Biological Markers for Alcoholism: A Vulnerability Model Conceptualization

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Although the title suggests that biological factors are of central importance to the present discussion, we do not wish to ignore the psychosocial or sociocultural contributions to the development of alcoholism. There appears to be a clear need to merge biological and psychosocial theories of alcoholism to fully understand the complex phenomenon which we recognize as alcoholism. Consequently, we have been led to merge these rather diverse etiological theories by proposing a vulnerability model for alcoholism (Hill, 1981). The vulnerability model is not new in the area of psychopathology. In fact, Zubin and colleagues have proposed such a model for conceptualizing a multitude of factors that appear to be responsible for the development of schizophrenia (Magaziner & Steinhauer, 1983; Zubin & Spring, 1977; Zubin & Steinhauer, 1981).

Although the vulnerability model proposed here is a new one, the idea that there is a "vulnerability" to alcoholism was first suggested by Jellinek in 1960. Jellinek hypothesized that each individual is endowed with "psychological vulnerability" to alcoholism. Although every individual has this vulnerability, widely varying degrees of vulnerability may be seen. Jellinek's model was an important step, viewing alcoholism as it did as a result of both cultural factors and factors within the individual. Antecedents of the vulnerability models can be found in the diathesis-stress models promulgated by Meehl (1962), Rosenthal (1970), Falconer (1965), and Slater and Slater (1944). Zubin (1963) first formulated his version of the model at about the time Meehl's seminal articles appeared. Jellinek may have been influenced by these models, in his attempt to apply the model to alcoholism.
While Jellinek termed these individual differences in risk for developing alcoholism "psychological vulnerability," his formulation did not speculate about the particular conditions that might produce greater psychological vulnerability; the internal milieu of the individual prone to alcohol problems remained elusive and essentially a "black box." This was in part because the search for biological markers had hardly begun 25 years ago. Obviously, within the "black box" one can place a variety of predisposing variables which are biological in nature and which may include biochemical, genetic, and neurophysiological factors. Impinging on the "black box" are a variety of psychosocial and sociocultural factors, including beliefs about alcohol's effects, cultural and familial sanctions for drinking, as well as the relative availability of alcohol to particular individuals. For example, a person who has a biological vulnerability to developing alcoholism may never express this vulnerability if he or she is raised in a culture that prohibits drinking, as is the case for individuals who are members of certain religious groups (Moslems, Latter Day Saints). Similarly, the individual with minimal biological vulnerability may, nevertheless, develop alcohol abuse or alcoholism in environments where alcohol is freely available and the norm for excessive drinking is present. The high rate of alcohol and drug problems seen among military personnel during the Vietnam War typifies such a situation. Of particular interest was the fact that those who continued to have problems when they came back to the United States were those having a family history of alcoholism or drug abuse problems (Robins, Helzer, & Davis, 1975).

Our present conceptualization is depicted in Figure 1, and is intended as a pictorial representation of some of the central concepts of a vulnerability model. By emphasizing both the biological and psychosocial
will undoubtedly alter the biological vulnerability of the individual--
a drink having more reward value because of its capacity to act temporarily
as a sedative.

It is important to compare the present vulnerability model for alcoholism
with the vulnerability model for schizophrenia as conceptualized by Zubin
and colleagues. In the model for schizophrenia, vulnerability is not
specified as either biological or psychosocial but rather is seen as a
general vulnerability that is constant throughout life. Psychosocial factors
are conceived of either as producing acquired vulnerability or as trigger-
ing events for the onset of episodes. In the present model, psychosocial
variables are similarly seen as potential triggering conditions for an
episode of heavy or abusive drinking. Unlike schizophrenia, development
of alcoholism requires an eliciting agent, exposure to alcohol. Therefore,
in the case of alcoholism, it is necessary to also consider psychosocial
or sociocultural conditions which may be conceived of as psychosocial
vulnerability factors.

For example, in most Western societies women tend to drink less than men.
Evidence has been presented suggesting this difference exists in all cultures.
Horton (1943), reporting on drinking customs of men and women in 30 cultures,
found that in 16 of these men drank more than women, in 14 they drank
equally, but in none of the cultures examined did women drink more than men.
Similarly, Child, Barry, and Bacon (1965) found sufficient information for
89 societies to classify the drinking of its members by sex. In 53, sex
differences were found, while in 36 drinking appeared to be equal, but
again, none were found in which women drank more than men. It would appear,
therefore, that women who reside in cultures that do not sanction drinking
might have a different psychosocial vulnerability for developing alcoholism than those living in more permissive cultures. It is clear that all women do not have equal biological vulnerability. That adopted daughters of alcoholic biological mothers have an increased risk for developing alcoholism (Bogman, Sigvardsson, & Cloninger, 1981) has been observed among 913 Swedish adoptees. However, it would be impossible to detect such a biological difference in cultures where psychosocial vulnerability for women is very low owing to specific prohibitions for drinking for women.

**Scientific Models of Etiology**

The foregoing scheme is an attempt to draw together the various factors that contribute to the development of alcoholism. A brief overview of the etiological models that have been suggested for alcoholism may clarify the proposed conceptualization.

The field of psychopathology, in general, has two primary types of etiological models: biological and environmental. The biological models include the factors within the individual (genetic, internal environmental, neurophysiological, and neuroanatomical), while the environmental models include factors in the field surrounding the individual (ecological, developmental, and learning models) (Zubin, Steinhauer, Day, & van Kammen, 1985). It should be borne in mind that these models are not independent but interact with all others. In the field of alcoholism, the general etiological models can be regrouped as follows: genetic, ecological, and developmental. While some might argue for giving learning theory models a separate status, there is sufficient overlap between learning theory conceptualizations and both the ecological and developmental models, as they apply to alcoholism, to include them in a single model. The neurochemical and neurophysiological models tend to lean toward the genetic, whereas the
ecological model emphasizes the environmental niche that the person occupies. From this general ecological model two specific types of environmental influences are proposed, each affecting the emergence of deviant drinking behavior: cultural influences in the form of nonfamilial environmental factors on the one hand, and familial influences on the other. Each of these models will be examined. We will begin by looking at the genetic model.

The Genetic Model

The genetic model is probably the most developed, drawing as it does on a variety of methodologies that have yielded results suggesting a genetic propensity for developing alcoholism. Though this propensity may perhaps not be both a necessary and sufficient condition, it may at least be a necessary condition for the development of alcohol-related problems. This might appear to overstate the case for genetics, given that some alcoholics appear to have a nonfamilial form (no first-degree biological relatives with alcoholism). We must remember, however, that not all individuals who carry a genotype express it.

Among the observations supporting a genetic vulnerability are greater concordance in drinking problems and in the greater similarity in quantity of alcohol consumed by monozygotic than dizygotic twins (Kaij, 1960; Partanen, Bruun, & Markkanen, 1966) and evidence from adoption studies that the risk for developing alcohol problems is elevated among adopted away offspring of alcoholics when contrasted with similar offspring of non-alcoholics (Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973). Other work using the adoption strategy has confirmed a greater risk among adoptees of alcoholic biological parentage than those without such parentage
(Bohman, Sigvardsson, & Cloninger, 1981; Cadoret & Gath, 1978). A further refinement of this methodology has included the discovery of subtypes of alcoholism varying by the degree to which environmental factors confer greater or lesser amounts of risk or protection from developing alcohol problems. Bohman et al. (1981) have proposed a "milieu limited" type of alcoholism in which the alcoholic may be characterized as having milder alcohol abuse and minimal criminality. Further, no history of treatment for alcoholism can be noted among the biological parents of such individuals. In this form, the postnatal environment is important in determining the frequency and severity of alcoholism expressed in adopted away sons of alcoholics. The other form, termed by Bohman et al. (1981) as the "male limited" type, is characterized by severe alcohol abuse, severe criminality, history of frequent treatment for alcoholism among biological fathers, but normal alcohol use in mothers. In this form, the postnatal environment does not affect the risk for developing alcohol-related problems among offspring. The "male limited" form appears to carry a greatly increased risk to relatives of index cases, a reported tenfold increase in Bohman's study and a fourfold increase in the Danish adoption study reported by Goodwin et al. (1973).

According to the genetic model, a genotype is transmitted from generation to generation either through a specific allele in a particular location on a specific chromosome, in the case of the single gene model, or through several alleles on the same or different chromosomes in the case of the polygenic model. Complicating the search for genetic markers is the fact that we presently cannot be certain about the genetic model which best describes the transmission of putative alleles. Thus, if we presume that
a single gene is responsible, specific research strategies must be utilized (e.g., use of large extended pedigrees) and appropriate steps taken to ensure that the data collected will allow for testing this possibility. Similarly, if a polygenic model is presumed to be responsible, other strategies might be indicated. The multifactorial model of transmission is one such model that tests for polygenic influences as well as environmental transmission.

