. Only beverage alcohol, a cultural artifact, gives them significance. If there were no such thing as an alcoholic drink these genetic variations would probably be as clinically inconsequential as hair color. Thus there is no justification for any notions of "genetic superiority" on the part of those who drink but are not alcoholic. They are merely lucky—so far.

This new knowledge is likely to have a profound social impact in

the coming years. Knowing that alcoholism is heritable should make it easier for us to rethink our cultural attitudes toward alcoholism and to accept it for what it is—a disease with a molecular basis, whose victims are worthy of our compassion.

The new knowledge will also have a powerful organizing and focusing effect on research on the fundamental mechanisms of alcoholism. This has already begun to occur, in fact, and the payoff will certainly be improved methods of treating and preventing this disease.

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INTRODUCTION

Modern research is making it increasingly evident that heredity is a major contributing cause of alcoholism and alcohol abuse in a large proportion of cases, and perhaps in nearly all cases.

The purpose of this report is to describe some of the significant new knowledge coming out of modern research on the genetics of alcoholism. The report is based on published research and on personal interviews with prominent investigators in the field. Several lines of recent research pointing to an inherited predisposition to alcoholism are discussed, including studies of twins, adoptees, and half-siblings; brain electrophysiology studies of the children of alcoholics; molecular studies of enzymes involved in alcohol metabolism; and selective breeding studies to produce strains of laboratory animals that not only prefer alcohol but drink it for its pharmacologic effects just as human alcoholics do. Research also is reviewed on the potential mechanisms of genetic influence on alcoholism, as well as on the search for physiological and biochemical markers that can identify individuals at risk. The amount of research going on in this new field is so prodigious[1] that only major highlights can be presented here.

Scientific studies of the inheritance of alcoholism have great potential for practical application. For example, it becomes both feasible and appropriate to search for specific physiological and biochemical indicators of this genetic susceptibility, so physicians can have a rational and convincing basis for counseling abstinence or strict moderation by individuals whose laboratory tests show them to be at risk.

An even more important benefit of studying the genetics of alcoholism is better understanding of the fundamental mechanisms involved in both the development of this complex disease and its clinical manifestations. Already, genetic studies have demonstrated heterogeneity in inherited alcoholism. At least two forms of inherited predisposition are known, and other forms will undoubtedly be discovered as research in this area continues. This process of refining disease classifications, of discovering and analyzing new subcategories of what were originally thought to be singular illnesses, is one of the most important

[1] A recent literature search by the National Clearinghouse for Alcohol Information yielded more than 700 articles published on this subject since 1980.

factors in the successes of modern medicine. In cancer research, for example, progress in basic understanding, diagnosis, treatment, and prevention accelerated as soon as scientists realized that they were dealing with, not one, but dozens of diseases. Knowing the specifics of any disease category allows more precise and more successful interventions to be designed, whether for prevention or therapy.

Genetic research on alcoholism provides a "compass" to guide research and generate hypotheses that link knowledge in diverse areas of the field. This integrative and stimulating effect is a major benefit of research on the genetics of alcoholism. Demonstrating that vulnerability to alcoholism has a genetic basis focuses the attention of many kinds of researchers on underlying mechanisms that may explain the phenomenon. Thus the observation by population geneticists that alcoholism tends to be more common in certain nationalities, ethnic or racial groups, or families, and that this clustering follows the laws of heredity, stimulates physiologists, biochemists, and molecular biologists to look for basic mechanisms that can account for the broader observations. Once these underlying mechanisms are understood, it becomes possible to design specific pharmacologic, nutritional, or other interventions to correct inherited defects, deficiencies, or other imbalances that are expressed as uncontrollable drinking.

This process of examining fundamental mechanisms involved in the genetic transmission of alcoholism is already occurring in the field of alcohol research. Although we are probably a long way from being able to alter the genes of susceptible individuals, research on the genetics of alcoholism has put us on the threshold of exciting new discoveries that will rapidly affect our understanding of the mechanisms of this baffling disease and the way we treat it and prevent it from starting.

EARLY STUDIES[2]

The involvement of heredity in alcoholism has been suspected since ancient times and was a fairly popular though not well founded belief in the Victorian period, especially among prohibitionists (1,2). The only basis for these early beliefs was the observation that alcoholism tends to "run in families," which in itself is not proof of genetic transmission since a shared environment could also explain the pattern. Most scientific research to separate the effects of heredity and environment in the transmission of alcoholism has occurred since the 1950s, and only in the last few years has it been conclusively shown that a substantial proportion of human alcoholics have genetically inherited a predisposition to acquire the disease.

In 1979, N.S. Cotton (3) reviewed 39 studies on the heredity of alcoholism that had been published over the preceding four decades and summarized findings on the families of 6,251 alcoholics and 4,083 nonalcoholics. The aggregate data from the thousands of alcoholics in these 39 studies showed that alcoholics were more likely than nonalcoholics to have an alcoholic father, mother, sibling, or distant relative. Almost one-third of any sample of alcoholics had at least one parent who was also alcoholic.

Heredity Versus Environment

These findings by Cotton and his predecessors were consistent with the idea that alcoholism is genetically transmitted. They did not prove it, however, because alternative explanations were not ruled out. What these studies showed was a statistical association between an individual's alcoholism and that of a close relative, but this could also be due to a shared environment that predisposes to alcoholism. Members of a family share many genes but they also share a common environment. Without further evidence, the aggregation of alcoholism in certain families can be explained just as readily by behavioral and sociocultural theories as by genetic ones (4).

Separating the effects of environment and heredity is a fundamental problem in studying the genetics of alcoholism, and scientists have used various methods to solve it. One approach to separating these effects is to compare alcoholism rates among identical twins who were

[2] Much of the information in this section was obtained from a review written for the National Institute on Alcohol Abuse and Alcoholism by Dr. T.-K. Li of Indiana University School of Medicine.

separated at an early age, with one brought up in an alcoholic home and the other brought up in a nonalcoholic home. Another is to compare alcoholism rates among identical twins versus fraternal twins. Yet another is to measure the rate of alcoholism among adopted-out children of alcoholics and compare it with the rate in a control group.

All such approaches to varying degrees separate the effects of environment and heredity. For example, if separated identical twins both tend to become alcoholic regardless of whether one of them is brought up by nonalcoholic adoptive parents, this favors the existence of hereditary factors in their alcoholism, since identical twins have virtually identical genetic makeup. Similarly, genetic factors are indicated if individuals with diverse genetic backgrounds are brought up in the same environment, as in the case of half-siblings, but show different susceptibility to alcoholism. Heredity is also implicated if people born to alcoholic parents, but removed from that environment at an early age through adoption, show a greater than expected rate of alcoholism.

Studies of Half-Siblings

Evidence for a genetic predisposition to alcoholism was found in a 1972 study of 69 hospitalized alcoholics who collectively had 164 half-siblings. M.A. Schuckit, D.A. Goodwin, and G.A. Winokur reported (5) that 20 percent of the half-siblings of these patients were also alcoholic. Furthermore, 62 percent of the alcoholic half-siblings had at least one biological parent who was alcoholic, while only 20 percent of the nonalcoholic half-siblings had an alcoholic biological parent. The investigators also found that the alcoholic half-siblings had not spent any more time in an alcoholic environment than the nonalcoholic half-siblings.

These results, which had high statistical significance, suggested that genetic predisposition was more important than childhood environment in influencing the development of alcoholism in this population.

Studies of the Adopted Children of Alcoholics

An even better separation of heredity and environment, and stronger evidence for genetic predisposition to alcoholism, was found in a study of the adopted-out sons of alcoholics in Denmark by D.W. Goodwin and his colleagues (6). Their study was based on a large sample population of 5,483 individuals who had been adopted in early

childhood. Using stringent criteria for diagnosing alcoholism, the investigators found that the sons of alcoholics who had been adopted by other families were more than three times as likely to become alcoholic as the adopted sons of nonalcoholics. They were also more likely to become alcoholic at an early age and to develop alcoholism serious enough to require treatment.

Confirmation of these earlier findings came in a 1978 study by Michael Bohman, who compared the rates of alcohol abuse in 2,324 adoptees and their biological parents in Sweden (7). The adoptees included 1,125 men and 1,199 women, all of whom had been born in the Stockholm area between 1930 and 1949 and had been adopted before the age of 3. The biological parents in the study sample included 2,261 mothers and 1,902 fathers. Histories of alcohol abuse in the study population were obtained from a variety of official sources. Bohman found that adopted sons whose fathers were alcoholic were three times more likely to become alcoholic than the adopted sons of nonalcoholic fathers, while adopted sons whose mothers were alcoholic were twice as likely to become alcoholic as those whose mothers were nonalcoholic.

