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Neurophysiological Phenotypic Factors in the Development of Alcoholism

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Alcoholism is clearly a genetically influenced disorder, but in many respects it is different from other disorders that follow a more traditional Mendelian mode of inheritance. In contrast to such disorders as cystic fibrosis, Huntington's chorea, and sickle-cell anemia, the development of alcoholism (at least in some individuals) depends on the interaction of genetically determined predisposing factors with environmentally determined precipitating factors. The search for genes is rather complicated because alcoholism is a common disorder with a number of features characteristic of complex diseases:

1. Clinical heterogeneity. Alcoholism has a variable age of onset and can involve a number of different symptoms. Because it might develop late in life, a person's status as an alcoholic could remain uncertain for a long period of time.
2. Reduced penetrance. Because of unknown genetic or environmental effects, not every individual who inherits the genes will develop the disorder.
3. Genetic heterogeneity. Single mutations at different genetic loci may result in clinically indistinguishable disease states.
4. Polygenic inheritance. The disorder might not be caused by any single gene, but could develop from additive effects of multiple genes.
5. Epistatic effects. The disorder might reflect the complex interactions between alleles at several loci.
6. Phenocopies. A substantial number of individuals without a disease genotype manifest alcoholism resulting from nongenetic causes.

The prospect for identifying genes involved in the predisposition toward alcoholism is clouded by these characteristics. Nevertheless, modern molecular genetic and data-

analytic techniques make the search for genes underlying complex disorders quite feasible (Chapter 14 Wilson and Elston, this volume, Chapter 14; Ott, 1993). The quest for genetic factors in alcoholism would be greatly aided if it were possible to identify trait markers of a vulnerability for alcoholism.

While alcoholic patients are known to differ from nonalcoholics in many biological ways, such differences cannot be regarded as unique factors in the development of alcoholism. Indeed, any differences between alcoholic and nonalcoholic individuals do not just reflect potential antecedent factors, but are seriously confounded by such deleterious effects of drinking as tolerance, physical dependence, possible malnutrition, organ damage, and cognitive impairment. For these compelling reasons, the study of biologic factors leading to the development of alcoholism cannot be properly conducted in alcoholic patients.

Because of the solid evidence for genetic factors in the development of alcoholism, the study of offspring of alcoholic patients should provide an important sample of individuals known to be at risk for its development. Moreover, the selection of young males (Cloninger, 1987) from families with a history of alcoholism (Hill et al., 1988; Pihl et al., 1990), and studied long before the development of alcoholism, should provide an optimal sample of individuals at high risk. Such a sample may be ideal for studying antecedent factors in alcoholism. The longitudinal study of nonalcoholic individuals at high risk for developing alcoholism appears to provide the best cost/benefit ratio for identifying possible trait markers of vulnerability. Indeed, identification of either markers or risk factors should be quite valuable in the development of specific prevention and treatment initiatives.

The search for potential predisposing genetic markers in alcoholism must not only be conducted in individuals at high risk for developing alcoholism, but must meet a specific set of criteria critical for the identification of a genetically influenced marker as follows:

1. Individuals from the general population should demonstrate that the trait:
   (a) Can be reliably measured and is stable over time.
   (b) Is genetically transmitted.
   (c) The so-called "abnormal" trait has a low base rate in the general population.
   (d) The trait in question can identify individuals at risk with a significant degree of accuracy and reliability.
2. Studies in patients should demonstrate that the trait:
   (a) Is prevalent in the patient population.
   (b) Is present during symptom remission, and is not just a state marker.
   (c) Occurs among first-degree relatives of the proband at a rate higher than that of the normal population.
   d) Segregates with the illness in affected relatives of the proband.

Electroencephalography and Event-Related Brain Potentials

To date, several potentially critical risk markers have been investigated. Possibly the most intriguing data have come from a variety of studies investigating the electrical

activity of the brain in both those at risk and controls. Some investigators have focused specifically on the spontaneous electrical activity of the brain, the electroencephalogram (EEG); others have examined the event-related brain potentials with the use of information-processing paradigms.

It is now well established that abstinent alcoholics manifest a number of EEG abnormalities, such as decreased alpha activity and increased delta, theta, and beta activity (for a review see Begleiter and Platz, 1972). Because these studies were conducted in abstinent alcoholics, it is difficult to determine if the EEG findings reflect the consequent deleterious effects of chronic alcohol intake or antecede the development of alcoholism. Indeed, many biological or behavioral anomalies observed in alcoholics reflect alterations in physiological and psychological systems constructed over many years of substantial ethanol intake.

Electroencephalogram Studies

In 1982 Gabrielli and his colleagues tested the hypothesis that young children (11–13 years of age) of alcoholic fathers manifest a higher percentage of fast EEG activity than children of nonalcoholic fathers. A number of EEG frequency bands were studied. However, only frequencies of 18–26 Hz and above showed absolute increases in activity. This EEG observation was characteristic of young males at high risk (HR) for alcoholism, although absolute increases in activity were also obtained for lower EEG amplitudes in each frequency band examined. It should be noted that the EEG amplitude findings in HR males were opposite to those observed in HR females. Although these investigators did not record the incidence and severity of other psychiatric disorders in the parents of the offsprings, they concluded that an excess of fast EEG activity may precede the development of alcohol abuse or alcoholism. Moreover, they suggest that this EEG pattern is heritable, and thus represents genetically influenced factors.

In a different study conducted by the same group of investigators, Pollock et al. (1983) examined several EEG frequencies including theta (3.51–7.03 Hz), slow alpha (7.42–9.46 Hz), fast alpha (9.75–12.10 Hz) energy, and mean alpha frequency in a sample of 19- to 21-year-old males at high and low risk for alcoholism. Risk for alcoholism was established by determining that each individual subject was the offspring of a father who had been in attendance at a psychiatric or alcoholism clinic. Drinking history was assessed for both HR and LR subjects, and was found not to differ significantly. In this study all subjects were administered a challenge dose of alcohol (0.5 g/kg). After alcohol ingestion HR individuals demonstrated greater decreases in fast alpha activity and greater increases in slow alpha activity. The decreases were obtained at 120 minutes postethanol, and the increases were observed at both 90 and 120 minutes postethanol.

Moreover, HR individuals manifested greater decreases in alpha frequency than did LR individuals at 30, 60, and 120 minutes post ethanol. In contrast to earlier findings by the same group (Gabrielli et al., 1982) reporting that HR subjects manifest increased beta activity before alcohol challenge, Pollock et al. (1983) did not find any EEG differences between HR and LR subjects before ethanol challenge. In a separate

report, Pollock et al. (1984) did not replicate the findings earlier reported by Gabrielli et al. (1982). While the HR subjects did not differ from the LR subjects in terms of alcohol consumption, they reported a significant subjective tolerance effect compared to the LR subjects. These findings suggest the HR subjects are more sensitive to the physiological effects of alcohol, including decreased subjective alcohol effects.