Briefly stated, the multifactorial model presumes that the liability to develop a disorder is the result of genetic factors, familial environmental factors and nonfamilial environmental factors (for example, cultural factors). From this model, predictions can be made about the mode of transmission of the disorder. For example, applying the multifactorial model to data collected for alcoholic and opiate abusing probands, including the assessment of these disorders in relatives of the probands, has previously allowed us to conclude that these two seemingly similar disorders (both involving addiction) are in fact transmitted independently within families (Hill, Cloninger, & Ayre, 1977). Familial transmission is demonstrated when a disorder tends to run in families. Genetic transmission is more difficult to demonstrate.

With regard to the genetic factors involved in the transmission of alcoholism, some geneticists have suggested that perhaps the combined effects of single genes against a background of polygenic influences would best describe the observed pattern of familial aggregation seen in alcoholic families. From this assumption a mixed-model approach has been offered. That is, the combined effect of single rare genes may contribute a significant proportion of the variance in some cases whereas polygenic influences
may be more influential in others. This model would also account for the heterogeneity of phenotypes seen among alcoholics.

The Ecological Model

For some time now ecological explanations have been offered for alcoholism. The ecological model has not produced as much scientific evidence for etiology as the genetic model has, though use of an ecological framework has elucidated a number of factors clearly associated with alcoholism. For simplicity, these factors can be categorized as being of two types: familial and nonfamilial. Among those factors that might be characterized as nonfamilial environmental factors are such things as the socioeconomic status of the individual, characteristics of the social milieu, including the religious orientation of the culture he or she occupies, and the social norms of the culture or subculture that either proscribe drinking or encourage it.

Familial environmental factors may well be of equal importance. Recently a number of researchers have begun to view the family as the social unit which directs the use of alcohol, through family interaction patterns and use of alcohol within the family.

Familial environment. Wolin and colleagues have, for example, characterized families which transmit alcoholism from parents to children as differing from those families that do not, in terms of the degree to which the presence of an alcoholic in the family circle either disrupts the performance of family rituals, or owing to coping efforts of the family, appears to minimally affect the performance of these rituals, if at all (Wolin, Bennett, Noonan, & Teitelbaum, 1980). A family ritual is defined by these researchers as a "symbolic form of communication that, due to the satisfaction that
family members experience through its repetition, is enacted out in a systematic fashion over time.” Included among these “rituals” are typical behaviors displayed during holidays, mealtimes, vacations and so forth.

To evaluate the impact of drinking on these rituals, families in which an alcoholic parent was present were asked to describe in detail the families' interaction and behavior during periods preceding and following the parent's heaviest drinking. The study was designed to determine if some families protect their most cherished family rituals more effectively than others and to assess whether this has any influence on transmission of alcoholism. The authors' conclusion was that ritual protection does make a difference. Extreme ritual disruption was significantly related to increased transmission of alcoholism to children, whereas ritual protection was associated with less transmission.

In short, alcoholism can be transmitted through nongenetic means, here in the form of familial environmental factors, though of course cultural transmission can occur as well. The value of the multifactorial model of transmission, as we indicated earlier, is that it makes no assumptions about the relative contribution of environmental or genetic factors and therefore appears well suited for the task of assembling a diverse set of variables that affect transmission of alcoholism from generation to generation and ultimately making predictions about risk within and across families. Other models of transmission have also been developed that similarly assess multiple factors for the potential contribution of both genes and environment (Morton, 1974).
The Developmental Model

Studies that reflect the developmental model have focused primarily on rearing patterns of children that are associated with later adult adjustment. This work has failed to identify any particular pattern consistently associated with the development of alcoholism. Adult alcoholics have been described as experiencing minimal parental supervision as children (McCord & McCord, 1962) and as having been the target of lax or inconsistent discipline (Robins, Bates, & O'Neal, 1962). That 50% of alcoholics in treatment have an alcoholic father may explain the lenient discipline of these children who later become alcoholic noted by some. Parental alcoholism has a major impact on the children of alcoholics. Studies concerning rearing practices of nonalcoholic parents of children who later develop alcoholism are also needed to answer the question of whether or not particular rearing practices (e.g., lenient discipline) have significant developmental influence. The increased level of disruption observed in households of alcoholics may provide greater predictive power as a developmental influence than any other aspect of child rearing. More work is also needed to understand how characteristics of the social network of children of alcoholics may provide buffering effects for the child (e.g., presence of a supportive nonalcoholic friend or relative).

Other theories of how developmental influences are mediated include studies on infant care and on early separation from parents, neither of which appear to have much effect on long-term outcome for any particular psychopathology (Becker, 1964; Caldwell, 1964; Yarrow, 1964). We suspect that, on the whole, Rosenthal's (1970) observation that child rearing is
less important than genetic loading in producing psychopathology in general may hold equally true for the development of alcoholism, though certainly having an alcoholic parent produces a distinct environment for the child.

**Social learning theory.** As mentioned previously, the social learning model has gained much acceptance as an etiological explanation for alcoholism. The basic tenet of the social learning theory is that the individual learns behavior, whether deviant or normative, through cognitive mediation (Bandura, 1969). Although the behavior may be maintained by external reinforcement, classical conditioning processes, or cognitive mediation, some of this learning occurs covertly in the form of modeling. From this theory one can predict that an individual will learn to become alcoholic by modeling the behaviors of alcoholics through a system of beliefs about the effects alcohol has on functioning.

In Bandura's early work he speaks of "no trial learning," in which new behaviors are most easily acquired through modeling. If the model has particular reward value, as parents certainly do, given their early ties to the emotional rewards of the child, learning of particular behaviors is facilitated. Further, in observing the parents' style of coping, the child learns to adopt similar modes of coping albeit maladaptive, in the case of the child who emulates an alcoholic parent.

For the child in an alcoholic home, communication patterns also are salient developmental factors since these homes are often characterized by the presence of disorders in the marital relationship as well as defects in the parent-child relationship. In fact, Jones (1968) has noted that the mothers of children who later became alcoholic, appeared uninterested in the child significantly more often than mothers whose children did not
become alcoholic. Robins et al. (1962) has characterized children seen in a child guidance clinic who later became alcoholic as frequently experiencing parental cruelty or desertion and general parental inadequacy. Although the homes of these children have generally been described as inadequate, further work is needed to determine if protective factors may operate in these homes in the form of social network characteristics. For example, does the presence of one healthy parent or other supportive adult buffer the stress of living in an alcoholic household? While no one individual in the alcoholism field may readily be identified as a social learning theorist, research on the effects that beliefs have on the use and misuse of alcohol follow most closely this theoretical orientation (Marlatt, 1976).

**Personality theory.** Within this discussion of developmental theories we will include personality theories of alcoholism. Placing personality theory under the developmental model may be controversial for some, since recent studies show that at least some of the similarity in personality types within families may be under genetic control. At any rate, we have arbitrarily placed personality theory in the developmental domain for the present. As will be seen in later discussion of the vulnerability model, we view personality variables as premorbid characteristics of the individual that are orthogonal to symptomatic aspects of a particular psychopathology, whether schizophrenia or alcoholism, such that they may not "cause" alcoholism but rather may serve as moderating variables. Whether or not personality characteristics are vulnerability indicators or moderating variables is still a debatable issue awaiting further research.

Personality variables were not always accorded this role in the etiology of alcoholism. In fact the "addictive" personality at one time
was considered the primary "cause" of alcoholism and substance abuse. This view not only attributed causality to personality but did so through a univariate explanation—one single personality type. This view probably emerged from psychoanalytic theory, which viewed the alcoholic as orally fixated, first dependent on the mother's breast, then excessively dependent on others for assistance, ultimately failing to get all the reassurance desired, finally turning to the bottle.

Recent research suggests that distinct personality types exist among alcoholics. Using the Minnesota Multiphasic Personality Inventory (MMPI) Nerviano and Gross (1983) have identified seven prominent subtypes: chronic severe distress, passive-aggressive sociopath, antisocial sociopath, reactive acute depression, severely neurotic psychophysiological, mixed character dysphoria, and paranoid alienated. Two of these subtypes, the passive-aggressive sociopath and the chronic severe distress type, have been replicated in a variety of studies (Morey & Blashfield, 1981; Skinner & Allen, 1982). Moreover, these subtypes appear to be correlated with different drinking styles and drinking problems, the distressed neurotics typically being heavier drinkers with more problems than the sociopathic alcoholics who drink more moderately and have fewer detrimental consequences (Skinner & Allen, 1982). The former subtype appears to use alcohol to alleviate distress and cope with life problems, whereas alcoholics of the latter type appear to use alcohol simply because of poor impulse control.

