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Alcohol Challenge With Sons of Alcoholics: A Critical Review and Analysis

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Studies are reviewed in which response to acute administration of alcohol was compared between individuals with and without family histories of alcoholism (FH+, FH-). This research represents a search for a psychobiological marker for alcoholism. A methodological critique of the procedures reported in this literature is then presented. Finally, a conceptual model is suggested in which differences in the response to alcohol between FH+ individuals and FH- individuals must be understood in relation to time after drinking alcohol. This Newtonian differentiator model proposes that sons of alcoholics exhibit acute sensitization as blood alcohol level rises and acute tolerance as blood alcohol level falls, compared with sons of nonalcoholics. Therefore, FH+ subjects find alcohol more rewarding because they accentuate the pleasurable, excitatory aspects of initial intoxication and attenuate the feelings of anxiety and depression that predominate as blood alcohol levels drop.

Alcoholism and drug abuse are the most prevalent psychiatric disorders (Robins et al., 1984). Approximately 30% of American men and 8% of American women have experienced serious problems with these drugs. However, the etiologies of alcoholism and drug abuse are unclear. This ambiguity may be due, in part, to the fact that long-term use of toxic drugs (such as alcohol) may obscure factors that play a role in the etiology of alcoholism and drug addiction. Therefore, comparisons of, for example, alcoholics with nonalcoholics may elucidate effects of the disorder without shedding any light on its causes.

One approach to studying causation is to investigate individuals who are at risk for the disorder but who are asymptomatic at the time of testing. Characteristics of at-risk individuals may reveal factors that promote development of the disorder. At the same time, these characteristics are not obscured by the long-term consequences of the abuse of alcohol and other drugs.

Alcoholism tends to run in families (Cotton, 1979). Therefore, individuals with a family history of alcoholism are at elevated risk for developing the disorder in late adolescence and adulthood. Whether this elevated risk is environmentally or genetically mediated (or both), offspring of alcoholics may have psychological or biological characteristics that play important etiological roles in the development of alcoholism. Empirical research over the last decade has attempted to identify these potentially causative factors in high-risk individuals.

One important technique for studying at-risk individuals is to administer alcohol challenges to high- and low-risk groups. The purpose of this procedure is to determine whether high-risk individuals have deviant responses to alcohol that could begin to explain their increased risk for alcoholism. Perhaps high-risk individuals respond to alcohol differently than low-risk individuals, which could have implications for their motivation to drink. For example, high-risk individuals might experience greater euphoria from alcohol, fewer adverse reactions such as nausea or hangover, or greater tolerance for the drug. These potential characteristics have direct implications for understanding at-risk status. Although it is clear that some individuals with a family history of alcoholism are more likely to become alcoholics themselves, it is not known what increases their morbidity. This question is equally valid for genetic, environmental, and interactional models of risk.

The purpose of this article is to review those studies in which offspring of alcoholics have been administered alcohol challenges, to critically evaluate the methodologies used in this paradigm, and to offer an integrative model that attempts to resolve the many discrepancies in this literature. A methodological critique is badly needed to evaluate procedures that have been used many times in this area of investigation and have become de facto standards despite their limitations. Although model building may seem premature in this relatively new field, the literature has grown so rapidly that integrative analysis is needed to provide a focus for continuing research.

The central question in studies in which high- and low-risk individuals are challenged with alcohol has been whether individuals with a family history of alcoholism (FH+) are more or less sensitive to alcohol than subjects with no such history (FH-). In other words, the focus has been on the relative magnitude of the response to alcohol. We address this issue in our critical review of the literature, in part because this has been such an overriding theme in these studies. However, our integrative model attempts to go beyond the differential sensitivity issue to the motivational implications of these data. We argue that the motivation to drink (or to avoid negative consequences of drinking) is a key issue that may provide a theoretical link between high-risk status and final manifestation of alcoholism.

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Psychobiological Markers

A psychobiological marker is a characteristic, other than symptoms of the disease itself, that identifies those individuals in the population who are most likely to develop a specific disorder. This characteristic may be measured using psychological or biological means. In the case of alcoholism, it is a characteristic that can be measured in children or adolescents (before the development of the disorder) that has significant power for predicting who will and will not show alcoholic behavior in adulthood. In other words, individuals who manifest this characteristic are more likely to develop alcoholism.

How do we identify psychobiological markers of alcoholism? A direct implication of the definition of psychobiological markers is that alcoholics themselves will be much more likely than nonalcoholics to display these characteristics. However, it is possible that a result of this disorder (i.e., prolonged drinking) is to change the marker so that it is no longer measurable. For example, suppose that there is a specific neuroendocrine marker for alcoholism; individuals who possess this neuroendocrine marker are much more likely to develop alcoholism than those without this characteristic. Researchers might therefore hope to discover this marker by comparing the neuroendocrine profiles of alcoholics and nonalcoholics. However, it is possible that prolonged drinking produces toxic effects that change or obscure this marker. Assuming that the neuroendocrine characteristic plays a significant role in the etiology of alcoholism, it is plausible (if not likely) that alcohol could have both short- and long-term effects on this neuroendocrine system. Therefore, it is easy to see that other means would be needed to identify this marker.