At the University of Connecticut, investigators have also been examining possible EEG differences between HR and LR subjects. Kaplan et al. (1988) recorded EEG frequencies between 2 Hz and 20 Hz; delta, theta, alpha, and beta. The male subjects ranged in age between 20 and 28 years, and were all social drinkers. Subjects classified as HR had a father diagnosed as alcohol dependent (DSM III) with additional first- and/or second-degree relatives with a similar diagnosis. Subjects with an alcohol-abusing mother were excluded from both groups. The authors found no statistically significant EEG difference between the two groups.

Another group of investigators at the University of California at San Diego studied similar potential EEG differences (Ehlers and Schuckit, 1990a). They recruited males (21 to 25 years old) using a questionnaire to assess the presence or absence of alcoholism in their families. An HR subject was identified as an individual who indicated the presence of some symptoms of alcoholism in his father. Both HR and LR were carefully matched on a myriad of important variables. The authors examined EEG frequencies in the 9- to 12-Hz range and the 12- to 20-Hz range. They observed that HR subjects manifested more energy in the 9- to 12-Hz range than did the LR individuals.

In a second study the same authors (Ehlers and Schuckit, 1990b) found no difference between the two groups in the 12- to 20-Hz range. It is somewhat puzzling that differences were not found, since this particular study was designed to replicate the previous result, which indicated that significant differences between the two were present in the 18- to 26-Hz band. It appears as if the differences in this frequency range were not examined by the investigators. As part of the same investigation, the authors reported that LR subjects classified as moderate drinkers had significantly more power in the 12- to 20-Hz range than did those individuals classified as low drinkers. This interesting relationship was not evident in the HR subjects. In conclusion, the authors stated that both genetic factors and drinking history contribute to an individual's EEG characteristics.

It should be pointed out that both the Pollock and the Ehlers laboratories have investigated fast frequency alpha in subjects at high risk for alcoholism. However, the results appear to be quite different. For example, Ehlers and Schuckit (1990b) report less physiological responsiveness and sensitivity to ethanol in the HR group compared to the LR group, whereas Pollock and her coworkers (1983) report more responsiveness and more sensitivity. In spite of these physiological differences it should be noted that both groups find that HR subjects report feeling less intoxicated than LR subjects after a single dose of alcohol (Schuckit, 1980, 1984; Pollock et al., 1983).

The relationship between prechallenge baseline EEG and postethanol effects is particularly significant in assessing the effects of alcohol. Propping (1983) observed that subjects manifesting poor alpha activity prior to ethanol are the ones who demonstrate

the most synchronization following ethanol ingestion. Individuals with average preethanol alpha activity exhibit minimal change after an alcohol challenge. Lukas et al. (1986) have demonstrated that the magnitude of ethanol-induced frequency decrease varies as a function of the baseline frequency.

The Genetic Influences. It is now well established that some aspects of the spontaneous EEG are under genetic influence. For example, Vogel (1970) has reported different genetic EEG variants. He has proposed that low-voltage and regular alpha follow an autosomal-dominant model of transmission, whereas poor alpha and diffuse beta are under polygenic control. Recent studies from Germany indicate that a specific variant of the EEG is represented by a major gene located on chromosome 20 (Steinlein et al., 1991).

In order to test possible differences in baseline EEG between HR and LR individuals we (Cohen et al., 1991) examined a wide range of EEG frequencies. Baseline EEG activity was recorded in a group of 19- to 24-year old individuals at risk for developing alcoholism as well as another group of well-matched LR individuals. The HR subjects were all individuals whose fathers were currently undergoing treatment for alcohol dependency (DSM 111-R criteria). Moreover, inclusion in the HR group required a high density of alcoholism in the family. In this group the average number of alcoholic relatives was 3.5 individuals. However, alcoholism in one's mother was cause for exclusion from the study. Candidates for the LR group were excluded if any first-or second-degree relatives was diagnosed as alcoholic. Any subject with major medical problems, taking medication, or with a history of psychiatric problems or drug abuse was excluded. A 128-second EEG record was obtained for each subject at each of the 21 electrodes in the 10–20 International System. A fast Fourier transform (FFT) was performed on the first 12, artifact-free, 4-second intervals. The resulting power spectral densities were summed and averaged at 0.25-Hz intervals over a range from 0.25 to 63.75 Hz. The integrals of power densities over frequency were calculated for the following frequency bands: slow alpha (SA: 7.5–10 Hz), fast alpha (FA: 10.25–12.75 Hz), slow beta (SB: 13–19.5 Hz), fast beta (FB-19.75-26 Hz). In this study, only EEG activity at electrodes P4, P3, O2, and O1 was examined. The initial selection of these electrode sites was dictated by the fact that they were common to most of the previous studies.

This study demonstrates that at the selected electrode sites, over a wide range of frequencies investigated, the EEG in HR individuals does not differ significantly from the EEG recorded from LR individuals.

While baseline EEG findings indicate significant interlaboratory discrepancies, we have recently completed a study (Cohen et al., 1993) in which, for the first time, the effects of two doses of alcohol were studied on both the ascending and descending limb of the blood alcohol curve. We hypothesized that HR individuals would manifest greater sensitivity to the reinforcing properties of alcohol on the ascending limb of the blood alcohol curve (Newlin and Thomson, 1990). Moreover, we also hypothesized that on the descending limb, the HR individuals would manifest greater acute tolerance

compared to the LR individuals (Schuckit et al., 1987). In keeping with findings in the literature (Schuckit, 1985), we found no statistically significant differences in the blood alcohol levels for the LR versus HR individuals under both the low- and high-dose conditions. We observed significant group differences in slow alpha activity between the HR and LR groups under alcohol only. During the ascending phase of the blood alcohol curve (BAC), the slow alpha activity increased under both low- and high-dose conditions. This increase is in agreement with the findings by Lukas and his collaborators (1986), who asserted that the production of slow alpha suggests greater reinforcing properties. Our results demonstrate that the magnitude of the increases were significantly greater in the HR than the LR subjects during the ascending BAC. These novel findings suggest that the HR individuals are more sensitive to the reinforcing effects of alcohol than are the LR individuals. During the descending phase of the blood alcohol curve for the low-dose condition, both groups showed decreases in slow alpha activity, though the magnitude of this decrease was significantly greater in HR than in LR individuals. Similarly, under the high-dose condition, LR subjects continued to show slow alpha increases, while the HR subjects manifested decreases. These findings suggest that HR individuals might manifest greater acute tolerance to the effects of alcohol.

While the aforementioned data from our laboratory provide a novel set of observations regarding the effects of alcohol on the ascending and descending limbs of the blood alcohol curve, the interpretation of the findings is complicated by the fact that the HR and LR individuals were all social drinkers. It is not possible, with the data at hand, to conclude that the observed effects are the direct consequence of differential genetic sensitivity and acute tolerance between HR and LR individuals. Indeed, while the effects of alcohol on EEG are different between HR and LR subjects, depending on the phase of the blood alcohol curve, they could well reflect an interaction between innate sensitivity and tolerance, and an individual's experience with alcohol. The issue of differential innate sensitivity and tolerance between HR and LR subjects can best be tested in individuals without experience with alcohol.

