Substance Abuse Vulnerability in Offspring of Alcohol and Drug Abusers

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There is clear evidence that a family history of alcoholism is a significant risk factor for the development of alcohol and other drug use disorders. Research also suggests that a family history of drug dependence increases the vulnerability of offspring for future development of drug abuse/dependence, although few such studies have been conducted.

This chapter will provide an overview of a number of areas of research on family history of substance abuse as a predictor of substance abuse vulnerability. First, epidemiological research on family history of alcohol and other drug use disorders will be briefly summarized. Next, laboratory research on potential physiological and behavioral markers for family history risk will be reviewed. There also will be a summary of several recent studies examining the predictive utility of putative markers for identifying those offspring at increased risk for substance abuse development. Finally, methodological limitations and future directions of the laboratory research will be discussed.

EPIDEMIOLOGICAL STUDIES OF FAMILY HISTORY OF ALCOHOL AND DRUG USE DISORDERS

Generally, three different human behavioral genetic methodologies have been used to examine the potential influence of family history of substance abuse: family studies, adoption studies, and twin studies (see review by Pickens and Svikis 1991). There has been convincing concordance across these different methodologies in findings of increased risk for alcohol and drug use disorders in male and, more recently, female family members of affected individuals.

Family History of Alcoholism as a Risk Factor for Alcohol Abuse/Dependence

Well-controlled family studies of alcoholism generally have shown a three- to ninefold increased risk of alcoholism among parents and

siblings of alcoholic subjects as compared with relatives of nonalcoholic subjects (Cotton 1979; Merikangas 1990). Approximately 25 percent of fathers and 5 percent of mothers of alcoholic probands meet diagnostic criteria for alcoholism. Typically, alcoholism risk in male relatives is consistently higher than in female relatives; however, this difference in risk appears to be related to different environmental or biological influences for men and women, and not to gender differences in genetic transmission of alcoholism (Merikangas 1990).

In the first rigorous adoption study on alcoholism, Goodwin and colleagues (1973) found a fourfold increased risk of alcoholism in adopted male offspring of alcoholic fathers as compared with adopted offspring of nonalcoholic fathers; no differential risk for female offspring was observed as a function of family history (Goodwin et al. 1977). A subsequent study by Cadoret and colleagues (1985) confirmed the elevated risk for sons of alcoholics, but also reported significantly increased rates of alcoholism among female offspring of alcoholics as compared with female offspring of nonalcoholics. Overall, average relative risk of alcoholism in male adoptees with as compared to without a family history of alcoholism is 2.4 and in female adoptees 2.8 (Merikangas 1990).

Twin studies have consistently found significantly higher concordance for alcoholism in monozygotic (MZ) twins who are genetically identical, as compared with dizygotic (DZ) twins, who on average share half of their genes (Hrubec and Omenn 1981; Kaij 1960; Kendler et al. 1992; Pickens et al. 1991). When the relative contribution of genetic and environmental factors to alcoholism risk was examined, genetic factors were found to exert a moderate to strong influence on development of the more severe disorder of alcohol dependence for both men (heritability estimate = 0.59) and women (heritability estimate = 0.42), but only modest influence on risk for the less severe disorder of alcohol abuse in men and no influence for alcohol abuse in women (Pickens et al. 1991).

Family History of Alcoholism as a Risk Factor for Drug Abuse/Dependence

To better understand the nature and extent of risk conferred by a family history of alcoholism, it is important to determine whether family history positive (FHP) offspring evidence increased risk for developing psychoactive drug use disorders in general or for alcohol disorders specifically. Several areas of research have suggested an

increased vulnerability to psychoactive substance abuse/dependence in persons with a positive family history of alcoholism.

In a study of self-reported alcohol and drug use by male college students, differences in substance use patterns and associated problems were found as a function of the extent of alcoholism in students' families (McCaul et al. 1990*a*). The greatest levels of alcohol and drug use were found for college students with a high density of alcoholism in their families (first- and second-degree affected relatives), an intermediate level for students with low alcoholism density families (first-degree affected relative(s) only), and the least in students with no affected relatives. Generally, students from high-density families reported: greater use of alcohol, marijuana, sedatives, and cocaine; a younger age at first alcohol intoxication and first use of marijuana; and more experience with less commonly used drug classes such as opiates and hallucinogens. Finally, a greater percentage of these students reported personal alcohol- or drug-related problems as well as family mental health care.

Using adoption study methods, Cadoret and colleagues examined the effects of alcoholism in the biologic parent on the subsequent development of drug use and abuse in the adoptee (Cadoret et al. 1986, 1995). Results indicated that alcohol abuse/dependence in a biological parent directly predicted drug abuse/dependence in the offspring. Additionally, antisocial personality in a biologic parent or psychiatric disturbance in an adoptive parent contributed to increased risk for drug abuse/dependence in the offspring (Cadoret et al. 1995).

In the only twin study to date of clinical drug use disorders, Pickens and colleagues (Pickens et al. 1991) found significantly higher concordance rates for drug abuse and/or dependence in MZ versus DZ male twins, but not female twins, when twins were identified on the basis of treated alcoholism in one member of the twin pair.

Family History of Drug Abuse as a Risk Factor for Drug Abuse/Dependence

Compared with alcohol abuse/dependence, there has been relatively little research on genetic contributions to risk for development of other psychoactive substance use disorders. Earlier clinical studies of genetic factors in drug use generally have focused on patterns of licit drug use by individuals in the general population. Twin studies have reported higher MZ than DZ concordance rates for: cigarette smoking (Kaprio et al. 1981), coffee and tea drinking (Pederson

1981), and tranquilizer use (Pederson 1981). There are a number of factors relevant to the dearth of research on genetic risk for illicit substance use disorders. Historically, there has been a greater emphasis on the role of environmental variables in the vulnerability to drug abuse; the lower population prevalence of drug abuse/dependence as compared with alcohol abuse/dependence makes research exceedingly more complex and difficult; and the illegal nature of much drug use decreases individual's willingness to volunteer for research protocols and increases the difficulty of locating and working with the population.

