

Potential Biological Markers in Individuals at High Risk for Developing Alcoholism

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IN THE PAST two decades a plethora of scientific evidence has been accumulated to support the notion that alcoholism is a familial disorder with the presence of genetic factors. It is now well established that sons of alcoholic fathers are approximately four times more likely to develop alcoholism compared to the male offspring of nonalcoholics.¹ Indeed, the evidence supporting the contribution of genetic factors in alcoholism is sufficiently compelling to warrant a search for markers of the genetic influence.

It should be noted that the antecedent factors or predisposition toward alcoholism might well be assessed with the use of various strategies. It may be possible to study genetic factors by comparing abstinent alcoholics to control subjects or by comparing abstinent alcoholics with a positive family history to abstinent alcoholics with a negative family history of alcoholism. While this particular strategy may yield interesting findings, the interpretation of the data may be confounded by significant differences in drinking history, differential age of onset of alcohol abuse, as well as numerous other clinical variables such as number and severity of withdrawal episodes, alcohol-related medical complications, etc.

A strategy typically used in the study of genetically determined disorders is the use of large family pedigrees. This powerful approach enables the investigator to study large families with alcoholism, and compare them to control families where alcoholism is absent. This particular strategy is most compelling if one studies genetically determined diseases such as Huntington's disease where the phenotypic expression is easily characterized and specific phenotypic markers are readily available. This approach is indeed most powerful to examine the pattern of inheritance. However this method is most difficult to implement without the availability of valid and reliable biological or behavioral markers.

In the last few years investigators concerned with the potential role of genetic factors in alcoholism have used the high risk paradigm. Comparing the sons of alcoholic fathers and nonalcoholic fathers is a useful approach for examining potential biological or behavioral factors associated with a predisposition for alcoholism. This particular strategy has been utilized in biological as well as behavioral investigations, and has already yielded promising data from various studies.

EEG

Some of the most promising investigations of potential biological markers for a predisposition to alcoholism come from various laboratories which study the electrical activity of the brain. In the last two decades a number of investigators have observed that the resting state electroencephalographic (EEG) activity recorded from awake male alcoholics manifests excessive high frequency activity (beta, fast EEG) and appears to be somewhat deficient in the appropriate production of lower frequency EEG activity such as alpha (for review see Begleiter and Platz²). Moreover, the production of fast EEG activity has been demonstrated to be genetically transmitted.³⁻⁵

These interesting EEG findings and the population genetics data in alcoholism suggested that an excess of fast EEG activity should be present in sons (but not daughters) of alcoholics. Gabrielli et al.⁶ tested this hypothesis in a sample of 265 Danish children. Among this large group of children the investigators found 27 children of alcoholics and compared them with children of normal parents. As expected, they observed that male children of alcoholics manifested excessive fast EEG activity compared to male controls. In addition they report that female offspring of alcoholics do not show this increase in fast EEG activity.

As early as 1968, Naitoh and Docter⁷ reported that the administration of alcohol to alcoholic subjects had primarily a stimulant-euphoriant effect, with the subjects reporting that they felt more alert and sociable than controls. Naitoh and Docter⁷ suggested the intriguing hypothesis that alcoholics drink in order to achieve the psychological state which is associated with an increase and slowing of alpha activity. A number of fundamental questions were raised by the observations of Naitoh and Docter,⁷ as follows: (a) Are individuals with poor alpha activity at greater risk to become alcoholics? (b) Are individuals at high risk for alcoholism more likely to show increased

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Supported by National Institute on Alcohol Abuse and Alcoholism Grants AA02686 and AA05524 and Grant 2529-A from The Scherman Foundation.

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production and slowing of alpha after alcohol administration? Answers to these questions might help delineate the possible relationship between biological markers and subsequent alcohol abuse or alcoholism.

A study conducted by Pollock et al.⁸ attempted to study the relationship between alcohol intake and alpha frequency and production in high risk individuals. Pollock and coworkers⁸ studied alpha activity in a group of males 19 to 21 years of age. They studied a group of 44 sons of alcoholics and a group of 28 controls matched for age and social class. They recorded the EEG 30, 60, and 120 min after the administrations of 0.5 g/kg of 95% ethanol. Blood alcohol level was taken at 40 and 130 min after alcohol administration. It is important to note that blood alcohol levels did not statistically discriminate between high risk and low risk individuals. However, the quantitative analysis of alpha activity revealed significant differences between the two groups. The high risk group demonstrated greater increases of slow alpha activity and greater decreases of fast alpha activity after alcohol ingestion than the control subjects. The high risk subjects also demonstrated greater decrease in alpha frequency after alcohol administration compared to control subjects.