This reasoning is equally applicable to responses to alcohol challenge. Alcoholics ought to have different responses to alcohol from nonalcoholics. If nothing else, they certainly ought to show greater tolerance for alcohol. However, this difference would not represent a psychobiological marker because it could easily be a result of prolonged drinking rather than a predisposing characteristic.

Therefore, research has been conducted with individuals at risk for alcoholism to identify characteristics that distinguish them from individuals at low risk for developing alcoholism. The rationale is the same whether the higher risk is due to genetic or environmental (or interactional) factors. Features that distinguish high- from low-risk groups may represent psychobiological markers for alcoholism. This is ultimately tested through long-term follow-up of those with and without the potential marker to determine who develops the disorder.

Alcoholism is not necessarily a single disorder with a unidimensional etiology. A marker may be present for one type of alcoholism but not for other types, or multiple markers may reflect different etiological pathways. One does not have to assume that alcoholism has a single etiological pathway to justify the search for psychobiological markers. However, consideration of this issue may change the way in which results are interpreted. Similarly, a psychobiological marker for alcoholism is not necessarily specific to the disorder. The specificity question requires empirical examination of other high-risk groups (such as individuals with a family history of schizophrenia) to determine whether the marker is specific to offspring of alcoholics.

Genetic Factors

There actually have been more reviews of genetic studies on alcoholism than the number of empirical studies on which the reviews comment. However, despite the large number of review articles, there have been very few critical reviews. Murray, Clifford, and Gurling (1983), Searles (1988), and Peele (1986) critically reviewed this literature and concluded that the evidence in favor of a genetic contribution to alcoholism is not strong. We briefly summarize the evidence in sufficient detail only to provide a background to alcohol-challenge studies. The high-risk paradigm does not depend on evidence for a genetic contribution to alcoholism; environmental risk is equally valid in the search for psychobiological markers for alcoholism. In addition, the study of offspring of alcoholics does not allow inferences concerning genetic versus environmental markers.

Much of the alcohol-challenge research has been motivated by evidence of genetic factors in alcoholism. Cotton (1979) reviewed evidence that alcoholism tends to run in families. She found that, of 4,329 alcoholic probands, 30.8% had an alcoholic parent, compared with 4.7% of 922 nonpsychiatric patients. This supports either genetic or environmental determination of alcoholism in many patients. Twin and adoption studies also have attempted to resolve the nature versus nurture question.

Overall drinking behavior, including normal social drinking, was reported to be significantly heritable in three studies of Scandinavian twins (Kaij, 1960; Kaprio et al., 1987; Partanen, Bruun, & Markkanen, 1966). However, in two other large twin studies, cited by Gurling, Murray, and Clifford (1981), no evidence was found for the heritability of normal drinking. Alcoholism concordance rates in twins were examined in four studies; Hrubec and Omenn (1981) and Kaij (1960) found evidence of significant heritability, whereas Gurling et al. (1981) and Partanen et al. (1966) found no such evidence. Differences in methodology and subject criteria may have contributed to the disparate results. However, in the two largest studies, Hrubec and Omenn (1981) and Partanen et al. (1966) found significant evidence for the heritability of alcoholism and overall drinking pattern, respectively.

The rationale behind adoption studies is that these designs allow separate relative measures of genetic and environmental components. Two large studies of northern European subjects with matched control groups (Bohman, 1978; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973) found alcoholism to be more common in adopted sons of alcoholics (SOAs) than in sons of nonalcoholics (SONAs). Both studies have been criticized on various grounds. Data for Bohman's entire adoptee population were presented in a later publication (Cloninger, Bohman, & Sigvardsson, 1981). When these data were presented in the format of Goodwin et al. (1973), the proband and control groups did not differ in alcoholism rates. Goodwin et al. (1973) found alcoholism in a significantly higher proportion of adopted SOAs, but heavy and problem drinking were more common among SONAs. When definitional criteria were redistributed to agree with common conceptions of alcoholism

(including almost every study to be cited in this review), no significant differences remained between groups.

In two smaller studies of half-siblings raised with or without an alcoholic parent, Goodwin et al. (1974) and Schuckit, Goodwin, and Winokur (1972) both found that alcoholism rates were not increased significantly by living with the alcoholic parent. Together, these twin, adoption, and half-sibling studies suggest a strong hereditary component to alcoholism. On critical examination, however, the evidence appears less strong.

The widely cited conclusion that SOAs are 3 to 5 times more likely to become alcoholic may not reflect genetic factors. However, even if it were a valid estimate, this would indicate much lower genetic loading to alcoholism than, for example, schizophrenia. Offspring of schizophrenics are approximately 12.3 times more likely to develop schizophrenia than are offspring of nonschizophrenics (Faraone & Tsuang, 1985). Apparently, the genetic hypothesis for alcoholism does not account for a large proportion of the variance no matter what estimates are used, and the risk ratio can give a very misleading representation of the strength of the effect.