Bohman selected 192 individuals from this group of 2,324 adoptees for more detailed study. The parents of these individuals had the most serious records of alcohol abuse. The 192 included 50 men and 50 women whose biological fathers were severely alcoholic, and 42 men and 50 women whose biological mothers were serious alcohol abusers. The subjects were compared with control groups matched on the basis of age, sex, age at adoption, occupational category of adoptive parents, and ages of the biological and adoptive parents when the child was born. Again the results pointed to genetic factors in alcoholism. Male adoptees whose biological fathers were severely alcoholic had a 20 percent incidence of alcohol abuse compared with 6 percent in the controls. Among male adoptees whose biological mothers had been reported for alcohol abuse, there was a 33 percent incidence of alcohol abuse compared with 19 percent in the control group (although the difference in this case was not statistically significant).

THE RELATIVE CONTRIBUTIONS OF HEREDITY AND ENVIRONMENT

These earlier studies on adoptees clearly showed that a genetic predisposition to alcoholism exists in some individuals. However, they did not address the question of how genetics and environment interact to produce alcoholism. Neither genetic nor environmental factors alone can explain alcoholism. Both are involved. But what are the relative contributions of these factors? Does environment affect the severity of alcoholism or alcohol abuse in a susceptible person? Are there subtypes of alcoholism that are due to varying contributions by heredity and environment?

Two factors complicate the search for answers to these questions. First, alcoholism is not a clinically homogeneous disease. For example, some alcoholics were well-adjusted as teenagers and worked regularly as young adults but in later years began to drink and became alcohol-dependent, but other alcoholics are antisocial persons who began a life combining delinquency, law-breaking, and alcohol abuse at an early age. Second, it is difficult to separate genetic and environmental effects within families, since children are influenced both by their genes and by their home environment.

Gene-environment interactions can be disentangled by studying people who were separated from their biological parents at an early age and raised by unrelated foster parents—such as the population of Swedish adoptees identified by Bohman in 1978 (7). This is a population for which environmental influences (but not genetic ones) of biological parents ended at a very early age, making the adoptive environment predominant.

The Swedish Adoption Studies

In collaborative investigations funded in part by the National Institute on Alcohol Abuse and Alcoholism, C. R. Cloninger, Bohman, and their colleagues (8–11) analyzed the Swedish adoptees to address four questions:

1. What characteristics of the biological parents influence the risk of alcohol abuse in the adoptees?
2. What characteristics of the adoptive parents influence the risk of alcohol abuse in the adoptees?
3. How do genetic and environmental factors interact in the development of alcohol abuse?

4. Is the genetic predisposition to alcoholism expressed in other psychopathological ways, depending on the environment experience and sex of the individual?

To answer these questions, the investigators selected 862 men and 913 women of known paternity who had been adopted before the age of 3 by nonrelatives. Six hundred twenty-seven or 35.3 percent of the adopted children had a biological parent known to be an alcohol abuser. The subjects were subdivided according to both congenital background and postnatal home environment. As before, extensive data about alcohol abuse, legal records, occupational status, and medical and social history were obtained for all adoptees and parents from official sources.

Each group was analyzed to determine how adoptees with particular types of congenital background react to different types of adoptive placement. Every possible combination of genetic background and environment was examined. The adoptees were divided into four subgroups according to degree of alcoholism (none, mild, moderate, or severe). To determine the role of heredity, several characteristics of the biological parents were examined to identify the ones that were most associated with a particular degree of alcoholism in the adoptees. To understand the role of postnatal environment, a similar analysis of adoptive parents was made to identify the most significant postnatal factors associated with particular degrees of alcoholism.

These studies identified two broad categories of alcoholic families: those in which only men develop alcoholism, and those in which both men and women may. There was a significantly greater prevalence of alcohol abuse in the adopted-out sons of alcoholic biological fathers than in the sons of nonalcoholic parents of either sex: 22.8 percent of the sons of alcoholic biological fathers were alcoholic, compared to 14.7 percent among sons who did not have an alcoholic biological parent. Also, twice as many of the adopted-out sons whose biological mothers were alcoholic were alcohol abusers than the sons of nonalcoholic parents of either sex: 28.1 percent of the sons of alcoholic biological mothers were alcohol abusers, compared to 14.7 percent of sons who did not have an alcoholic biological parent.

The effect of parental alcoholism on adopted women was more complex. The frequency of alcohol abuse was more than three times higher in the adopted-out daughters of alcoholic mothers than in the daughters of nonalcoholic parents: 10.8 percent of the daughters of

alcoholic biological mothers were alcohol abusers, compared to 2.8 percent of daughters who did not have an alcoholic biological parent. There was a statistically insignificant excess of alcoholism among adopted-out women whose fathers had mild alcohol abuse and no encounters with police or courts (3.9 percent versus 2.8 percent), but there was no excess of alcoholism in the daughters of fathers with more severe alcohol abuse or legal misconduct.

Alcohol abuse in the adoptive parents was not associated with alcohol abuse in the adoptees, ruling out the possibility that alcoholism in the adoptees could have been due to their imitating alcohol abuse by their nonbiological parents. In fact, the percentage of alcohol abusers among the men reared by an alcoholic adoptive parent was lower than in the other male adoptees—13 percent versus 18 percent. The only significant risk factor in the adoptive parents was low occupational status of the adoptive father.

These findings provide strong evidence that biological inheritance can be a major factor in the development of alcohol abuse and alcoholism. Further analysis of the data led to the conclusion that two kinds of genetic predisposition to alcoholism exist—milieu-limited and male-limited—and that these predispositions differ significantly in the severity of the alcoholism they give rise to and also in the relative influence of heredity and environment.

Milieu-Limited Alcoholism

This is the more common type of genetically influenced alcoholism, and it occurs in both men and women (accounting for most alcoholics among both males and females). It is called milieu-limited because its occurrence and severity in susceptible offspring are influenced by the postnatal environment. Thus milieu-limited alcohol abuse requires both a genetic predisposition and environmental provocation. Analysis of the data showed that if only one of these factors was present the risk of alcohol abuse was lower than in the general population. If both were present, however, the risk was doubled and the severity was determined by the degree of postnatal provocation.

Milieu-limited alcohol abuse is usually not severe, typically goes untreated, and is associated with mild, untreated, adult-onset alcohol abuse in either biological parent. The biological parents also show few if any encounters with the legal system. The controlling effect of environment on this form of alcoholism is demonstrated by the finding that a more severe milieu-limited alcoholism requiring hospital care

may occur in susceptible sons growing up in particular environments, especially those associated with low social status or unskilled occupation of the adoptive father.

Male-Limited Alcoholism

This is a severe type of hereditary predisposition, found only in men. It is less prevalent (about 25 percent of all male alcoholics in the general population) than milieu-limited alcoholism and appears to be unaffected by the environment. In families with male-limited susceptibility, alcohol abuse was nine times greater in the adopted sons regardless of their postnatal environment. Male-limited susceptibility is associated with severe alcoholism requiring extensive treatment in the biological father, but it is not associated with alcohol abuse in the biological mother. The biological father also tends to have a record of serious law-breaking. Male-limited alcoholism frequently develops in adolescence, is often accompanied by serious encounters with the law, and is associated with episodes of extensive treatment. Postnatal environment has no influence on the risk of developing male-limited alcoholism, but it may influence its severity; adoptees with this form of alcoholism generally were not as severely alcoholic as their fathers, possibly reflecting the advantages of their having been brought up in better homes or other environmental factors.

The male-limited type of susceptibility in a family does not increase the risk of alcohol abuse in the daughters. However, the Swedish adoption studies revealed that it greatly increases the chances of a woman developing a psychosomatic condition called diversiform somatization, characterized by frequent complaints of pain or discomfort, without any physiological basis, in various parts of the body (11).

The prominent features of milieu-limited and male-limited alcoholism are summarized in table 1 (adopted females) and table 2 (adopted males).

