Risk Markers for Alcoholism in High-Density Families

Shirley Y. Hill
Stuart R. Steinhauer
Timothy R. Smith
Jeannette Locke

Alcoholism and Genetics Research Program
Western Psychiatric Institute and Clinic
University of Pittsburgh School of Medicine

This review summarizes the efforts of our research program to identify markers for alcoholism risk, which broadly fall within the domain of temperament and those which may be described as attentional or information-processing capacities. Analyses of three-generation pedigrees that include minor children at higher risk of becoming alcoholic indicate that event-related potential characteristics differ between high- and low-risk children. Newer results concerning cardiac responsivity both in minor children and adult high-risk individuals are presented. These results suggest a relationship between personality or temperament on the one hand, and cardiac responsivity on the other. Additional neurobehavioral markers are addressed including static ataxia. Recent segregation analyses and linkage to particular DNA segments are also included.

Alcoholism ranks among the most commonly occurring psychiatric disorders in the general population. Furthermore, it appears to have a higher probability of transmission in families than most psychiatric disorders including the affective disorders (Merikangas, Leckman, Prusoff, Pauls, & Weissman, 1985). Adoption data suggest that this higher rate of transmission occurs even in the absence of exposure to the alcoholic parent (Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973). Moreover, alcoholism appears to breed “true to type” even among the substance abuse disorders (Hill, Cloninger, & Ayre, 1977; Pohlisch, 1933). Early studies by the St. Louis group indicate that comorbid psychiatric conditions in the proband alcoholic are reflected in elevated rates of comorbidity in relatives (Pitts & Winokur, 1966; Winokur & Clayton, 1967). Given this historical perspective, it is not surprising that the “genetics of alcoholism” has become such a timely topic.

Appreciation for the assistance of many individuals who made this publication possible is gratefully acknowledged. These include both former and current staff of the project, particularly Linda Wastyn, for editorial and statistical help, and Christopher Aston, for genetic analyses. The help of the families who gave their time to this project is also greatly appreciated. This research was supported by a grant from the National Institute of Alcohol Abuse and Alcoholism (AA-05909).

Correspondence and requests for reprints should be sent to Shirley Y. Hill, Alcoholism and Genetics Research Program, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.
Quantification of Risk

One disturbing trend, however, has been the tendency to assume that the high rates of transmission seen in alcoholic families are due entirely to genetic factors. Although a few thoughtful reviews give exception to this (Lester, 1988; Peele, 1986), the majority presume the exclusivity of genetic factors. Though few alcoholism researchers would agree with the statement that most of the variance in alcoholism outcome is attributable to genetic factors, many of the research designs employed to seek psychobiological predictors have made that assumption through designs that have contrasted “family history positive” and “family history negative” groups. The apparent underlying assumption is that the presence of a single first-degree relative is evidence for a genetic predisposition. This is not necessarily so.

Recently, we submitted two of our pedigrees to a quantitative analysis of risk using computer programs designed for this purpose (MENDEL). In collaboration with Dr. Stephen Matthyssse of Harvard University, we demonstrated that two pedigrees, both of which would be classified as family history positive, had vastly different likelihoods of sporadicity. (A sporadic family is one in which factors other than genetic ones have etiological significance.) In one case, the likelihood was less than 7%, and the other was over 80%. This example underscores the need to take alcoholism studies beyond categorical groups to quantified risk estimates. Although some investigators have attempted to quantify familial loading by various techniques (Alterman, 1988; McCaul, Tukkan, Svikis, Bigelow, & Cromwell, 1990; Pandina & Johnson, 1990; Stabenau, 1984; Volicer, Volicer, & D'Angelo, 1983), none have demonstrated that the estimates provided by these techniques are predictive of alcoholism on a case-by-case basis. This would require a longitudinal follow-up. A better strategy might be to use more sophisticated computer programs familiar to geneticists. For example, POINTER (Lalouel & Morton, 1981) is a program that calculates complex segregation analysis and provides estimates of recurrence risk (the likelihood that a given individual will become affected) for particular individuals given their particular family background. Longitudinal follow-up to confirm the predictive power of the estimated risks could then be used to test these estimates.