The question of whether predrinking characteristics of the EEG pattern (or the initial brain state) partially determines whether alcohol will have a stimulating or depressant effect would appear to be a fruitful area of investigation particularly within the high risk paradigm. The potential relationship between a specific subjective state and a particular characteristic of brain activity which modulates either the craving for, or the response to alcohol may have fundamental implications for both the search for biological markers as well as the search for drugs capable of inducing the appropriate changes in the brain state responsible for abusive alcohol intake.

Evoked Potentials

While the EEG is a measure of the spontaneous electrical activity of the brain, evoked brain potential (EP) techniques measure the specific electrical response of the brain to external sensory stimuli. With the use of computer technology as well as mathematical techniques it is possible to measure the salient features of evoked potentials which are related to sensory, perceptual, cognitive, or affective responses to the evoking stimuli. The use of various evoked potential techniques can provide important information about the integrity of different brain systems.

In the last decade, the use of several evoked potential techniques has demonstrated the presence of various functional abnormalities in the brains of abstinent alcoholics (see reviews by Porjesz and Begleiter⁹⁻¹¹). A number of studies have shown that the Brainstem Auditory Evoked Response (BAER) recorded in abstinent alcoholics manifests an abnormality in conduction velocity compared to those recorded in matched control subjects.^{12, 13} Brainstem

transmission time is significantly prolonged in abstinent alcoholics. With the use of different cognitive paradigms¹⁴⁻¹⁹ Porjesz and Begleiter have reported that the amplitude of the late positive component (P3) of the event-related potential (ERP) is significantly reduced in abstinent alcoholics compared to controls.

Neurophysiological deficits in sensory processes (BAER) as well as cognitive processes (P3) were originally presumed to be the consequence of alcoholism. Additional investigations examining the possible recovery of the aforementioned neurophysiological deficits uncovered differential outcome in recovery over time.¹¹ Brain stem deficits were observed to recover in chronic alcoholics hospitalized over a three month period. Changes in the P3 voltage of the ERP did not show any change in abstinent alcoholics hospitalized over a similar 3-month period. Similar P3 amplitude deficits were observed in chronic alcoholics abstinent for 2 to 5 years.

Begleiter, Porjesz, Bihari, and Kissin²⁰ hypothesized that deficits in P3 voltage of the ERP may antecede the onset of chronic alcohol abuse and may be present in males at high risk for alcoholism. The investigators decided to test this hypothesis in a select group of individuals who had never had exposure to alcohol and were at high risk for alcoholism according to population genetic studies. ERPs were recorded from 25 young sons of alcoholic fathers and 25 control boys matched for age, socioeconomic status, school grade, and who had no family history of alcoholism. The experimental paradigm consisted of a complex visual mental rotation task to identify the orientation of a target stimulus. The high risk group showed a significantly reduced amplitude of the late positive component (P3) of the ERP. This pattern of results (low voltage P3 amplitude) is quite similar to results obtained in abstinent alcoholics,¹¹ originally presumed to be solely the consequence of alcoholism. These similar findings in ERPs obtained in young, nondrinking sons of alcoholics are particularly interesting because they were obtained without administering alcohol to the subjects.

The reduced P3 voltages of the ERP obtained in young sons of alcoholics have recently been replicated in an older population.²¹ Using the identical experimental paradigm as Begleiter et al.,²⁰ O'Connor et al.²¹ recorded ERPs in an older (20-25 years of age) group of sons of alcoholic fathers and matched controls. None of the subjects manifested signs of problem drinking. In agreement with the observations reported by Begleiter et al.,²⁰ these investigators observed a significantly reduced amplitude of the P3 component of the ERP in the high risk males.

Because of the striking similarity in P3 deficits between abstinent alcoholics and males at high risk for alcoholism, Begleiter, Porjesz, and Bihari²² used the BAER to assess the auditory pathway in young boys at high risk for alcoholism. The investigators examined 23 sons of alcoholics (7-13 years old) and 23 control boys matched for age, socioeconomic status, and school grade. In contrast

to the P3 voltage findings, no significant difference in the BAER was found between high risk and low risk boys. These results suggest that the BAER abnormalities observed in abstinent alcoholics are likely to be the consequence of alcoholism whereas the P3 deficits seen in both abstinent alcoholics and individuals at high risk for alcoholism may be antecedents of alcoholism.