Some Caveats

Although these studies demonstrate the existence of two forms of inherited predisposition to alcoholism, as well as an association between alcoholism and a tendency to get into trouble with the law, the investigators caution against certain unwarranted conclusions. First, the existence of alcohol abuse in an individual does not in itself indicate agenetic susceptibility to alcoholism. There are many sporadic (i.e., nonfamilial) cases of alcoholism, and many alcoholics do not have par-

ents with the characteristics associated with vulnerability to alcoholism. (The investigators concede, however, that the parents of an alcoholic could be genetically predisposed to alcoholism themselves yet not develop the disease because their exposure to alcohol may have been limited by sociocultural factors.) Second, while the combination of teenage onset of alcohol abuse and legal misconduct in the biological parents of moderate alcohol abusers may suggest the presence of an underlying psychological disorder, such as antisocial personality, it is hard to know whether a tendency to violate the law is a cause or a consequence of alcoholism. The analysis of the Swedish adoptees suggested that the tendency to break laws was a secondary complication of alcohol abuse, not a cause of it.

Table 1. Effect of alcoholism in biological parents on the frequency of alcohol abuse in 913 adopted Swedish women[1]

Characteristics of biological parents	Frequency of alcoholism[2] in adopted-out daughters
Only mother abused alcohol	10.3% (2.8%)[3]
Only father abused alcohol	3.9% (2.8%)[3]
Mother and father both abused alcohol	9.8% (2.8%)[3]
Father severely alcoholic, with serious legal encounters (usually male-limited alcoholism)	No excess of alcoholism, but high frequency of diversiform somatization[4]

[1]From Bohman, M.; Sigvardsson, S.; and Cloninger, C.R. Maternal inheritance of alcohol abuse: Cross-fostering analysis of adopted women. *Archives of General Psychiatry* 38:965-969, 1981, *and* Bohman, M.; Cloninger, C.R.; von Knorring, A.-L.; and Sigvardsson, S. An adoption study of somatoform disorders. III. Cross-fostering analysis and genetic relationship to alcoholism and criminality. *Archives of General Psychiatry* 41:872-878, 1984.

[2]This is the milieu-limited type of alcoholism, the only form of genetic predisposition to alcoholism identified in women by the Swedish adoption studies.

[3]Percentages in parentheses are alcoholism rates in adopted-out daughters who did not have an alcoholic biological parent.

[4]Diversiform somatization is a psychosomatic condition characterized by frequent complaints of pain or discomfort, without any physiological basis, in various parts of the body. Male adoptees whose biological fathers were severely alcoholic and had serious encounters with the law were likely to develop the male-limited form of hereditary alcoholism, which suggests that the genetic factors that lead to male-limited alcoholism are expressed as somatization in women. From Bohman, M.; Cloninger, C. R.; von Knorring, A.-L.; and Sigvardsson, S. An adoption study of somatoform disorders. III. Cross-fostering analysis and genetic relationship to alcoholism and criminality. *Archives of General Psychiatry* 41:872-878, 1984.

Table 2. Prominent features distinguishing two types of genetic predisposition to alcoholism in 862 adopted Swedish men[1]

	Type of predisposition	
Distinguishing feature	Milieu-limited	Male-limited
Prevalence in adopted men	19%	4%
Characteristics of biological parents		
Father	Mild alcohol abuse, minor legal encounters, no treatment	Severe alcohol abuse, serious legal encounters
Mother	Mild alcohol abuse, minor legal encounters	No alcohol abuse, no legal encounters
Postnatal environment	Determines both frequency and severity of alcoholism in susceptible sons	No influence on frequency, but may influence severity
Severity of alcoholism	Usually isolated or mild problems, but may be severe	Usually recurrent or moderate problems, but may be severe
Relative risk in genetically predisposed sons[2]	2 with postnatal provocation, 1 without postnatal provocation	9 regardless of postnatal environment

[1]Adapted from Cloninger, C.R.; Bohman, M.; and Sigvardsson, S. Inheritance of alcohol abuse. *Archives of General Psychiatry* 38:861-868, 1981.

[2]Relative risk is the ratio of the risk of alcoholism in congenitally predisposed sons to that in others. A relative risk of 1 means there is no difference in risk of alcoholism between congenitally predisposed sons and others.

Significance of the Swedish Adoption Studies

The studies of the Swedish adoptees provide a clear demonstration of genetic heterogeneity in alcoholism and gene-environment interaction in its development. By taking into account the interaction of heredity and environment this research has reconciled conflicting results of earlier studies. By demonstrating the critical importance of sociocultural influences in most alcoholics, this research suggests that major changes in social attitudes about drinking can significantly reduce the prevalence of alcoholism, regardless of genetic predisposition.

Finally, these studies indicate the importance of considering genetic heterogeneity in future research on either the biomedical or sociocultural aspects of alcohol abuse. The following section illustrates the point.

Alcohol Abuse and Alcoholism in Combat Veterans: A Speculation

The discovery by Cloninger and colleagues that the expression of a major type of hereditary predisposition to alcoholism is strongly influenced by environment (milieu-limited alcoholism) has potential significance for other areas of alcohol research, especially studies of alcoholism rates in defined populations. Knowledge that there is such a thing as milieu-limited alcoholism allows data on alcoholism prevalence in such populations to be viewed in a new way. A recent study of the prevalence of alcohol abuse and alcoholism in Korea and Vietnam combat veterans is a case in point.

Drs. L. Branchey, W. Davis, and C. S. Lieber, of the Veterans Administration Medical Center and Mount Sinai School of Medicine, Bronx, New York, recently published the results of their study to determine the prevalence of alcohol abuse and alcoholism (12) among veterans of the Korean and Vietnam Wars. The investigation grew out of several reports published between 1975 and 1980 showing a high prevalence of alcohol-related problems among Vietnam veterans. One study found that nearly a third of Vietnam veterans surveyed 8–12 months after their return to civilian life were problem drinkers. Another survey of Vietnam veterans made 2 years after their military service ended found that 39 percent had developed at least one alcohol-related problem and that 16 percent were alcoholics. Other studies provided similar findings: alcohol-related problems were significantly higher in Vietnam War veterans than in a matched control group of nonveterans; high levels of alcohol consumption and binge drinking were more prevalent in Vietnam veterans than in other Vietnam era veterans, veterans of other wars, and nonveterans; and the rate of heavy drinking among Vietnam veterans increased with the severity of combat exposure. High prevalence of alcohol abuse has also been observed in Korean War veterans.

Branchey and colleagues wanted to know how long these effects persist in war veterans. They also wanted to explore further the effect of exposure to combat on the prevalence of alcoholism and alcohol abuse, so their study population consisted of matched groups of nearly equal

numbers of randomly selected combat and noncombat veterans (103 total). The severity of the combat experience was assessed by raters who had no knowledge of the presence or absence of an alcohol problem.

The study revealed dramatic differences in the prevalence of alcohol problems in the two groups. Nearly two-thirds of the noncombat veterans had never developed an alcohol problem, but just the opposite was true in the combat veterans: two-thirds of them were either alcohol abusers, active alcoholics, or alcoholics in remission, and the severity of alcoholism in this group was related to the amount of time spent in combat.

The investigators concluded that there is a significant association between exposure to the extreme stress of combat and excessive alcohol consumption and that this can persist for more than a decade after the stressful events.

This is a reasonable conclusion, although a less likely hypothesis is that individuals with characteristics making them more prone to alcohol problems are more likely to be assigned to combat service. In either case, we are now entitled to wonder, in view of the findings from the Swedish adoption studies, how many of these veterans with combat-associated alcoholism might have inherited the milieu-limited type of genetic predisposition and needed only a stressful environment to become alcoholic, with the severity of the alcoholism depending on the amount of environmental provocation.

The Limitations of Human Studies

The studies described in the previous sections clearly show that heredity is at work in many cases of human alcoholism. However, the demonstration of that fact raises many more questions. *How* is alcoholism genetically transmitted? What specific genes are involved? What particular laws of genetics apply in the transmission of susceptibility to alcoholism? How would specific kinds of matings affect the genetic risk of alcoholism?

For moral, ethical, legal, and economic reasons, humans are unsuitable subjects for research to answer questions regarding the details of genetic transmission. Scientists cannot manipulate human breeding, they only observe its results. Only animals are suitable for the kind of controlled breeding studies that are required to answer questions about the mechanisms of genetic susceptibility to alcoholism.

ANIMAL STUDIES

Perhaps the strongest evidence of a genetic predisposition to alcoholism comes from animal breeding experiments yielding strains that prefer to drink alcohol.

Most animals have a strong aversion to alcohol. The key phrase here is "most animals." In any sizeable population of animals, say, a colony of laboratory rats, a range of preferences will be found. At one extreme there will be a small number of rats that almost totally avoid alcohol solutions. At the other extreme there will be a few rats that voluntarily consume significant quantities of it. The majority of animals will fall between these two extreme levels of aversion and preference.

