Genetics and Biological Markers of Risk for Alcoholism

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Synopsis.....................................

Substantial scientific evidence has accumulated that both genetic and environmental factors predispose the development of alcoholism in certain individuals. Evidence has accumulated to indicate that alcoholism is a heterogeneous entity arising from multiple etiologies. The demonstrated role of genetics in increasing the risk of alcoholism has promoted the search for biological markers that could objectively identify individuals who are genetically predisposed to alcoholism. Identifying such markers could allow for early diagnosis, focused prevention, and differential and type-specific treatment of alcoholism. Promising markers have been provided by research in electrophysiology, endocrinology, and biochemistry. Recent advances in molecular genetics are offering prospects for direct analysis of the human genome to determine elements that provide predisposition to, and protection from, alcoholism. Recent advances in research and new knowledge gained by the alcoholism treatment community and the lay public are helping to diminish the societal damage caused by alcohol abuse and alcoholism and to change prevailing attitudes about them.

THE DEBATE about whether "nature" or "nurture" is the prime determinant of risk for alcoholism continues to consume substantive energy and resources (for example, *Traynor and McKelvry v. Turnage*, argued in the Supreme Court of the United States) (*1*). However, behavioral genetics research long ago provided the means to examine the relative contributions of genetics and environment to behavioral differences among individuals (*2*). The application of these techniques to the study of human populations has demonstrated that both the environment (nurture) and inherited factors (genetics, or nature) play a role in predisposing a person to alcoholism.

In the 19th century, Sir Francis Galton studied the relative contribution of the environment and inherited factors in determining human behavior. His conclusions (*3*) that "nature prevails over nurture" when one studies a particular stratum of a population have met considerable resistance because these conclusions have, at times, been generalized indiscriminately to many questions on the determinants of behavior.

The formula $Vp = V_G + V_E$ states that the "phenotypic variance" (Vp), or the range of characteristics of individuals in a population, is the *sum* of the environmentally determined variance (V_E) in the characteristics and the genetically determined variance (V_G) in the characteristics (*2*). That is, both environment and genetics are involved. This formula does not indicate the relative contributions of environment and genetics in determining a particular phenotype—for instance, alcoholism. Relative contributions must be determined by experiment.

Familial Factors

The hypothesis that genetic factors have a role in alcoholism is based on observations that alcoholism runs in families. Cotton surveyed the literature on the families of 6,251 alcoholics and 4,083 families of nonalcoholics (*4*). The most striking finding of the survey was that "regardless of the nature of the population of non-alcoholics studied, an alcoholic is more likely than a non-alcoholic to have a mother, father or more distant relative who is an alcoholic." A similar conclusion was reached by Goodwin (*5*) in an earlier review of family studies of alcoholism.

The literature on families of alcoholics also demonstrates the relatively consistent finding that other forms of mental illness such as schizophrenia and other major psychoses are not found at higher

frequencies in families of alcoholics compared with the general population (4, 5). Although a number of studies have indicated that depression and psychopathological features are more frequently observed in relatives of alcoholics than in nonalcoholic families, the incidence of alcoholism was found to be higher than any other form of mental illness in families of alcoholics.

The available data on the families of alcoholics support the contention that alcoholism runs in families, but the data are not sufficient to conclude that genetic factors play a role in the etiology of alcoholism. The social system of the family may be an important and possible overriding determinant in the development of alcoholism. Kaufman (6), who summarized the family system variables that are important in the genesis of alcoholism, concluded that a search for a simple model of an alcoholic family is not realistic and that more complex interactive models are needed to describe the determinants of alcoholism. The needed interactive variable may be genetics.

Studies of identical (monozygotic, or MZ) and fraternal (dizygotic, or DZ) twins and adoption studies are needed to develop such models and to quantify the genetic and environmental contributions to individual differences in behavior. In one of the earliest completed studies, Kaij (7) examined 174 sets of twins and demonstrated that the concordance rate for alcoholism was 71 percent in MZ twins, but only 32 percent in DZ twins. A later study by Hrubec and Omenn (8) again demonstrated a significantly greater concordance for alcoholism in MZ twins than in DZ twins. In this study, 26 percent of MZ twins but only 12 percent of DZ twins were concordant for alcoholism. Although there remains some controversy in the area of twin studies of alcoholism (see, for example, an editorial by Gurling (9)), most studies support the hypothesis that genetic factors make a significant contribution to the etiology of alcoholism.