Although a number of other personality tests exist, the MMPI has been most frequently administered clinically to alcoholic subjects. A number of MMPI profile configurations have been observed among alcoholics and certain scales appear to be more consistently elevated than others among alcoholics.
in treatment. These include elevations on Scale 4 (the Psychopathic Deviate Scale) with additional elevations on Scale 2 (Depression) and Scale 7 (Psychasthenia) (see Owen & Butcher, 1979). Elevations on Scale 4 are thought to reflect impulsivity and low frustration tolerance as well as disregard for social norms. Included in the Scale 4 elevation is a general tendency not to profit from past experience, especially negative reinforcement contingencies. The other two elevations, Scales 2 and 7, usually are taken as indicators of subjective distress, the former scale being associated with low mood, despair, and pessimism about the future whereas the latter is associated more with obsessive rumination and worry.

Particular scale elevations appear to be more characteristic of alcoholics in treatment than of prealcoholic individuals who will later become alcoholic though information is currently limited. A few longitudinal studies have been completed in which persons who later became alcoholic were assessed before the possible confounding effects of drinking were manifest. Hoffmann, Loper, and Kammeier (1974) compared MMPI protocols of alcoholics undergoing treatment with their protocols obtained when they were college freshmen. Next they compared the subjects' college protocols with those of their non-alcoholic classmates. From these comparisons they found that two of the clinical scales were elevated among the prealcoholics, Scale 4 (Psychopathic Deviate) and Scale 9 (Hypomania), suggesting that these individuals were more gregarious, impulsive, and nonconforming than their peers who did not become alcoholic. While no significant maladjustment in the form of subjective distress was seen among the protocols of the prealcoholics, onset of alcoholism produced a different picture, the alcoholics now showed clear evidence of subjective distress, manifest as elevations on both the
Psychasthenia and the Depression scales, as well as continued elevations on Scale 4.

Other longitudinal studies have suggested that the potential alcoholic or drug abuser can be identified by a constellation of traits well before they begin to use these substances. The Oakland Growth Study (Jones, 1968, 1971), a prospective study of female and male adolescents who were followed into adulthood, revealed particular personality characteristics as a function of gender. The male adolescents who later became problem drinkers were described as "undercontrolled, impulsive and rebellious," while the females were described as "self-defeating, pessimistic, withdrawn, guilty, and depressive." Others, including Jessor and Jessor (1977, 1978) and Kandel (1978, 1980), have noted that adolescents could be identified as future users of addictive substances by their independence, rebelliousness, and failure to value conventional institutions. Although the MMPI was not administered in these studies, one wonders if the constellation of traits described by these observers might be the essence of what the Psychopathic Deviate scale measures. At any rate, it now appears that certain premorbid personality characteristics may accompany later development of alcoholism.

The Search for Etiology

As is abundantly clear from the foregoing review, each model makes a unique contribution to understanding the factors that may be responsible for the development of alcoholism. Each model fails, however, to explain why one individual becomes an alcoholic and another does not. Even if alcoholism were completely determined by genetic factors, we could expect that some individuals would carry the genotype but not express the disorder because of incomplete penetrance. Clearly, there is a need to merge the various
theories and models into a super-model to adequately explain the etiology of alcoholism. We propose that a vulnerability model similar to that previously proposed by Zubin and his colleagues for schizophrenia may offer greater explanatory power when considering the diverse expression of alcohol abuse patterns and outcome. Rather than postulating that alcoholism is a disease or at least a biological condition, on the one hand, or a defect in social learning on the other, the vulnerability model attempts to incorporate relevant findings from both the biological and psychosocial domains.

Though this view may seem heretical to those accustomed to viewing alcoholism as a chronic disease state, in which the alcoholic is considered to be, lifelong, a "recovering alcoholic," we propose that alcoholism is an episodic disorder, developing in the vulnerable individual when subjected to exogenous or endogenous stressors. When the episode of drinking terminates the individual returns to his or her premorbid level of functioning. For those with good premorbid functioning, we consider the end of the episode and the return to their premorbid niche a recovery, or at least a remission. For those with poor premorbid functioning, it is difficult to know whether the effects of an episode have ended, since a return to the premorbid level still may not enable them to function as well as others. They may be mistakenly considered as persisting in their episode of drinking. However, a minority of individuals who are biologically vulnerable who undergo stressors necessarily develop episodes. In fact, some highly vulnerable individuals may never develop an episode of excessive drinking at all.

Among the moderating variables which may prevent development of an episode are: the individual's premorbid personality, characteristics of
his/her social network, and the ecological niche which he/she occupies. That not all vulnerable individuals develop episodes is illustrated in the Danish adoption study. The majority (73%) of offspring of alcoholics adopted away shortly after birth (Goodwin et al., 1973) did not develop alcoholism as adults, though of course the risk was higher among this group than in a matched control group (18% versus 5%) by age 30 when they were assessed. The moderating variables of premorbid personality, supportive (perhaps nondrinking) social networks, and favorable ecological niches may cushion the impact of the stressor so that the episode is aborted.

Recent work by Marlatt and others who have examined the features of successful relapse prevention among treated alcoholics attests to the fact that triggering events play a major role in determining whether an individual who has displayed abusive drinking will relapse or go on to be symptom free. Marlatt and Gordon (1980) suggest that most relapses can be accounted for by four situational categories. Two of the categories are interpersonal and consist of situations in which the individual feels frustrated and angry and is unable to express these feelings, or feels incapable resisting the social pressure exerted by others to drink. The remaining two categories consist of situations in which the individual experiences negative emotional states such as anxiety, depression, or boredom. These observations have led Marlatt and Gordon to propose a cognitive behavioral model of relapse in which a person's expectations of competency interact with the availability and effectiveness of coping strategies to determine the response to situations in which drinking might occur.

Our present vulnerability model assumes that alcoholism is episodic. This assumption could be challenged in the case of the chronic alcoholic
who does not achieve remission and goes on to progressively more entrenched drinking which may result in severe medical problems and sometimes death. In fact, one of the tenets of the disease model is that alcoholism is a progressive illness ending in death if not arrested once and for all. Yet recent epidemiological data suggest that not all alcoholics show a progressive course. A number of studies have examined in detail the drinking patterns of persons diagnosed as alcoholics at one point in time and followed them for periods of up to 20 years (Clark, 1974; Fillmore, 1974; Pettinati, Sugeran, DiDonato, & Maurer, 1982; Polich, Armor & Braiker, 1981; Rohan, 1975). For example, a 1980 four-year follow-up of a subsample of persons who were part of the original Rand study (Polich et al., 1981) found that 18% of their subjects were drinking without problems or symptoms of dependence. The "typical" drinking pattern appeared to be one characterized by much changing back and forth between levels of consumption. They noted that some individuals when examined at multiple points in time continued to improve, while others deteriorated, with most alternating between relatively improved and unimproved status. Similar conclusions were reached by Fillmore (1974) in her 20 year follow-up; many drinkers with numerous and severe problems were later found either to have markedly improved or to have different problems. Clark (1974) suggests: "None of this fits with the disease model of alcoholism insofar as that model implies keeping early symptoms and early problems and adding others as time passes."

The Diagnosis of Alcoholism-Implications for Scientific Breakthroughs

When Jellinek first began to classify the types of alcoholisms which he had observed in the 1940s, systematic nomenclature for psychopathology had
not been developed to the degree it has today. Jellinek's writing predated such classification systems as the Research Diagnostic Criteria (RDC) and the American Psychiatric Association's DSM-III by more than thirty years. Without the benefit of the large-scale epidemiological studies which were to take place much later, it is to Jellinek's credit that he was able to recognize so many different forms of alcoholism. Although RDC and DSM-III have their problems, they nevertheless represent considerable achievement for both psychology and psychiatry in making a systematic descriptive approach to diagnosis available to both clinicians and researchers.

The question then becomes, Have we come far enough in systematizing our diagnoses of alcohol-related problems? Probably not. To the same extent that Jellinek relied on his astute clinical judgment to describe the alpha, beta, and gamma alcoholic, DSM-III relied on the clinical judgment of a panel of experts in the alcohol field to come up with a definition of alcoholism. What then is the reliability and validity of the alcohol-related diagnoses using this classification system?

With the development of semistructured interviews such as the Schedule for Affective Disorders and Schizophrenia (SADS) and structured ones like the Diagnostic Interview Schedule, whose forerunner was the Renard Diagnostic Interview, it became possible to check the reliability of the diagnosis of alcoholism and following the advent of DSM-III, that of alcohol abuse and alcohol dependence. Reliability checks using these instruments suggest that clinicians can agree upon diagnoses of individuals having alcohol-related problems using the schema outlined in DSM-III.

The definition of alcoholism provided by the panel of experts convened by the American Psychiatric Association departed from earlier versions of
the DSM by distinguishing between alcohol abuse and alcohol dependence (the latter probably most akin to alcoholism). The need to make this distinction undoubtedly came from the experts' clinical observations that some people can have a number of problems associated with alcohol use (e.g., job loss, marital difficulty) yet not be physically dependent on it.

Prior to DSM-III the clinician had the choice of either placing a "case" for diagnosis into either an "alcoholic" or "not alcoholic" category. Obviously, if problems with alcohol fall along a continuum, this is a most unsatisfactory solution. Thus DSM-III overcame this problem, at least in part, by introducing a milder form of alcohol problems, namely, alcohol abuse.