Because alcoholism is a complex disorder, its etiology and pathogenesis are most likely the result of both genetic and environmental factors (Hill, Aston, & Rabin, 1988; Hill, Steinhauer, & Zubin, 1987). Unraveling the relative contributions of particular genes and environments and their additive or interactive effects requires complex data sets that include large numbers of related individuals. Accordingly, nuclear families and extended pedigree data provide one important source for uncovering such relationships. Moreover, multigenerational pedigrees provide the opportunity for assessing the relative contribution of genetic and familial environmental factors as well as cultural transmission.
Nosological Considerations

Alcoholism appears in many forms. Nevertheless, there is some regularity in the signs and symptoms of alcoholism so that an endpoint phenotype can be described and studied. Owing to the large amount of family data collected in St. Louis using the Feighner Criteria (Feighner et al., 1972), we strictly adhered to this definition throughout our work. (Briefly, at least one symptom from three out of four symptom groups is required for "definite alcoholism.""

However, both in treated and community samples, one sees alcoholic individuals who carry dual diagnoses. This may arise because the second disorder is common in the population (e.g., affective disorder) or because there is a common underlying diathesis. Furthermore, some alcoholics may have developed their alcoholism because of a strong genetic diathesis whereas others may have arisen solely because of environmental causes. (The attempt by Cloninger, Bohman, & Sigvardsson [1981] to describe a Type I [milieu type] and a Type II [more genetically predisposed] form is recognition of this problem.) Unlike other pedigree studies (e.g., St. Louis) which included comorbid cases, we restricted our study to "pure" types who do not carry a dual diagnosis and have an absence of these in first-degree relatives. This reduction of heterogeneity enabled us to identify clinical, biological, and genetic characteristics of persons with alcoholism alone, thus avoiding the possibility that the markers found would only be indicators of nonspecific psychopathology.

Because of the heterogeneity problem, the goal of our ongoing research effort has been to identify more discriminating indicators of risk for developing alcoholism by limiting our study to a highly selected sample where two or more male alcoholic probands and their families (parents, all siblings, and minor offspring) were available. Furthermore, we excluded families with other psychiatric illnesses (antisocial personality was allowed) from our affected families and excluded both alcoholism and all psychiatric illnesses from our control families. This strategy provided us with extended pedigrees of male alcoholic probands with which to begin to identify discriminating markers for risk and to describe the pattern of transmission of the disorder.

We chose this strategy of examining only highly selected families for two reasons: (1) understanding biological mechanisms is facilitated by increasing the homogeneity of the sample under study; and (2) comorbid conditions may well mask identification of those psychobiological markers that could be useful in understanding the etiology and, ultimately, the prevention, of alcoholism. Selection of families through two alcoholic probands eliminates families with a single alcoholic individual who may be a "sporadic" case and thus tends to increase homozygosity (Matthysse & Kidd, 1981) so that if a marker gene is present, it is more easily detected.

Developmental Issues

Understanding the etiology of alcoholism requires searching for promising "markers," including both behavioral and genetic ones, across the life span.
(Behavioral characteristics may have known genetic mediation, but are contrasted with gene products such as DNA sequences investigated through restriction fragment enzyme techniques [RFLPs].) Searching for markers across the life span is necessary because as individuals age, their cumulative use of alcohol and drugs increases. In some cases, the marker of interest may be changed by alcohol consumption. With regard to alcohol affecting the marker of interest, it is worthy of note that early reports by Cruz-Coke (1965) and Cruz-Coke and Varela (1965) indicated that alcoholics displayed a red–green color blindness more often than nonalcoholics, suggestive of a sex-linked disorder. However, later reports (Fialkow, Thuline, & Fenster, 1966) indicated that long-term use of alcohol alters liver function sufficiently to produce a high rate of false-positive color-blind individuals. Thus, when alcoholics in remission were tested, the marker status changed.

Because different behaviors emerge at different points in development, it is conceivable that critical differences between high- and low-risk groups would be apparent only at certain developmental stages. Alternatively, performance may be similar, but, when age-matched groups are contrasted, one group shows a developmental lag with respect to the other. A major goal of our research program has been to adopt a developmental perspective on the process of becoming alcoholic, utilizing both neurobehavioral techniques (e.g., event-related potentials, baseline sway) and measures of temperament for understanding this process. To date, we have identified and located 190 minor offspring of our proband alcoholics and their siblings as well as offspring from control families who are currently between the ages of 8–18 years. These children represent a rich resource for a prospective longitudinal follow-up for two reasons: (1) they, like their parents and grandparents, have been characterized diagnostically through structured psychiatric interviews; and (2) biological marker data are available for all three generations. Included in this report are data based on the first 80 children we assessed.