The obvious disparity among baseline EEG findings from different laboratories as well as, in some cases, within laboratories might be explained by a number of factors. The ascertainment procedures for the recruitment of HR individuals varies greatly across laboratories. In some cases, college students (Ehlers and Schuckit, 1990a, 1990b) were selected and the presence of alcoholism in one relative determined with the use of a questionnaire. In other studies, the HR individuals were recruited through fathers attending treatment facilities for alcoholism, and the presence of multiple affected relatives was necessary (Cohen et al., 1991; Kaplan et al., 1988). These are indubitably the most disparate recruitment procedures, yet other investigators adopted still different procedures (Pollock et al., 1983). Possibly one of the most compelling explanations for divergent baseline EEG findings in HR subjects is the fact that the EEG is typically obtained under conditions in which the subject's task is poorly defined. As a result, the investigator has no control over the subject's mental activity, including attentional and motivational factors. While recording the EEG affords an

opportunity of examining the spontaneous activity of the brain, the uncontrolled mentation could produce excessive variability in the derived EEG variables.

Event Related Potentials

The event-related potentials (ERPs) represent a set of neurophysiologic techniques generally sensitive to the functional integrity of the brain. In addition to being sensitive to sensory aspects of information processing, ERPs are quite useful in indexing neurophysiological concomitants of complex cognitive tasks (Hillyard et al., 1978; Donchin, 1979). ERPs consist of an amalgam of characteristic components that typically occur within 100 ms for basic sensory processes reflecting the physical attributes of a sensory stimulus. Components occurring after 100 ms are more influenced by psychological factors and the information-processing demands of the task. One of the major advantage of ERPs is that they can easily be recorded in conjunction with, or without, any behavioral response, as well as with both attended and unattended stimuli.

In recent years a great deal of attention has focused on the P3 component of the ERP. This is a positive component that occurs between 300 and 600 ms after stimulus, and is also related to stimulus significance. For the past two decades we have investigated the P3 component of the ERP in abstinent alcoholics using a variety of different paradigms. We have repeatedly observed that they manifest a significantly reduced P3 component compared to matched normal control subjects (Porjesz and Begleiter, 1985). These findings have been replicated by a number of different investigators (Patterson et al., 1987; Emmerson et al., 1987; Pfefferbaum et al., 1987; 1991; Branchey et al., 1988). It should be noted, however, that while other components of the ERP show significant differences between abstinent alcoholics and controls, the P3 component does not change much over long abstinence periods (Porjesz and Begleiter, 1985).

Because of the protracted anomaly of the P3 component in abstinent alcoholics, we hypothesized that a decrease in its voltage did not necessarily reflect the deleterious effects of chronic alcohol abuse. Instead, we examined the possibility that this anomaly anteceded the development of alcoholism in young males at risk. Starting in 1980, we initiated a series of neurophysiological studies in various groups of HR individuals. In our first study, we studied young boys between the ages of 7 and 13 who had no prior exposure to alcohol or any illicit drugs (Begleiter et al., 1984). We selected boys whose fathers had received a diagnosis of alcohol dependence (DSM III) and were in treatment for alcoholism. Indeed it is important to note that all the HR subjects were recruited from treatment facilities. We excluded boys whose mothers had either ingested alcohol during pregnancy or who drank excessively after birth. The LR group consisted of healthy, normal boys matched to the HR subjects for age, socioeconomic status, and school grade. They were included in the study only if they had no prior experience with alcohol or other substances of abuse, and if they had no first- or second-degree relatives with a family history of alcoholism or other psychiatric disorder. With the exception of latter factor, the same exclusion criteria were used in both the LR and HR groups.

In this study a complex visual paradigm was developed. The target stimulus was an infrequently occurring aerial view of a head with the nose and either the left or right ear included, and rotated in one of two possible positions. This paradigm yielded four different targets, namely, nose up and right ear, nose up and left ear, nose down and right ear, and nose down and left ear. These target stimuli were randomly interspersed among nontargets (ovals). Subjects were required to press one of two microswitches to the targets, as quickly and accurately as possible, indicating whether the right or left ear stimulus was presented. The easy condition included all target stimuli with the nose up, and the difficult condition included all targets with the nose down.

The results of this experiment represent a novel set of observations in which we noted that the P3 amplitude was significantly smaller in the HR compared to the LR groups for all target stimuli. This group difference was most significant at the parietal electrode.

The study was the first to indicate that P3 amplitude is significantly reduced in young boys at high risk for alcoholism, without exposure to alcohol. This finding is quite interesting because it is so strikingly similar to ERP results obtained in abstinent alcoholics. Since our initial observation in HR subjects, a number of laboratories have replicated our observations. At the University of Connecticut, O'Connor and colleagues used the same visual stimuli and task, and reported that in a group of young adult males at risk for alcoholism the P3 amplitude was significantly reduced compared to a matched control group (O'Connor et al., 1986). Whipple et al. (1988) used a complex visual task in a group of young male subjects similar to subjects examined in our laboratory (Begleiter et al., 1984), and noted a significantly reduced P3 amplitude in the HR group compared to the LR group. In a subsequent study, Whipple et al. (1991) once again reported a decrease in P3 amplitude in young HR subjects, and noted that this finding can only be observed if a sufficiently challenging cognitive task is used in the ERP paradigm.

In yet another study by O'Connor et al. (1987) the authors reported a decrease in the amplitude of the P3 component of the ERP obtained in HR subjects. The investigators recorded the ERP in HR and LR males using two different visual tasks. In both conditions the P3 amplitude was significantly smaller in HR compared to LR individuals.

Begleiter et al. (1987) studied another group of sons of alcoholics to determine whether the reduced P3 amplitudes observed in past studies was modality or task specific. A modified auditory oddball task was used in which subjects pressed a button in response to rarely occurring tones presented at a random rate. Twenty-three matched pairs of HR and LR males between the ages of 7 and 16 were studied; all subjects were carefully interviewed to ascertain that they had no exposure to alcohol or illicit drugs. The HR subjects were all sons of alcoholic men who manifested early onset alcoholism, a high rate of recidivism, and were from families in which there was a multigenerational incidence of alcoholism. As in the previous visual study, the HR males manifested significantly reduced P3 amplitudes compared to the LR subjects. These findings suggest that the reduced P3 voltage typically observed in HR subjects may not be task or modality specific.

Most recently in another auditory target selection task, we noted that adolescent HR males manifest lower amplitude P3 voltage compared to LR individuals. In this paradigm

(modified after Hillyard et al., 1978), rare or frequent tones were randomly presented rapidly (600–800 ms ISI) to either the right or the left ear. The rare tones to a specific ear were designated as targets, and the subjects pressed a button as quickly as possible. The same rare tones to the opposite ear were to be ignored. In the absence of other ERP differences between groups, HR subjects manifested reduced P3 amplitude components to target stimuli when compared to LR subjects. The amplitude to both the rare attended (P3b) and unattended (P3a) stimuli were of lower voltage in HR subjects, suggesting that HR individuals manifest greater difficulties in probability matching than LR subjects.