Using family study methods, Merikangas and colleagues (1992) examined rates of drug use and other psychiatric disorders in the first-degree relatives of opiate-dependent, treated probands. Overall, 69 percent of the siblings of opiate-dependent probands reported use of at least one illicit drug, and 63 percent of the siblings met diagnostic criteria for substance abuse. Most of the siblings with drug abuse reported using a variety of substances. For all drugs, over 90 percent of siblings who tried any illicit drug went on to develop substance abuse. Clearly, the siblings of opiate-dependent probands are an exceedingly high-risk group for substance use disorders.

These investigators also examined the relationships between parental psychiatric disorders and sibling disorders in the relatives of opiate abusers. Maternal alcohol abuse was significantly related to sibling drug abuse, and maternal anxiety or depression was associated with elevated rates of alcoholism, drug abuse, and anxiety or depression in the siblings. In contrast, paternal disorders were specifically predictive of elevated risk for the same disorder in the siblings; that is, paternal alcoholism was significantly associated with sibling alcohol abuse, drug abuse with drug abuse, and antisocial personality with anxiety/depression (Merikangas et al. 1992). These findings suggest greater specificity for transmission of risk of psychiatric disorders between affected fathers and their offspring than between affected mothers and their offspring; however, the small numbers of drug-abusing mothers makes these conclusions tentative.

SEARCH FOR MARKERS THAT MAY BE RELATED TO INCREASED RISK FOR SUBSTANCE USE DISORDERS IN FHPs

These converging lines of evidence for a familial influence on the development of substance abuse/dependence have led to the study of offspring of alcoholics who have not yet themselves developed the disorder. The goal of this research is identification of physiological,

subjective, and/or behavioral markers that are associated with and therefore predict increased risk for development of alcohol dependence in FHP individuals. FHP males and females have been studied while sober and intoxicated from alcohol or other drugs. Potential risk factors may include underlying psychological or biological basal abnormalities that are generally expressed and do not occur solely in the presence of alcohol. On the other hand, hypothesized risk factors may be highly specific to alcohol and may only come into play when alcohol has been ingested. Indeed, many researchers have hypothesized family history differences related to the reward or reinforcement value of alcohol and other psychoactive drugs.

The high-risk research paradigm that has been used to investigate potential markers has been conceptually quite simple. A sample of adolescent or young adult offspring of alcoholics (FHP) is recruited and assessed for the presence/absence or magnitude of the putative marker. Offspring with no familial alcoholism (FHN) are matched to the FHP subjects on a number of potentially important variables, including age, gender, years of education, height/weight ratio, typical and maximum drinking, and recent and lifetime drug use. Typical exclusion criteria include: the Michigan Alcoholism Screening Test (MAST) score suggestive of alcohol problems; DSM-III-R Axis I diagnosis in the subject; significant medical history; and evidence of maternal alcoholism, particularly during pregnancy. Assessments can be conducted with or without an alcohol challenge, depending on the whether the marker is hypothesized to operate under baseline conditions or differentially in the presence of alcohol.

Baseline Differences Between FHP and FHN Youth

A variety of psychological and biological variables have been studied in sober FHP subjects, including body sway, perceptual motor functioning, personality measures, school performance, verbal abilities, abstraction/ conceptual reasoning, and neurological and biochemical measures. The most consistent and robust finding has been reduced amplitude in the P300 component of event-related potentials (ERPs) elicited by visual stimuli in young FHP subjects as compared with FHN subjects (Begleiter et al. 1984; Hill et al. 1988; Steinhauer et al. 1987; Whipple et al. 1988). For example, Hill and Steinhauer (1993) reported significantly reduced P300 amplitudes during a visual discrimination task in multigenerational, high-density FHP prepubertal boys compared with their age-matched FHN controls; interestingly, no significant differences were observed as a

function of familial alcoholism in young female subjects. It is thought that ERPs reflect memory updating operations during information processing. Importantly, there is evidence that P300 amplitude and latency are genetically influenced. The importance of familial alcoholism as a determinant of P300 deficits has received further support from two recent studies with adult alcoholics (Cohen et al. 1995; Pfefferbaum et al. 1991). Across five brain areas (frontal, central, parietal, occipital, and temporal), Cohen and colleagues (1995) found no differences in P300 amplitude between low-density alcoholics and controls; in contrast, high-density alcoholics showed significant P300 reductions in every brain region compared with controls. Differences in resting EEG activity have not been reliably obtained as a function of family alcoholism history (Cohen et al. 1991; Kaplan et al. 1988; Pollock et al. 1983).

FHP youth also have been shown to have increased body sway (static ataxia) in the absence of alcohol as compared with FHN youth (Hegedus et al. 1984; Hill et al. 1987; Lipscomb et al. 1979). For example, Hill and colleagues (1987) examined sway in 8- to-14-year-old males and females. On average, FHP youth had 3.3 male and 0.3 female first- and second-degree relatives who were alcoholic. Over repeated trials with eyes open and closed, FHP youth evidenced greater body sway both front to back and side to side than FHN youth. Interestingly, many of these same measures now are being examined in young offspring of drug abusers. However, the hypotheses under investigation in this research relate primarily to the effects of in utero drug exposure on these youth and not potential genetic risk markers.