Studies of twins have been used to assess whether a person's physiologic (for example, electroencephalographic (EEG)) responses to ethanol, similarities in drinking patterns, and the metabolism of ethanol by a person are in part under genetic control (10–12). Such studies have further demonstrated that genetic factors play an important role in individual responses to alcohol, alcohol metabolism, and drinking patterns, as well as in the development of alcoholism. The contribution of environmental variables to producing similarities or differences between twins depends in great part on the measure being studied. Thus, MZ twins demon-

'The studies of the molecular genetics of alcohol and aldehyde metabolizing enzymes provide the first opportunities to use molecular probes of the human genome as markers of predisposing factors as well as protective factors in alcoholism.'

strate almost identical EEG responses to alcohol, while the concordance values for drinking patterns and alcoholism in MZ twins indicate a substantive contribution of environmental variables, as well as genetics, to the twins' characteristics.

The interaction of genetic and environmental factors in the development of alcoholism can also be studied by comparing individuals who have been adopted soon after birth with those who have been raised by their biologic parents. Such adoption studies have focused on the development of alcoholism in subjects whose biologic parents are alcoholics and who are raised by their natural parents or by adoptive families in which there is no alcoholism. These studies also have examined children born to nonalcoholic parents and raised in their own or foster nonalcoholic families. The most detailed and extensive adoption studies have been conducted by Cloninger and coworkers (13). These studies agree with the earlier work of Goodwin (14) and demonstrate that (a) adopted sons of alcoholic biologic parents are four times more likely to become alcoholic than adoptees whose biologic parents were not alcoholic; (b) sons of alcoholic biologic parents are more likely to be classified as alcoholic at an earlier age than their peers; and (c) daughters of alcoholic fathers, although not demonstrating a greater incidence of alcoholism, exhibit a high incidence of somatic anxiety and frequent disabling physical complaints.

Further analysis of the data collected by Bohman (15) demonstrated that the population of alcoholics being studied could be segregated into two prototypic groups. Both groups were characterized by the severity of their problems with alcoholism (for example, age of onset, violence associated with drinking, and attitude toward drinking) and, more recently, by personality traits (for example, novelty seeking) (16). The adoption studies are therefore notable not only for substantiating a genetic contribution to the development of alcoholism, but also

Heterogeneity of Alcoholism: Distinguishing Characteristics

Distinguishing features	Type 1 alcoholism	Type 2 alcoholism
Characteristics of biological parents:		
Father	Minor alcohol abuse; Minor legal encounters	Severe alcohol abuse; Serious legal encounters
Mother	Mild alcohol abuse; Minor legal encounters	No alcohol abuse; No legal encounters
Postnatal environmental characteristics		
	Determines frequency and severity of alcoholism in susceptible sons	No influence on frequency, but may influence severity
Severity of alcoholism		
	Usually isolated, less severe problems, but may be severe	Usually recurring, moderate to severe problems
Characteristics of alcohol-related problems:		
Usual age of onset	After 25 years	Before 25 years
Spontaneous alcohol seeking (inability to abstain)	Infrequent	Frequent

Distinguishing features	Type 1 alcoholism	Type 2 alcoholism
Characteristics of alcohol-related problems: (cont'd.)		
Fighting and arrests when drinking	Infrequent	Frequent
Physiological dependence (loss of control)	Frequent	Infrequent
Guilt and fear about alcohol dependence	Frequent	Infrequent
Personality characteristics:		
Novelty seeking	Low	High
Harm avoidance	High	Low
Reward dependence	High	Low
Relative risk in genetically predisposed sons		
	Two times, with postnatal provocation; No difference without postnatal provocation	Nine times, regardless of postnatal environment

NOTE: Relative risk is the ratio of the risk of alcoholism in congenitally predisposed sons to the risk in others. A relative risk of 1 means there is no difference in risk of alcoholism between congenitally predisposed sons and others.
SOURCES: References 13, 16, and 54.

for underscoring the fact that alcoholism, as defined by current psychiatric criteria (17), is a heterogeneous entity that probably involves a number of genetic as well as environmental factors.