In order to determine if the P3 findings in high risk individuals were modality or task specific, Begleiter, Porjesz, Rawlings, and Eckardt²³ have recently studied auditory-evoked potentials in another group of high and low risk boys. An auditory oddball paradigm was developed in which subjects pressed a button to discriminable infrequent stimuli. In this study, all subjects were instructed to stress accuracy over speed. The subjects were 23 young boys (7–16) who were sons of alcoholic fathers and 23 control boys without a family history of alcoholism matched for age, school grade, and socioeconomic status. The subjects in this study were carefully interviewed to ascertain that they had no exposure to alcohol or other illicit drugs.

It is important to note that the young sons of alcoholics tested by Begleiter et al.²³ meet the criteria for male-limited (Type 2) alcoholism as proposed by Cloninger.²⁴ All of the young high risk boys came from families in which familial alcoholism occurred only in males, was highly heritable, gave rise to severe early onset alcoholism with a high rate of recidivism requiring extensive treatment, and was accompanied by the occurrence of petty criminality. These data were obtained by conducting clinical examinations. The neurophysiological deficits observed in young male offspring of male-limited alcoholics is intriguing in light of neurochemical deficits found only in male-limited alcoholics as well as high risk individuals.²⁵ These neurochemical findings will be reviewed in a subsequent section.

The results of this recent study by Begleiter et al.²³ indicate that boys at high risk for alcoholism manifest significantly reduced amplitudes of the P3 component of the ERP. The reduced P3 voltage found in this auditory study indicates that P3 reduction in high risk males does not seem to be modality or task specific but seems to be present in the visual as well as auditory modality in easy and difficult tasks, and in speed as well as accuracy conditions.

Reduced P3 voltages in high risk subjects without the administration of alcohol have been replicated in three different laboratories: by O'Connor et al.,²⁶ by Whipple et al.,²⁷ and by Steinhauer et al.²⁸ As these findings have now been obtained by various laboratories under different experimental conditions, these findings seem to be generalizable.

Other investigators have reported differences in P3 between high risk and low risk individuals only after the administration of either alcohol or placebo. Elmasian et al.²⁹ studied the P3 component as well as the slow wave component of the ERP in three separate groups of subjects

each consisting of five matched pairs (five high risk and five low risk); one group served as the placebo group, the second group received a low dose of alcohol, and the third group was administered a high dose of alcohol. The subjects were male college students between 20 and 25 years of age who were primarily social drinkers. The investigators observed a significant decrease in the amplitude of the P3 component in the high risk compared to the low risk subjects. However this finding was observed after the administration of either alcohol or placebo. The investigators suggest that all subjects expected to receive alcohol; however, only high risk subjects manifest a specific expectancy for alcohol characterized by an unusual brain event. It is also suggested by the investigators that higher than normal alcohol intake in the mothers of high risk individuals might result in altered brain physiology.

Another study conducted by Neville and Schmidt³⁰ examined the late positive component of the ERP between young adults at risk for alcoholism and low risk individuals. This study did not involve the ingestion of alcohol or placebo, and therefore eliminated expectancy for alcohol as a potential confounding factor. Moreover the mothers of all subjects were interviewed to determine the use of alcohol and other drugs. Group differences in the late component of the ERP were observed.

In a subsequent study Schmidt and Neville³¹ recorded ERPs in high and low risk males while they performed a visual language task. All subjects were social drinkers. The investigators found that the amplitude of the N430 component was significantly smaller in men at high risk compared to men at low risk for alcoholism. Moreover, the latency of the N430 was directly related to the amount of alcohol consumed per occasion in the high risk group. These results imply that neuronal function associated with language processes are affected by family history of alcoholism, and the interaction between family history and alcohol consumed per occasion. Taken together the neurophysiological studies conducted in populations at high risk for alcoholism indicate rather clear differences between high and low risk individuals. While many questions remain unanswered, these preliminary findings appear quite intriguing and merit further neurophysiological investigations.