More recently we (Porjesz and Begleiter, 1990) attempted to again replicate our P3 findings in males between 19 and 24 years of age. The sample consisted of the offspring of carefully diagnosed (DSMIII-R/RDC) male alcoholics selected from high-density families (mean number of alcoholic family members = 4). While this procedure is not foolproof, it provides a modicum of safety against selecting children of male alcoholics considered to be sporadic cases. Individuals with mothers who abused alcohol before, during, or after pregnancy were excluded. Controls were matched to the sons of male alcoholics on the basis of age, education, and socioeconomic status. They were selected from families in which there was no history of alcohol abuse or alcoholism in any first- or second-degree relatives. The HR and LR subjects were carefully matched on drinking history, including duration and quantity–frequency information.

In this experiment we used a visual task that consisted of an easy and difficult line orientation discrimination. We have in the past demonstrated that abstinent alcoholics manifest significantly reduced P3 with the use of this paradigm. The stimuli consisted of a nontarget (vertical line) and two different targets: an easy discrimination target that deviated from the vertical by 90° (horizontal line), and a difficult discrimination target that deviated from the vertical by only 3°. The subject performed a reaction time task (RT), responding as quickly as possible to all nonvertical stimuli. In this study, we replicated our previous findings (Begleiter et al., 1984, 1987) of significantly decreased P3 voltage in HR individuals compared to LR subjects. This finding was obtained in an older group of HR and LR subjects and replicates the work of O'Connor and his colleagues (1986, 1987). The largest difference in P3 voltage was obtained from the easily discriminable target, and is identical to our results with abstinent alcoholics (Porjesz et al., 1987). This P3 voltage difference was most significant at the Pz and Cz electrodes where P3 amplitude is typically maximum. Taken together these data indicate that with the use of a moderately challenging visual task the P3 voltage is significantly reduced in HR individuals compared to LR subjects.

Taken together, the ERP findings discussed so far indicate that P3 amplitude of the ERP is significantly reduced in HR compared to LR subjects. These results relate to both attended (P3b) and unattended (P3a) stimuli, and may be present in visual and auditory studies.

Some Conflicting Studies

Despite the general consensus that P3 amplitude is of lower voltage in HR than in LR subjects, there are some studies that have failed to replicate these findings. In various

studies conducted by investigators in California, conflicting ERP results have been reported. One early study by Elmasian et al. (1982) examined the P3 and slow-wave components of the ERP in HR and LR male college students (age 20–25) under placebo, low, and high doses of alcohol. It should be noted that different groups, each consisting of only five pairs of subjects, were used for each dose. After alcohol or placebo administration, significantly lower P3 amplitudes were observed in the HR as compared to the LR subjects. The authors explained their results in terms of differential expectancies for alcohol characterized by different neuroelectric events. Moreover, the investigators suggested that the findings could be due to the higher than normal alcohol intake in the mothers of the HR subjects.

Investigating ERPs in male college students with and without family histories of alcoholism, Polich and Bloom (1987, 1988) and Schuckit et al. (1988) did not find P3 amplitude differences between groups. Further, using a simple auditory oddball paradigm, Schuckit et al. (1988) did not find any ERP differences between HR and LR individuals before or after placebo and ethanol. Following a high dose of ethanol (1.1 ml/kg), P3 latency delays returned to baseline values more rapidly in the HR subjects. It should be noted that the initial placebo effects observed in HR subjects by Elmasian et al. (1982) could not be replicated by this group (Polich and Bloom, 1988). However, the ERP results of all these studies were all obtained with relatively small samples.

An inverse relationship between the amount of alcohol consumption and the amplitude of P3 was reported by Polich and Bloom (1987) without the administration of ethanol in the laboratory. However, this relationship was only apparent for a difficult intensity discrimination task in the HR subjects. The authors conclude that the HR subjects are more sensitive to the effects of ethanol than the LR subjects. When a similar intensity discrimination study was carried out in the visual modality, no correlation between P3 characteristics and amount of alcohol consumed was found (Polich et al., 1988). Furthermore, in yet another study designed to replicate Elmasian et al. (1982), Polich and Bloom (1988) not only did not replicate their previous findings of a placebo effect in the HR group, but in addition they noted a correlation between P3 latency and amount of alcohol consumed. Taken together, these findings relating alcohol consumption to P3 characteristics do not appear to be robust.

In the same laboratory, using samples drawn from the same population at the University of California San Diego, the ERP findings are not readily replicable. Previous alcohol consumption has been found to correlate with P3 amplitude only, particularly in HR subjects (Polich and Bloom, 1987), to correlate with P3 latency only (Polich and Bloom, 1988), and to be uncorrelated with any previous drinking variables (Polich et al, 1988). The relationship between P3 characteristics and drinking history has also produced contradictory findings in other laboratories. O'Connor et al (1986) reported no relationship between any P3 characteristics and drinking history, while Steinhauer et al. (1987) found such a correlation. In addition to correlations between P3 characteristics and drinking history, Schmidt and Neville (1985) have reported a correlation between the N430 latency and the number of drinks ingested per occasion in HR subjects only.

Baribeau et al. (1987) examined HR and LR subjects, who were further subdivided according to the amount of alcohol consumed (heavy vs. light drinkers). They used an auditory selective attention paradigm in which rare and frequent tones were randomly presented to either the right or left ear at an irregular rate. Subjects were instructed to count the targets in one designated ear and ignore those in the other ear. Although the light drinkers did not exhibit reduced P3 amplitude, they did manifest somewhat smaller P3 voltages in the inattention condition. High-risk subjects manifested significantly larger N100 components than LR subjects in the attention condition, which suggests that the HR subjects may have found the tone discrimination task to be difficult, and hence needed to muster greater resources. It appears that the subject sample used in this study is somewhat atypical since it represents an older group of HR individuals, with an age range of (19–35) and a mean age of 27 (HR: heavy drinking), 22 (HR: light drinking, 24 (LR: heavy-drinking), and 25 (LR: light-drinking). It is certainly reasonable to assume that this older group of HR subjects has already passed the age when alcoholism develops, and thus represents an atypical sample of HR, perhaps endowed not with risk factors but with protective mechanisms. In fact, the increase in the N100 component above that obtained for the LR subjects suggests the presence of atypical factors. A study by Hill et al. (1988) reports increased cognitive efficiency in nonaffected siblings of alcoholics. These investigators observed shorter P3 latencies in the nonaffected siblings of alcoholics, and suggest that this phenomenon may indicate the presence of protective factors against the development of alcoholism.