A compilation of the distinguishing features of the two types of alcoholism described by Cloninger and coworkers (13) is shown in the box. Cloninger has cautioned (16), however, that these two subgroups of alcoholics may be "polar extremes" of a continuous variable rather than "discrete disease entities."

Family, twin, and adoption studies show that the risk for alcoholism is determined by genetic factors as well as by environment. The degree of genetic contribution depends on the subtype of alcoholism being examined and on the alcohol-use trait being studied. The conclusion that there is a significant genetic component to alcoholism, as is indicated, leads to the realization that the individuals who are at greater risk for becoming alcoholic because of inherited (genetic) factors are biologically different from individuals who have few or no inherited factors that predispose them to alcoholism.

Search for Markers

This realization sets the stage for the search for "markers" to identify the individuals at increased risk for alcoholism. The markers of increased risk, or predisposition, may be the actual elements that

are mechanistically involved in the etiology of alcoholism, or they may be factors that in themselves do not predispose to alcoholism but are closely correlated with the development of alcoholism in an individual. Individual differences that can act as markers of a predisposition for alcoholism could be behavioral, physiologic, or biochemical. Given the array of possible markers, research has followed a pattern in which measurable differences between alcoholic and control subjects were initially considered as candidate markers. Clearly, differences between alcoholic and control subjects can be a result of years of alcohol consumption by the alcoholic (state markers) rather than differences associated with a predisposition to alcoholism (trait markers). Therefore, researchers have considered that a candidate trait marker either has to continue to be present during long periods of abstinence or should be present before the development of alcoholism in an individual. In certain instances, studies of animal models of alcoholism have been extremely informative in distinguishing state and trait markers.

Given the evidence that children of alcoholics are at greater risk for developing alcoholism (4, 5, 7, 8, 10–14), one would expect that the prevalence of a candidate trait marker would be significantly greater in a population of individuals who have a positive family history of alcoholism. More important, the candidate marker should predict, with a high degree of accuracy, the individuals who, when followed longitudinally, will develop alcoholism. A major caveat to be considered when assessing the utility of a candidate marker is that the probable heterogeneous nature of alcoholism may not allow for the generation of a single marker that can identify all individuals at risk for alcoholism. But even given the many difficulties and caveats, research on trait markers in alcoholism is providing some tantalizing insight into the future for the diagnosis of increased risk for alcoholism.

Physiological Markers

Measurement of brain electrical activity using scalp electrodes provides a noninvasive assessment of brain function. Two types of measurements have been commonly used in this regard. Electroencephalographic measures provide for the characterization and quantitation of the spontaneous electrical activity of the brain. Measures of evoked event-related potentials (ERPs) provide knowledge of the responses of the brain to external sensory stimuli. ERPs can be measured from a number of areas of the scalp after the delivery of a discrete sensory stimulus. Auditory and visual stimuli have been used most often in studies of alcoholics or of offspring of alcoholics.

The measurement of some of the later phases of ERPs has provided the most intriguing prospects for developing trait markers for increased risk for alcoholism. The P300 component of an ERP is a large positive deflection that occurs approximately 300–500 milliseconds after the presentation of a stimulus. The P300 component can be significantly enhanced in response to a relevant "target" stimulus presented within a series of frequently occurring nontarget stimuli. Porjesz and Begleiter (18, 19) found that P300 amplitudes were significantly diminished in alcoholics compared with control subjects when either relevant target stimuli or nontarget visual stimuli were presented. In a followup study of the alcoholic subjects during 4 months of abstinence, the subjects continued to manifest this "sensory-filtering" deficit.