Definitional Issues

One approach to the definitional problems (American Psychiatric Association, 1980; National Council on Alcoholism, 1972) noted earlier is to examine the alcoholic behavior found to be heritable in the genetic studies. Cloninger et al. (1981) described two forms of alcoholism on the basis of a multivariate analysis of their complete male adoptee data. Type 1, or milieu-limited, alcoholism usually was mild (only one registration for alcohol abuse) and, depending on the postnatal environment, could become severe (with hospitalization or treatment required). Type 2, or male-limited, alcoholism was moderate (two or three registrations for alcohol abuse, no treatment) and independent of environmental influence. There was an apparent logical problem with this formulation, however, because this moderate and highly heritable form of alcoholism usually occurred in sons of fathers with severe and extensively treated alcoholism (Cloninger, 1983). Moreover, Cloninger et al. reported that sons with severe alcoholism tended to have fathers with mild alcoholism, which they suggested is a less strictly heritable form of alcoholism. Public registration data is biased by the presence of antisocial behavior in both the fathers and sons. Antisocial behavior is much more likely to be called to the attention of authorities, so that it is more likely to be represented in the register.

Goodwin et al. (1973), on the other hand, found that heavy and problem drinking did not significantly differentiate adopted SOAs and adopted SONAs. Only alcoholism, determined by very strict and severe criteria, was found to be inherited. The limitations of Goodwin et al.'s study have already been discussed, and because of the small numbers and lack of replication, these results should not be overinterpreted. Nevertheless, Goodwin et al.'s results indicate a categorical difference in heritability between alcoholism with two (or fewer) related problems and alcoholism with three (or more) related problems. Cloninger et al. (1981) reported the highest heritability in a group roughly similar to the problem drinkers of Goodwin et al.'s study, although there was a higher percentage of problem drinkers among the control subjects than among the SOAs (14% vs. 19%) in the latter study.

One additional point should be mentioned before leaving this topic. Abel and Lee (1988) found that exposing rat sires to alcohol led to changes in offspring behavior. This raises the thorny issue of whether the heritable component of alcoholism is really due to genetic transmission in the traditional sense of the term or to changes in the sperm of the father resulting from exposure to alcohol. It is also possible that both effects are present. This issue requires further research before firm conclusions can be drawn. The implications of these results, if replicated, are that it may be necessary to study the grandsons of alcoholics when the father is not alcoholic. Another approach would be to restrict FH+ groups to individuals with alcoholic brothers and sisters rather than parents. These studies have not yet been performed.

Alcohol-Challenge Studies

Alcohol-challenge studies with the sons and daughters of alcoholics have had scientific influence beyond their number, in part because the results have been accepted without consideration of the theoretical and methodological assumptions made in this research paradigm. In this section, we summarize those studies in which SOAs (and one study of daughters of alcoholics) were given alcohol in challenge doses so that deviant responses in the high-risk group could be measured. The types of measures that have been used in these studies include blood alcohol concentration (BAC), acetaldehyde levels, other biochemical measures, electroencephalography (EEG), self-reported intoxication, static ataxia (body sway), other motor and cognitive measures, and a range of autonomic measures.

A central focus for this research paradigm has been the question of whether offspring of alcoholics are more or less sensitive to the effect of alcohol. The results on this question have been remarkably inconsistent, particularly because, at first glance, this seems to be a simple and straightforward question. Whether the offspring of alcoholics are more sensitive to alcohol is an important conceptual issue for which integrative analyses are needed. A summary of studies focusing on this issue is presented in Table 1.

Blood Alcohol Concentration

Schuckit (1981) hypothesized that alcohol metabolism is under genetic control and measured peak BAC in nonalcoholic college men who were FH+ ($n = 20$) or FH– ($n = 20$). In this and other studies, Schuckit used criteria similar to those of the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; American Psychiatric Association, 1980) without tolerance or withdrawal requirements. The groups were matched for demography, drinking history, and height:weight ratio. Subjects were administered 0.75 ml/kg of 95% ethanol, and BAC was measured regularly with blood drawn from a venous catheter for 5 hr. Blood alcohol curves for the two groups were almost identical. A review of other studies in which BAC was measured in SOAs revealed no group differences in average or peak BAC in any study (Lipscomb & Nathan, 1980; O'Malley & Maisto, 1985; Pollock et al., 1983a; Schuckit, 1984a, 1984b, 1985a;