**Study Design**

The overall goal of our research has been to identify patterns of markers that might identify those individuals most vulnerable to developing alcoholism. We expect that results of this study would lead to developing markers of vulnerability to alcoholism, permitting early detection of the alcoholism-prone individual. Educational programs for guiding such individuals in the use of alcohol could then be applied.

The research design we used is somewhat unique. Multiple pedigrees selected through the presence of at least two male alcoholic siblings were identified over the past 6 years. A typical pedigree may be seen in Figure 1. Only those pedigrees with an absence of other psychiatric problems were included. A severe form of alcoholism resulted. (Recurrence risks for 10-year-old children from our pedigrees indicate an overall rate of alcoholism by age 20 that is approximately three times greater than the population prevalence.) With the availability of both alcoholic and nonalcoholic adult
siblings, their children, and their parents, which our study families afforded, it was possible to begin to separate the antecedents of alcoholism from its consequences. For example, if both alcoholic and nonalcoholic members of a sibling pair have a given trait, it may be provisionally considered a diathesis indicator, whereas if only the alcoholic member shows the marker, it may be the result of long-term use of alcohol.

Over the past 6 years, an extensive data base has been amassed, which includes both laboratory-based psychobiological marker assessments, as well as behavioral and self-report measures of psychopathology. Although we used family history techniques to derive information about deceased relatives or second- and third-degree relatives of our proband alcoholics, the majority of our assessments were made by direct clinical interviews followed by extensive assessment of cognitive and personality functioning.

The foregoing review summarizes the efforts of our research program to pursue markers that broadly fall within the domain of personality or temperament, and others that are conventionally thought of as attentional or information-processing capacities. One theoretical link between these seemingly disparate domains would appear to be the functional state of the nervous system. Different states of physiological activation can be expected to alter both the way information is processed centrally, and how the individual more or less consistently presents himself or herself to the world (temperament variables). These relatively enduring traits or temperament variables need to be distinguished from state variables that may arise from alcohol use if they are to provide explanatory power.

RESULTS

Overview

This report gives brief highlights of our studies, which were based on over 100 affected and control pedigrees, ascertained through the Alcoholism and Genetics Research Program at the University of Pittsburgh. These include: (1) electrophysiological and neurobehavioral characteristics of high-risk individuals; (2) recent attempts to model the transmission of alcoholism using these affected pedigrees; (3) personality and temperament indicators in high-risk individuals that appear to be independent of long-term alcohol use; and (4) new findings on possible temperament differences in children of alcoholics that might predispose them to alcoholism.

Auditory Event-Related Potentials (ERP) in Adult High-Risk Relatives

Recently, a great deal of attention has been focused on ERPs as possible biological markers for alcoholism risk. It is now well established that chronic alcoholics exhibit deviations in ERP characteristics (Porjesz & Begleiter, 1982; Porjesz, Begleiter, & Samuelly, 1980). There is considerable consistency in results obtained for the P300 component of the ERP for individuals at risk.
Pedigree 62

Legend

- Male; female unaffected
- Male; female affected
- Male; female affected status unknown
- Male; female deceased
- Age at interview
- Age at interview of proband
- Diagnosis from interview
- Diagnosis from family history
- Age of onset from interview

Figure 1. A typical Pittsburgh pedigree showing multigenerational alcoholism.
for alcoholism who are not themselves alcoholic (Begleiter, Porjesz, Bihari, & Kissin, 1984; Elmasian, Neville, Woods, Schuckit, & Bloom, 1982; Neville & Schmidt, 1985; Whipple & Noble, 1986), though there have been reports that failed to find differences between high- and low-risk groups (Polich & Bloom, 1987). P300 refers to a scalp-positive component, which occurs with a latency of approximately 300 msec (Donchin, 1979; Sutton & Ruchkin, 1984) and is related to stimulus evaluation, whereas components with latencies of 200 msec or less (e.g., P50, N100, P200) tend to be associated primarily with the physical characteristics of the stimuli presented. (N100 amplitude also is related to general levels of attention.)