The irreversible nature of the P300 deficits in alcoholics suggested that these deficits may be inherent characteristics of these subjects and may have been present prior to the onset of alcoholism. To test this possibility, Begleiter and coworkers (20) examined young (7–13 years old) sons of alcoholic fathers and control boys matched for age and socioeconomic status from families with no history of alcoholism. The experimental paradigm involved a complex visual task. When the ERPs were analyzed, the sons of alcoholic fathers were found to have a pattern of P300 response quite similar to the pattern found in abstinent alcoholics and significantly different from the P300 pattern found in sons from nonalcoholic families. Although some controversy still exists regarding the influence of task requirement (21) and the characteristics of the subject population (that is, sons of type 1 versus type 2 alcoholics) on the robustness of the witnessed deficits in P300 ERPs in sons of alcoholics, these measures have opened a fruitful area for the study of heritable markers of risk for alcoholism.

Electroencephalographic studies have also demonstrated long-lasting differences between alcoholic and control subjects. Particularly, alcoholics have been shown to manifest an excessive proportion of fast, or beta, EEG activity (22). Gabrielli and coworkers (22) also studied children of alcoholics and compared the results with those obtained from children of nonalcoholic parents. Interestingly, these investigators observed that male children of alcoholics demonstrated excessive fast EEG activity

compared with control children. Further studies focusing on EEG responses to administered alcohol in young adult children of alcoholics (23) have demonstrated that individual responses to alcohol in terms of EEG activity may be influenced by whether or not an individual is a son of an alcoholic father. The electrophysiologic studies of offspring of alcoholics, in total, provide a solid foundation for the search for markers of predisposition to alcoholism and a foundation for the search for etiological mechanisms for alcoholism.

Subjective measures of the response to ethanol have also been investigated in an attempt to identify a genetically linked trait marker for a predisposition to alcoholism. It has been reported that individuals with an alcoholic first-degree relative—that is, family history positive (FHP) subjects—showed a decreased response to ethanol compared with matched family history negative (FHN) subjects. To measure the subjective responses to consumed alcohol, subjects completed a questionnaire measuring aspects of intoxication ranging from pleasant feelings to feelings of discomfort (24). In these studies, there was no difference in the baseline mood (before ethanol administration or during placebo administration) between the two groups.

More objective measures of the response to ethanol have also been examined in FHP and FHN individuals. Static ataxia, or body sway, a measure of psychomotor performance, has been used to evaluate baseline differences between children of alcoholics and children of nonalcoholics. Static ataxia also has been used to measure differences in the response to ethanol of these groups. Measurement of static ataxia involves placing a harness around the upper body and asking subjects to stand still with their arms and feet in a particular position (usually with their arms folded across the chest or at their sides and with their feet close together) and with their eyes open or closed. The harness is attached to cords which are connected to sensors that measure lateral or anterior-posterior movement. A movement platform method has also been used to assess body sway.

In several studies, it has been found that FHP individuals show greater baseline body sway than FHN individuals (25, 26). The ability of a subject to control body sway at a given blood ethanol level has been suggested as a measure of ethanol tolerance (25). When body sway was measured after consumption of ethanol, it was found to be less in FHP than in FHN individuals. This was observed even when the subjects were matched for drinking history and were assessed at the same blood ethanol levels and even when heavy drinkers were excluded (that is, the effect of tolerance was theoretically minimized) (27). In this particular study, in contrast to earlier studies, FHP and FHN subjects were not found to differ in baseline (during placebo administration) body sway. However, the data are consistent with the hypothesis that those with a positive family history of alcoholism have a decreased psychomotor response to ethanol. Nonetheless, the possible influences of ethanol tolerance, the baseline differences between the groups, and the importance of the subtype of alcoholism being studied, need further investigation.