According to DSM-III, an alcohol abuser is one who exhibits symptoms in two broadly defined categories: (A) pathological use, and (B) impairment in social or occupational functioning. The symptoms must also have been present for at least one month for a diagnosis of alcohol abuse to be correctly applied. Examples of pathological use listed are: need for daily use, drinking despite medical complications, binges, and blackouts. Impairment in social or occupational functioning due to alcohol use includes loss of job, legal difficulties, and arguments or violence with friends, family, or acquaintances while drinking.

The alcohol dependent person in DSM-III terminology is one who exhibits symptoms from either of the broad categories of pathological use or impairment in social or occupational functioning. In addition, to be labeled alcohol dependent, the individual must also display evidence that he or she has tolerance to the effects of alcohol or has experienced withdrawal symptoms.
Although these are far from perfect as definitions covering the vast spectrum of alcohol abuse problems, with or without dependence, nevertheless, we can describe the characteristics of people whom clinicians (the APA experts) have seen in their clinical practices and whom they know to be alcoholic. The emphasis is here placed on the word "know" because diagnosis of alcoholism, like diagnosis of all other psychiatric problems, is circular insofar as that clinicians diagnose the psychiatric disorder and then proceed to enumerate the characteristics of those individuals so labeled. Diagnosis becomes noncircular when the same diagnostic entity is observed over time and found to be consistent, that is, the alcoholic diagnosed at point A in time does not, for example, become schizophrenic at point B. To further validate a diagnostic entity, it is also useful to have information about treatment outcome and response to particular treatments. If, for example, a patient appears to be either severely depressed or possibly schizophrenic and shows no improvement after a course of antidepressants or ECT but responds well to one of the neuroleptic medications, our hunch that the patient was suffering from schizophrenia is further confirmed. So too, the various alcoholisms need to be studied with respect to treatment outcome and consistency across time. Finally, unraveling phenomenological aspects of the disorder associated with known markers for alcoholism would appear to be an important next step.

Markers

Since 1973, when the results of the Danish adoption study were released and the clear contribution of genetics to the development of alcoholism was fully realized, there has been increased attention to finding "markers" for alcoholism. While this is a laudable endeavor, the results of this search
may turn out to be less fruitful than we had hoped because of our current lack of clarity in the alcoholism field as to what constitutes a "marker" and how to recognize one. It is our intent that the conceptualization provided by the present vulnerability model may direct our search in a more efficacious way.

The general parameters of our vulnerability model include the following variables: (1) the degree of vulnerability of the individual; (2) the necessary triggering events for eliciting an episode; (3) moderating factors that ameliorate or exacerbate the triggering event so that the episode is either aborted or actually experienced; (4) the time course of the episode; (5) the termination of the active episode; and (6) any residual effects of the episode.

The degree of vulnerability is gauged by measuring the indicators. The triggering events are the life events and endogenous events that impinge on the individual at the time of the development of the episode. Even though an individual may be highly vulnerable, based on the presence of the indicators, and even though he or she may have undergone considerable life event stressors, that person need not develop an episode if the social network, ecological niche and premorbid personality can absorb the stress the person is experiencing. However, once an episode begins, it will continue until there is intervention either by the individual or by some therapeutic agent. But episodes do not last forever, though the vulnerability tends to persist and even recovered alcoholics are still at high risk of relapse. Of course, after a chronic bout of alcoholism there is a tendency for residual effects to persist and these residual effects make it difficult to investigate the original premorbid vulnerability.
A vulnerability model allows for some individuals being at greater risk for a particular disorder though they have not ever developed the disorder and may never do so. Diabetes mellitus is one such condition that can now be characterized by biological "vulnerability markers." Specifically, juvenile onset diabetes has been found to be associated with particular HLA antigens. Obviously, when we speak of an association we mean that the frequency of a particular HLA variant is higher among the affected group; it does not mean that every case with the illness will have the marker nor that every person with the marker will have the illness. However, should two unaffected individuals who carry the marker have children, we can specify how much their children's risk is increased over population rates as a result of having such parentage.

Applying the vulnerability model to alcoholism requires that we find ways of identifying those who are vulnerable, regardless of whether they have ever displayed alcoholic behavior or even heavy drinking. This means finding indicators or "markers" of performance (neuropsychological, neurophysiological), measures of psychosocial functioning (e.g., participation in family and social networks), or other characteristics (profiles from personality tests). Ideally, these indicators would identify individuals who are either alcoholic and currently in an episode (drinking without significant periods of sobriety) or alcoholic and in remission (sobriety of six months duration), or unaffected individuals with a higher risk for developing alcoholism (persons with multiple blood relatives with alcoholism). The ideal marker is one that occurs only in alcoholics and not in normal controls or in other nonalcoholic psychiatric patients.
Further, the marker or pattern of markers should be present in "high risk" individuals (blood relatives of alcoholics) more frequently than is seen in the normal population.

Specific cultural, ecological and social support or personality characteristics may modify the likelihood of developing an episode in the presence of a triggering event because they serve as buffering agents (i.e., they are moderating variables). Such variables can either amplify or diminish the immediate effects of stress and subsequent drinking behavior. Thus it is convenient to differentiate between the various types of indicators: vulnerability markers, episode markers, and moderating variables (Hill, 1981; Zubin, Magaziner, & Steinhauer, 1983; Zubin & Spring, 1977).

For some of the indicators we cannot yet state unequivocably that they are, for example, vulnerability markers rather than moderating variables. As one illustration of this, we have suggested earlier that individuals raised in certain religious environments may be imbued with such a persistent aversion to alcohol use such that throughout life and even in other environments that encourage drinking, these individuals will be more likely to remain abstinent. We have earlier denoted as psychosocial vulnerability this lifelong persistent psychological (attitudinal) stance. When similar kinds of environmental variables produce relatively transient modifications in the psychosocial environment of the individual, we prefer to classify them as moderating variables.

Before reviewing the evidence obtained thus far on a variety of putative markers for alcoholism, let us attempt to distinguish the various types of markers and the conditions under which they must be observed if they are to
have even tentative value in terms of discovering the etiology of alcoholism. We in the behavioral sciences have extended the term "marker" beyond its usual more limited boundaries as used in genetics. In genetic studies the term marker usually refers to a characteristic or trait given at birth through one's genetic heritage that endures as for example, whether one has type O or B blood. Usually genetic markers have simple unequivocal patterns of inheritance and heritable variations common enough to be classified as genetic polymorphisms. Of course an enduring, heritable trait like type O or B blood is not necessarily a "marker" for a particular illness just because the frequency of the genetic marker is higher among a particular group of individuals having the illness. To be considered a "marker" the blood group or other variant should distinguish affected from nonaffected individuals, should distinguish relatives of affected individuals from individuals without such a family history, and additionally should show linkage with affected status. That is, within families there should be segregation of the marker with the disease status. Because the science of alcoholism is still in its infancy, we really have no markers as such. We have a number of indicators, however, which we will review.

First, we will look at the types of indicators that can be studied to clarify the etiology of alcoholism. We have outlined the conditions under which one would be able to distinguish a vulnerability indicator from an episode or residual indicator. We will here use the term "marker" because we are considering the idealized case at a point in time when marker status has been demonstrated for some of our more promising indicators. At present, a number of indicators appear to differentiate alcoholics from
nonalcoholics (e.g., impaired performance on particular neuropsychological tests; elevations on MMPI subscales). All of these are candidates for status as vulnerability indicators, or perhaps markers; but because they are most often identified after the individual becomes an alcoholic, it is impossible to determine if these are indicators of an episode alone, disappearing when the person becomes sufficiently detoxified, or are persistent characteristics of the individual both during and after the episode, that is, they are vulnerability indicators or ultimately vulnerability markers.