Neurochemistry

The search for biological markers has not been restricted to neurophysiological studies but has also yielded some interesting preliminary neurochemical findings. Monoamine oxidase (MAO) is an enzyme involved in the metabolism of neurotransmitters in the central nervous system. This enzyme is also found in blood platelets where it can easily be measured. In the last decade a myriad of studies have all reported low MAO levels in alcoholics compared to controls.^{32–39}

In 1980, Puchall et al.⁴⁰ measured platelet MAO in a large group of nonalcoholic college student and their

parents. The researchers observed a significant correlation between MAO in parents and offsprings. College students who manifested low levels of platelet MAO had parents who also showed low levels of MAO. It should be noted that the occurrence of alcohol abuse and alcoholism among the parents of the low MAO subjects was significantly higher than among parents of high MAO probands. These findings raise serious doubts about the possibility that low platelet MAO typically found in alcoholics are the direct result of alcohol abuse or alcoholism.

While these findings are interesting it should be noted that Schuckit⁴¹ found no statistically significant difference in MAO level between men with a positive family history of alcoholism and those with a negative family history of alcoholism. The investigator measured MAO before and 180 min after the administration of alcohol. While statistical significance was not reached, there was a trend in the same direction, with lower MAO levels in males with a positive family history of alcoholism.

The many replications of low MAO levels in abstinent alcoholics and the demonstration that MAO levels appear to be under genetic control⁴² suggest that low MAO levels may antecede the development of alcoholism in male-limited alcoholics. A study by Alexopoulos et al.⁴³ investigated MAO levels in alcoholic patients and their first-degree relatives. A significant relationship was found between MAO levels which were low in both alcoholics and their first-degree relatives.

A recent set of observations would suggest that low MAO levels may not be prevalent in all alcoholics but may only be found in certain alcoholics. A study by von Knorring et al.²⁵ indicates that two types of alcoholism may be differentiated by platelet MAO activity. The investigators studied 36 outpatient alcoholics and 34 control subjects without a family history of alcohol abuse or alcoholism. The alcoholic patients were further classified as either Type 1 (milieu-limited) or Type 2 (male-limited) alcoholics. This subclassification was accomplished on the basis of age of onset, severity of the disease, social consequences, frequency and severity of legal problems, and family history. The investigators reported that platelet MAO levels were significantly lower in the Type 2 alcoholics compared to the Type 1 alcoholics. The distribution of MAO activities was essentially the same in the controls and the milieu-limited alcoholics.

A number of other studies have attempted to examine various biological variables in order to differentiate individuals at high risk for alcoholism from control subjects. Such attempts include studies of blood acetaldehyde⁴⁴ and prolactin.⁴⁵ The lack of experimental replication for the aforementioned biochemical studies do not make these variables viable candidates as potential biological markers. At present there is no compelling evidence to indicate that rates of alcohol metabolism are associated with the risk for alcoholism.^{46, 47}

Concluding Remarks

It is quite obvious that in the last 5 years there have been some significant research developments in the study of individuals at high risk for alcoholism. A number of biological as well as behavioral variables have already been reported to differentiate subjects at high risk for alcoholism from individuals at low risk. However, it is at present totally unknown whether the myriad of variables which have already been identified are indeed predictive of subsequent alcohol abuse or alcoholism. Prospective longitudinal research is absolutely essential in order to evaluate the validity, reliability, and predictability of those variables as potential phenotypic markers for a predisposition toward alcoholism. These longitudinal studies can be considered high risk for the investigator unless a set of well-delineated variables with high potential can be culled for longitudinal studies.

The following criteria are necessary for the identification of a potential biological marker:

1. Studies of subjects from the general population should show that the trait (*a*) can be reliably measured and is stable over time (Table 1); (*b*) is genetically transmitted (Table 2); (*c*) the "abnormal" trait has a low base rate (Table 3); (*d*) identifies individuals at risk (Table 4).

2. Studies in patients should show that the trait (*a*) is prevalent in the patient population (Table 5); (*b*) is present during symptom remission (Table 6); (*c*) occurs among the first-degree relatives of the index case at a rate higher than that of the normal population (Table 7); (*d*) segregates with the illness in affected relatives (Table 8).

Tables 1-4 indicate results of neurophysiological tests (EEG, sensory EPs, and long latency ERPs) of subjects in the general population for each of these criteria, respectively. The criteria for the identification of a potential phenotypic marker are only discussed within the context of neurophysiological experiments, as they provide the most compelling data to qualify as biological markers. As can be seen in each of these tables, neurophysiological measures appear very promising in terms of the above criteria.