Alcoholic Rats

This normal distribution of animal behaviors is the starting point for breeding experiments to produce strains of rats that either consistently reject alcohol or consistently prefer it. Basically the approach is to mate the animals at the two extremes of alcohol preference only with their own kind. After several generations of such selective breeding, two strains can be produced that "breed true" and are quite opposite in their reaction to alcohol solutions; one strain consistently produces alcohol-avoiding offspring, and the other consistently produces alcohol-preferring offspring.

Such divergent genetic strains are being used as models for the study of human alcoholism in laboratories around the world. An example of the results of such selective breeding is the P (alcohol preferring) and NP (nonpreferring) rat strains developed by T.-K. Li and his colleagues at the Indiana University School of Medicine (13) with grant support from the National Institute on Alcohol Abuse and Alcoholism. Similar rat lines have been developed by the Research Laboratories of the State Alcohol Monopoly in Finland (14).

The nonpreferring strain might be thought of as the animal equivalent of the human who abstains or drinks very little, while the preferring strain might be considered the equivalent of the human alcoholic (with an unequivocal demonstration of the genetic transmission of alcoholism thrown into the bargain).

The P rats have been shown in several studies to meet most of the requirements of an animal model of alcoholism. They voluntarily drink large quantities of alcohol solution to achieve high blood alcohol

levels. They will actually work to obtain alcohol by pressing a lever, even when food and water are readily available. If allowed to drink these high levels for long periods they will become physically dependent on alcohol, develop tolerance to its depressive effects, and become susceptible to the withdrawal syndrome. These behaviors are identical to those seen in human alcoholism. Recently a final major requirement was established in these models. The requirement has to do with why these animals prefer alcohol.

Before it can be concluded that an alcohol-preferring rat strain is an ideal model of human alcoholism and its genetic transmission, it is necessary to demonstrate that the strain drinks alcohol for its pharmacologic action and not for its taste, smell, or caloric value. It must be shown that an animal drinks alcohol voluntarily, chronically, and in large amounts for no other reason but to obtain a pharmacologic effect, just as human alcoholics do. Without such evidence the existence of an alcohol-preferring rat strain only proves the genetic transmission of a preference for alcohol, for whatever reasons, but not necessarily the genetic transmission of the full range of characteristics that define true alcoholism.

It is not easy for human beings to know the inner motivations of rats that plainly prefer to drink alcohol, but Dr. Li and his colleagues have succeeded in doing so (15). Their method has demonstrated that P rats inherit, not a gustatory or olfactory preference for alcohol, but a tendency to consume large amounts of alcohol for its pharmacologic effects.

To eliminate the possibility that rats sought alcohol for its taste or smell the Indiana scientists used an apparatus that automatically delivered either plain water or an alcohol solution directly into the stomachs of male P and NP rats whenever they consumed either of two neutrally flavored drinking water solutions (almond or banana). The device gave the animals freedom of movement within their cages, including free access to food and drinking water.

The idea was to train the animals to associate a particular flavor in their drinking water with the presence or absence of a pharmacologic effect from the intragastric alcohol infusion, without giving them the opportunity to taste or smell what was entering their stomachs. The investigators reasoned that if animals of the alcohol-preferring strain consistently consumed a large amount of the flavored water that was paired with intragastric alcohol infusion, then it could be inferred that

they had learned to associate that particular flavor with pharmacologic effects from alcohol and not with its taste or odor.

That is exactly what the investigators found. The P rats drank up to 14 times more of the flavored water that was linked to alcohol infusion than the NP rats did. In fact, their rate of consumption in some experiments was higher than it is in free-choice alcohol drinking by P rats, suggesting that the taste of alcohol may be slightly aversive even in these alcohol-preferring animals. The P rats self-infused as much as 9.4 grams of alcohol per kilogram of body weight per day compared to only 0.7 grams per kilogram per day in the NP rats, and reached blood alcohol levels as high as 0.450 percent.[3] In human terms, this is roughly the difference between drinking a fifth of whiskey every day and having a daily glass of beer.

Significantly, the level of alcohol self-administration by the P rats dropped drastically when conditions were altered to cause water instead of alcohol to be intragastrically infused. When the original conditions were restored, however, the alcohol self-administration behavior returned within 4 days. This ability to extinguish alcohol-seeking behavior by removing the alcohol that reinforces it, then to restore that behavior by bringing back the reinforcer, is fully consistent with the idea that the P rats like alcohol for its pharmacologic effect on the central nervous system.

Implications for the Inheritance of Alcoholism in Humans

These studies by Li and his colleagues do more than demonstrate that the P and NP rats are good animal models for alcoholism research. They also have important theoretical implications as to the role of genetics in human alcoholism. These rat lines were developed for ethanol preference and nonpreference, and it is now very evident that P rats prefer alcohol because of its effects on their central nervous systems. The ability to develop such animal strains by selective breeding is itself proof that both alcoholism and resistance to alcoholism can have a genetic basis.

It can be argued, of course, that rats are not humans. But the biomedical literature is so replete with examples of interspecies similarities, particularly at the subcellular and molecular levels where the basic

[3] For comparison, the legal permissible limit for blood alcohol in drivers in most States is 0.100–0.150 percent.

processes of inheritance occur, that it would be unwise to give much weight to that argument. Rats and humans do have very different aggregations of genes, but the basic genetic mechanisms are the same in both species, and many of the gene products (i.e., proteins) are very similar, including the enzymes involved in alcohol metabolism.

If rodents can inherit alcoholism there is little reason to doubt that humans can too, especially when independent genetic studies of humans, such as those described earlier in this report, point to the same conclusion.

MECHANISMS INVOLVED IN ALCOHOLISM RISK

The studies described in preceding sections observed only a behavioral phenomenon—alcoholism—and provided strong evidence that it can have a genetic basis. But strictly speaking, behavior, as such, cannot be inherited. Only genes can, and the immediate products of genes are proteins. Behavioral characteristics arise from the genes and their products, but remotely, and furthermore they are strongly influenced by environment.

It is therefore insufficient merely to say that the risk of the behavior pattern, alcoholism, is inherited and let it go at that. We need to know what *physical* characteristics people inherit that make them vulnerable to develop the alcoholic behavior pattern. Specifically, how do their anatomical, physiological, and biochemical systems differ from those of people who are not susceptible? And by what mechanisms do these differences become expressed as alcoholism? Such questions have more than theoretical importance; they can lead to discoveries that help us understand how alcoholism develops and devise better ways to treat and prevent it. Merely proving that alcoholism can have a genetic basis, and asking no further questions, gets us nowhere.

Several hypotheses in this area are being studied, but they fall into two broad categories: those involving genetic variations in the enzymes of alcohol metabolism and those involving genetic variations in the structure and function of nerve cells. Studies in each category are presented below.

Enzyme Variations

Sensitivity to the effects of alcohol varies greatly among individuals. Some people can remain conscious after drinking a quantity of alcohol that would cause others to "pass out," become comatose, or even die. Others are so sensitive to alcohol that just one or two drinks can produce acute discomfort accompanied by facial flushing, elevated skin temperature, and a rapid pulse. These individual variations in response to alcohol are probably due to differences in the ability to metabolize alcohol, to innate differences in the central nervous system's sensitivity to alcohol, or to differences in the capacity to adapt rapidly to the presence of alcohol (acute tolerance).

The body's major chemical pathway for the metabolism of alcohol requires the action of two enzymes—alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH). The process, occurring

mostly in the liver, involves three steps: first, alcohol is converted to acetaldehyde by the action of ADH; second, acetaldehyde is converted to acetic acid by the action of ALDH; finally, acetic acid is converted by a series of enzymes to carbon dioxide and water. Considerable scientific attention is being focused on the molecular structure and function of ADH and ALDH to determine how genetic variations in their properties might account for individual differences in alcohol sensitivity and susceptibility to alcoholism. A major area of study is the comparison of alcohol metabolism in different races.

Racial Differences in the Metabolism of Alcohol

There is evidence of a high prevalence of alcohol sensitivity among Orientals or people of Oriental derivation (Chinese, Japanese, Koreans, American Indians, and Eskimos). Signs of sensitivity—rapid facial flushing, elevated skin temperature, and increased pulse rate—after consuming moderate amounts of alcohol appear to be common among Orientals but are seen in only 5 percent of Caucasians. Recent studies suggest that these differences are based on genetic variation in the enzymes involved in alcohol metabolism. Distinctive molecular differences have been found in ADH and ALDH in Orientals and Caucasians.