The Effects of Alcohol Challenges on Offspring of Alcoholics

A wide range of variables also have been studied using an alcohol challenge procedure in which responses of adult male offspring of alcoholics and matched FHN males are examined following equal doses of alcohol. Early reports were generally consistent in findings of decreased sensitivity to ethanol on a number of measures in FHP as compared with matched FHN subjects at equivalent blood alcohol levels. For example, FHP subjects have demonstrated less subjective intoxication (O'Malley and Maisto 1985; Pollock et al. 1986; Schuckit 1980*b*, 1984), decreased body sway (Schuckit 1985), and less impairment on the pursuit rotor task (Schuckit 1980*a*). With an increasing number of laboratories engaged in this area of research, there has been increasing diversity in the results of alcohol challenge studies. In the laboratory of the author and her colleagues (McCaul et

al. 1990*b*), findings indicated that FHP subjects reported significantly greater subjective effects of ethanol than FHN subjects. In the same study, the author and colleagues failed to find ethanol-induced differences in body sway between FHP and FHN subjects. Similar findings of increased or no difference in ethanol sensitivity for FHP subjects have been reported by other laboratories for a variety of measures including: body sway (Behar et al. 1983; Lipscomb et al. 1979; O'Malley and Maisto 1985), subjective ratings of ethanol effects (Behar et al. 1983; de Wit and McCracken 1990; Vogel-Sprott and Chipperfield 1987; Wilson and Nagoshi 1988); electrophysiological responses (Ehlers and Schuckit 1990; Pollock et al. 1983); heart rate (Wilson and Nagoshi 1988); facial flushing (Schuckit and Duby 1982); resting muscle-tension scores (Schuckit et al. 1981); psychomotor tasks (Vogel-Sprott and Chipperfield 1987; Wilson and Nagoshi 1988); and attenuation of stress response (Finn and Pihl 1987; Levenson et al. 1987). Thus, results from a number of laboratories have yielded conflicting evidence of the direction and magnitude of FHP versus FHN group differences following ethanol ingestion.

A number of studies have examined stress-response dampening in high-risk males (Finn and Pihl 1987; Levenson et al. 1987; Sher and Levenson 1982). Specifically, multigenerational FHP compared to FHN males have been shown to have increased cardiovascular, skin conductance, and muscular reactivity to aversive stimuli (e.g., unavoidable shock) when sober, and to have significantly larger decrements in reactivity to these stimuli following alcohol ingestion (Finn and Pihl 1987, 1988; Finn et al. 1990). Stewart and colleagues (1992) have shown this stress-dampening effect to be dose dependent, with heart rate decreases evident only at moderate to high alcohol doses in FHP subjects. Most recently, the specificity of alcohol stress-dampening effects was examined by comparing cardiovascular and muscular reactivity in two groups known to evidence cardiovascular reactivity to novel stimuli when sober—multi-generational FHP males and males with a family history of essential hypertension (HT) (Conrod et al. 1995). Importantly, results indicated that alcohol ingestion was associated with greater decreases in heart rate and muscle tension in FHP as compared with HT or FHN subjects. Pihl and colleagues (1990) hypothesized that increased responsivity to stimulation when sober coupled with large reductions in reactivity following alcohol ingestion may differentially negatively reinforce alcohol use in FHP males, thereby increasing their risk for development of alcoholism.

To date, only one laboratory study has examined ethanol self-administration in FHP and FHN youth. Using a relatively restrictive choice procedure that paced drinking behavior, this study found no difference in choices of ethanol drinks over placebo drinks, or in the amounts of ethanol consumed within choice sessions (de Wit and McCracken 1990).

Finally, despite many endocrine studies in alcoholics, little research has been published on the neuroendocrine axes as a marker for a familial predisposition for alcoholism. Schuckit and coworkers found that FHP males had blunted plasma ACTH, cortisol, and prolactin responses to an acute ethanol challenge compared to FHN subjects (Schuckit and Gold 1988; Schuckit et al. 1983, 1987*a*, 1987*b*); in contrast, Moss and coworkers (1989) reported comparable effects of ethanol on prolactin secretion in their sample of FHP and FHN males. In adolescents, Behar and coworkers (1983) did not demonstrate any differential cortisol response to ethanol as a function of family history. More recently, Gianoulakis and coworkers (1989) found that acute ethanol challenge produced a small but significant rise in plasma beta-endorphin (co-secreted with ACTH) in multigenerational FHP offspring compared to FHN subjects.

The Effects of Other Drug Challenges in Offspring of Alcoholics

As described earlier, differential responsiveness to ethanol is thought to be one potential mechanism for the observed differences in risk of alcoholism in FHP males. In order to better understand the nature of the risk conferred by a family history of alcoholism, it is important to determine whether FHP offspring show different dose-response relationships for drug classes other than alcohol, thereby suggesting increased risk for developing substance abuse disorders in general.

Recent studies in the author's laboratories used the alcohol challenge method to examine the pharmacological specificity to ethanol of FHP versus FHN response differences. Specifically, dose-effect functions for a variety of physiological, subjective, and psychomotor measures were established in FHP and matched FHN subjects for the short-acting barbiturate secobarbital. The well-documented cross-tolerance, similarity in intoxicating and withdrawal effects, and common mechanism of action at the GABA-benzodiazepine receptor complex between ethanol and barbiturates made this an interesting drug class for examining the sensitivity of FHP males to other drug classes. A single dose of ethanol was included in the design to allow for an explicit comparison of the magnitude of effect with

secobarbital. FHP subjects reported greater ethanol effects than FHN subjects on almost all subjective measures. Following the high dose of secobarbital, FHP but not FHN subjects showed elevated subjective effects, although these effects were less pronounced and evident in fewer measures than following ethanol. These findings suggest that family history differences partially generalize to another drug class that is cross-tolerant with alcohol and has a common mechanism of action.