Two tasks are typically employed in our laboratory: counting of an infrequent tone while ignoring frequent tones, and later, a choice reaction task in which a different finger press is performed for infrequent versus frequent tones. At least one frequent tone occurs after every rare tone (two rare tones never occur in a row), and the subject is informed of this contingency at the onset of testing. Using the probability of a rare tone followed by a frequent, two frequencies in a row, or a frequent followed by a rare, results in conditional probabilities of 1.00, .67, and .33. Results are analyzed with respect to these probabilities as previous work has indicated a strong relationship between conditional probability and amplitude of the P500 component (Steinhauer & Zubin, 1982). Details of this methodology have been published elsewhere (Hill, Steinhauer, Park, & Zubin, 1990; Hill, Steinhauer, Zubin, & Baughman, et al., 1988; Steinhauer, Hill, & Zubin, 1987).

Although results for a number of components could be discussed, our discussion is limited to those obtained for the P300 component. We have found that, among adults, the peak latency of P300 occurs later in affected (alcoholic) siblings as compared to unaffected ones (Figure 2). This effect remains even when controlling for alcohol use. This is particularly important because recurrence risk is highly correlated with latency of P300 (.33 condition) among our minor children, particularly among boys, who have not yet begun to drink alcohol (r = .46, df = 17, p = .028). Therefore, we have speculated that within high-risk families, those who do not succumb to alcoholism may possess protective factors such as more efficient information processing. Unlike minor children, adult high-risk subjects do not show auditory P300 amplitude differences, suggesting that a search for biological markers for risk must take into account developmental considerations. This shorter latency in nonalcoholic siblings also is accompanied by greater levels of achievement orientation. In fact, the nonalcoholic brother has higher levels of achievement than controls (Hill, Zubin, & Steinhauer, 1990).

ERP Assessments in High-Risk Children

Auditory.

When sons and daughters of male alcoholics were compared with age-matched controls, they were found to differ in a number of ways (Hill, Steinhauer et al., 1990). Among the most interesting findings was a decrease
Figure 2. P300 latency as a function of the conditional probability of a presented target for the alcoholic proband and his family members performing the Choice Reaction Task. Note the shorter latency for the unaffected (nonalcoholic) sibling.

in P300 amplitude (auditory) for the high-risk children when compared to the controls in two probability conditions (.67 and 1.00), which is in agreement with Begleiter et al.’s (1984) finding (visual) for an all-male sample (Figure 3). This decrease in amplitude was not seen in the .33 condition. We viewed the .33 condition as a more difficult condition for the subject because it evokes greater utilization of processing resources. This is evidenced by the fact that this rare condition produces a larger amplitude and longer latency relative to the other two conditional probabilities (Steinhauer & Zubin, 1982). We speculated that task difficulty may determine whether or not a reduction in amplitude is seen.

Another intriguing finding from our auditory paradigm was that greater negativity was seen for the high-risk children at the frontal electrode beginning at approximately N250. This finding is of interest because of developmental changes in N250: Frontal negativity in children decreases in adolescence and throughout the life span (Friedman, Brown, Vaughan, Cornblatt, & Erlemeyer-Kimling, 1984). Because both groups were of comparable age, a possible developmental lag among the high-risk children is suggested.

Visual Task.

Recently we implemented the visual ERP paradigm of Begleiter et al. (1984) in our laboratory. This task is a more difficult task than the auditory
P300 Amplitudes – Choice Reaction Task

Children

Figure 3. P300 amplitude as a function of the conditional probability of a presented target. Children from control families display higher amplitude when performing the Choice Reaction Task than do children from alcoholic families.

oddball paradigm used in our laboratory and those typically used by others (Pfefferbaum, Rosenbloom & Ford, 1987). In this task, subjects are presented with an outline of a head with one ear present. The task is to press a button indicating whether it is a left or right ear. When the nose points upward, the ear is to the same side of the body as the responding hand, a relatively easy task. However, when the nose points downward, the ear is to the opposite side of the body as the responding hand so the task is difficult in comparison. Blank trials requiring no response also are included. P300 responses are typically recorded to stimuli requiring a response. Results of the visual task given to the first 48 children tested show that whereas control children show large P300s for the more difficult as compared with the easy condition, high-risk children show the opposite effect (a significant group by condition effect). The difficult condition requiring more attention to the task appears to normalize the responses of the high-risk children. (There were no differences in error rates, false alarms, misses, or incorrect responses, between the groups.)