Preliminary studies suggest that a high proportion of Orientals, perhaps 90 percent, have a form of ADH that is far more active than the ADH found in Westerners and therefore converts alcohol to acetaldehyde more rapidly. Oriental populations also have a high prevalence of a genetically based deficiency in ALDH, the enzyme that metabolizes acetaldehyde produced from alcohol by ADH. Such individuals, perhaps half of all Orientals, are sensitive to alcohol because they eliminate acetaldehyde much more slowly. When ALDH is deficient, alcohol consumption leads to high blood acetaldehyde levels and consequent unpleasant symptoms. This genetically based ALDH deficiency may help explain the very low prevalence of alcoholism among Orientals: individuals deficient in the enzyme are likely to avoid alcohol and the unpleasant sensations it causes, while individuals who are not deficient in ALDH would lack this protection against alcoholism.

Interestingly, the rapid and unpleasant accumulation of acetaldehyde (a highly toxic compound) following the consumption of alcohol, which occurs naturally in many Orientals, is deliberately invoked when alcoholic patients are given the drug disulfiram (Antabuse) to deter them from drinking. Disulfiram acts by inhibiting acetaldehyde dehy-

drogenase, causing acetaldehyde to accumulate rapidly and produce very unpleasant symptoms when alcohol is consumed. Since many Orientals have an inborn inefficiency in eliminating acetaldehyde, they can therefore be considered to have a built-in deterrent to alcohol abuse because they get a disulfiram-like reaction from drinking alcohol. Consistent with this are recent studies from Japan (16,17) showing that ALDH deficiency is less common in Japanese alcoholics than in the general Japanese population.

The study of molecular variations among the alcohol metabolizing enzymes is important for understanding the basic mechanisms that determine individual genetic resistance or susceptibility to alcoholism.

Many studies have demonstrated that the human liver, where about 85 percent of alcohol metabolism takes place, contains multiple forms of the enzymes responsible for that metabolism, each of which is inherited. Structurally, each of these variants is very similar to its counterparts, differing only in one or just a few amino acid constituents out of the hundreds of amino acids that comprise the enzyme molecule. Small though they are, these structural differences can have a great effect on the functional properties of the enzyme, either speeding up its action or slowing it down, and thus accelerating or delaying the elimination of alcohol from the body.

Since there are so many such variants—20 for ADH so far, and probably more awaiting discovery—many combinations are possible among individuals. These discoveries have led to several hypotheses concerning the role of enzyme variants in human alcoholism. A prominent one is that the particular combination of variant alcohol-metabolizing enzymes that individuals inherit can affect both their ability to handle alcohol and their susceptibility to alcoholism.

Why Do We Have Alcohol-Metabolizing Enzymes?

A broader issue is why animals and humans even have enzymes to metabolize ethyl alcohol. Certainly they could not have evolved ADH and ALDH so they can drink alcoholic beverages and produce a toxic compound like acetaldehyde. Even though animals can metabolize ethyl alcohol, most of them have an aversion to it. So do many people, although drinking alcohol has been part of human culture since prehistoric times. How then did mammalian species happen to evolve such enzymes, when alcohol consumption could not have been a factor in their evolution?

The answer is that these enzymes, including ADH (which comprises 5 percent of the total protein in liver), evolved for a totally different purpose—the chemical conversion of certain alcohols produced by the body itself. These alcohols, including a class called biogenic amine alcohols, are normal physiological compounds and are nonintoxicating. It is purely fortuitous that ADH also works chemically on ethyl alcohol.

If that is so, then it is also purely fortuitous — and far from a moral issue—that some people are genetically more sensitive than others to an enzyme substrate that is, after all, unnatural even for those who tolerate it well. The implication is that people who inherit a metabolic predisposition to alcoholism probably have alcohol-metabolizing enzymes that function well within the normal range—as long as they let those enzymes work only on their natural substrates.

Neurochemical and Neurophysiological Variations

Alcohol affects every system of the body, but its greatest, most immediate, and most visible effects are on the central nervous system. This makes the central nervous system, particularly the brain, a primary target of research on mechanisms underlying inherited susceptibility to alcoholism.

The Nerve Cell

The fundamental unit of the nervous system is the neuron, or nerve cell, which has a long extension called the axon and several shorter extensions called dendrites. The function of nerve cells is to transmit electrical impulses to other nerve cells as well as to structures outside the nervous system (e.g., muscles and glands). A typical nerve cell receives a messenger chemical called a neurotransmitter from other nerve cells through specific receptor sites on its dendrites, changes the chemical signal to an electrical signal, and sends the electrical signal through the axon. When the electrical signal reaches the tip of the axon, the nerve cell releases molecules of neurotransmitter that pass through a tiny region called the synapse and are taken up by specific receptors on the dendrites of adjacent nerve cells. This process can be repeated many times to transmit signals throughout the nervous system. (See figure 1.)

The propagation of an electrical signal along a nerve cell is based on the movement of sodium and potassium ions back and forth

FIGURE 1. TYPICAL NEURONS

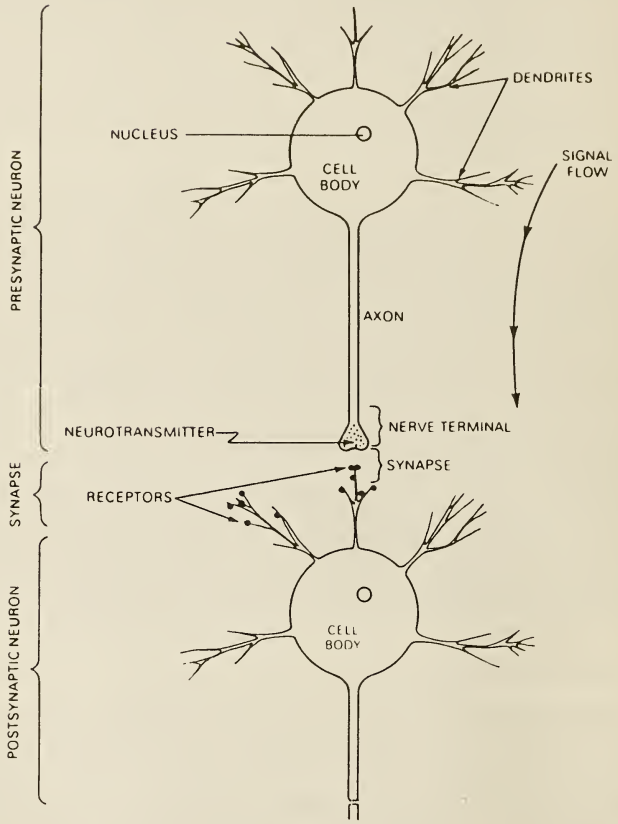


Figure 1. Typical neurons. The interrelationship of a pair of neurons is indicated. A neuron consists of a cell body and two types of extensions—dendrites and an axon. Specific receptors on dendrites receive neurotransmitter molecules from the axons of adjacent neurons. This sets up an electrical impulse in the receiving neuron that is transmitted through the neuron to the nerve terminal at the tip of its axon. Arrival of the impulse at the nerve terminal causes release of neurotransmitter molecules (indicated in the figure by dots), which diffuse across a small gap (the synapse) to receptors on the dendrites of the next neuron. This triggers another impulse in the receiving (postsynaptic) neuron. The process can be repeated many times to send signals throughout the brain and the rest of the nervous system. Susceptibility to alcoholism could involve genetic variations in several aspects of this system. (Source: *Fifth Special Report to Congress on Alcohol and Health*, 1983).

through the lipid membrane that encloses the cell. The movement of these ions through the membrane is regulated by the enzyme sodium-potassium ATPase, whose molecules are embedded in the cell membrane.

All of the complex features of the self—thoughts, emotions, actions—are based on these chemical and electrical processes occurring in billions of nerve cells in the brain at any instant. Several features of this system could be involved in inherited predisposition to alcoholism and are being investigated from that perspective. Alcohol could interfere with numerous processes involved in nerve cell function, and if there is inherited variation in these processes it could result in either neurochemical vulnerability or resistance to alcoholism. Among the leading neurochemical hypotheses are the following:

- Individuals predisposed to alcoholism might have nerve cell membranes that are less sensitive to the permeability-altering effects of alcohol, which would affect the movement of sodium and potassium ions and the propagation of nerve impulses.
- Predisposition might be based on inherited variations in the sensitivity of sodium-potassium ATPase and other membrane enzymes to inhibition by alcohol. This also would affect the transmission of nerve impulses, which depend on enzymic regulation of the flow of ions through the nerve cell membrane.
- Inherited predisposition to alcoholism may be based on inherited variations in neurotransmitter release and uptake systems involved in the chemical propagation of nerve impulses between nerve cells.
- Persons predisposed to alcoholism may produce abnormal amounts of tetrahydroisoquinolines, morphine-like compounds that may be involved in alcohol addiction.
- Predisposition may be based on inherited variations in the brain's neurochemical mechanisms for reinforcing certain behaviors.