Several drug challenge studies have been conducted comparing the effects of benzodiazepines in family history-positive and -negative subjects. Two studies have reported increased euphoric responses following alprazolam or diazepam administration as measured by the morphine benzedrine group (MBG) Scale of the Addiction Research Center Inventory (Ciraulo et al. 1989; Cowley et al. 1992; 1994). Also, Schuckit and colleagues (1991*b*) reported that intravenous (IV) diazepam administration significantly increased growth hormone in FHP as compared with FHN males; however, in the same study, no differences were observed in subjective effects, body sway, prolactin, or cortisol levels as a function of family history status (Schuckit et al. 1991*a*; 1991*b*). In contrast, Cowley and colleagues (1994) reported that FHP males evidenced less sensitivity to diazepam effects on two eye movement tasks (peak saccadic eye movement velocity and average smooth pursuit eye movement gain), self-rated sedation and memory (repetition, recall, and recognition).

A recent investigation examined the functional responsitivity of the GABA-benzodiazepine receptor complex as a function of familial alcoholism (Volkow et al. 1995). Specifically, effects of lorazepam were studied on regional brain glucose metabolism using positron emission tomography in subjects with and without a family history of alcoholism. Results indicated lower basal metabolic levels and a blunted drug response in the cerebellum of FHP subjects; no family history differences were observed in whole-brain glucose metabolism or in cortical or subcortical activity. FHP subjects also evidenced somewhat less motor impairment following lorazepam administration compared to FHN subjects, and impaired motor response following drug administration was found to be positively correlated with cerebellar metabolism. Overall, these findings suggest the involvement of the GABA-benzodiazepine receptor complex in sensitivity to alcohol and benzodiazepine effects.

Finally, using a self-administration paradigm, no significant differences were observed in frequency or amount of diazepam choices

by FHP and FHN males (de Wit 1991). Also, no differences were observed on ratings of drug liking, drug identification, Digit Symbol Substitution Test, or mood, although observer-rated signs of intoxication (e.g., slurred speech, trouble walking, talkativeness, drowsiness) were elevated following diazepam ingestion in FHP subjects only.

To date, there have been no alcohol or drug challenge studies in offspring of drug abusers.

MARKERS AS PREDICTORS OF SUBSTANCE ABUSE DEVELOPMENT

Several followup studies have been conducted to examine the predictive utility of the various measures that have been investigated as potential markers for alcoholism risk. Such work will be critical in determining the functional significance of the various differences that have been observed in behavioral and physiological studies of high-risk youth.

Schuckit (1994) reported findings from an 8- to-12-year followup of 223 men who participated in the alcohol challenge research conducted in his laboratory over the last decade. Remarkably, all subjects were located and only 1 percent of subjects declined participation in the followup interview. At the time of the followup interview, 34 percent of FHP subjects and 13 percent of FHN subjects had developed DSM-III-R alcohol abuse or dependence. Subjects who had developed alcohol abuse or dependence at followup had scored significantly lower on ratings of subjective high and had evidenced less body sway following alcohol administration in the earlier laboratory study; these effects were obtained independent of family history status. These findings suggest that decreased alcohol sensitivity may place individuals at increased risk for the subsequent development of alcoholism.

Berman and colleagues (1993) reported 4-year followup data on alcohol and drug use among FHP and FHN boys who had completed ERP assessment as preadolescents prior to substance exposure. A summary score of substance use was derived using an adolescent behavior questionnaire that elicited self-report data on use and/or effects of alcohol, tobacco, caffeine, marijuana, pills and other drugs, and on delinquency. Independent of family history status, P300s of lowest amplitude were associated with highest substance use scores at

followup. When corrected for subjects' age, there was a significant relationship between the combination of reduced amplitude and increased latency of target and nontarget P300 and substance use scores; however, the combination of these variables accounted for less than a quarter of the variance in the adolescent substance use measure. These findings suggest that while P300 measures may be predictive of subsequent development of substance use, other variables will need to be included in the model to more accurately predict risk.

Finally, the predictive utility of psychomotor sensitivity was examined using followup data from the Colorado Alcohol Research on Twins and Adoptees (CARTA) project (Rodriguez et al. 1993). Initial sensitivity on three psychomotor measures following alcohol ingestion was used to predict self-reported alcohol consumption collected annually over a 4-year period. For male subjects, decreased sensitivity to rail walking was associated with increased reports of alcohol use at year 2. For females, increased sensitivity on hand steadiness was associated with increased reports of alcohol use at year 2. The investigators suggested that overall results indicated at best a relatively weak relationship between psychomotor sensitivity and subsequent alcohol use since a relationship was observed for only one of three measures, at only one of four timepoints, and was opposite in direction for males and females.

METHODOLOGICAL LIMITATIONS AND FUTURE RESEARCH DIRECTIONS

Refinements in Proband Ascertainment for High-Risk Studies

There has been considerable variation in the definitions of a positive family history of alcoholism used to recruit and characterize subjects across high-risk studies. For example, definitions have varied as to the proximity and extent of affected family members. In some early studies, probands were considered positive for a family history of alcoholism if a sibling had an alcohol problem; other more recent research has required that the proband's father, grandfather, and at least one other first- or second-degree relative meet diagnostic criteria for alcohol abuse/dependence. Further, there has been substantial variability in the rigor of the assessment methods and criteria for identifying a positive family history. Assessment strategies have included the Michigan Alcoholism Screening Test (Selzer 1971) (adapted to apply to the subject's mother or father), Family History-Research Diagnostic Criteria (Andreasen et al. 1977, 1986), Feighner

criteria (Feighner et al. 1972), or DSM-III-R criteria (American Psychiatric Association 1987). Such variability in subject selection criteria could certainly be expected to contribute to the discrepant findings across laboratory studies with FHP youth.

Genetic factors, as compared with environmental factors, are more likely to be major determinants of alcoholism in families with high-density patterns of alcoholism than in families with only one affected member. Thus, many of the study subjects that met criteria for participation in earlier research may not be genetically at risk for the disorder (Tarter 1988) or may differ in the degree of risk conferred by their familial alcoholism characteristics (Cloninger 1988). Indeed, this research is made even more challenging by the fact that even if a subject is FHP, he or she may not have inherited the marker or be at increased risk. It is important that only approximately 25 percent of FHP male offspring and fewer than 10 percent of FHP female offspring go on to develop substance use disorders as adults (Cloninger et al. 1981).