More recently, we (Porjesz and Begleiter, 1992) investigated the effects of alcohol on visual ERPs in HR and LR subjects. Twenty-four pairs of male HR and LR subjects (19–24 years of age) were administered a placebo, a low dose of alcohol (0.5 ml/kg), and a high dose (0.8 ml/kg) mixed with three parts of ginger ale on three separate randomly determined occasions. A visual ERP paradigm involving easy and difficult line orientation discrimination was used. ERPs and subjective measures of intoxication were recorded preethanol and after 20, 60, 90, and 130 minutes following alcohol ingestion. Blood alcohol levels were recorded at 10 minute intervals throughout the entire experiment, but no significant differences were obtained between groups in terms of blood alcohol curves.

As mentioned earlier, before alcohol ingestion the amplitude of P3 to all target stimuli was significantly smaller in the HR compared to the LR subjects. Alcohol ingestion did not affect the difference in P3 amplitude initially observed between the two groups. While there was a tendency for alcohol to decrease the amplitude of the P3 component of the ERP in both groups, this finding did not reach statistical significance. During the ascending phase of the blood alcohol level, however, the HR group manifested a significantly larger percent decrement in P3 amplitude to all targets, compared to the LR group. This interesting finding perhaps indicates greater sensitization to alcohol in the HR subjects on the ascending limb of the blood alcohol curve (Newlin and Thomson, 1990).

We have obtained similar findings with slow alpha EEG activity in our laboratory (Cohen et al., 1993), where we found more of an increase in the HR group following an alcohol challenge. It should be noted that while no significant difference in P3

latency occurred between groups prior to alcohol ingestion, the high dose of alcohol significantly increased the latency of P3 to the difficult target in both groups of subjects. This effect was maximal between 60 and 90 minutes postethanol, namely at peak and early descending phase of the blood alcohol curve. The HR group recovered more rapidly to prealcohol levels in contrast to the LR subjects, who manifested a delay that lasted the length of the postethanol experiment. These findings replicate the results of Schuckit et al. (1988), who noted that HR subjects recover more quickly from ethanol-induced P3 delays. This result suggests that on the descending limb of the blood alcohol curve, HR subjects manifest a faster recovery (tolerance) to the effects of alcohol.

In this experiment, the N1 amplitude of the ERP was significantly decreased by alcohol starting at 20 minutes, particularly to the nontarget stimulus. This result was more pronounced at occipital sites for the LR compared to the HR group. While the N1 amplitude to nontargets remained depressed in the LR group throughout the experiment, it recovered by 90 minutes for the HR group. Once again, these results suggest that the HR subjects manifest more tolerance to alcohol compared to the LR group. The N1 amplitude did not decrease to the difficult target, and was only somewhat decreased to the easy target. These results are in agreement with the findings by Roth et al. (1977), indicating that attentional factors can vitiate the actions of alcohol on the N1 amplitude of the ERP. These findings also support the observations of Campbell and Lowick (1987) that indicate that the largest alcohol effects are typically obtained when attention is mobilized the least (to nontargets). The differential effects of alcohol on N1 amplitude between HR and LR groups are quite similar to the behavioral effects reported by Schuckit (1984), which suggest that the HR subjects exhibit more acute tolerance to alcohol than the LR group. It is quite obvious for the aforementioned data that ERP measures provide very sensitive indices of state and trait variables related to alcohol ingestion and alcoholism. Different ERP characteristics are sensitive to different aspects of this multifaceted problem.

Because of the striking similarity in P3 findings between abstinent alcoholics and sons of alcoholics, we decided to investigate the integrity of the brainstem potentials in young boys at risk for alcoholism. We had in the past observed brainstem anomalies in abstinent alcoholics (Begleiter et al., 1981). For our experiment, we recorded the auditory brainstem potentials in 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 amplitude findings, no significant difference in the brainstem potentials were noted between HR and LR boys. These results suggest that the brainstem abnormalities represent a potential state marker, that is, the consequence of alcohol abuse. In contrast, the significantly low-voltage P3 in both abstinent alcoholics and HR subjects seemingly antecedes the development of alcoholism, and may be considered a potential trait marker.

Conclusion

A review of the ERP data in individuals at risk for developing alcoholism indicates that the P3 component is characterized by low voltage. Except in a few studies noted earlier, this finding is quite robust. Indeed, in a recent meta-analysis of all ERP studies

in HR and LR subjects, Polich et al. (1994) conclude that the amplitude of the P3 component of the ERP reliably discriminates between HR and LR subjects. Recently, Pfefferbaum et al. (1991) conducted a path analysis using family history of alcoholism and drinking history to predict the amplitude of P3 in abstinent alcoholics, concluding that family history is in fact the only significant predictor. These interesting data provide an important link between P3 studies of alcoholics and subjects at risk for alcoholism, indicating that P3 characteristics are genetically influenced and supporting the notion that low P3 voltages in HR individuals represent a trait rather than a characteristic state. There is substantial evidence indicating that several neurophysiological characteristics (EEG, ERP) are under genetic control. The P3 component has been demonstrated to be significantly more similar in MZ twins than in control subjects (Polich and Burns, 1987). In addition, ERP's deficits have been reported to be similar in abstinent alcoholic fathers and their young sons (Whipple et al. 1988). The aforementioned data suggest that the reduced P3 voltage may provide a phenotypic marker for alcoholism. It remains to be determined with longitudinal studies, however, whether HR subjects manifesting low P3 voltages are in fact those who in subsequent years develop alcoholism, drug abuse, or other psychiatric conditions.

Behavioral Reaction to Alcohol

Another promising area of research that has produced interesting findings deals with the subjective behavioral reaction of subjects at high risk to a challenge dose of alcohol. Much of this research has been carried out by Schuckit and his colleagues at the University of California at San Diego. Schuckit (1980) was the first to note that HR men reported significantly lower levels of subjective feelings of intoxication after drinking. In his studies, carried out since 1978, a questionnaire has been used to identify male students and staff at the university at elevated risk for alcoholism. The questionnaire uses a highly structured format to collect information on demographic variables as well as pattern of alcohol and drug intake. In addition, personal, medical and psychiatric information, and family history of major psychiatric disorders are all collected. From these completed questionnaires, those sons of alcoholics, who were drinkers but had not experienced major life problems from alcohol, drugs, or other psychiatric problems were selected as subjects at high risk for developing alcoholism. It should be noted that all HR subjects were carefully matched with LR subjects on several important variables including age, sex, race, educational level, quantity and frequency of drinking, substance intake history, height-to-weight ratio, and smoking history.

All individuals selected for this series of studies were tested on three separate occasions with a placebo, 0.75 ml/kg of ethanol, and 1.1 ml/kg of ethanol. The ethanol was given as a 20% by volume solution in a sugar-free, noncaffeinated beverage, which was consumed over a 10-minute period. Before any liquid was administered, all subjects were tested on a variety of cognitive and psychomotor tasks, mood, and anxiety scales, to establish baseline levels of functioning. After ingesting each beverage all subjects were tested for a period of 4 hours in order to note their subjective reactions to

the placebo or the two doses of alcohol. Before challenges, both the HR and LR subjects reported similar expectations to the effects of alcohol. After ethanol ingestion, both groups manifested similar blood alcohol curves. Nevertheless, after drinking 0.75 ml/kg of ethanol, approximately 40% of the HR subjects reported feeling less intoxicated than did the LR subjects.