Although these results for the visual task are quite preliminary, they suggest that the focusing of attention through a more difficult requisite task tends to normalize the performance of the high-risk children. This is in accord with our auditory findings: High-risk children were equivalent to controls when the task difficulty was increased (.33 condition as compared to .67).

Results of our ERP assessments using both auditory and visual paradigms across an age span of over 60 years (children, parents, and grandparents all received ERP assessment) suggested to us that the processing difficulties seen in high-risk individuals are most apparent in the least challenging situations. Could it be that a challenging situation serves to focus the attention of the high-risk individual so that when full-processing capability is brought to bear,
few differences between high- and low-risk groups are seen? Should this principle be found to hold true with future work, it may have important implications for ameliorating educational deficits reported for high-risk children.

**Cardiac Responsivity in Adult High-Risk Relatives**

**Baseline Heart Rate.**

A particularly striking finding emerged from analyses of the cardiac responsivity of the adult members of our pedigrees (Hill, Steinhauser, & Zubin, in press). The mean heart rate for all siblings, affected or unaffected, who come from the high-risk families was elevated with respect to controls (see Figure 4). The significant effect of family type (affected versus control) was present even when a number of covariates were removed (i.e., recent alcohol consumption, cigarettes, and caffeine). This finding could not be attributed to alcohol use because our unaffected siblings from the affected families had similar levels of alcohol consumption to the control siblings. Furthermore, no differences were observed in frequency of smoking or overall physical conditioning.

**Prestimulus Heart Rate in Adults**

![Graph showing prestimulus heart rate in adults](image)

**Figure 4.** Prestimulus heart rate at IBI-1 is plotted for both auditory tasks for each of the three adult subject groups: Affected (alcoholic sibling) and unaffected (nonalcoholic sibling) from the high-risk families and controls from the low-risk families. (IBI:0 represents the interbeat interval during which the stimulus is presented).
Response to Certainty/Uncertainty.

In addition to recording of baseline heart rate, the paradigms used to elicit the ERPs also allow for measurement of heart-rate acceleration and deceleration. Cardiac deceleration is associated with the anticipation of a potentially relevant stimulus. During the Counting task, when the individual anticipates that the next stimulus is irrelevant as, for example, when a target has just occurred (subject has been told two targets never occur in a row, a certain event), there is a failure to decelerate and continued acceleration to the previous event occurs. In contrast, uncertain (or unpredictable) stimuli are always preceded by deceleration, followed by acceleration during the poststimulus evaluation. Adult individuals from affected families show a significantly smaller difference in their response to certainty and uncertainty under conditions of minimal task demand (Counting) than do controls (Figure 5). We suggest that this represents decreased attentional processing during the anticipatory period. However, as task demand is increased by requiring a motor response to all stimuli (Choice RT task), members of both control and affected families generate anticipatory deceleration to all events including all “certain” stimuli. In parallel, the greater processing demand of the Choice RT task also tended to normalize the auditory ERP responsivity of high-risk children (Hill, Steinbauer et al., 1990). Taken together, this failure to discriminate certain and uncertain conditions under minimal task demand for ERP and cardiac paradigms suggests that individuals at risk for developing alcoholism may be subject to problems in attentional focusing. The nature of the attentional problem is subtle and requires evaluation of how subjects perform, both behaviorally and psychophysiologicaly, under different levels of task difficulty.

Cardiac Reactivity in High-Risk Children: Relationship to Personality, Temperament, and Psychiatric Status.

In addition to our laboratory measures of cardiac responsivity, we have been assessing cardiac response in children to two types of stress: (1) a mental arithmetic task, and (2) the anticipation of a blood draw. The mental arithmetic task is performed immediately before the child begins the auditory and visual paradigms in the ERP laboratory, whereas the response to the stress of a blood draw is recorded at Children’s Hospital where children are routinely taken to obtain blood samples for other measures of interest.