As described earlier, in a report by the author's research team (McCaul et al. 1990*a*), differences in self-reported alcohol and drug use patterns and associated problems were found as a function of extent of family alcoholism history. The greatest levels of alcohol and drug use were found for college students with a high density of alcoholism in their families (first- and second-degree affected relatives), an intermediate level for students with low alcoholism density families (first-degree affected relative(s) only), and the least in students with no affected relatives. Generally, students from high-density families reported greater use of alcohol, marijuana, sedatives, and cocaine; a younger age at first alcohol intoxication and first use of marijuana; and more experience with less commonly used drug classes such as opiates and hallucinogens. Finally, a greater percentage of these students reported personal alcohol- or drug-related problems as well as family mental health care. While similar findings have been reported in offspring of treated alcoholic probands (Merikangas et al. 1985), this was the first report of the significant role of density of familial alcoholism in determining the onset, amount, and broad extent of substance use in a diverse population of college males. These results are in line with earlier findings by Schuckit and Sweeney (1987) that men with a high density of familial alcoholism tended to report a higher frequency of drinking days, an earlier age of drinking onset, and more life problems than males with low density or unaffected families.

The importance of family density of alcoholism as a determinant of ethanol effects is further supported by a secondary analysis of alcohol challenge data from the author's laboratory (McCaul et al. 1991*b*). In general across physiological, psychomotor, and subjective measures, responses of subjects with a high density of familial alcoholism were significantly greater than either low-density or FHN subject responses; indeed, there were no differences between low-density and FHN subjects. Also, using laboratory methodology, Finn and Pihl (1987) demonstrated significant differences in resting heart rate and change in heart rate to a shock stressor for multigenerational family history-positive subjects as compared with low-density and FHN subjects, but no differences on these measures between low-density and FHN subjects. Thus, both epidemiological and laboratory studies have shown extent of familial alcoholism to be an important determinant of alcohol ingestion and effects.

While improved specification of family history status may be the most important subject selection criteria targeted for refinement, a number of other issues important in subject selection also should be addressed.

First, there needs to be increased restrictions on prior alcohol use of subjects enrolled in laboratory research. When subjects already have initiated use, the potential effects of differential prior exposure to alcohol/drugs on research outcomes cannot be ruled out. It is important to ensure that subjects have had no or only minimal prior alcohol exposure in research examining baseline differences between FHP and FHN subjects and that no symptoms of alcohol abuse or tolerance have developed in subjects included in alcohol challenge research.

A second area of consideration in subject selection is improved matching of FHP and FHN subjects. Investigators need to be sure to match on the variety of variables that may affect their results, including gender, race, typical and maximal alcohol use, other drug use, and, if administering a drug challenge, body composition.

Third, investigators need to consider the impact of the sociodemographic diversity in their subjects. In earlier research, many laboratories have recruited only college-enrolled subjects. In so doing, investigators may well be selecting individuals who are at reduced risk for problems compared to the general population. Finally, family history research would benefit from better characterization of subjects' personality characteristics, particularly

antiscoial personality (ASP) tendencies and symptoms. Such traits may be important determinants of baseline characteristics as well as alcohol/drug responses and should be characterized in the study sample.

Refinements in Laboratory Methods for High-Risk Studies

In addition to the suggested refinements in subject ascertainment, several methodological issues need consideration in designing laboratory research examining the effects of familial alcoholism.

First, several investigators have suggested that it is important to examine potential biphasic effects of alcohol in family history research. For example, Newlin and Thomson (1990) suggested that sons of alcoholics demonstrate greater acute sensitization during ascending blood alcohol levels and acute tolerance during descending blood alcohol levels as compared with sons of nonalcoholics. Given the rapid achievement of peak blood alcohol levels in many subjects, early and frequent collection of dependent measures would be necessary to detect such ascending blood alcohol effects. There is also evidence of family history differences in postsession "hangover" or withdrawal effects (McCaul et al. 1991*a*; Newlin and Pretorius 1990), suggesting the importance of extending data collection periods beyond the acute challenge session.

Second, this area of research could benefit from the inclusion of a range of biological and behavioral measures in the same studies. All too often, reports focus on either biological (e.g., hormonal or neurophysiological data) or behavioral-dependent measures, thus limiting the interpretation of study findings.

Third, investigators should consider increased standardization of procedures (e.g., alcohol/drug doses; timing of data collection procedures) and dependent measures (e.g., subjective report measures; hormonal measures; psychomotor tasks) to facilitate comparisons across studies.

Finally, as described earlier, it will be important in future research to evaluate subjects' long-term alcohol/drug use status to determine the predictive utility of proposed markers. Ultimately, laboratory measures that demonstrate significant differences as a function of family history will be informative only to the extent that they predict differences in alcohol and/or drug use patterns in adult FHP offspring.

SUMMARY

Epidemiological research has clearly demonstrated the importance of a family history as a determinant of future alcohol and, possibly, drug use in offspring of alcoholics. Laboratory studies have examined a wide range of potential markers both in the presence and absence of alcohol challenge, which may predict those subjects at high risk for the future development of alcoholism. While this body of research has yielded several replicable differences in FHP and FHN subjects, it also has been marked by many discrepancies in outcomes across studies. Future refinements in subject ascertainment and laboratory methodologies may help to bring greater procedural uniformity and consistency in study outcomes.

REFERENCES

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 3d ed. Revised*. Washington, DC: American Psychiatric Association, 1987.

Andreasen, N.C.; Endicott, J.; Spitzer, R.L.; and Winokur, G. The family history method using diagnostic criteria: Reliability and validity. *Arch Gen Psychiatry* 34:1229-1235, 1977.