Tables 5-8 indicate results of neurophysiological tests in patients for each of the criteria of a phenotypic marker, respectively. As these tables indicate, neurophysiological measures meet the criteria for the identification of a marker in most of these patient-related criteria except those that have not yet been examined. Studies are underway to investigate whether neurophysiological measures segregate with the illness in the affected relatives. Thus, on the basis of currently available data, it appears that neurophysiological measures are likely candidates as potential markers of alcoholism.

Further studies must of necessity heed recent data which indicate that alcoholism is a heterogeneous disease with multiple clinical types of alcohol abuse. Studies of high risk populations should obtain detailed clinical characterization of alcoholism in the family, since it is now estab-

Table 1. Marker Can Be Reliably Measured and is Stable Over Time

Test-retest correlations:	6-18 months
EEG (frequency analysis)	0.62-0.87
Short latency EP (sensory)	0.81-0.96
Long latency EP (cognitive)	0.79-0.93

Table 2. Marker Should Be Genetically Transmitted

	MZ	DZ
EEG (all frequencies)	0.61-0.79	0.23-0.34
EEG (alpha only)	0.69-0.81	0.31-0.37
Early EP (sensory)	0.78-0.86	0.34-0.35
Late EP (cognitive)	0.64-0.81	0.32-0.38

Table 3. Marker (Abnormal) Manifestation Should Have a Low Base Rate in Normal Population

EEG (all frequencies)	Abnormal less than 5%
Early EP (sensory)	Abnormal less than 4% (?)
Late EP (cognitive)	Abnormal less than 4% (?)

Table 4. Marker Should Identify Individuals at Risk

EEG	Current data on correct identification not available
Early EP (sensory)	Does not appear useful to identify individuals at risk
Late EP (cognitive)	35% of sons of all alcoholic fathers 87% of sons of Type 2 alcoholic fathers

Table 5. Marker Should Be Prevalent in the Patient Population

EEG abnormalities	Approximately 56% of short-term abstinent alcoholics
Early EP (sensory)	Approximately 61% of short-term abstinent alcoholics
Late EP (cognitive)	Approximately 74% of short-term abstinent alcoholics

Table 6. Marker Should Be Present during Symptom Remission

EEG abnormalities	Approximately 19% of long-term abstinent alcoholics
Early EP (sensory)	Approximately 7% of long-term abstinent alcoholics
Late EP (cognitive)	Approximately 43% of long-term abstinent alcoholics

Table 7. Marker Should Occur among First-Degree Relatives of Patients at a Rate Higher Than That of "Normal" Population

EEG	Significantly higher incidence of EEG abnormalities in high risk individuals compared to control subjects
Early EP (sensory)	Not available
Late EP (cognitive)	Significantly higher incidence of late EP abnormalities in first degree relatives of patients compared to normal population

Table 8. Marker Should Segregate with the Illness in Affected Relatives

EEG	Data not available
Early EP (sensory)	Data not available
Late EP (cognitive)	Only preliminary data available

lished that different types of alcoholism may be correlated with different gene-environment interactions. Investigators should no longer focus on statistical techniques which attempt to compare group means from high risk versus low risk populations. More attention needs to be focused

on outliers as well as the presence of different distributions or populations within the high risk group. Studies of subjects at high risk for alcoholism should not only focus on abstainers or mild drinkers, but should include drinkers as well for possible comparisons.

At present, studies on high risk populations have been limited to male subjects. There is need to investigate daughters of alcoholics and to compare them to sons of alcoholics. Moreover, there is need to assess the relationship between various potential markers and the pattern of incidence of alcoholism in first- and second-degree relatives.

It is becoming increasingly obvious that the development of alcoholism is not likely to be the result of a single biological or behavioral factor. Indeed the disease of alcoholism is likely to reflect the complex interactions of biological and behavioral predisposing factors in conjunction with environmental precipitating factors. Therefore it is incumbent upon future investigators to evaluate biological as well as behavioral variables, simultaneously, and to assess their interactions.

While studies involving young individuals at high risk for alcoholism cannot examine the pharmacogenetics of alcohol, the effects of alcohol should be evaluated in older subjects at high risk for alcoholism. Initial sensitivity, tolerance, as well as the reinforcing properties of alcohol should be studied in populations at high risk. Biological and behavioral studies of high risk populations could lead to the development of valid and reliable phenotypic markers which may eventually be used in family studies in conjunction with molecular genetics.

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