In addition, all children are given an age-appropriate modification of the MMPI. The only trait on which high-risk children were different from controls was on Social Introversion. Intrigued by observations by Kagan and colleagues that temperamentally fearful children display consistently higher heart rates (Garcia-Coll, Kagan, & Reznick, 1984; Kagan, Reznick, Clarke, & Snidman, 1984; Kagan, Reznick, Snidman, Gibbons, & Johnson, 1988; Reznick et al., 1986), we investigated this relationship by correlating prestimulus heart rate (from our Counting and RT paradigms) with the Social Introversion scale from the MMPI for all subjects (high-risk and controls). Based on a sample of 26, we obtained an $r$ of .39 ($p < .025$; see Figure 6). Restricting our data
Cardiac Deceleration in Adults
Certainty-Uncertainty Differences

Figure 5. Heart rate differences between IBI-1 and IBI+1 for the certain (1.0) condition and uncertain (.33 and .67) conditions are plotted for each of the three adult subject groups for the Counting Task.

to high-risk children (Figure 7), the results were even stronger ($r = .61$, $p < .011$). Using controls only, the results were not significant. In Figure 7, it may be noted that extreme scores are indicated in closed circles. This is of interest because of the 14 children who were at high-risk, we calculated that approximately 3–4 children will become alcoholic in the next 10 years. Perhaps the most extreme on both measures may turn out to be those who later develop alcoholism. Through longitudinal follow-up, we will be able to determine if these “outliers” on the psychobiological indicators develop alcoholism.

Stimulated by these findings, we began to look at the types of K-SADS diagnoses that were more prevalent among our high-risk children. A number of these children carried consensus diagnoses of Separation Anxiety, Overanxious disorder, and Simple Phobia. In fact, of the 13 children with any Axis I disorder, 8 had one of these diagnoses. There was a significant positive correlation between presence of an anxiety-related disorder and the magnitude of the heart-rate increase in response to the blood draw (point biserial $r = .31$, $p < .05$). When we examined the larger sample of children for whom K-SADS assessments have been completed and analyzed ($N = 68$) and used the presence of any Axis I diagnosis of psychopathology to compare members of our high- and low-risk groups, we found that children who were at high
Figure 6. A correlation between the prestimulus heart rate (Counting Task) and scores from the Social Introversion scale of the MMPI has been demonstrated for children.

Risk for developing alcoholism were 2.2 times as likely to have a diagnosis. The majority of diagnoses seen among these high-risk children can be characterized as anxiety- or fear-related.

Results of Sway (Static Ataxia) Assessment in Children

We have reported results of sway assessments utilizing a mechanical measure of sway in children from our high-density pedigrees (Hill, Armstrong, Steinhauser, Baughman, & Zubin, 1987). These high-risk children were found to sway more when compared to children of controls. Because the children averaged 11 years of age, they had not begun to experiment with alcohol or drugs. Also, the sway measurements were elicited without administration of alcohol. These results confirm other published studies (Lester & Carpenter, 1985; Lipscomb, Carpenter, & Nathan, 1980) indicating that this may be a robust marker. We have begun to investigate sway using a sensitive movement platform (computerized force plate). Additionally, we have been evaluating a number of “soft” neurological signs that might be present in these children.
Prestimulus Heart Rate vs Social Introversion
High Risk Children Only

Figure 7. A robust correlation of prestimulus heart rate with Social Introversion is seen when scores for only the high-risk children are plotted. Some children were considered “extreme scorers,” having both higher heart rates and higher scores on the SI scale than the other high-risk children. It is hypothesized that these children may be at the highest risk for becoming alcoholic in adulthood.

Based on analysis of 68 children, we find that balance and gait assessments from the neurological battery indicate a correlation with performance on the movement platform.

Comparison of Temperament in High- and Low-Risk Adults and Children

Our studies in personality have not only been directed toward identifying differences between alcoholics and normal controls, but more importantly, attempting to identify differences between high-risk nonalcoholic individuals and normal controls. Analysis of MMPI data (unpublished) indicates a host of differences between alcoholics and normal controls. Moreover, alcoholics differ from their nonalcoholic siblings in a number of ways. Of particular interest is an elevation in Scale 8 (schizophrenia) among nonalcoholic siblings of alcoholics when compared to controls. (Alcoholics were significantly higher
than their nonalcoholic brothers.) Although this elevation would not be in the clinically important range \((T > 70)\), nevertheless, it indicates that nonalcoholic adult siblings from affected families have significant elevations relative to controls though one is alcoholic and the other not. Additionally, we have taken a behavioral-genetic approach to understanding variations in personality using intraclass correlations to look at covariations in siblings. Where brother pairs are both alcoholic, a greater similarity is seen over discordant pairs of siblings (Hill, Zubin et al., 1990).