Andreasen, N.C.; Rice, J.; Endicott, J.; Reich, T.; and Coryell, W. The family history approach to diagnosis: How useful is it? *Arch Gen Psychiatry* 43:421-429, 1986.

Begleiter, H.; Porjesz, B.; Bihari, B.; and Kissin, B. Event-related potentials in boys at risk for alcoholism. *Science* 225:1493-1496, 1984.

Behar, D.; Berg, C.J.; Rappaport, J.L.; Linnoila, M.; Cohen, M.; Bozevich, C.; and Marshall, T. Behavioral and physiological effects of ethanol in high-risk and control children: A pilot study. *Alcohol Clin Exp Res* 7:404-410, 1983.

Berman, S.M.; Whipple, S.C.; Fitch, R.J.; and Noble, E.P. P3 in young boys as a predictor of adolescent substance use. *Alcohol* 10:69-76, 1993.

Cadoret, R.J.; O'Gorman, T.W.; Troughton, E.; and Heywood, E. Alcoholism and antisocial personality. Interrelationships, genetic and environmental factors. *Arch Gen Psychiatry* 42 (2):161-167, 1985.

Cadoret, R.J.; Troughton, E.; O'Gorman, T.W.; and Heywood, E. An adoption study of genetic and environmental factors in drug abuse. *Arch Gen Psychiatry* 43:1131-1136, 1986.

Cadoret, R.J.; Yates, W.R.; Troughton, E.; Woodworth, G.; and Stewart, M.A. Adoption study demonstrating two genetic pathways to drug abuse. *Arch Gen Psychiatry* 52(1):42-52, 1995.

Ciraulo, D.A.; Barnhill, J.G.; Ciraulo, A.M.; Greenblatt, D.J.; and Shader, R.I. Parental alcoholism as a risk factor in benzodiazepine abuse: A pilot study. *Am J Psychiatry* 146:1333-1335, 1989.

Cloninger, C.R. Etiologic factors in substance abuse: An adoption study perspective. In: Pickens, R.W., and Svikis, D.S., eds. *Biological Vulnerability to Drug Abuse*. National Institute on Drug Abuse Monograph 89. DHHS Pub. No.(ADM)88-1590. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1988.

Cloninger, C.R.; Bohman, M.; and Sigvardsson, S. Inheritance of alcohol abuse. *Arch Gen Psychiatry* 38:861-868, 1981.

Cohen, H.L.; Porjesz, B.; and Begleiter, H. EEG characteristics in males at risk for alcoholism. *Alcohol Clin Exp Res* 15(5):858-861, 1991.

Cohen, H.L.; Wang, W.; Porjesz, B.; and Begleiter, H. Auditory P300 in young alcoholics: Regional response characteristics. *Alcohol Clin Exp Res* 19(2):469-475, 1995.

Conrod, P.J.; Pihl, R.O.; and Ditto, B. Autonomic reactivity and alcohol-induced dampening in men at risk for alcoholism and men at risk for hypertension. *Alcohol Clin Exp Res* 19(2):482-489, 1995.

Cotton, N.S. The familial incidence of alcoholism. *J Stud Alcohol* 40:89-116, 1979.

Cowley, D.S.; Roy-Byrne, P.P.; Godon, C.; Breenblatt, D.J.; Ries, R.; Walker, R.D.; Samson, H.H.; and Hommer, D.W. Response to diazepam in sons of alcoholics. *Alcohol Clin Exp Res* 16(6):1057-1063, 1992.

Cowley, D.S.; Roy-Byrne, P.P.; Radant, A.; Hommer, D.W.; Greenblatt, D.J.; Vitaliano, P.P.; and Godon, C. Eye movement effects of diazepam in sons of alcoholic fathers and male control subjects. *Alcohol Clin Exp Res* 18(2):324-332, 1994.

de Wit, H. Diazepam preference in males with and without an alcoholic first-degree relative. *Alcohol Clin Exp Res* 15(4):593-600, 1991.

de Wit, H., and McCracken, S.G. Ethanol self-administration in males with and without an alcoholic first-degree relative. *Alcohol Clin Exp Res* 14(1):63-70, 1990.

Ehlers, C L., and Schuckit, M.A. EEG fast frequency activity in the sons of alcoholics. *Biol Psychiatry* 27(6):631-41, 1990.

Feighner, J.; Robins, E.; Cruze, S.; Woodruff, R.; Winokur, G., Munoz, R. Diagnostic criteria for use in psychiatric research. *Arch Gen Psy* 26:57-63, 1972.

Finn, P.R., and Pihl, R.O. Men at high risk for alcoholism: The effects of alcohol on cardiovascular response to unavoidable-shock. *J Abnorm Psychol* 96:230-236, 1987.

Finn, P.R., and Pihl, R.O. Risk for alcoholism: A comparison between two different groups of sons of alcoholics on cardiovascular reactivity and sensitivity to alcohol. *Alcohol Clin Exp Res* 12:742-747, 1988.

Finn, P.R.; Zeitouni, N.C.; and Pihl, R.O. Effects of alcohol on psychophysiological hyperreactivity to nonaversive and aversive stimuli in men at high risk for alcoholism. *J Abnorm Psychol* 99:79-85, 1990.

Gianoulakis, C.; Beliveau, D.; Angelogianni, P.; Meaney, M.; Thavundayil, J.; Tawar, V.; and Dumas, M. Different pituitary beta-endorphin and adrenal cortisol response to ethanol in individuals with high and low risk for future development of alcoholism. *Life Sci* 45(12):1097-1109, 1989.

Goodwin, D.W.; Schulsinger, F.; Hermansen, L.; Guze, S.D.; and Winokur, G. Alcohol problems in adoptees raised apart from alcoholic biological parents. *Arch Gen Psychiatry* 28:238-243, 1973.