We have outlined a number of strategies to enable us to differentiate between episode markers and vulnerability markers, as seen in Tables 1 and 2. The plus sign indicates that the marker is present; a minus sign means the marker is absent. But in order to properly classify the potential marker, we need to know its status both during and after the episode. Because the onset of alcoholism is insidious, it is sometimes difficult to know when the episode of alcoholism began. A period of heavy drinking lasting many years often precedes bona fide alcoholism. Also, since alcohol use may affect the marker under study, even in quantities typically consumed by non-alcoholic individuals, more and more research designs utilize children who presumably have not begun to drink to get around this problem. The next step is to determine the status of the marker after the episode is over. If we didn't have enough problems defining the onset of the episode, we now must figure out when the episode ended! There certainly is no unanimity on this issue. While all can agree that an alcoholic off alcohol in a detoxification ward has ended his drinking episode, not all would agree about when the effects of drinking have passed. But if we can assume that the drinking episode has ended (the person is abstinent), and that the acute
Table 1
Types of Markers by Episode and Postepisode Status

<table>
<thead>
<tr>
<th>Marker</th>
<th>Episode</th>
<th>Postepisode</th>
<th>Type of Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>+</td>
<td>Vulnerability</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>-</td>
<td>Episode</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>+</td>
<td>Residual</td>
</tr>
<tr>
<td>D</td>
<td>-</td>
<td>-</td>
<td>Nondifferential</td>
</tr>
</tbody>
</table>

Note: (+) marker present; (-) marker absent
Table 2
Types of Markers by Preepisode, Episode, and Postepisode Status

<table>
<thead>
<tr>
<th>Marker</th>
<th>Preepisode</th>
<th>Episode</th>
<th>Postepisode</th>
<th>Type of Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Vulnerability</td>
</tr>
<tr>
<td>B</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Episode</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Vulnerability</td>
</tr>
<tr>
<td>D</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Normalized by Episode</td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Residual</td>
</tr>
<tr>
<td>F</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Normalized by Episode</td>
</tr>
<tr>
<td>G</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Residual</td>
</tr>
<tr>
<td>H</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Nondifferential</td>
</tr>
</tbody>
</table>

Source: Adapted from Zubin & Steinhauer, 1981

Note: (+) marker present; (-) marker absent
neurotoxic effects of the alcohol have subsided, then it may be reasonable
to look at the marker at some arbitrary point, say, after approximately
one month off alcohol.

Insert Table 1 about here

Insert Table 2 about here

In the schema we have outlined, A is definitely a vulnerability marker
since it characterizes the person both during and after the episode whereas
B is definitely an episode marker since it is present during the episode
but disappears when the episode ends. C is normal during the episode
but shows a residual effect in the postepisode period, indicating that it
may reflect the effect of the episode rather than vulnerability to developing
alcoholism. D indicates that the marker in question is absent both during
and after the episode and hence is not a marker for alcoholism. It has been
included here simply for logical clarity.

In order to determine whether C is merely present because of past
alcohol consumption, that is, as a residual effect of the episode, we also
need to know the status of the individual during the preepisode period.
If the alcoholic exhibited the marker during the preepisode period, we
could no longer regard it as a residual effect. Perhaps, we have here a
vulnerable individual whose drinking during an episode alters the marker expression, but without the drinking we would see the marker throughout: pre, during, and following the episode.

In order to take into account the preepisode status, we have expanded the table (see Table 2). Here again A is a definite vulnerability marker and B is a definite episode marker. C is a vulnerability marker which changes toward control subject levels during an episode; at present this type of marker is purely speculative for alcoholism. However, one example of this type of marker can be seen in schizophrenia where homovanillic acid (HVA) appears to normalize during acute stages of schizophrenia (Post, Fink, Carpenter, & Goodwin, 1975). D reflects the normalization of the indicator as a result of an episode, the marker disappears in the post-episode period. Again, whether this type of marker will actually be found among alcoholics is yet to be determined.

E shows the residual effect of the episode since it was absent in the preepisode period but developed in the postepisode. An example of this is the disruption in sleep continuity and suppression of slow wave sleep mentioned earlier, which tends to develop during a drinking bout and can remain in evidence for as long as 1-2 years after the alcoholic achieves sobriety (Adamson & Burdick, 1973). F indicates that the episode normalized the marker, causing it to disappear in the postepisode period. One possible example of this would be a tendency for prealcoholics to exhibit higher levels of mania than those who never become alcoholic (elevation of Scale 9--MMPI). The mania levels could remain elevated during drinking, but as the person experiences withdrawal (subclinical withdrawal may go on for many months), it might be expected to normalize toward nonalcoholic
Table 3
Types of Markers Based on Presence in Probands and Their First-Degree Relatives

<table>
<thead>
<tr>
<th>Marker</th>
<th>Pre-Episode</th>
<th>Episode</th>
<th>Post-Episode</th>
<th>First-Degree Relatives</th>
<th>Type of Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Vulnerability</td>
</tr>
<tr>
<td>AA</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>*</td>
<td>Vulnerability</td>
</tr>
<tr>
<td>B</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Episode</td>
</tr>
<tr>
<td>BB</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Vulnerability</td>
</tr>
<tr>
<td>CC</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Vulnerability, Nonfamilial</td>
</tr>
<tr>
<td>D</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Vulnerability, Change by Episode</td>
</tr>
<tr>
<td>DD</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Vulnerability, Nonfamilial, Change by Episode</td>
</tr>
<tr>
<td>E</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Residual Effect of Episode</td>
</tr>
<tr>
<td>EE</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>F</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Vulnerability, Change by Episode</td>
</tr>
<tr>
<td>FF</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Vulnerability, Nonfamilial, Change by Episode</td>
</tr>
<tr>
<td>G</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Residual Effect of Episode</td>
</tr>
<tr>
<td>GG</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>H</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Nondifferential for Alcoholism</td>
</tr>
<tr>
<td>HH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Invulnerability</td>
</tr>
</tbody>
</table>
Note: (+) marker significantly more frequent in alcoholics and/or their first-degree relatives than in normal controls during designated period; (-*) marker significantly less frequent in alcoholics and/or their first-degree relatives than in normal controls during the period; (-) marker not differential during the period; (?) doubt whether the pattern across the periods occurs in nature.
levels. Because withdrawal is often associated with depression, increasing scores on the Depression scale may bring scores on the Mania scale more toward normal values. G, like E, demonstrates the residual effect of the episode. A good example of this is the lowered scores on the Category test of the Halstead Reitan battery which has now been reported in a number of studies (Goodwin & Hill, 1975; Parsons & Leber, 1982). H is a nondifferential marker.

Another way of determining the character of the marker is to examine the siblings of the probands. Because siblings have in common, on the average, 50% of their genes and share a common environment, study of the siblings aids us in determining whether the putative marker is a vulnerability marker, an episode marker, or possibly both. Table 3 shows the possibilities when the status of the sibling is considered. The heading "first degree relatives" is used because in fact one can also examine either the probands' natural parents or children, since both share half of their genes on average. Two points need mentioned. First, we assume in this table that the sibling or parent is not affected by alcoholism. Secondly, when one speaks of a control group in this situation, we mean that the controls are free of alcoholism and other psychiatric disorders as are their first-degree relatives. Individuals who carry the genotype for alcoholism or psychiatric disorders, even though they are phenotypically healthy, must be excluded to avoid stacking the cards against finding markers among the alcoholic families even when they exist.

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Insert Table 3 about here

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In Table 3, A remains a vulnerability marker, its character confirmed by its presence in siblings. AA is apparently a permanent characteristic of the proband but not of the sibling and hence might qualify as a non-familial marker. B remains an episode marker, while BB is not easy to explain and may be an impossible marker. C and CC are vulnerability indicators which change during an episode, C being more likely a familial marker while CC is not. D is definitely a vulnerability marker which disappears during and after an episode, so that siblings who develop an episode would lose the marker. DD on the other hand shows the effect of the episode only. E may be regarded as representing a residual effect of the episode but is not a vulnerability marker. EE is absent during the preepisode but present during and after the episode and also occurs in siblings. Only a follow-up of the siblings can reveal the significance of this type of marker. It is also possible that this pattern will not emerge in a real data set. F represents a marker of vulnerability that disappears in the proband who develops an episode but that may have a familial basis, since the siblings also exhibit the marker as well. FF is similarly a vulnerability marker that changes during an episode and presumably is nonfamilial since siblings do not exhibit it. G shows the residual effect of the episode and might be further elucidated by follow-up of the siblings. GG is a bit of a puzzle since it seems to appear only after an episode and is present in the siblings. H is nondifferential for alcoholism while HH can be examined only by follow-up.