Endocrinological responses to ethanol in FHP and FHN individuals also have been examined. Plasma levels of cortisol and prolactin increase after ethanol is ingested, and differences in these responses, have been reported between FHP and FHN men. FHP and FHN subjects in one study, after ingesting a 0.75 ml per kg dose of ethanol, showed similar initial increases in prolactin, but prolactin levels dropped more rapidly in the FHP subjects than in the FHN subjects (28). This finding was replicated by using a design that incorporated a placebo and two ethanol doses (29). Similarly, FHP men in another study showed a decreased cortisol response after ethanol ingestion (30). As in the earlier study, subjects were carefully matched for drinking history. Consequently, their decreased response to ethanol may well be an indicator of a predisposition to alcoholism. The possible influence of prior ethanol consumption and the cortisol and prolactin responses to ethanol in defined subtypes of alcoholics, however, are factors that need further evaluation. This latter distinction is particularly important when one considers that the subjects in most of these studies are college students, and this population is not likely to include a large proportion of type 2 alcoholics.

As mentioned above, it seems likely that no one marker will be adequate to identify all individuals at increased risk for becoming alcoholic. It has been demonstrated that measurement of a combination of variables provides a better discrimination of FHP and FHN individuals (31). The most realistic goal at present would appear to be identification of the fewest number of variables that will provide the maximum specificity and sensitivity for classifying subjects at risk for developing alcoholism.

Biochemical Markers

Biochemical markers of a predisposition to alcoholism would consist of gene products, or closely

linked gene products, that predispose an individual to ethanol-related problems. It has often been assumed that a biochemical marker for a predisposition to alcoholism should be present prior to alcohol consumption. Such a marker possibly could be a biochemical variable that is altered differently by alcohol in individuals who are predisposed to alcoholism, compared with individuals who have no predisposition.

The enzyme monoamine oxidase (MAO) has been suggested as a possible marker for alcoholism or a predisposition to alcoholism. MAO is a mitochondrial enzyme involved in the metabolism of biogenic amines. There are two forms of MAO, each having different substrate specificities and inhibitor sensitivities as well as different tissue distributions. The brain, for example, contains both MAO A and MAO B, while the B form is found in human platelets. Platelet MAO activity is under genetic control (32), and low platelet MAO activity has been suggested as a marker for schizophrenia and several other psychiatric disorders, as well as for alcoholism.

In at least a dozen studies, mean platelet MAO activity has been reported to be significantly lower in alcoholics than in controls (33–35). Included are studies that evaluate from approximately 20 to 100 active or abstinent alcoholics and matched controls. However, substantial variability in MAO activity has been noted within alcoholic and control populations, leading to significant overlapping in activity between these groups. There are a number of possible explanations for such variability. A recent study, for example, demonstrated that the maximum velocity (V_{max}) for platelet MAO, but not the affinity (K_m) for substrate, was altered in alcoholics, compared with controls (34). If a single low substrate concentration is used to measure MAO activity, variability may be more prevalent.

As for all potential markers, particularly those measured in alcoholics, it is necessary to determine whether the observed difference is an effect of alcohol consumption or whether it represents an inherent characteristic of the individuals. In animal studies, little change in brain MAO activity was evident when mice or rats were fed ethanol chronically (36, 37), suggesting that MAO activity is not easily altered by prior consumption of ethanol. However, platelet MAO activity in alcoholics was found, in several studies, to fluctuate after cessation of alcohol intake (38, 39). In part, these fluctuations may be due to changes in platelet production that have been documented during intoxication and withdrawal in some alcoholics, be-

cause newly matured and released platelets have high levels of MAO activity. Such possible additional sources of variability emphasize the difficulties of evaluating genetic markers in alcoholics and also demonstrate the value of using populations such as twins or FHP and FHN individuals. In a study involving a small group of FHP and FHN men, there was a trend toward lower platelet MAO activity in the group with alcoholic relatives (35). In a more recent study, when alcoholic subjects were divided into type 1 and type 2 subtypes, it was found that type 2 alcoholics had significantly lower platelet MAO activity than controls, while the activity in type 1 alcoholics was similar to that in controls (40). In another study, it was reported that teenage boys who were abusers of multiple drugs and who exhibited personality traits consistent with type 2 alcoholism had low platelet MAO activity (41).