In addition to a decreased level of subjective intoxication in HR subjects compared to LR subjects, similar findings were obtained with a measure of body sway. While there were no differences in body sway before or after placebo administration between HR and LR subjects, significant differences emerged subsequent to the ethanol challenge. The LR subjects manifested a significantly greater increase in body sway after drinking the 0.75ml/kg dose of ethanol than did the HR group (Schuckit, 1985).

Most of the work investigating subjective intoxication after a challenge dose of ethanol in HR and LR individuals has been conducted by Schuckit and his colleagues (Schuckit et al., 1991a; 1991b; Schuckit, 1992). A number of studies by other investigators have been reviewed by Pollock (1992) and Newlin and Thomson (1990). It should be noted that the metaanalysis by Pollock (1992) reviews all the published studies that utilize a challenge dose of alcohol in HR and LR subjects. The author concludes that data from several studies support a less intense alcohol reaction in the group of males at risk of developing alcoholism.

In order to determine the pharmacological specificity of this effect, Schuckit and his colleagues compared the challenge effects of ethanol and diazepam (0.1 and 0.2 mg/kg of diazepam) in a large group of HR and LR subjects. In contrast to the results with the alcohol challenge, the diazepam challenge did not differentiate the two groups at high and low risk for developing alcoholism. This suggested to the authors that the postchallenge effects between HR and LR are indeed specific to alcohol. The authors further speculated that a decreased intensity of reaction to low doses of alcohol would make it more difficult for HR individuals to identify an oncoming state of intoxication. A deficient ability to detect a state of intoxication in oneself could seriously jeapordize one's ability to stop drinking and lead to drunkeness followed by stupor. With the currently available data it is not possible to determine if HR subjects manifest more innate tolerance to the effects of alcohol or are indeed more insensitive to its pharmacological effects. All the subjects recruited in these studies are at least in their 20s and all are social drinkers so it is quite likely that the presence of innate tolerance in HR subjects is interacting with varying degrees of exposure to alcohol.

Now, some 8 to 12 years after the initial study, Schuckit and his colleagues are carrying out a follow-up study to interview the majority of subjects tested. Although this study is currently in progress, some intriguing preliminary results are already available. For example, a decreased intensity of reaction to alcohol, as initially assessed, appears to be a reliable predictor of alcohol abuse. Moreover, the current data also indicate a potential trend toward subsequent cocaine and marijuana problems.

Neuropsychological Deficits

A number of studies have suggested that sons of alcoholics have difficulty attributing meaning to potentially relevant stimuli, resulting in a characteristic pattern of hyperac-

tivity. Alcohol consumption serves a salutory function by significantly reducing this pattern.

For several decades investigators have reported that sons of alcoholics are characterized by excessive impulsivity (Cadoret et al., 1980; Tarter et al., 1984b; Knop et al., 1985), while others have described sons of alcoholics as hyperactive (Cantwell, 1972; Morrison and Stewart, 1973; Goodwin et al., 1975; Rydelius, 1981; 1983; Alterman et al., 1982; Tarter et al., 1984). In general, these studies depict sons of alcoholics as individuals who are unable to alter their behavior in ways commensurate with social expectations and mores. More recently Cloninger (1987) has identified a number of behavioral characteristics typical of sons of alcoholics, describing them as low in reward-dependence, high in novelty-seeking, and low in harm-avoidance. These traits imply that they are socially detached, impulsive, and overly confident. Moreover, Cloninger (1987) asserts that these traits are genetically influenced, and render sons of alcoholics particularly susceptible to the development of alcoholism.

A number of investigators have argued that the behavioral characteristics that have been identified in sons of alcoholics are the result of deviations in temperamental traits (Tarter et al., 1985; Zucker and Lisansky-Gomberg, 1986; Johnson and Rolf, 1990). These authors have proposed a developmental approach, and suggested that some of these temperamental traits are genetically determined (Plomin, 1983).

A group of investigators at McGill University have conducted a series of studies to assess the information-processing characteristics of sons of alcoholics. With the use of psychophysiological measures the Montreal investigators have found that sons of alcoholics manifest significant hyperactivity to external stimulation. Finn and Pihl (1987, 1988) reported that young nonalcoholic sons of alcoholics with extensive multigenerational family histories of alcoholism were characterized by increased heart rate and decreased digital blood volume amplitude (DBVA) when anticipating and receiving mild electric shock. In a subsequent study, Finn et al. (1990) observed the same pattern of cardiovascular hyperreactivity among HR subjects before and after receiving avoidable and unavoidable signaled electric shock. Moreover, these subjects manifested larger electrodermal orienting responses, shorter latency responses, and slower rates of habituation to novel nonaversive stimuli. In addition to these abnormalities in cued psychophysiological responses, HR individuals manifest an increased sensitivity to the stress-response dampening effects of alcohol intake.

The first study assessing the effects of alcohol on psychophysiological measures was conducted by Sher and Levenson (1982). The authors found that HR subjects were characterized by increased baseline heart rate after administration of alcohol and by decreased heart acceleration in response to stressors. In a subsequent study, Levenson et al. (1987) observed that alcohol ingestion reduced some aspects of cardiovascular reactivity as well as general somatic activity to self-disclosing speech and electric shock in HR individuals.

Alcohol has been consistently shown to normalize the exaggerated stress response typically manifested by HR subjects. A number of investigators have reported that alcohol intoxication dampens the psychophysiological responses of HR to aversive stimulation (Finn and Pihl, 1987; 1988; Finn et al., 1990; Peterson et al., 1990). It should be noted that abstinent alcoholics manifest significant reduction in electroder-

mal reactivity (Coopersmith and Woodrow, 1967; Garfield and McBreaty, 1970) after alcohol ingestion. Taken together, the findings in abstinent alcoholics and HR subjects suggest that alcohol has a major salutory effect in that it significantly reduces the effects of various stressors. In the short term, the consumption of alcohol by HR individuals may be perceived as an adaptive means to cope with unpleasant situations. The alcohol effects just described indicate that HR subjects may find alcohol more reinforcing than LR individuals. This is quite consistent with findings by Cohen et al. (1993) and by Porjesz and Begleiter (1993), who reported that HR individuals manifest sensitization on the ascending limb of the blood alcohol curve and tolerance on the descending limb of the blood alcohol curve.