Table 1
Summaries of Alcohol-Challenge Studies

Study	Sample	*N*	Measure	SOA vs. SONA
Schuckit (1981)	College students	SOA = 20 SONA = 20	BAC	*ns*
Lex, Lukas, Greenwald, & Mendelson (1988)	Women	DOA = 6 DONA = 6	BAC	*ns*
Utne, Hansen, Winkler, & Schulsinger (1977)	General population	SOA = 10 SONA = 10	Alcohol elimination	*ns*
Schuckit & Rayses (1979)	College students	SOA = 20 SONA = 20	Acetaldehyde	SOA greater
Schuckit & Duby (1982)	College students	SOA = 30 SONA = 30	Flushing	SOA greater
Behar et al. (1983)	General population (8–15 yrs old)	SOA = 11 SONA = 11	Acetaldehyde, cortisol, norepinephrine, beta-endorphin	*ns*
Schuckit, Shaskan, Duby, Vega, & Moss (1982)	College students	SOA = 11 SONA = 11	Monoamine oxidase activity	*ns*
Schuckit, O'Connor, Duby, Vega, & Moss (1981)	College students	SOA = 22 SONA = 22	Dopamine-B-hydroxylase	*ns*
Schuckit (1984a)	College students	SOA = 20 SONA = 20	Cortisol	SOA less
Schuckit, Gold, & Risch (1987b)	College students	SOA = 30 SONA = 30	Cortisol	SOA less
Moss, Yao, & Maddock (1989)	College students	SOA = 10 SONA = 10	Cortisol	*ns*
Schuckit, Parker, & Rossman (1983)	College students	SOA = 44 SONA = 44	Prolactin	SOA less
Schuckit, Gold, & Risch (1987a)	College students	SOA = 30 SONA = 30	Prolactin	SOA less
Schuckit, Risch, & Gold (1988)	College students	SOA = 18 SONA = 18	Adrenocorticotropic hormone	SOA less
Swartz, Drews, & Cadoret (1987)	Adoptees	SOA = 17 SONA = 12	Epinephrine	SOA greater (stress induced)
Newlin & Thomson (1990), Exp. 1	College students	SOA = 9 SONA = 9	Autonomic	SOA greater
Newlin & Thomson (1990), Exp. 2	College students	SOA = 11 SONA = 14 SONA = 10	Autonomic	SOA greater
Schuckit, Engstrom, Alpert, & Duby (1981)	College students	SOA = 20 SONA = 20	Electromyograph	SOA greater
Lipscomb, Carpenter, & Nathan (1979), Exp. 1	College students	SOA = 12 SONA = 12	Static ataxia	*ns*
Lipscomb & Nathan (1980)	College students	SOA = 12 SONA = 12	Static ataxia	*ns*
O'Malley & Maisto (1985)	College students	SOA = 24 SONA = 24	Static ataxia	*ns*
Schuckit (1985a)	College students	SOA = 34 SONA = 34	Static ataxia	SOA less
Newlin & Thomson (1990), Exp. 2	College students	SOA = 11 SONA = 14	Static ataxia	SOA greater
Lex, Lukas, Greenwald, & Mendelson (1988)	Women	DOA = 6 DONA = 6	Static ataxia	DOA less
Lipscomb & Nathan (1980)	College students	SOA = 12 SONA = 12	Intoxication	*ns*
Schuckit (1980c)	College students	SOA = 20 SONA = 20	Intoxication	SOA less
Schuckit (1984b)	College students	SOA = 20 SONA = 20	Intoxication	SOA less
Schuckit (1985a)	College students	SOA = 34 SONA = 34	Intoxication	*ns*
O'Malley & Maisto (1985)	College students	SOA = 24 SONA = 24	Intoxication	SOA less
Vogel-Sprott & Chipperfield (1987)	College students	SOA = 21 SONA = 22	Intoxication	*ns*
Moss, Yao, & Maddock (1989)	College students	SOA = 10 SONA = 10	Intoxication	SOA less
Finn & Pihl (1987)	College students	SOA = 24 SONA = 12	Intoxication	*ns*
Lex, Lukas, Greenwald, & Mendelson (1988)	Women	DOA = 6 DONA = 6	Intoxication	*ns*

Table 1 (*continued*)

Study	Sample	*N*	Measure	SOA vs. SONA
Kaplan, Hesselbrock, O'Connor, & Depalma (1988)	General population	SOA = 25 SONA = 24	Intoxication	SOA greater
Nagoshi & Wilson (1987)	College students	SOA = 35 SONA = 35	Intoxication	SOA greater
Moss, Yao, & Maddock (1989)	College students	SOA = 10 SONA = 10	Mood	SOA greater
Pollock et al. (1983)	General population	SOA = 31 SONA = 17	EEG alpha	SOA greater
Elmasian, Neville, Woods, Schuckit, & Bloom (1982)	General population	SOA = 15 SONA = 15	P300 amplitude and latency	SOA less
Schuckit, Gold, Croot, Finn, & Polich (1988)	College students	SOA = 21 SONA = 21	P300 latency	SOA less
Kaplan, Hesselbrock, O'Connor, & Depalma (1988)	General population	SOA = 25 SONA = 24	EEG alpha	*ns*
Vogel-Sprott & Chipperfield (1987)	College students	SOA = 21 SONA = 22	Motor tasks	SOA greater
Nagoshi & Wilson (1987)	College students	SOA = 35 SONA = 35	Motor tasks	*ns*
Levenson, Oyama, & Meek (1987)	College students	SOA = 112 SONA = 131	Stress-response dampening	SOA greater
Finn & Pihl (1987)	College students	SOA = 24 SONA = 12	Stress-response dampening	SOA greater
Swartz, Drews, & Cadoret (1987)	Adoptees	SOA = 17 SONA = 12	Stress-response dampening (epinephrine)	SOA greater

Note. SOA = son of alcoholic parents; SONA = son of nonalcoholic parents; BAC = blood alcohol concentration; DOA = daughter of alcoholic parents; DONA = daughter of nonalcoholic parents; EEG = electroencephalograph.