Goodwin, D.W.; Schulsinger, F.; Knop, J.; Mednick, S.; and Guze, S.D. Psychopathology in adopted and nonadopted daughters of alcoholics. *Arch Gen Psychiatry* 34:1005-1009, 1977.

Hegedus, A.M.; Tarter, R.; Hill, S.Y.; Jacob, T.; and Winsten, N.E. Static ataxia: A possible marker for alcoholism. *Alcohol Clin Exp Res* 8:580-582, 1984.

Hill, S.Y., Armstrong, J.; Steinhauer, S.R.; Baughman, T.; and Zubin, J. Static ataxia as a psychobiological marker for alcoholism. *Alcohol Clin Exp Res* 11(4):345-348, 1987.

Hill, S.Y., and Steinhauer, S.R. Assessment of prepubertal and postpubertal boys and girls at risk for developing alcoholism with P300 from a visual discrimination task. *J Stud Alcohol* 54:350-358, 1993.

Hill, S.Y.; Steinhauer, S.R.; Zubin, J.; and Baughman, T. Event-related potentials as markers for alcoholism risk in high density families. *Alcohol Clin Exp Res* 12:545-554, 1988.

Hrubec, S., and Omenn, G.S. Evidence of genetic predisposition to alcoholic cirrhosis and psychosis: Twin concordances for alcoholism and its biological end points by zygosity among male veterans. *Alcohol Clin Exp Res* 5:207-215, 1981.

Kaij, L. *Alcoholism in Twins*. Stockholm: Almqvist and Wiksell, 1960.

Kaplan, R.F.; Hesselbrock, V.M.; O'Connor, S.; and De Palma, N. Behavioral and EEG response to alcohol in nonalcoholic men with a family history of alcoholism. *Neuropsychopharmacology Biol Psychiatry* 12:873-885, 1988.

Kaprio, J.; Koskenvuo, M.; and Sarna, S. Cigarette smoking, use of alcohol, and leisure-time physical activity among same-sexed adult twins. In: *Twin Research 3, Part C: Epidemiological and Clinical Studies*. New York: A.R. Liss, 1981.

Kendler, K.S.; Heath, A.C.; Neale, M.C.; Kessler, R.C.; and Eaves, L.J. A population-based twin study of alcoholism in women. *JAMA* 268(14):1877-82, 1992.

Levenson, R.W.; Oyama, O.N.; and Meek, P.S. Greater reinforcement from alcohol for those at risk: Parental risk, personality risk, and sex. *J Abnorm Psychol* 96:242-253, 1987.

Lipscomb, T.R.; Carpenter, J.A.; and Nathan, P.E. Static ataxia: A predictor for alcoholism? *Br J Addict* 74:289-294, 1979.

McCaul, M.E.; Svikis, D.S.; Turkkan, J.S.; and Bigelow, G.E. Alcohol and drug use by college males as a function of family alcoholism history. *Alcohol Clin Exp Res* 14(3):467-471, 1990*a*.

McCaul, M.E.; Turkkan, J.S.; Svikis, D.S.; and Bigelow, G.E. Alcohol and secobarbital effects as a function of familial alcoholism: Acute psychophysiological effects. *Alcohol Clin Exp Res* 14(5):704-712, 1990b.

McCaul, M.E.; Turkkan, J.S.; Svikis, D.S.; and Bigelow, G.E. Alcohol and secobarbital effects as a function of familial alcoholism: Extended intoxication and increased withdrawal effects. *Alcohol Clin Exp Res* 15(1):94-101, 1991*a*.

McCaul, M.E.; Turkkan, J.S.; Svikis, D.S.; and Bigelow, G.E. Family density of alcoholism: Effects on psychophysiological responses to ethanol. *Alcohol* 8:219-222, 1991*b*.

Merikangas, K.R. The genetic epidemiology of alcoholism. *Psychol Med* 20:11-22, 1990.

Merikangas, K.R.; Rounsaville, B.J. and Prusoff, B.A. Familial factors in vulnerability to substance abuse. In: Glantz, M., and Pickens, R., eds. *Vulnerability to Drug Abuse*. Washington, DC: American Psychiatric Association Press, 1992.

Merikangas, K.R.; Weissman, M.M.; Prusoff, B.A.; Pauls, D.L.; and Leckman, J.F. Depressives with secondary alcoholism: Psychiatric disorders in offspring. *J Stud Alcohol* 46(3):119-204, 1985.

Moss, H.B.;Yao, J.K.; and Maddock, J.M. Responses by sons of alcoholic fathers to alcoholic and placebo drinks: Perceived mood, intoxication, and plasma prolactin. *Alcohol Clin Exp Res* 13:252-257, 1989.

Newlin, D.B., and Pretorius, M.B. Sons of alcoholics report greater hangover symptoms than sons of nonalcoholics: A pilot study. *Alcohol Clin Exp Res* 14(5):713-716, 1990.

Newlin, D.B., and Thomson, J.B. Alcohol challenge with sons of alcoholics: A critical review and analysis. *Psychol Bull* 108(3):383-402, 1990.

O'Malley, S.S., and Maisto, S.A. Effects of family history and expectancies on responses to alcohol in men. *J Stud Alcohol* 46:289-297, 1985.

Pederson, N. Twin similarity for usage of common drugs. In: Gedda, L.; Parisi, P.; and Nance, W., eds. *Twin Research 3: Epidemiological and Clinical Studies.* New York: Alan R. Liss, 1981.

Pfefferbaum, A.; Ford, J.M.; White, P.M.; and Mathalon, D. Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcohol Clin Exp Res* 15(5):839-850, 1991.

Pickens, R.W., and Svikis, D.S. Genetic influences in human substance abuse. *J Addict Dis* 10:205-214, 1991.