Markers for Alcoholism

Heterogeneous etiology. The search for markers for alcoholism is a complicated one, owing to the heterogeneity of the disorder and the fact that
alcoholics and their first-degree relatives show higher rates for a number of psychiatric illnesses than those expected in the general population. Families of alcoholics show increased rates of affective disorders (Behar & Winokur, 1979; Dunner, Hensel, & Fieve, 1979) and anorexia nervosa (Eckert, Goldberg, Halmi, Casper, & Davis, 1979). Increased rates of sociopathy and Briquet's Syndrome have also been reported. However, there does appear to be a tendency for alcoholism to "run true to type" in the sense that alcoholics appear to have higher rates of alcoholism in their families than any other psychopathology (Cotton, 1979; Hill et al., 1977). Nevertheless, we cannot ignore the increased rates of other psychopathology. These increased rates of other psychopathology may be due to the fact that persons with psychiatric problems may drink in an attempt to modify psychiatric symptoms or it may simply reflect the heterogeneous nature of alcoholism. (There may be different forms.) To date, we have not come very far in specifying the subtypes of the disorder. Two systems frequently referenced are: (1) the primary/secondary distinction, originating with the St. Louis group (Goodwin & Guze, 1979), and (2) the familial/nonfamilial distinction described by many investigators (Frances, Timm, & Bucky, 1980; Goodwin, 1983). Little is currently known about the reliability and validity of these distinctions. Even when such data are available, we suspect that improved diagnostic typologies will have limited value unless we can identify trait-related markers. At any rate, armed with more precise typologies for diagnosing more homogeneous groups of alcoholics, we can now proceed to search for markers in accordance with the hypotheses emanating from the model we have outlined for understanding the etiology of alcoholism. Several of the potential markers available to us will be discussed.
Metabolism. Because alcohol is a drug, it is understandable that the search for what might be genetically transmitted has included studies looking at the metabolism of alcohol. Alcohol is eliminated from the body predominantly by metabolism in the liver. Oxidation of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) is followed by nicotinamide-adenine dinucleotide (NAD)-dependent oxidation by aldehyde dehydrogenase (ALDH) to acetate. The enzyme alcohol dehydrogenase has received attention in recent years (Li, Bosron, Dafeldecker, Lange, & Vallee, 1977; von Wartburg, 1979) because three gene loci have been identified: ADH-1, ADH-2, ADH-3. Two common alleles occurring at two of the loci have particular polypeptides associated with them (B-1, B-2, and gamma 1, gamma-2). Depending on the genotype, isoenzymes can be formed by a combination of these subunits. Isoenzymes containing an "atypical" subunit, B-2, have higher enzymatic activity than those composed of "normal" subunits. The atypical subunit is far more common among Orientals who, because of their lower rates of alcoholism, appear to be protected in some way. The higher enzymatic activity of the "atypical" isoenzyme could increase elimination rates and lead to production of greater amounts of acetaldehyde, a substance associated with physiological discomfort.

Wolff has demonstrated that increased vasomotor response to alcohol can be elicited in over 80% of Orientals and American Indians (Wolff, 1972, 1973) as contrasted with 5% of Caucasians. The differential response appears to be present independent of alcohol exposure since Oriental infants show greater peripheral dilation than Caucasian infants following parenteral administration of ethanol. This increased vasomotor response includes flushing, abdominal discomfort, muscle weakness, dizziness,
tachycardia, and hypotension. These aversive symptoms have together been implicated as a "protective factor." This factor may indeed be a vulnerability marker which is changed by an episode of drinking, similar to the situation previously outlined for marker D. The high rates of alcoholism among North American Indians and increasing rates of alcoholism among the Japanese suggest that if the "flush reaction" is a protective factor, it can easily be modified through drinking.

Behavioral markers. For convenience, we have placed the Oriental "flush" among the behavioral markers because identification of this marker was by incidental behavioral observations. Obviously it has biochemical underpinnings as previously noted in our discussion of "atypical" ALDH. A second behavioral marker that has received much attention is the statistically significant difference in the subjective "high" experienced by individuals receiving alcohol in a laboratory setting as a function of whether or not they had a positive family history for alcoholism (Schuckit, 1980). College students were sent questionnaires soliciting participation in a study concerning alcohol use. The questionnaire included questions about drinking behavior of first-degree relatives. Using this information, Schuckit set out to contrast the response to alcohol administration in two groups of individuals: (1) those without a first-degree relative with alcohol problems (Family History Negative) and (2) individuals with such a history (Family History Positive). Students who were themselves alcohol abusers were carefully excluded from the study. The two groups were matched on demographic variables and drinking history. Two significant findings emerged: Those with a positive family history of alcoholism rated themselves lower on a global rating scale of intoxication despite
comparable blood alcohol levels and had significantly higher blood acetaldehyde levels. The acetaldehyde findings (Schuckit & Rayses, 1979) remain somewhat controversial due to the difficulties which a number of investigators have had in measuring acetaldehyde accurately (Eriksson, 1980).

That Family History Positive (FHP) subjects rated themselves lower on the subjectively experienced "high" produced by alcohol ingestion than the Family History Negative (FHN) ones, suggested to Schuckit that the seeds of abuse could be found in this phenomenon. Due to the fact that more alcohol would need to be consumed for the FHP individual to feel high, it would be expected that these individuals might develop alcohol tolerance sooner. Also, because one biological variant, acetaldehyde, appeared to be linked to a genetic predisposition to alcoholism (FHP), Schuckit proposed that alcohol could have a differential effect on reward centers in the central nervous system of FHP and FHN subjects. We were intrigued by these findings and wondered if they could be replicated. Secondly, if replicated, would they be due to the pharmacological effects of alcohol on brain tissue, a result of beliefs about alcohol learned only in the families of alcoholics, or perhaps due to both? As his dissertation research Jonathan Rightmyer undertook in our laboratory the task of designing an experiment that would allow replication of Schuckit's study and test these alternative explanations of FHP/FHN differential responsivity. Ultimately we chose the balanced-placebo design, a design frequently used in studies in which the relative contribution of the subjects' beliefs about alcohol effects are pitted against its actual pharmacological effects. This called for four experimental cells, a
two-by-two design in which the subject either received alcohol or did not and was told either that he would receive alcohol or that he would receive only the mixer (tonic water).

The Subjective High Assessment Scale (SHAS) was administered to both FHP and FHN young men (mostly college students) both before and after they consumed the appropriate beverage (tonic or 0.5 g/kg alcohol). All subjects were interviewed extensively about their drinking experience to rule out any potential differences in alcohol tolerance. No significant effects on the individual's subjective assessments of the alcohol induced "high" as a function of family history were found using the SHAS. However, a number of other interesting findings emerged. The Mood Adjective Checklist (MACL) (Nowlis, 1964) assessments and other scales from the SHAS used in Rightmyer's study revealed a number of family history effects. Some of these were interactions between family history and beliefs (instruction/expectancy) while others were interactions between family history and beverage consumed (pharmacological effects). For one scale, "Concentration," from the MACL, both beverage and expectancy effects were noted as a function of family history of alcoholism (Rightmyer & Hill, unpublished). Because of the potential importance of finding biological differences in the way alcohol affects brain reward systems, further work on the subjective effects of alcohol appears indicated in families with varying levels of vulnerability.

Currently we are studying vulnerability to alcoholism using multiplex families evaluated for performance on a number of variables. A multiplex family is one in which, after ascertaining an affected proband, one selects families who have at least one other affected sibling and one other
unaffected sibling. In this way the acute effects of episodes of illness can be partialed out using a cross-sectional design. The advantages are clear given the time required to conduct a prospective study of prealcoholic individuals and wait for some to become alcoholics. Also included in our study were control families chosen because of an absence of psychopathology in the index case or in first- and second-degree relatives.

As mentioned previously, elevation in the Psychopathic Deviate scale (Pd) of the MMPI is a common finding in the profiles of alcoholic subjects. Whether this elevation in Pd is an episode marker or vulnerability marker is an important question. If it is only an episode marker, then it would be useful in predicting relapse among alcoholics, perhaps, but not discriminating as a marker among nonalcoholics for the purpose of determining who will later become alcoholic. On the other hand, if the Pd scale is a vulnerability marker, it might ultimately be used as a screening tool, to channel those with higher scores into prevention programs of some sort, particularly if other risk factors are present as well. As mentioned previously, Hoffmann et al. (1974) found Pd elevations in individuals who later became alcoholics. Our own data appear to confirm these findings for Pd as a possible vulnerability marker.

Like others, we found significant elevations in clinical scales when we contrasted our affected (alcoholic) subjects with the nonalcoholic, nonpathological control group. Five significant differences were observed (see Figure 2). The affected individuals were significantly higher on Pd, Ma, Pt, Sc, and Pa than the normal controls. To determine whether any of these scale elevations might be vulnerability markers, we chose to contrast the unaffected siblings of the alcoholics with the normal
controls. Because in neither group were there alcoholics, we reasoned that any differences observed would be due to some personality characteristic of individuals at high risk for becoming alcoholics. Three significant differences were found (see Figure 3). The high-risk individuals had significantly greater Pd, Hy, and Sc scale scores. Because Pd and Sc were higher in the alcoholics than in normals, it would appear that these two characteristics may prove to be vulnerability markers. Because of the convergence between our data and those of Hoffman et al. (1974), we are most confident about the Pd finding as a marker. It is not yet known whether elevations in the Psychopathic Deviate scale will eventually turn out to be a vulnerability marker for alcoholism or simply a moderating variable present in families of alcoholics, in the terminology of the multifactorial model, a familial-environmental factor.

Insert Figure 2 about here

Insert Figure 3 about here

Concordance for drinking. Although not a marker as such, concordance in drinking behavior among genetically related individuals should follow some predictable pattern if drinking behavior has a genetic basis.
The evidence suggests a fairly high concordance. Kaij (1960) studied 174 Swedish twin pairs selected because one member of the pair had appeared on the national register of alcohol abusers. Using a five-point scale from abstention to chronic alcoholism, he found about twice the concordance in monozygotic twins (Mz) (53%) as in dizygotic twins (Dz) (28%) in terms of having the same grade of drinking (1-5). He also found greater concordance when the chronically alcoholic proband was a member of a monozygotic twin pair (70%) than a member of a dizygotic pair (32%). Partanen et al. (1966) in Finland failed to find greater concordance in monozygotic than dizygotic twins for "out of control" drinking or "consequences of drinking." These twins were drawn from a general population sample, whereas Kaij's sample was chosen from the registry of alcohol abusers. However, in both frequency and quantity per occasion, there was greater concordance in the monozygotics than the dizygotics Partanen studied suggesting a genetic influence in drinking. Heritability estimates were 0.39 for frequency and 0.36 for quantity per occasion.