Schuckit, O'Connor, Duby, Vega, & Moss, 1981; Schuckit, Parker, & Rossman, 1983). Lex, Lukas, Greenwald, and Mendelson (1988) reported no significant differences in BAC between FH+ and FH– women given 0.56 g/kg alcohol.

Utne, Hansen, Winkler, and Schulsinger (1977) measured alcohol elimination rate in adoptees from the Danish adoption study (Goodwin et al., 1973). Ten SOAs were randomly selected, and 10 SONAs were matched for age and age at adoption. A dose between 0.27 and 0.36 g/kg ethanol was administered intravenously, and alcohol elimination rate was calculated from the linear portion of the blood alcohol curve. No significant differences were found.

Lipscomb and Nathan (1980) examined 24 college men who were light or heavy drinkers and FH+ or FH–. The criteria for alcoholism were (a) the subject received medical treatment for alcoholism and (b) the subject was considered alcoholic by medical or religious authorities. Subjects were rewarded for accuracy in estimating BAC while receiving a programmed series of drinks. No group differences were found in the accuracy of BAC estimation for any session.

Acetaldehyde

Although it is relatively clear that SOAs and SONAs do not differ in BAC following consumption of alcohol, it is possible that they differ in terms of metabolites of alcohol. Schuckit and Rayses (1979) examined acetaldehyde levels in college students with (n = 20) and without (n = 20) first-degree relatives with alcoholism. Acetaldehyde, a metabolite of ethanol, causes facial flushing and nausea in many Asians (Harada, Agarwal, Goedde, Tagaki, & Ishikawa, 1982; Newlin, 1989; Wolff, 1972). It is not clear what characteristics of acetaldehyde buildup or facial flushing are protective against the development of alcoholism in Asians who flush in response to alcohol (Newlin, 1989). In contrast, Schuckit and Rayses (1979) suggested that acetaldehyde may mediate short-term effects of alcohol, such as heightened subjective intoxication. This apparent contradiction has not been resolved. Schuckit and Rayses (1979) gave their subjects 0.5 ml/kg 95% ethanol and mixer and measured acetaldehyde from blood samples taken at baseline and every 30 min for 180 min. Following alcohol administration, FH+ subjects had significantly higher acetaldehyde concentrations than did FH– subjects.

Shortly after publication of the Schuckit and Rayses (1979) study, Ericksson (1980) criticized their methodology and suggested that their results were based on mainly artifactually formed acetaldehyde. Subsequently, Schuckit and Duby (1982) assessed acetaldehyde concentrations with a method that had been modified to include Eriksson's (1980) suggestions for avoiding artifact. Schuckit and Duby (1982) compared 30 FH+ and a matched group of 30 FH– nonalcoholic college men. The procedure, described previously, involved administration of 0.59 g/kg 95% ethanol with mixer; blood samples were taken regularly for 5 hr. In addition, facial flushing was measured by ear plethysmograph and by observation (a technician, blind to experimental condition, using an ad hoc 7-point scale). Despite methodological problems, significantly more FH+ subjects (39%) than FH– subjects (13%) showed plethysmograph-measured flushing increases of 50% or more up to 60 min after consuming alcohol. Data were not presented more clearly for groups. A significant positive correlation (r = .88) was reported between observational flushing measured for 90 min and acetal-

dehyde levels for all 60 subjects. The two flushing measures, however, were not correlated. Schuckit and Duby admitted that "absolute acetaldehyde values are uncertain because of disagreements in the literature about methodology (p. 417)."

One other group of researchers (Behar et al., 1983) measured acetaldehyde in SOAs ($n = 11$) and SONAs ($n = 11$). Behar et al. recruited the children of hospitalized alcoholics who met the Feighner et al. (1972) criteria for primary alcoholism. SOAs and sons of parents with no family history of alcohol or psychiatric disorder were catheterized for blood samples and administered a drink containing 0.5 ml/kg ethanol. Breath and blood acetaldehyde were measured repeatedly for several hours, as were plasma cortisol, norepinephrine, epinephrine, and beta-endorphin levels. Behar et al. (1983) reported that blood acetaldehyde levels were not significantly different for the two groups at baseline or after consuming alcohol. Blood and breath acetaldehyde values were not correlated with each other. No significant differences between groups were found for plasma epinephrine, norepinephrine, cortisol, or beta-endorphin.

To summarize, the finding of equivalent BACs in SOAs and SONAs has been a very consistent one in this literature. Apparently, SOAs and SONAs do not differ in the pharmacokinetics of alcohol. Results concerning acetaldehyde must be considered highly tentative given the difficulty in measurement and failures to replicate.

Serum Biochemical Measures

Schuckit, Shaskan, Duby, Vega, and Moss (1982) measured platelet monoamine oxidase (MAO) activity after alcohol administration in nonalcoholic college men. Fifteen SOAs were matched with 15 SONAs on demographics, height:weight ratio, and drinking history. Subjects were screened for drug abuse and affective disorder. After fasting overnight, subjects were catheterized and given 0.59 g/kg ethanol with mixer. Platelet MAO activity was measured at baseline and 180 min after drinking. No significant group differences were found for baseline or 180-min blood MAO values.