Hypotheses Involving the Nerve Cell Membrane

The transmission of signals through and between nerve cells depends on the function of neurotransmitter releasers and receptors, enzymes, and channels for the movement of ions. All of these components are proteins embedded in the cell membrane, which is mostly lipid.

Several studies have shown that alcohol lowers the viscosity (i.e., increases the fluidity) of the nerve cell membrane, and it is reasonable to suppose that anything that disturbs the cell membrane could interfere with the specialized membrane proteins involved in neurotransmission. Reduction of membrane viscosity by alcohol occurs only up to a point, however; in mice chronically treated with alcohol, subsequent alcohol administration produced no further changes in membrane viscosity (18). This suggests that behavioral tolerance to alcohol may be associated with tolerance of cell membranes to alcohol-induced decrease in viscosity.

The role of genetics in this phenomenon is strongly indicated by the results of a study comparing alcohol's effects on neuronal membranes from two genetic strains of mice that differ in their sensitivity to alcohol. D.B. Goldstein and colleagues (19) compared long-sleep (LS) mice (sensitive to alcohol) and short-sleep (SS) mice (less sensitive to alcohol), and found that nerve cell membranes from the more sensitive strain (LS) were more susceptible to the viscosity-lowering effects of alcohol. In view of these findings it is conceivable that a human with inherited susceptibility to alcoholism is like the SS mouse, with nerve cell membranes that are genetically resistant to the fluidizing effect of alcohol.

Hypotheses Involving Membrane-Bound Neuronal Enzymes

The membrane-bound enzyme sodium-potassium ATPase is an "ion pump" responsible for the movement of sodium and potassium ions through the cell membrane. It participates in neurotransmission by maintaining correct concentrations of these ions on either side of the membrane. Studies have shown that brain alcohol levels achievable by beverage consumption can inhibit sodium-potassium ATPase, but only in the presence of the neurotransmitter norepinephrine. This could explain the alcohol sensitivity of brain areas that have norepinephrine-containing nerve cells.

As with membrane viscosity changes, sodium-potassium ATPase becomes resistant to inhibition by alcohol after chronic exposure. This invites the same kind of speculation that has been made in the case of membrane viscosity; that is, genetic predisposition to alcoholism may involve forms of sodium-potassium ATPase that show atypical sensitivity (or resistance) to inhibition by alcohol. Thus a genetically predisposed individual could be expected to have sodium-potassium ATPase that was less sensitive to alcohol.

Hypotheses Involving Neurotransmitters

A neurotransmitter is a chemical substance that is released from the tip of an axon when the electrical nerve impulse arrives. The release mechanism requires the movement of calcium ions into the cell membrane. The released neurotransmitter molecules then move across the synapse and are bound to receptor sites on the dendrites of adjacent neurons. This sets off another electrical nerve impulse in the adjacent neuron.

The binding of a neurotransmitter to a receptor is very specific; a given type of neurotransmitter will bind only to a receptor site that is designed to receive it. Like a key and a lock, the fit must be right before anything can happen. Since at least 40 different neurotransmitters have been identified (and there may be as many as 200 undiscovered), there must also be a multitude of receptor types.

It is reasonable to suppose that a system with this complexity and these exacting requirements of fit could be easily disrupted by a foreign substance like alcohol. This is indeed the case. It has been shown that under certain conditions alcohol inhibits the calcium uptake part of the neurotransmitter release process, but that the inhibition is reduced by chronic exposure to alcohol (20). Other studies have shown that alcohol interferes with the release of the neurotransmitters norepinephrine, dopamine, and gamma-aminobutyric acid as well as their recognition by their receptors (21–23). Chronic alcohol administration changes the picture somewhat; rats and mice chronically given alcohol showed increased norepinephrine release and further decrease in dopamine release (24).

One finding in this area also points to a possible genetic mechanism for the inheritance of alcoholism susceptibility: mice bred for resistance to the behavioral effects of alcohol showed more resistance to the effects of alcohol on dopamine release (25). Thus predisposition to alcoholism could be due in part to genetic variations in the protein molecules involved in neurotransmitter release and reception.

Hypotheses Involving Tetrahydroisoquinolines

Tetrahydroisoquinolines (TIQs) are potent morphine-like neurochemicals formed by the chemical combination of acetaldehyde (a major product of alcohol metabolism) and neurotransmitters. The chemistry of these combinations is well known and involves an interaction between the oxygen atom of acetaldehyde and an amino group on

the neurotransmitter. The structural similarity of some TIQs to morphine and its derivatives has led to the hypothesis that opiate addiction and alcoholism may share a common addictive mechanism involving specific receptors in the brain that bind both opiates and TIQs.

In 1977 Myers and Melchior (26) reported that infusions of the TIQ tetrahydropapaveroline into the brain caused normally alcohol-avoiding animals to choose alcohol in moderate doses. Later Myers and colleagues (27) reported similar effects in monkeys. There is also evidence that TIQs are produced spontaneously in the brain.

These findings have led to the hypothesis that excessive drinking by humans could be caused by metabolic abnormalities that result in excessive production of TIQs. If this hypothesis is correct, it is reasonable to think that at least some of these abnormalities could be genetic, and that inherited propensity to become alcoholic might also be due to genes that cause overproduction of TIQs.

Hypotheses on Alcohol as a Reinforcer

Depending on the circumstances, alcohol can either depress the central nervous system or excite it. While most earlier studies focused on its depressive effect, scientific attention in recent times has turned to its excitatory effect. Many investigators now believe that alcohol is sought more for its excitatory actions, and that humans (and animals) drink alcohol because these excitatory effects are rewarding. In psychological terms, alcohol is "reinforcing"—it makes people "feel good."

Like all psychological phenomena, reinforcement has underlying neurochemical mechanisms. Most researchers agree that alcohol is a reinforcer, that its reinforcement arises from specific mechanisms within the brain, and that these mechanisms, which constitute the brain's reward system, are probably located in a specific cluster of nerve cells.

Several researchers have studied the reward system and have implicated certain brain neurochemicals in the reinforcing properties of alcohol. Alcohol may make many people "feel good" because it alters the levels of the neurotransmitters dopamine and norepinephrine, as well as opiate peptides, in a specific brain region. Subjectively, these neurochemical changes are experienced as excitation, and because that experience can be pleasurable, both people and animals will seek alcohol again.

In view of the neurochemical basis of reinforcement, it seems very likely that an individual's genetic predisposition to alcoholism could be

due to inheritance of neurochemical mechanisms in the brain's reward center that are abnormally responsive to alcohol. Such individuals may become alcoholic because alcohol is abnormally stimulating and abnormally rewarding to them.

MARKERS OF INHERITED SUSCEPTIBILITY TO ALCOHOLISM

Studies of human alcoholic families, together with animal breeding experiments, leave little doubt that heredity plays a very important role in determining an individual's susceptibility to alcohol abuse and alcoholism. By itself, however, such knowledge has little practical application in the prevention of alcoholism. The urgent need is to identify specific genetically based physiological or biochemical markers that show unequivocally the existence of an inherited susceptibility to alcohol abuse.

The search for such markers is now a very active area of research and involves many laboratories worldwide. The search is based on the genetic concept of *pleiotropy*, the ability of a single gene to affect more than one visible or measurable characteristic. Since alcoholism is a complex disease probably involving many such genes, a genetic makeup that predisposes an individual to become alcoholic should be manifested in many ways that can be measured in the laboratory, even if the ultimate manifestation—problem drinking or alcoholism—has not yet developed.

Investigators are examining a number of physiological and biochemical factors that may indicate predisposition to alcoholism, including brain waves, enzymes involved in alcohol metabolism, and blood levels of alcohol metabolites.

Neurophysiological Markers

Alcohol has marked effects on the nervous system and behavior, although these effects vary greatly among individuals, possibly for genetic reasons. It has begun to seem plausible that the genetic susceptibility to alcoholism might be expressed in alterations in certain neurobehavioral functions that can be measured in the laboratory. If this hypothesis is correct, a powerful new tool for early detection and prevention could become available. Appropriate tests of brain function could allow potential alcoholics to be identified and counseled before heavy drinking started.