Two other twin studies are worthy of mention. One was a sample of twins gleaned from among the 600,000 juniors who took the National Merit Scholarship Questionnaire Test (Loehlin, 1972). Greater concordance was found among Mz twins than among Dz twins for questions related to heavy drinking among the 850 twins identified in this sample. Jonsson and Nilsson (1968), in their study of 1500 Swedish twin pairs, also found greater concordance among the Mz twins than the Dz twins in the quantity consumed.

All of these findings taken together suggest that genetic influences operate to make concordance of drinking patterns more similar among
relatives, with those sharing the greater proportion of their genes even more similar. It should be noted that environmental factors play an important role as well. Harburg, Davis, and Caplan (1982) have noted that children of alcoholics are less often social drinkers than children of nonalcoholics because they either model the affected parent, becoming heavy drinkers, or shun the negative aspects of drinking altogether by becoming abstainers. Once again, the vulnerability model proposed here would explain these two seemingly contradictory sets of data. That is, a certain proportion of highly vulnerable individuals will never develop an episode of heavy drinking or alcohol abuse because of moderating variables that cushion the impact of the stressful life event.

Neurological, Neuropsychophysiological and Neuropsychological Markers

We will begin by discussing the evidence that neurological dysfunction may predict the development of alcoholism. This theory has received increasing attention in recent years largely because a number of investigators have pointed to a possible relationship between childhood hyperactivity and later development of alcoholism. The studies have either begun looking at the family histories of children in treatment for hyperactivity (Cantwell, 1972; Morrison & Stewart, 1971) or started with alcoholic probands and assessed their hyperactivity retrospectively (Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1975; Tarter, McBride, Buonpane, & Schneider, 1977). Only two studies have looked at drinking in hyperactive adolescents. In one the assessment was made cross-sectionally (Mendelson, Johnson, & Stewart, 1971) where hyperactive children were found to use greater amounts of alcohol, and in the other where prospective data were collected. In the latter no significant relationship was found except for those who
persisted in antisocial behavior (Gittelman, Mannuzza, Shenker, & Bonagura, 1985). At present the association between hyperactivity and alcoholism appears to be no greater than it is for any other psychiatric disorder. Thus, while hyperactivity was previously considered a marker for alcoholism, it now appears to be a nonspecific marker for psychiatric illness. Such has been the fate of other markers such as the Dexamethasone Suppression Test (DST). While responsivity on this test was originally thought to be specific for depression, it was later found to be present in other psychiatric states.

Another indicator of neurological functioning that has received attention recently is static ataxia. The report by Lipscomb, Carpenter, and Nathan (1979) that measures of static ataxia differentiated young men with or without a family history of alcoholism was based on somewhat of a serendipituous finding. The design of that study included administering alcohol to young men and determining their tolerance to ethanol using a variety of behavioral assessments both before and after the alcohol administration. The use of static ataxia measures to determine alcohol tolerance had been anticipated several years before by Goldberg (1943) in Sweden who made extensive tests of alcohol tolerance in alcoholics, heavy users, and controls. The serendipity was in finding that persons with a family history of alcoholism differed, at baseline, from those without such a history. A number of attempts to replicate this work have largely been successful. A study of 1200 school children who were administered the static ataxia test show clear differences as a function of family history (Lester & Carpenter, 1985). In our first investigation of this phenomenon, children of alcoholics, normal controls, and children of
depressives were found to differ on static ataxia using an apparatus patterned after Lipscomb's setup (Hegedus, Tarter, Hill, Jacob, & Winsten, 1984). These results were quite encouraging because they suggest a specificity of this marker for alcoholism. Further work is currently in progress in our laboratory assessing children of affected and unaffected siblings from our highly selected multiplex families described earlier.

Neuropsychological differences between family history positive and negative subjects have been reported by Schaeffer, Parsons, and Yohman (1984) suggesting that some of the neuropsychological deficits seen in alcoholics and previously considered a consequence of drinking, may in fact be vulnerability markers. Neuropsychological tests performed on children whose biological fathers were alcoholic have revealed a number of deficits when their performance is contrasted with children without alcoholic biological parents (Drejer, Theilgaard, Teasdale, Schulsinger, & Goodwin, 1985). These include a greater number of errors on the Category Test (Halstead-Reitan Battery), lower WAIS Vocabulary scores, and poorer performance on the Porteus Maze Test among the children of alcoholics. Our ongoing study of multiplex families is assessing the replicability of the Category Test data.

Neurophysiological markers. The ensuing discussion will focus on the neurophysiological model as one approach to understanding the etiology of alcoholism. Our premise is that observation of overt behavior alone may not be sufficient for understanding why some individuals persist in behaviors that appear to us to be maladaptive. A neurophysiological analysis may provide insights into which systems may be involved in particular psychopathologies and how information in those systems is processed.
Information processing demands may vary over a wide range of complexity, from minimal processing activity to tasks that require a great deal of attention and interpretation by subjects, and the level of the demands may aid us in the detection of neurophysiological markers.

Many different task demands have been placed on alcoholic subjects varying from those that passively record resting heart rate or EEG to those that measure heart rate changes or EEG characteristics during a problem solving task while the subject is actively processing information. The latter results in a group of electrical potentials that can be recorded from the scalp and which are collectively known as Event-Related Potentials (ERPs). These should be distinguished from brain-stem evoked responses which have provided a major neurological tool for detecting intact or deviant reactivity of the nervous system at very early (1-10 msec) stages of processing. These are elicited under relatively passive conditions, whereas the ERP is elicited when relatively more complex processing is required. Certain psychophysiological measures are especially useful for studying ongoing information processing activities because they occur with relatively short latency (approximately 1000 msec or less). These may be contrasted with the temporal resolution of other recently developed techniques for understanding brain functioning (e.g., PET scan, cerebral blood flow), each of which provides an indication of metabolic activity, but integrate activity over much longer periods of time, and are thus not capable of monitoring reactions to discrete types of events, as can be accomplished with ERPs.

Among the variety of measures available, the long-latency components of the ERP have proven to be the most closely related to information
processing activity across different experiments. The most prominent aspects include the P300 component, a scalp-recorded positivity with a latency of approximately 300 msec, which was first noted by Sutton, Baren, Zubin, and John in 1965, and related long-latency activity such as slow-wave and processing negativity, as well as the contingent negative variation (CNV) which precedes an expected imperative stimulus. A number of earlier components have been identified and studied including N100, which is clearly related to selective attention.

Brain function has been studied in alcoholics by conventional EEG and by computer averaged Event-Related Potentials (ERPs). The EEGs of chronic alcoholics have been described as poorly synchronized and deficient in alpha activity (Docter, Naitoh, & Smith, 1966). Also, it has been shown that 12-year-old sons of alcoholics show an excess of high frequency activity (Gabrielli et al., 1982). Further, there is evidence that alpha activity is genetically determined (Vogel, Schalt, Kruger, Propping, & Lehnert, 1979) and that persons at higher risk for alcoholism may be deficient in alpha activity (Propping, Kruger, & Mark, 1981). Because alcohol consumption elicits alpha activity in normals (Propping, Kruger, & Janah, 1980), particularly those with low baseline levels, it has been suggested that alpha activity may be a marker for alcoholism (Pollock et al., 1983). Pollock and colleagues have shown that high risk individuals (sons of male alcoholics) display greater increases in slow alpha energy following alcohol administration than individuals from a matched control group. Propping et al. (1981) similarly found alcohol to have a greater synchronizing effect on individuals with borderline alpha EEG, all of whom were either alcoholics or their relatives.
**Event-Related Potentials.** Neville, Snyder, and Bloom (1982) were the first to observe that alcohol administration has different effects on ERP in individuals with a first-degree relative who is alcoholic (Family History Positive) than those without such a history. Because these subjects were not matched for drinking habits, the results could not be interpreted unambiguously. Therefore, in their second study this variable was more closely monitored in 10 subjects, 5 each who were either Family History Positive (FHP) or Family History Negative (FHN) (Elmasian, Neville, Woods, Schuckit, & Bloom, 1982). Subjects with a positive family history showed significantly reduced amplitudes for the P300 component of the ERP when making decisions about task relevant stimuli. Also, the latency of the positive component and reaction times to correctly detected targets were significantly later in individuals with a positive family history. Recently a visual discrimination task was administered to children of alcoholics and children of nonalcoholics with differences being seen primarily in the amplitude of the P300 component (Begleiter, Porjesz, Bihari, & Kissin, 1984). This was the first demonstration of changes in information processing in a high risk group of subjects without the confounding effects of current or previous alcohol consumption. All of the subjects were preadolescent and had been screened for having never used alcohol. The second aspect of this study that should be emphasized is that these results were found without the necessity of administering alcohol to the subjects.