Pickens, R.W.; Svikis, D.S.; McGue, M.; Lykken, D.T.; Heston, L.L.; and Clayton, P.J. Heterogeneity in the inheritance of alcoholism. *Arch Gen Psychiatry* 48:19-28, 1991.

Pihl, R.O.; Peterson, J.; and Finn, P. Inherited predisposition to alcoholism: Characteristics of sons of male alcoholics. *J Abnorm Psychol* 99(3):291-301, 1990.

Pollock, V.E.; Teasdale, T.W.; Gabrielli, W.E.; and Knop, J. Subjective and objective measures of response to alcohol among young men at risk for alcoholism. *J Stud Alcohol* 47:297-304, 1986.

Pollock, V.E.; Volavka, J.; Goodwin, D.W.; Mednick, S.S. Gabrielli, W.F.; Knop, J.; and Schulsinger, F. The EEG after alcohol in men at risk for alcoholism. *Arch Gen Psychiatry* 40:857-861, 1983.

Rodriguez, L.A.; Wilson, J.R.; and Nagoshi, C.T. Does psychomotor sensitivity to alcohol predict subsequent alcohol use? *Alcohol Clin Exp Res* 17(1):155-161, 1993.

Schuckit, M.A. Biological markers: metabolism and acute reactions to alcohol in sons of alcoholics. *Pharmacol Biochem Behav* 13(Suppl. 1):9-16, 1980*a*.

Schuckit, M.A. Self-rating of alcohol intoxication by young men with and without family histories of alcoholism. *J Stud Alcohol* 41:242-249, 1980*b*.

Schuckit, M.A. Subjective responses to alcohol in sons of alcoholics and control subjects. *Arch Gen Psychiatry* 41:879-884, 1984.

Schuckit, M.A. Ethanol-induced changes in body sway in men at high alcoholism risk. *Arch Gen Psychiatry* 42(4):375-9, 1985.

Schuckit, M.A. Low level of response to alcohol as a predictor of future alcoholism. *Am J Psychiatry* 151:184-189, 1994.

Schuckit, M. A., and Duby, J. Alcohol-related flushing and the risk for alcoholism in sons of alcoholics. *J Clin Psychiatry* 43(10):415-418, 1982.

Schuckit, M.A.; Duthie, L.A.; Mahler, H.I.M.; Irwin, M.; and Monteiro, M.G. Subjective feelings and changes in body sway following diazepam in sons of alcoholics and control subjects. *J Stud Alcohol* 52(6):601-608, 1991*a*.

Schuckit, M.A.; Engstrom, D.; Alpert, R.; and Duby. J. Differences in muscle-tension response to ethanol in young men with and without family histories of alcoholism. *J Stud Alcohol* 42:918-924, 1981.

Schuckit, M.A.; Gold, E.; and Risch, C. Plasma cortisol levels following ethanol in sons of alcoholics and controls. *Arch Gen Psychiatry* 44:942-945, 1987*a*.

Schuckit, M.A.; Gold, E.; and Risch, C. Serum prolactin levels following ethanol in sons of alcoholics and controls. *Am J Psychiatry* 144:854-859, 1987*b*.

Schuckit, M.A., and Gold, E.O. A simultaneous evaluation of multiple markers of ethanol/placebo challenges in sons of alcoholics and controls. *Arch Gen Psychiatry* 45:211-216, 1988.

Schuckit, M.A.; Hauger, R.L.; Monteiro, M.G.; Irwin, M.; Duthie, L.A.; and Mahler, H.I.M. Response of three hormones to diazepam challenge in sons of alcoholics and controls. *Alcohol Clin Exp Res* 15(3):537-542, 1991b.

Schuckit, M.A.; Parker, D.C.; and Rossman, L.R. Ethanol-related prolactin responses and risk for alcoholism. *Biol Psychiatry* 18:1153-1159, 1983.

Schuckit, M.A., and Sweeney, S. Substance use and mental health problems among sons of alcoholics and controls. *J Stud Alcohol* 48(6):528-34, 1987.

Selzer, M.L. The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. *Am J Psychiatry* 127:1653-1658, 1971.

Sher, K.J., and Levenson, R.W. Risk for alcoholism and individual differences in the stress-response-dampening effect of alcohol. *J Abnorm Psychol* 91:350-367, 1982.

Steinhauer, S.R.; Hill, S.Y.; and Zubin, J. Event-related potentials in alcoholics and their first-degree relatives. *Alcohol* 4:307-314, 1987.

Stewart, S.H.; Finn, P.R.; and Pihl, R.O. The effects of alcohol on the cardiovascular stress response in men at high risk for alcoholism: A dose response study. *J Stud Alcohol* 53:499-506, 1992.

Tarter, R.E. The high-risk paradigm in alcohol and drug abuse research. In: Pickens, R.W., and Svikis, D.S., eds. *Biological Vulnerability to Drug Abuse*. National Institute on Drug Abuse Monograph 89. DHHS Pub. No.(ADM)88-1590. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1988.

Vogel-Sprott, M., and Chipperfield, B. Family history of problem drinking among young male social drinkers: Behavioral effects of alcohol. *J Stud Alcohol* 48(5):430-436, 1987.

Volkow, N.D.; Wang, G-J.; Genleiter, H.; Hitzemann, R.; Pappas, N.; Burr, G.; Pascani, K.;Christopher Wong, C.; Fowler, J.S.; and Wolf, A.P. Regional brain metabolic response to Lorazepam in subjects at risk for alcoholism. *Alcohol Clin Exp Res* 19(2):510-516, 1995.

Whipple, S.; Parker, E.S.; and Noble, E.P. An atypical neurocognitive profile in alcoholic fathers and their sons. *J Stud Alcohol* 49:240-244, 1988.

Wilson, J.R., and Nagoshi, C.T. Adult children of alcoholics: Cognitive and psychomotor characteristics. *Br J Addict* 83:809-820, 1988.

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