Scientists exploring this new area of research are coming up with very encouraging findings. Neurophysiological techniques are producing evidence that supports the importance of genetic factors in the development of alcoholism, as well as the hypothesis that appropriate

measurements can identify individuals at risk even before they take their first drink.

Brain Wave Studies

The event-related potential (ERP) technique was recently used by Drs. Helen J. Neville and Albert L. Schmidt at the Salk Institute, San Diego, in NIAAA-supported research comparing electrical phenomena in the brains of nonalcoholic young men with or without a family history of alcoholism (28). In the ERP technique electrodes are attached to the scalp to detect, amplify, and characterize electrical events in the brain that result from different sensory stimuli or specific mental processes.

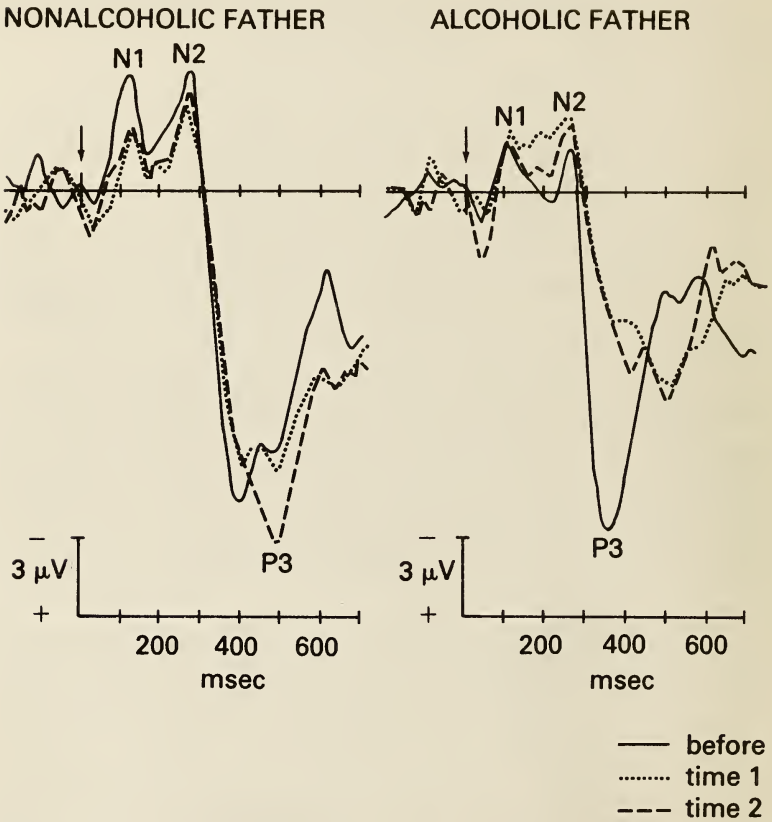
Half of the 30 subjects had fathers who were judged to be alcoholic; the other half had no family history of alcoholism. ERPs were recorded during a vigilance task that required a subject to press a button in response to short tones that occurred very rarely. The recordings, made before and after ingestion of either alcohol or a placebo, revealed significant differences in brain electrical activity—notably a feature called the P3 wave—in the two groups, whether alcohol was administered or not (figures 2a and 2b).

Several other studies using such electrophysiological techniques have also revealed peculiar and apparently genetically based electrical phenomena in the brains of people at risk for alcoholism. Drs. Henri Begleiter and B. Porjesz of the Department of Psychiatry, College of Medicine of the State University of New York, Brooklyn, have published several studies in this area with research support from the National Institute on Alcohol Abuse and Alcoholism.

In a recent paper (29) Drs. Begleiter and Porjesz report on their investigation of the possibility that the sons of alcoholics show brain aberrations that are present before any exposure to alcohol. The two investigators compared 25 boys, aged 7-13 years, who were sons of alcoholic fathers, and a matched group of boys with no familial history of alcoholism. None of the boys in either group used alcohol or drugs.

They found that the P3 wave had a markedly reduced amplitude in these young sons of alcoholic fathers. This discovery is especially significant in view of other research that shows marked alterations of the P3 wave in the brains of abstinent alcoholics and in young adult men whose fathers were alcoholic. The investigators are now searching for a possible cluster of neurophysiological alterations in children at high risk for alcoholism.

Figure 2a: *Alcohol Administration*—ERP



Nonalcoholic sons of alcoholic fathers have different brain wave patterns. Event-related potentials—electrophysiologic phenomena in the brain associated with sensory stimuli or specific mental processes—have been found to differ significantly in the sons of alcoholic and nonalcoholic fathers. The 30 subjects in the study were normal young men who were moderate social drinkers. Half of the subjects' fathers were judged to be alcoholic based on loss of employment or broken marriage due to excessive drinking. The other half had no family history of alcoholism.

Figure 2a. Striking differences were found in the amplitude and shape of the P3 wave in the two kinds of subjects after administration of an alcohol dose (0.56 grams/kilogram body weight). Alcohol produced an immediate and substantial reduction in P3 amplitude in the sons of alcoholic fathers that persisted at least 30 minutes (right side of figure). In contrast, there was only a slight reduction in P3 amplitude in the sons of nonalcoholic fathers.

Figure 2b: *Placebo Administration*—ERP

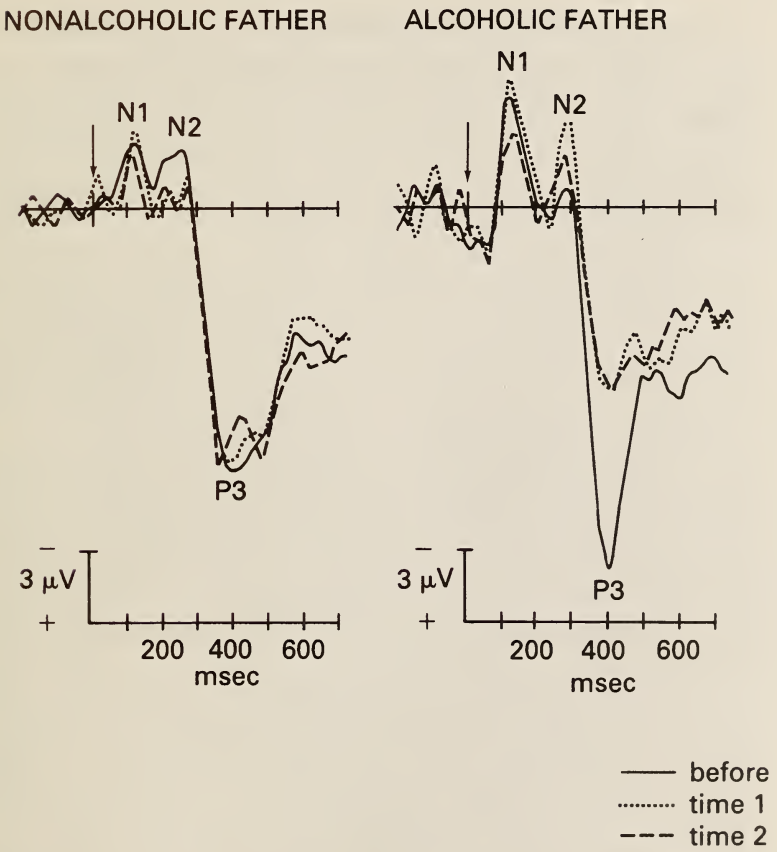


Figure 2b. Differences in P3 amplitude response also were found in the sons of alcoholic and nonalcoholic fathers when alcohol was expected but a placebo was administered instead. Mere expectation of receiving alcohol immediately caused a large reduction of P3 amplitude in the sons of alcoholic fathers that persisted at least 30 minutes (right side of figure). Alcohol expectancy produced no significant change in P3 amplitude in the sons of nonalcoholic fathers (left side of figure).

(Source: Elmasian, R.; Neville, H.; Woods, D.; Schuckit, M.; and Bloom, F. Event-related brain potentials are different in individuals at high and low risk for developing alcoholism. *Proceedings of the National Academy of Sciences, U.S.A.* 79:7900-7903, 1982.)

Studies of Neuromuscular Coordination

A number of studies have shown an association between disturbances in the regulation of movement by the nervous system and increased risk for developing alcoholism. For example, patients with a condition called essential tremor are more likely to have a history of alcoholism, and relatives of alcoholics are more likely to have a tremor disorder than relatives of nonalcoholics (4).

Hyperactivity is also associated with the risk for alcoholism. Hyperactive children are more likely to have an alcoholic biological father, hyperactive teenagers are more likely to abuse alcohol, familial alcoholics report more symptoms of hyperactivity during their childhood, and signs of hyperactivity have been observed in children who eventually became alcoholic (4).