Another enzyme, dopamine-B-hydroxylase (DBH), is also thought to be important in regulation of mood states and psychiatric disorders. Schuckit, O'Connor, et al. (1981) compared 22 FH+ nonalcoholic college men and a matched sample of FH– nonalcoholic men. After an overnight fast, subjects were catheterized and tested for DBH level by a technician blind to group. Subjects then drank 0.59 g/kg 95% ethanol and mixer, and blood samples were drawn every 30 min for 180 min. DBH levels at baseline and 180 min were analyzed, and no significant differences between groups were found. Post hoc correlational analyses fielded a significant positive relationship between drinks or drinking day and DBH level in FH+ men, which ran counter to experimental hypotheses.

Plasma cortisol was measured by Schuckit (1984a) for 20 pairs of nonalcoholic college men. Subjects with alcoholic first-degree relatives and matched subjects with no alcoholic first-degree relatives were catheterized after an overnight fast and given a drink containing 0.59 g/kg 95% ethanol. Venous blood was sampled at baseline and regularly for several hours. The groups differed significantly at 15, 30, 240, 270, and 300 min after alcohol consumption, with FH+ subjects lower in plasma cortisol. When data were analyzed as percent change from baseline, group differences were significant only at 240, 270, and 300 min after consumption. Schuckit did not rule out possible circadian changes in cortisol levels as an alternative explanation for the group differences.

Schuckit, Gold, and Risch (1987b) replicated these results in a later study that was placebo controlled. Following placebo, FH+ subjects had smaller increases in cortisol levels, which were significant only at 30 min after consumption. There were very small differences between groups at the low (0.75 ml/kg) ethanol dose, but larger differences at 90, 120, 150, and 180 min after consumption for the high ethanol dose. In this same study (Schuckit et al., 1987b), prolactin differences were greatest at the low ethanol dose.

Moss, Yao, and Maddock (1989) attempted to replicate Schuckit's cortisol results with 10 SOAs and 10 SONAs. They found no differences in cortisol levels as BAC rose or as it fell. Because the sample was so small, this may not represent a failure to replicate.

Serum prolactin (PRL) levels were measured in SOAs and controls in two studies. PRL, an anterior pituitary hormone, has been found to be elevated in chronic alcoholics (e.g., Van Theil & Lester, 1976). Schuckit et al. (1983) administered 0.59 g/kg 95% ethanol to 44 FH+ and 44 matched FH– nonalcoholic college men. The methodology was the same as for Schuckit (1984a), and samples were collected regularly for 4 hr after alcohol administration. Post hoc analyses found the two groups to differ significantly at 150 min after ethanol administration, with FH+ subjects showing lower PRL levels. This effect was replicated in a second experiment that included a placebo control (Schuckit, Gold, & Risch, 1987a) with 30 FH+ and 30 matched FH– subjects. In three separate sessions, each beginning at 9:00 a.m., subjects drank a placebo, 0.75 ml/kg ethanol, and 1.1 ml/kg ethanol, in random order, and blood was drawn every 30 min for 180 min. Thirty and 60 min after alcohol consumption, levels of PRL following the low dose were lower among FH+ subjects than among FH– subjects; following the higher dose, PRL levels were lower for FH+ subjects at 90, 120, and 150 min. There were no significant differences for placebo.

In an effort to determine whether the neuroendocrine differences in response to alcohol between SOAs and SONAs are due to central rather than peripheral events, Schuckit, Risch, and Gold (1988) assayed adrenocorticotropic hormone (ACTH) in 18 matched pairs of SOAs and SONAs. SOAs had lower levels of ACTH approximately 90 to 180 min after drinking the higher dose of alcohol (1.1 ml/kg).

In multivariate analysis (Schuckit, Risch, & Gold, 1988) of the same cortisol and PRL data from the earlier study (Schuckit et al., 1987a, 1987b), stepwise discriminant analysis revealed that maximum "terrible" feelings on the Subjective High Assessment Scale (SHAS; Judd et al., 1987) explained the most variance, followed by maximum low-dose PRL level, maximum high-dose cortisol level, and 210-min high-dose cortisol level. Not surprisingly, these same variables exhibited significant classification rates in a jackknife procedure. Seventy percent of the FH+ and 83% of the FH– subjects were correctly classified into their respective groups. In a principal-components analysis of the data, the subjective high measures segre-

gated differently from the biochemical measures, although the first three factors significantly discriminated between groups.

The findings concerning stress hormones (particularly prolactin and cortisol) have been relatively consistent from Schuckit's laboratory. SOAs appear to have greater acute tolerance to alcohol (i.e., more rapid recovery from alcohol-induced changes) in relation to these neuroendocrine measures. Whether the greatest difference between SOAs and SONAs has been at the high or low dose has been less consistent. The differences in these hormones have typically been found well after alcohol was administered, usually from one to several hours after drinking. Moss et al.'s (1989) apparent failure to replicate is consistent with the high variability of these measures and does not seriously challenge the earlier results.