**Is Alcoholism Transmitted as a Multifactorial Component or Is There Evidence for a Single Major Gene?**

Although it is unlikely that something as complex as alcoholism can be accounted for by a single gene, we thought it useful to determine if there were evidence for a major effect. Should alcoholism follow a mixed model (major effect in the presence of a multifactorial background), demonstration of a major effect would make the search for a gene more plausible. Because we had a large number of highly selected pedigrees available, we set out to determine if a major effect might be present, and if so, if it were recessive or dominant. The unified mixed model of Lalouel and Morton (1981) was used to analyze the segregation of alcoholism in 35 affected nuclear families. A segregation analysis (Aston & Hill, 1990) provided significant evidence for familial transmission and suggested that the underlying liability to definite alcoholism was, in part, controlled by a major effect with or without an additional multifactorial component. The hypothesis that the major effect was due to a single major locus with Mendelian transmission was rejected. Absence of this major effect also was rejected. The non-Mendelian character of this major effect may be due to confounding a Mendelian major locus with phenocopies or with differential expression between the sexes. It may be as simple as two Mendelian major loci acting in concert, it may be several such loci, or there may really be segregation distortion occurring. However, an increased sample size is necessary to delineate further the components of the genetic model for the underlying liability to definite alcoholism, a goal which we are currently pursuing.

**Search for the Susceptibility Gene.**

Although the primary focus of our research has not been on either doing a genome scan, or investigating a battery of candidate genes, we were in a position to perform preliminary linkage analyses on a small number of red cell antigens and marker antigens from the HLA histocompatibility locus. This was possible because we had collected blood samples for over 6 years as part of our attempt to verify paternity of all participating subjects. Based on data collected from 30 affected pedigrees, we found suggestive evidence of linkage of a putative alcohol susceptibility (AS) gene to blood markers on chromosome 4. Linkage was found between this putative AS gene and the MNS system \((\text{lod score} = 2.02,\) at a recombination frequency of .007; Hill,
Aston et al., 1988). The addition of new families placed the lod score as high as 2.49 at a recombination frequency of 0.00 (95% confidence interval: 0.00–0.10). However, recently, we found that the lod score had dropped considerably. We are pursuing additional families and additional loci in the vicinity of the MNS locus to determine if the suggestive linkage will disappear altogether or be confirmed.

CONCLUSIONS

First, we identified information-processing characteristics, utilizing event-related potentials and cardiac activity in adult subjects, which distinguish individuals from high- and low-risk families. For example, adult members of high-risk families (both alcoholic and nonalcoholic) show elevated heart rates relative to controls. Moreover, we identified within-family variations in processing activity (nonalcoholic brothers display a shorter latency of the P300 component). We explored these variables in children, because high-risk children show greater heart-rate change to the stress of the blood draw. Second, we utilized our extensive pedigree data to complete a segregation analysis providing important information regarding the mode of transmission of alcoholism. From this analysis, quantified risks for developing alcoholism have been specified for offspring that can then be correlated with marker status. Third, we tested 80 children and uncovered some interesting information-processing characteristics. High-risk children (a) show a developmental delay in N250 relative to controls, and (b) show P300 deficits that can be corrected by attentional focusing. Additionally, these children show evidence of specific neurological soft signs (greater body sway in controlled conditions). Moreover, they appear to have more anxiety-related disorders.

These findings led to the following working model. By adulthood, members of high-risk families, whether alcoholic or not, show higher baseline heart rates suggestive of either higher activation or greater anxiety. Young children from these families, more often than controls, show anxiety-related disorders. Thus, this activation factor may be thought of as a necessary, though not sufficient, condition for developing alcoholism. Some members of high-risk families display information-processing characteristics which indicate that performance is improved under conditions of attentional focusing. Inasmuch as this cannot be practically accomplished at all times, high-risk individuals who later become alcoholic may show less cognitive competence in early childhood, making school situations less rewarding. This may explain why two siblings from high-risk families may be discordant for alcoholism. For example, we found that the nonalcoholic adult male sibling has a shorter latency of P300 and a higher need for achievement (MPQ scores) when compared to his alcoholic siblings.

In summary, the rich resource which our database provides has allowed us to extract results that have moved across domains (temperament and activation) to integrate findings from one or more of these areas. Moreover, because of the three-generation data base that now includes over 400 indi-
individuals assessed by face-to-face interview and laboratory testing, we are in a unique position to chart the course of vulnerability across the life span.

REFERENCES