Another condition associated with risk for alcoholism is static ataxia, characterized by impaired ability to maintain equilibrium while standing. In late 1984, Andrea Hegedus and colleagues at the University of Pittsburgh School of Medicine reported findings from their NIAAA-supported study comparing static ataxia in the sons of alcoholic fathers and the sons of nonalcoholic fathers who were either normal or suffered from depression (30). The boys in all three groups were 12–13 years old.

The investigators found that static ataxia was significantly more prevalent among the sons of alcoholic fathers than among boys in the other two groups. There was no difference, however, between the sons of normal fathers and depressive fathers, which indicates that the increased ataxia in the sons of alcoholics cannot be merely the consequence of living in a home with a psychiatrically disturbed parent. The investigators conclude that static ataxia may be a biological marker for alcoholism susceptibility.

Enzyme Markers

An individual whose body produces a variant of ADH or ALDH that causes acetaldehyde to accumulate can be said to have a genetic marker—in this case a genetic marker of relative *non*susceptibility to alcoholism. As stated earlier, this is fairly common among Orientals.

While it is useful to be able to identify enzyme variants that are markers of genetic resistance to alcoholism, the search for reliable markers of genetic susceptibility among the variant forms of ADH and ALDH continues. Some recent advances in this area are described below.

Genetic Variations in Human Alcohol Dehydrogenase

At least 20 different forms of human ADH have been discovered in recent years. These variant ADHs, called isozymes, are all similar in that they consist of two protein subunits and have about the same molecular weight. They differ, however, in details of molecular structure that affect the rate at which they convert alcohol to acetaldehyde. On the basis of their electrophoretic properties (i.e., the rate at which they will move when subjected to an electrical current), the 20 human ADH variants have been grouped into three broad classes, Class I, Class II, and Class III. Class I ADH includes three closely related ADH molecules, which have been termed alpha-ADH, beta-ADH, and gamma-ADH. Until recently, the existence of alpha-, beta-, and gamma-ADH was based only on electrophoretic evidence.

An NIAAA-supported molecular genetic analysis of the Class I ADH genes by collaborating scientists at two campuses of the University of California (31) has now confirmed the existence of these three distinct molecular types of Class I ADH. Drs. Gregg Deuster, G. Wesley Hatfield, and Moyra Smith used sophisticated molecular biology methods to show the molecular distinctiveness of alpha-, beta-, and gamma-ADH. Their analysis also suggests that all three ADH genes probably are located on the same chromosome and have evolved by successive duplication of a primordial gene. ADHIndianapolis is an example of one of the 20 variant forms of alcohol dehydrogenase discovered in humans (32–34). It gets its name from the locality where it was first discovered, by NIAAA-funded scientists at the Indiana University School of Medicine. ADHIndianapolis was found in 29 percent of liver specimens from Black Americans. So far, it has not been found in Whites.

Other variants of ADH have been found among Orientals. About 80-90 percent of Japanese studied, for example, have either ADH2 2-1 or ADH2 2-2, which differ structurally and functionally from the ADH found predominantly in Caucasians (ADH2 1-1). These Oriental ADH variants convert alcohol to acetaldehyde much more rapidly than the ADH variants found in Caucasians, perhaps contributing to the flushing reaction so common among Orientals.

Genetic Variations in Acetaldehyde Dehydrogenase

Scientists at the City of Hope Research Institute, Duarte, California, are among several alcohol researchers examining molecular differences in acetaldehyde dehydrogenase in Orientals and Caucasians. Drs.

Akira Yoshida, Gordon Wang, and Vibha Dave, of the Department of Biochemical Genetics, recently reported the results of their comparison of molecular properties of ALDH in the livers of Caucasians and Japanese (35). The livers, obtained at autopsy, included 10 from Japanese persons and 4 from Caucasians. Among the 10 Japanese livers, 5 had only half the amount of ALDH activity of Caucasian livers. The results are explained on the basis of the existence of two major forms of the enzyme: ALDH1 and ALDH2. In the five Japanese livers deficient in ALDH activity, only the ALDH1 type was present as an active enzyme. However, sensitive immunological tests revealed the presence of a protein similar to ALDH2 in these five livers, but lacking in enzyme activity. The investigators believe that a mutation of the gene controlling the production of ALDH2 in such individuals is responsible for the presence of an inactive form of ALDH2, resulting in only half the normal amount of ALDH activity, and all of it due to ALDH1. Three other Japanese livers were found to have functional forms of both ALDH1 and ALDH2, but the ALDH2 in these individuals lacked full activity. These individuals were judged to be heterozygous for genes controlling the production of ALDH2; that is, half of the ALDH2 molecules in these individuals were inactive.

In summary, this study has revealed three genetic patterns of ALDH that help determine sensitivity to alcohol: functional ALDH1 and ALDH2 both present (predominantly Caucasians); functional ALDH1 and nonfunctional ALDH2 (some Japanese); and functional ALDH1 and only partly functional ALDH2 (some Japanese).

CONCLUSION

The evidence for genetic mechanisms in some forms of human alcoholism is compelling. It is important to realize, however, that even if heredity is involved in alcoholism it is no cause for adopting a fatalistic attitude. Environment is also involved, and while we cannot alter our own heredity, we can alter our environments. A proper environment or an appropriate intervention can prevent milieu-limited alcoholism despite the existence of a genetic component, and even if the more serious male-limited form of hereditary alcoholism cannot be prevented, it can at least be mitigated by environment or intervention.

Knowledge that alcoholism has both genetic and environmental components can have important practical applications. Prevention of alcohol abuse and alcoholism would certainly be one important application of this new and growing knowledge. If reliable biological indicators of alcoholic predisposition can be found, then individuals who have those indicators can know the unique risks they face and can make informed choices about drinking.

Another practical application is improved treatment. It is already clear, partly from genetic studies, that alcoholism is not a single disease entity. By clarifying the nature of subcategories of alcoholism, genetic studies can point the way to more specific and more effective therapies based on fundamental mechanisms and the genetic uniqueness of individuals.

Future Research

The consensus among alcohol scientists is that research in the field of alcoholism genetics will proceed on the two broad fronts already described in this report:

1. Population studies to detect hereditary patterns of alcoholism, as with the Swedish adoptees, will no doubt be extended to other groups for which adequate family history records are available. Eventually, such studies may identify several new subcategories of inherited predisposition.
2. Laboratory researchers in the alcohol field will be guided increasingly by a genetic perspective, and this will sharpen their search for specific physiological and biochemical traits that are strongly associated with inherited predisposition to alcoholism. The identification of these associated traits will in turn lead to productive mechanistic hypotheses and theories

on how genetic variations at the molecular and cellular levels become expressed as uncontrollable drinking by the whole organism.

Both approaches are needed. They are also mutually supportive, so we should expect to see increasing cooperation between population geneticists and laboratory scientists in the alcohol field.

The Case for Optimism

Only 10 years ago, Jack H. Mendelson, a prominent alcoholism specialist at Harvard University, wrote this discouraging summation of existing knowledge about the causes of alcoholism:

> No specific biologic, psychologic, or social variable has been shown to have high predictive value for determining which individuals are at high risk to develop and sustain problem drinking behavior. There are no known psychologic tests which can reliably differentiate alcohol abusers from normal drinkers. Many theories have purported to explain the causation of alcoholism in terms of psychodynamic factors, personality profiles, psychosocial developmental and growth characteristics, nutritional idiosyncrasies, allergic disorders, and specific and nonspecific metabolic derangements. To date, none of these theories of the causation of alcohol abuse or alcohol addiction have significant support from well-controlled laboratory and clinical investigations . . . The contribution of specific genetic and environmental factors which may enhance the risk for development of alcohol-related problems has not been clarified.(36)

The "state of the art" in alcohol research has improved tremendously since that was written. The contribution of genetic and environmental factors that enhance the risk for developing alcohol-related problems has now been greatly clarified by the Swedish adoption studies. A number of very promising biochemical and physiological markers of risk have also been identified — including genetic enzyme variants, variations in membrane phenomena in the central nervous system, and characteristic patterns of electrophysiological functioning in the brains of people at risk of alcoholism. Finally, excellent animal models of inherited alcoholism are now available, and they will greatly facilitate the search for reliable markers of susceptibility, understanding of the fundamental mechanisms responsible for alcoholism, and the design of specific pharmacological interventions to prevent it and treat it.

These developments in alcoholism genetics, most of which have

occurred only in the past 10 years, have laid the groundwork for dramatic advances in the coming decade.

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