These data suggest that much of the variability and overlapping observed both in studies of alcoholics and control subjects and of FHP and FHN men may arise from the failure to distinguish subtypes of alcoholism. In spite of the variability, the relatively consistent finding of low platelet MAO, particularly in those individuals with a highly heritable form of alcoholism, suggests that MAO enzyme activity may be useful as a trait marker for alcoholism. The specificity of this marker to alcoholism remains to be evaluated, however, because, as mentioned earlier, platelet MAO activity may also be low in individuals with schizophrenia and other mental disorders.

Another characteristic of MAO that might be useful in distinguishing alcoholics and controls is the susceptibility of the B form of the enzyme to inhibition by ethanol in vitro. In a group of 53 alcoholics and 17 controls, matched for age, race, and socioeconomic status, inhibition of platelet MAO activity by ethanol was found to be significantly greater in alcoholics than controls when a high substrate concentration was used to assay MAO activity (33). The difference was not associated with race, smoking, or illicit drug use, and there was no significant correlation with age, duration of problems with alcohol, or time since the last alcoholic drink. The latter data suggest that the difference in the properties of MAO is not a reflection of chronic ethanol consumption, but may be an inherent characteristic of alcoholics.

Adenylate cyclase (AC) is another enzyme localized in platelets and lymphocytes that has recently been investigated in alcoholic subjects. This enzyme is activated by hormones and neurotransmitters and

catalyzes the conversion of adenosine triphosphate (ATP) to the ubiquitous intracellular "second messenger," cyclic $3',5'$-adenosine monophosphate (cyclic AMP). In a study of 94 male alcoholics and 31 matched controls, basal (unstimulated) platelet AC activity was the same, but stimulation of AC by fluoride, guanine nucleotides, and prostaglandin E_1 was significantly lower in the platelets of alcoholics than in the platelets of controls (33). As for the inhibition of MAO activity by ethanol, lower fluoride-stimulated platelet AC activity was not associated with smoking, race, or illicit drug use and was not significantly correlated with the duration of problems with alcohol or time since the last consumption of alcohol. In fact, in this study, platelet AC activity was lowest in alcoholic individuals who had reportedly abstained from alcohol for 1–4 years. The data suggest that low platelet AC activity could be a genetically influenced characteristic of alcoholic subjects. Discriminant analysis, using the values for ethanol-inhibited MAO activity and fluoride-stimulated AC activity, was able to provide correct classification of 75 percent of alcoholics and 73 percent of controls.

A more recent analysis of platelet AC activity involved a group of Swedish male alcoholics and controls. The results indicated that fluoride- and guanine nucleotide-stimulated AC activities were again significantly lower in platelets of alcoholics than in platelets of controls, and a significant *negative* correlation was found between fluoride-stimulated AC activity and time since the last consumption of alcohol. These findings again suggest that lowered platelet AC activity is not a reversible effect produced by chronic ethanol consumption. Furthermore, in these individuals, there was a significant effect of hereditary factors on platelet AC activity, in that activity was lowest in individuals who had a higher number of alcoholic first-degree relatives (42). It has also been reported that in Japanese alcoholics, *in vitro* stimulation of platelet AC activity by ethanol was lower than in controls, and this difference was not reversed at 4 weeks after withdrawal (43).

Overall, the data suggest that platelet AC characteristics may represent a trait marker for predisposition to alcoholism. The actual site of this marker may be G_s, the guanine nucleotide-binding protein that couples receptors to AC, because stimulation of AC by a number of agents acting via G_s is reduced in platelets of alcoholics. It has also been reported that adenosine-stimulated AC activity is lower in *lymphocytes* of alcoholics compared with controls (44), and there is a preliminary report of decreased guanine nucleotide-stimulated AC activity in lymphocytes of alcoholics (41). When lymphocytes from alcoholics were grown, *ex vivo*, in culture, they recovered their responsiveness to adenosine and had higher cyclic AMP levels than cells from controls. However, the cultured lymphocytes from alcoholics continued to be much more sensitive to the effect of ethanol in vitro than lymphocytes from control individuals (46). Studies with lymphocytes have, therefore, provided further evidence that differences in AC activity may represent an inherent characteristic of the cells of alcoholic subjects.