This study was a seminal contribution to the alcoholism literature, pointing out as it did the potential usefulness of Event-Related
Potentials for uncovering a possible biological risk for developing alcoholism. Two other studies have looked at the P300 responding of adult children of alcoholics. In one of these (O'Connor and Hesselbrock, 1985), two visual tasks were used while subjects were either sober or mildly intoxicated. The amplitude of P300 was reported to be smaller for young men at greater risk (all had alcoholic fathers) than those with minimal risk (fathers and other first degree relatives were not alcoholic). These results are in accord with Begleiter's findings for younger children of alcoholics. In the second study Polich and Bloom (1985) compared normal subjects and individuals at risk for developing alcoholism using an auditory oddball task. In all, 24 male subjects were evaluated, 12 with a family history of alcoholism and 12 without. A positive history was defined as having a father who met DSM III criteria for alcoholism. No significant differences for either latency or amplitude of the P300 were found between the two family history groups. A significant correlation between P300 amplitude and the quantity of alcohol consumed on any one occasion was also observed. This effect appeared to be greater for the family history positive as contrasted with the family history negative subjects and was elicited only when task difficulty was increased.

Utilizing our highly selected multiplex families, we have investigated the possibility that ERP characteristics may be markers for vulnerability to alcoholism. In our laboratory, a modification of the "oddball" task is used. Normally, when subjects are asked to count a rare auditory or visual stimulus embedded in a sequence of different but more frequent stimuli, a large P300 response is evoked by the rare event (Donchin, 1977).
Our subjects are informed that two "rare" stimuli (high-pitched tones) never occur in a row, so that every high tone is followed by a frequent stimulus, a low-pitched tone. Thus, the frequent tone which follows a rare, counted tone is predictable (probability = 1.00), while after a frequent tone, either another frequent tone may occur (probability = .67) or a rare tone may be presented (probability = .33). The subject's task is to report the number of rare target tones at the end of every block of trials. Normal subjects show a large amplitude P300 response to the rare tone, a smaller P300 to the unpredictable frequent tone (i.e., the repeated frequent tone, probability = .67), and the smallest response to the predictable frequent tone which follows each rare tone (probability = 1.00).

Some comments are needed regarding the task requirements. All subjects are required to count rare tones, but are not required to pay attention to sequences, even though some information is made available to them at the outset. In the analyses of the data, only blocks of trials for which the subject has counted accurately (within 3 counts) are included, so that in general all subjects considered have been performing adequately. Insuring adequate performance is a necessity before inferring that P300 is reduced because of processing difficulty. Some reports of reduced P300 amplitude in demented patients have also noted that performance was poor in those subjects. Thus the reduced P300 may merely reflect poor performance on the task in such experimental paradigms that allow inattention. We also used a reaction task in which subjects are asked to make a response on either of two switches, either "right" or "left," which is counterbalanced over blocks for the rare and frequent tones.

As in Figure 4, we observed longer latency for P300 in the counting
UNAFFECTED
CONTROL

15 μV

.5 SEC

5b
task (though here nonsignificant) between alcoholics and controls. Were we to stop here we could only conclude that we have suggestive evidence for an episode marker; that is, alcohol exposure may be providing cognitive changes that are reflected in neurophysiological responding. As seen in Figure 5, we also found significant latency differences when the unaffected siblings were compared with normal nonalcoholic controls, suggesting that we may have a vulnerability marker. Of course the nonaffected siblings might have been drinking more than controls indicating merely an episode marker. However, two aspects of our methodology suggest alternatives: (1) we asked all subjects to refrain from using alcohol or drugs for 48 hours before testing; (2) extensive alcohol-use questions were determined for both groups and verified by liver enzyme measures. The liver enzymes SGOT, SGPT and GGPT are elevated in heavy drinkers, particularly GGPT. We rejected from analysis any subject whose self-report did not match expectations about alcohol effects on liver functioning.

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Insert Figure 4 about here
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Insert Figure 5 (a) & 5 (b) about here
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When we made the same comparison with the choice-reaction task, we saw the same significant differences between the two affected siblings
and their unaffected siblings in both the .33 and the .67 probability conditions, lending further support to our hypothesis that latency of P300 may be a vulnerability marker (see Figures 6 and 7).

To further assess the meaning of the finding, it is useful to examine the possibility that the marker is under genetic control. There is evidence that ERP waveforms are heritable. An example is provided by data obtained in our laboratories for the .33 probability condition of the counting task (see Figure 8). Four pairs of subjects are displayed who vary in their genetic similarity to each other. The unrelated individuals are least congruent in the wave forms elicited, whereas the non-twin siblings show more resemblance, which is similar to the dizygotic twin pair, with monozygotic twins showing the greatest congruity. This is what one would expect based on the shared genes of these groups. Dizygotic twins are no more closely related genetically than siblings sharing as they do half of their genes on average, whereas monozygotic twins share all their genes.
AFFECTED
UNAFFECTED

.5 SEC
Summary

As the foregoing review indicates, we have made considerable progress in identifying a number of promising metabolic, behavioral, and neurophysiological markers for assessing risk for developing alcoholism. As previously noted, the term "marker" has been extended beyond its current usage in genetic marker studies where typically a blood marker has been used to elucidate the genetic transmission of particular diseases. In these studies the "ideal" marker is one which is itself an inherited characteristic that is polymorphic (there exist two or more discrete forms that are commonly found in the population), has an established mode of inheritance, is unaffected by the presence of the episode (e.g., the ABO system is unaffected by presence of a disorder), and is localizable to a particular chromosome. Few potential markers satisfy all these requirements, yet it is important to keep this in mind as we search for "markers" for vulnerability to developing alcoholism.

We have proposed a vulnerability model for alcoholism in an attempt to sort out which potential markers hold promise for identifying individuals who are at risk. We have chosen to look at vulnerability from both biological and psychosocial perspectives realizing that some people may carry biological markers as part of their genetic heritage yet never develop episodes of abusive drinking because they lack psychosocial vulnerability. For example, women appear less likely to
develop alcoholism than men because of cultural factors that reduce the chance that they will become heavy drinkers. The greater risk for heavy drinking among men than women appears, however, to be independent of the particular cultures. As mentioned earlier, among the 30 cultures assessed for male and female drinking practices, in no instance did women drink more than men, and in 16 men drank more than women.

In the vulnerability model proposed, we assume that alcoholism is not a continuous disorder but that vulnerability, whether biological or psychosocial, is. This vulnerability may remain latent throughout life or may become manifest when triggers sufficient to produce an episode occur. These triggers may be life events or changes in the internal milieu. For example, biological changes may well produce a major affective disorder which in turn may lead to alcohol abuse. That some individuals have only one major episode of abusive drinking and never return to excessive use of alcohol attests to the fact that alcoholism should not be conceived of as a lifelong disease. Therapeutic intervention should be aimed at preventing its initial occurrence or its recurrence.

We view the identification of markers for vulnerability as essential to achieving this goal. Each of the models of alcoholism should be investigated to provide markers by which the etiological factors can be determined. Once such markers are available, it may be possible to identify individuals prone to alcoholism even before episodes of heavy drinking occur. Although intervention efforts designed to reach all segments of the population might be desirable, they may be impractical owing to inevitable limitation of resources. Therefore, identifying those at
greatest risk would make it possible to design intensive intervention for those who might benefit most.

By establishing the various indicators of vulnerability, episode, and postepisode characteristics, it may become possible to detect the presence of vulnerability long before alcoholism develops and through educational procedures perhaps forestall the development of even the first episode or relapses in recovered individuals. Unlike other mental disorders, we can actually hope to prevent alcoholism since there is no endogenous disease process without alcohol consumption.

We hope that by presenting the current accomplishments of the "marker" movement, and noting the gaps still needing to be filled, will engender a new wave of research interest in detecting vulnerability to alcoholism that will redound to the well-being of individuals at high risk for alcoholism.
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Additional References


- Reference Omission

Whipple, Berka, Poland, & Nobel, 1984.
FIGURE 7. (a) Latency of P300 for the .67 probability condition in the auditory Choice Reaction Task: means of probands and affected brothers versus unaffected brothers.

(b) Superaverages for ERPs obtained from Pz electrode site for each group during the auditory Choice Reaction Task (.67 probability condition).

FIGURE 8. Event-Related Potentials elicited at six electrode sites by an infrequent auditory stimulus (.33 probability condition) during the Counting Task. P300 is the positive (downward-going) wave, which is most prominent at the Cz and Pz locations, at approximately 300 msec. Data are presented for four pairs of subjects varying in their degree of familial relationship. (Note that the data for both of the nontwin siblings are scaled down relative to the other subjects.)