Electroencephalography

Pollock et al. (1983) reported EEG results from a subset of their longitudinal high-risk sample after the administration of 0.5 g/kg of 95% ethanol in currant juice. EEG data were collected from 31 SOAs and 17 control subjects in groups that did not differ in weekly alcohol consumption or in mean BAC. There were no overall main effects for risk, but SOAs showed significantly greater increases than controls in slow alpha energy at 30 min and 120 min after drinking. Decreases in fast alpha energy were found for both groups 30 and 60 min after drinking. Differences in mean alpha activity (combined fast and slow alpha) were significantly greater for SOAs at 30, 60, and 120 min after drinking for all scalp locations except the left occipital. Results including subjects previously dropped because of incomplete data suggested that the differences in mean alpha frequency were localized to the right and posterior scalp regions. Pollock et al. suggested that the changes in alpha frequency after alcohol consumption may reflect SOAs increased sensitivity to alcohol's effects.

Kaplan, Hesselbrock, O'Connor, and Depalma (1988) studied EEG responses to alcohol (two 12 oz. beers) in 25 SOAs and 24 SONAs. Both groups showed increases in alpha activity after drinking; there were no significant differences between groups. However, for SOAs, alpha activity was correlated with desire to drink alcohol, but for SONAs, it was correlated with perceived intoxication.

Using a weak criterion for primary alcoholism ("if drinking behavior interfered with his marriage or job"), Elmasian, Neville, Woods, Schuckit, and Bloom (1982) compared 15 SOAs and 15 SONAs matched for drinking habits, height:weight ratio, age, sex, and socioeconomic status. Each group was divided into three subgroups of 5 subjects each, who received either a placebo, a low-dose alcoholic drink (0.59 g/kg), or a high-dose alcoholic drink (0.94 g/kg), administered early in the morning after fasting. Subjects were asked to press a button in response to a target tone, and event-related potentials were recorded. For SOAs, both alcohol and placebo caused reduced amplitude and increased latency of response. The differences between groups were significant even though alcohol reduced the amplitude of the P300 component in both groups. SOAs were also less accurate at identifying target stimuli. It should be noted that the groups were extremely small in this study.

In a more recent study, Schuckit, Gold, Croot, Finn, and Polich (1988) found no differences in P300 latency between 21 FH+ and 21 FH– subjects after placebo or 0.75 ml/kg alcohol doses. However, FH+ subjects demonstrated a more rapid return to baseline in P300 latency after drinking the high (1.1 ml/kg) dose of alcohol (measured at 240 min).

The results with EEGs have been very tentative. Clearly, more research is needed before drawing conclusions concerning differences between SOAs and SONAs in terms of EEG responses to an alcohol challenge. This is potentially fertile ground for research.

Static Ataxia

Alcohol causes a robust increase in static ataxis, or body sway (Moskowitz, Daily, & Henderson, 1974). Static ataxia has been measured with a rope-and-pulley system to which subjects are connected with a harness. Measurements are made while the subject is standing, with eyes open or eyes closed.

Static ataxia has been used as a measure of motor performance in a number of studies of SOAs. Lipscomb, Carpenter, and Nathan (1979, Exp. 1) selected 12 male FH+ subjects whose first- or second-degree relatives had been treated for alcoholism or who were considered alcoholic by religious or medical authorities. Twelve male FH– subjects were matched for drinking pattern. Light and problem drinkers were excluded. Subjects were administered a series of drinks programmed to yield a peak BAC of 0.08%. Twice before and six times after alcohol consumption, body sway was measured by the movement of ropes attached to the subject's back and side while he stood with eyes open. FH+ subjects swayed significantly more than FH– subjects at baseline, although postdrinking sway showed no group differences when baseline scores were used as a covariate.

Lipscomb et al. (1979, Exp. 2) reported further data obtained from unselected and unmatched subjects. Twenty-one FH+ and 46 FH– subjects were exposed to the same drinking procedure, but sway was measured with subjects' eyes closed as well as open. FH+ subjects swayed significantly more than FH– subjects with eyes closed but not with eyes open, apparently at baseline.

Lipscomb and Nathan (1980) administered low, moderate, or high doses of alcohol to 12 FH+ and 12 FH– subjects who were heavy or light drinkers. Body sway was measured with subjects' eyes open (the same method that Lipscomb et al. (1979) used) but was collected only in the first session. No group differences were found.

Schuckit (1985a), in a study of 34 FH+ and 34 FH– nonalcoholic college men, measured body sway after placebo, low (0.75 ml/kg) or high (1.1 ml/kg) doses of alcohol. Schuckit measured body sway with the method of Lipscomb et al. (1979); subjects' eyes were open. Schuckit measured each subject three times for each measurement period and averaged the results. No significant group differences were found for baseline or placebo measurements, but FH+ subjects showed significantly less sway than FH– subjects 135 min after a low dose of alcohol. The difference was not significant for the high-alcohol dose. In an apparent attempt to replicate this effect, Schuckit and Gold (1988) found the low-dose body-sway measurement to be weakly related to familial history of alcoholism and entered the

measurement after a number of other biochemical measures in a jackknife classification procedure. Body-sway results for both the low and high doses were found on the second factor to emerge in a principal-components analysis, and this factor accounted for 14% of the variance.