In addition to the study of specific enzyme activities that may reflect a predisposition to alcoholism, some attempts have been made to link the predisposition to alcoholism with other characteristics that are known to be inherited. For example, a significantly higher phenotype frequency of HLA antigen (human leukocyte antigen) CW3 was found in chronic alcoholics than in controls; this difference became even more distinct when alcoholics were subdivided according to whether they had liver disease (the CW3 phenotype frequency was higher in individuals with liver disease) (47). HLA antigens are proteins on the surface of cells that identify a tissue, and they are coded for by genes on chromosome 6. Another type of linkage was suggested in a study of 11 serological markers in alcoholics. In the original study of alcoholics and their nonalcoholic first-degree relatives, associations were reported between alcoholism and two blood groups, as well as a serum protein (48). A more recent preliminary report on 30 families in which alcoholism was segregated also included a reanalysis of the earlier data and revealed a linkage with the MNS blood marker, which is coded for by a gene on chromosome 4. Another locus (GC) on chromosome 4 also gave some evidence of linkage (44).

Such linkage studies require a careful choice of subjects and are still in the early stages. However, in combination with other types of research, they may eventually provide important information on the locus of genetic material associated with a predisposition to alcoholism.

Although the bulk of this review has centered on markers for predisposition to alcoholism, it has become clear over the past several years that the development of alcoholism involves an interplay between positively predisposing factors and factors that may produce an aversion to alcohol and thus protect an individual from becoming an alcoholic. An example of such a protective factor may be the

inherited inability of some individuals to metabolize acetaldehyde, which is produced from ingested alcohol. The adverse physiologic responses of these individuals to the elevated levels of acetaldehyde in the circulation may act to diminish alcohol consumption.

A variant in human liver aldehyde dehydrogenase was described in the early part of this decade (50). More recently, molecular genetic studies have demonstrated a structural mutation in certain individuals in the gene coding for a human aldehyde dehydrogenase that has a high affinity for acetaldehyde (51). This structural mutation leads to a loss of the enzyme's ability to oxidize acetaldehyde. Population studies (52) have shown that the mutant enzyme and the diminished ability to metabolize acetaldehyde are prevalent among the Mongoloid populations (for example, approximately 44 percent of the Japanese exhibit the aldehyde dehydrogenase deficiency). The increased levels of circulating acetaldehyde after ethanol ingestion in subjects with an aldehyde dehydrogenase deficiency and the resultant flushing and other noxious consequences of acetaldehyde toxicity may be determinants of a lower incidence of alcoholism among Orientals. Goedde and Agarwal (53) have indicated that the frequency of the deficient aldehyde dehydrogenase phenotype in alcoholics in treatment programs in Japan is much lower than the frequency of this phenotype in the normal population or in patients in treatment for other mental illness. The studies of the molecular genetics of alcohol and aldehyde metabolizing enzymes provide the first opportunities to use molecular probes of the human genome as markers of predisposing factors as well as protective factors in alcoholism.

The scientific investigation of markers for ascertaining the risk of developing alcoholism is growing rapidly. Behavioral, physiologic, biochemical, and molecular genetic indicators of predisposition are being developed. The advances in this area have a multitude of implications beyond the obvious utility of being able to identify more accurately people at risk. The demonstration of the presence of biologic markers of predisposition should clearly promote the acceptance of the role of biology and genetics in the development of alcoholism. The availability of such markers should allow for swifter progress in elucidating the etiology of various forms of alcoholism. Differential diagnosis with the use of markers can provide for specifically focused treatment programs and circumscribed and directed prevention efforts.

The beneficial aspects of research on markers for predisposition to alcoholism, however, have to be matched by progress in a number of related areas for the full potential of this work to be realized. Destigmatization of alcoholism is a necessity, and the conceptualization of alcoholism as a moral weakness should no longer be accepted. Research on effective treatment and prevention modalities needs to be accelerated.

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