The neuropsychological findings summarized earlier have resulted in a rather consistent set of inferences that attempt to relate the behavioral characteristics of HR subjects to potential brain processes. Several authors, such as Tarter et al. (1984a; 1988), Pihl et al. (1987), Gorenstein (1987), Peterson and Pihl (1990), have postulated that the pattern of behavioral deficits typically manifested by HR subjects is quite analogous to that displayed by individuals with dysfunction of the prefrontal cortex. This notion has of late received substantial support from an elegant study by Peterson et al. (in press), who have reported a significant relationship between the performance of HR subjects on two tests of prefrontal cortex function [Self-ordered Pointing test (Petrides and Milner, 1987) and Wisconsin Card Sort Test (Milner, 1964)], and their cardiovascular hyperreactivity to anticipation and receipt of electric shock.

Individuals who manifest dysfunction of prefrontal cortex typically manifest impulsivity, hyperactivity, antisocial behavior, and a strong tendency to avoid stimuli with delayed gratification (Luria, 1980; Damasio, 1986). Such individuals have difficulties with moderate to long attention span, and are quite prone to conduct disorder. Zucker and Lisansky-Gomberg (1986) and Sher (1992) have noted that individuals who develop serious difficulties with alcohol typically demonstrate poor school performance, more truancy, and completion of fewer school years.

Conclusion

As of now, a review of the literature on males at risk of developing alcoholism indicates that two specific set of features are characteristically observed in those individuals without the use of alcohol.

1. Specifically, in the absence of alcohol, HR males manifest neurophysiological characteristics, such as a significantly reduced amplitude of the P3 component of the ERP. This finding reflects an inability of HR subjects to differentiate relevant from irrelevant stimuli. While this robust finding has been replicated in many different laboratories with different experimental paradigms, the lack of unanimity among them can in part be attributed to differences in subject populations (see metanalysis by Polich et al., 1994). The clinical criteria for diagnosis of alcoholism in the father and the general method of diagnostic assessment contribute considerably to differences in the samples studied. For example, some studies require only one symptom of alcoholism for the father to quality for inclusion in the HR group. The number of affected relatives varies

greatly across studies. Some investigators select HR individuals from families where only a single individual manifests symptoms of alcoholism, while others select only HR subjects from multigenerational or high-density families. The selection of HR subjects from families where only one individual is affected increases the risk of selecting an individual from a family where alcoholism is not genetically influenced, but represents a sporadic case or phenocopy.

The issue of comorbidity for other psychiatric problems is also treated quite differently by various investigators. Some assert that alcoholism is a single, unique disorder that must be studied in the absence of other potentially confounding psychiatric disorders, while others maintain that it may not be a single and unique entity devoid of influence by other psychiatric disorders such as antisocial personality and anxiety disorders. As a result, some studies include HR individuals who manifest antisocial behavior or other psychiatric symptoms, while others clearly exclude such individuals. Because alcoholism is such a heterogeneous disease, the inclusion or exclusion of individuals in HR studies is quite likely to vary significantly across studies, and thus have a significant effect on outcome findings.

Another variable that is highly likely to influence study outcome is the age range of the selected population. In a study of traits potentially relevant to the development of alcoholism, it is critical to select subjects before they pass through the age of maximal risk. The selection of somewhat older individuals (25–40 years of age) is likely to yield a sample comprising subjects who may manifest protective factors instead of risk factors. Several investigators have published data obtained in a sample of older individuals. In addition, there are a number of demographic and environmental variables, such as education, scholastic achievement, socioeconomic status, nutritional deficiencies, and home environment, that could potentially influence the search for risk factors. It is quite obvious that subject selection remains a major problem in the conduct of research designed to identify markers for the development of alcoholism in HR individuals. Nevertheless, it is quite remarkable that in light of all of the aforementioned problems, there exists a substantial body of neurophysiological research indicating that HR individuals may be reliably differentiated from LR individuals.

2. Several psychophysiological characteristics differentiate HR from LR individuals. As reviewed earlier, a number of studies have demonstrated that HR subjects show increased heart rate and decreased digital blood volume amplitude when anticipating or faced with unpleasant stimuli. This pattern of cardiovascular hyperreactivity is indicative of impaired autonomic regulation. These data are seemingly consistent with the neurophysiological findings and indicate that HR subjects have difficulty placing potentially relevant stimuli into a meaningful context. This inability (reduced P3) leads to inappropriate autonomic reactivity (cardiovascular hypperreactivity). The affective/motivational response of HR subjects to internal and external stimuli is not commensurate with the significance of such stimuli. Some authors have elected to interpret this emotional instability to be concommitant with the development of temperamental traits that may be genetically influenced. It has been postulated that the hyperactivity, disinhibition, and emotional lability observed in HR subjects reflect a dysfunction of neural systems in the prefrontal region of the brain.

The second set of characteristics that differentiate HR from LR individuals is observed in response to a challenge dose of alcohol. Several studies indicate that after such a dose HR subjects report a less intense subjective reaction on the descending limb of the blood alcohol curve when compared to LR individuals. This finding implies that HR subjects may be more tolerant or more insensitive to the negative effects of alcohol. Because social drinkers are typically used in these studies, it is difficult to attribute the results to the potential presence of innate tolerance. Nevertheless, these results imply that this decreased subjective feeling of intoxication could lead to an inability to cease drinking alcohol.

Another group of studies indicates that HR individuals are particularly sensitive to the stress-dampening effects of alcohol. Indeed, for HR subjects alcohol reduces stress and normalizes their autonomic responses. For this group of individuals, alcohol appears to have an adaptive if not salutory effect. While studies that assess the subjective reaction to alcohol find a decreased effect in HR subjects, those studies that measure its stress-dampening effects find increased sensitization in HR subjects.

This seeming discrepancy can be explained by the differential time of measurement between these studies. For example, some studies record the dependent variables on the ascending limb of the blood alcohol curve, while others obtain their measures on the descending limb. It is important to note that recent neurophysiological studies indicate that subsequent to a dose of alcohol, HR subjects manifest increased sensitization on the ascending limb of the blood alcohol curve. Since this sensitization is only seen on the ascending limb, it might be speculated that HR subjects find the effects of alcohol more positively reinforcing than do the LR subjects. This would naturally lead to increased alcohol ingestion. On the descending limb of the blood alcohol curve the alcohol effects that differentiate the HR from the LR subjects are quite different from those on the ascending limb. Indeed, on the descending limb, the HR subjects manifest more tolerance or insensitivity to the effects of alcohol, which indicates that they are less sensitive to the detrimental or negative effects of alcohol.

In general, the behavioral, psychophysiological, and neurophysiological findings in HR subjects in response to a challenge dose of alcohol are interesting. The potential discrepancy between those studies that purport to find tolerance and those that indicate greater sensitization may easily be resolved by studying all individuals on both the ascending and descending limbs of the blood alcohol curve.

At present, the neurophysiological and psychophysiological data obtained in the absence of alcohol, and the behavioral, psychophysiological, and neurophysiological data obtained in response to a challenge dose of alcohol best differentiates HR from LR subjects. Taken together these data strongly support the conclusion that objective quantifiable measures differentiate reliably between them.

While the aforementioned findings may have identified a number of putative markers, several questions remain unanswered. With the exception of the neurophysiological variables, the heritability of the measures reviewed previously is not established. Therefore, these measures (i.e., subjective reaction to alcohol and stress-dampening effects of alcohol) do not meet the criteria for a genetic marker as defined at the beginning of this chapter.

This issue does not vitiate the potential use of these measures in predicting subsequent alcoholism or drug abuse. It does, however, limit the use of these measures in searching for the genes involved in the predisposition toward alcoholism. The most efficacious search for the genetic predisposition toward alcoholism must of necessity involve reliable and highly heritable markers. However, it is critical to remember that heritable biological factors will most likely not elucidate all of the etiological factors involved in alcoholism. The final development of alcoholism most probably represents the interaction between biological and environmental factors.

While the group of putative markers reviewed earlier does differentiate HR from LR subjects reliably, it remains to be determined whether these putative markers are related to one another, and the potential nature of this relationship. To date, not a single study has attempted to study all of the potential markers in one set of subjects. It should be noted, however, that different groups of investigators select HR and LR subjects using different ascertainment and assessment procedures. To the extent that alcoholism is a clinically heterogeneous condition, it may well be that various investigators are studying different subgroups of this disorder. Nevertheless, it would be of great importance to study all of the putative markers in one group to assess their relationships, and to better delineate the potential characteristics of different subgroups of individuals at risk to develop alcoholism.

Despite the diversity of ascertainment and assessment procedures, the use of various dependent variables, and the different time of testing on the ascending and descending limb of the blood alcohol curve, an interesting pattern of results is emerging from the myriad of studies reviewed here. In general, sons of alcoholics (HR) manifest impaired neurophysiological, autonomic, and behavioral regulation. They demonstrate an inability to differentiate relevant from irrelevant stimuli, are insensitive to interoceptive cues, and are hyperreactive to seemingly threatening or noxious stimuli. Alcohol consumption significantly reduces the negative consequences of this impaired regulation, and in that sense, appears to have greater rewarding properties for the HR as compared to the LR individuals. These greater reinforcing properties may thus lead to increased drinking on the part of the HR individuals. For example, the behavioral studies suggest that HR subjects are more insensitive or tolerant to the negative effects of alcohol intake on the descending limb of the blood alcohol curve. This decreased intensity of reaction to alcohol in HR subjects would prevent them from experiencing both the short- and long-term negative consequences of drinking. This inability to fully experience the negative consequences of alcohol could also lead to increased alcohol intake.

The notion of increased sensitization on the ascending limb of the blood alcohol curve and decreased reaction on the descending limb of the blood alcohol curve (Newlin and Thomson, 1990) is supported by recent neurophysiological studies in HR subjects. In that sense, sons of alcoholics are at high risk of developing alcoholism because they are quite susceptible to the immediate short-term reinforcing properties of alcohol, and are impervious to the negative consequences of alcohol intoxication. This impairment of behavioral regulation leads the HR individual to seek short-term gratification at the expense of long-term detriment. As drinking progresses and depen-

dence develops, behavioral dysregulation becomes exacerbated, resulting in the progressive loss of control.

Some authors (Tarter et al., 1984) have suggested a developmental deficit in temperament based on a disturbance in arousal, while others (Cloninger, 1987) have proposed that HR individuals possess a number of specific heritable personality traits. While behavioral dysregulation is characteristic of alcoholism, it is not specific to this disorder. Indeed, behavioral dysregulation is typical of all of the addictive disorders. It has been proposed (Miller and Brown, 1992) that risk for alcohol and other drug abuse occurs in conjunction with behavioral problems characteristic of impairment in self-regulatory control. These authors suggested that risk markers for self-regulatory problems might include poor academic work, impulsive–aggressive behavior accompanied by disciplinary problems, and a variety of reckless driving offenses as young adults. It is of fundamental significance to note that poor attention span, impulsivity, insensitivity to interoceptive cues, hyperreactivity to potentially noxious stimuli, and risk-taking are typically found in HR individuals. All of these signs suggest a pattern of regulatory processes that are seemingly impaired in individuals at risk to develop alcoholism. Moreover, it is critical to note that for HR subjects, alcohol or drug use may well serve adaptive functions, which tend to normalize various processes (Kissin and Hankoff, 1959). For individuals at risk of developing alcoholism, the use of alcohol may have short-term salutory effects.

In reviewing the literature on HR individuals we have attempted to cull findings from research areas that provide the largest and most consistent body of data. To be sure, we have excluded some findings not as a result of bias, but primarily because several findings are quite preliminary, or are represented by just a few isolated results that could not be properly assessed at this time. As can be seen from this review, most of the data in this area of research have been published in the last decade. Indeed, it is quite remarkable how productive this research area has been in just ten years. As mentioned earlier, several findings appear to be quite reliable and promising. As a result, there is currently some cause for cautious optimism.

A number of interesting parallels are beginning to emerge between the HR findings and the results obtained with genetically bred strains of rodents. HR individuals manifest sensitization to alcohol on the ascending limb of the blood alcohol curve and tolerance on the descending limb of the blood alcohol curve; an identical set of findings obtains with rats genetically bred to manifest preference for alcohol (Lumeng et al., this volume). We have reviewed the neurophysiological deficits in HR individuals. There are a number of neurophysiological deficits that have been noted in genetically bred rats preferring alcohol when compared to nonpreferring rats (Marzoratti et al., 1988; Ehlers et al., 1991). While it is not currently possible to equate or even compare the human and animal neurophysiological data, the presence of anomalies in both species is potentially important.

It is interesting to note that rats preferring alcohol manifest increased motoric activity to a novel environment compared to nonpreferring rats, since hyperactivity has been noted in subjects at risk to develop alcoholism. While some interesting similarities are beginning to emerge between the human and animal research, it would be quite

premature, if not inappropriate, to assume identity. While much remains to be done before valid similarities can be established, these interesting data provide an unprecented window of opportunity that is likely to guide research for the next decade.

The identification of valid and reliable genetic markers of risk to develop alcoholism has begun in earnest, and is critical to the search for the genes that influence the development of alcohol dependence. Several putative markers have been evaluated in cross-sectional studies. The value of any potential marker, however, will be significantly increased by testing its predictive power in the conduct of longitudinal studies. Moreover, we need to assess the relationship of all the putative markers in several different populations of individuals at risk of developing alcoholism. While the current epidemiological data indicate that males are at higher risk than females, it is critical to implement similar studies in females. It is important to determine if similar putative markers exist in them, as well as assessing the predictive value of such markers for the development of alcoholism or other psychiatric conditions.

The identification of genetic trait markers that are correlated with a predisposition to develop alcoholism will not only be critical for identifying potential genes but will be equally important in elucidating the etiological factors involved in the development of alcoholism. A better understanding of the causes of alcoholism will naturally result in the development of more rational and effective treatment procedures and the implementation of efficacious primary prevention initiatives.

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