Newlin and Thomson (1990) recorded the static ataxia of 11 SOAs and 14 SONAs on a stabilometer board before alcohol consumption and as BAC increased during four separate sessions with 0.5 g/kg alcohol. SOAs showed greater alcohol-induced increases in static ataxia in the first and second (but not the third and fourth) sessions with alcohol.

One pilot study of women differing in family history of alcoholism has been reported. Lex et al. (1988) studied 6 FH+ and 6 FH– women who were given 0.56 g/kg ethanol; body sway was measured on a stabilometer platform. FH– women had significantly lower sway scores at a number of measurement points following alcohol consumption.

In summary, the results with static ataxia have been promising but inconsistent. Because static ataxia is a very reliable measure of the effect of alcohol, it would seem to be an appropriate measure for family-history studies. However, the methodology may be inadequate to yield consistent results across different laboratories. We would particularly expect different results from rope-and-pulley systems and stabilometer measures of static ataxia. A further complication is that the static ataxia measures may not differentiate between inner ear disturbances and the hyperactivity (or hypoactivity) caused by alcohol. Methodological research is needed to improve these measurement systems before definitive research can be carried out.

Subjective Responses to Alcohol

Schuckit (1980c) examined self-ratings of intoxication in 20 FH+ and a matched control group of 20 FH– nonalcoholic college men. After fasting and catheterization, subjects received 0.59 g/kg 95% ethanol. The SHAS, consisting of positive and negative adjectives relevant to mood, was administered every 30 min for 180 min after alcohol consumption. FH+ subjects reported significantly less subjective intoxication than did controls on both the SHAS and a 10-point ad hoc scale of "feeling high." However, FH– men had significantly higher BACs 60 min after drinking. Almost all of the SHAS items on which FH– subjects rated themselves significantly higher were positive in tone (e.g., "sexy," "joyful," "enjoy self," etc.).

Schuckit (1984b) later reexamined subjective intoxication after placebo, low, or high doses of alcohol. Matched groups of 20 FH+ and FH– nonalcoholic college men were examined using the methodology described for Schuckit (1980c), except that they received the three different levels of alcohol in three randomly ordered sessions. Subjects completed an ad hoc questionnaire before the first session, describing how they expected to feel after receiving alcohol. After drinking, they used a 36-point scale to indicate drug effect and intoxication at regular intervals for 4 hr. The two groups were similar in their expectations of intoxication level. No group differences were found for subjective intoxication after drinking a placebo beverage. For the low dose of alcohol (0.59 ml/kg 95% ethanol), mean self-ratings of drug effect and intoxication were lower for FH+ subjects. The group differences for the high dose (1.1 ml/kg) were not significant. Schuckit provided an interesting hypothesis for the findings, namely, that FH+ individuals do not accurately perceive intoxication until they are drunk and intoxication has become obvious.

Schuckit (1985a) again assessed subjective intoxication in a study of body sway in 34 FH+ and a matched group of 34 FH– nonalcoholic college men. The procedures were identical to those reported in Schuckit (1984b), with the addition of the body sway assessment. Results showed that, for the high-alcohol dose, ratings of intoxication correlated positively ($r = .30$) with body sway and that, for FH+ subjects, body sway correlated negatively ($r = -.28$) with number of alcoholic relatives.

In a later multivariate analysis of various responses to an alcohol challenge, Schuckit and Gold (1988) found that maximum terrible feelings after the high dose of alcohol was the best single independent discriminator between FH+ and FH– men and that maximum terrible feelings loaded highly on the first factor in a principal-components analysis; this factor accounted for 46% of the total variance.

Another assessment of subjective intoxication in SOAs was conducted by O'Malley and Maisto (1985). Twenty-four nonalcoholic college-student SOAs and a matched group of 24 SONAs were examined. Diagnostic criteria for parental primary alcoholism were the same as in Schuckit (1980c), with the additional requirement of treatment for alcoholism. All subjects were moderate to heavy drinkers. Subjects in each group received placebo, a low dose (1.3 ml/kg), or a high dose (2.58 ml/kg) of 80 proof alcohol. Perceived intoxication (indicated on an 8-point scale), mood, and internal sensations were self-reported on two separate occasions after drinking. No group differences were found on measures of estimated quantity of alcohol consumed or expected effects of alcohol. Regardless of dose (including placebo), SOAs reported feeling significantly less intoxicated than did SONAs and reported less behavioral impairment at peak BAC. Two of six factors from the Sensation Scale, "central stimulant" and "anesthetic" were self-reported lower by SOAs. In a post hoc multiple regression analysis, O'Malley and Maisto found that scores on the preassessment of expectancy accounted for more of the variance in self-reports of intoxication in SOAs than in SONAs and that BAC contributed equally to both groups.

Vogel-Sprott and Chipperfield (1987) found no differences in self-reported intoxication between 21 FH+ men and 22 FH– men after they consumed 0.83 ml/kg of alcohol. Nagoshi and Wilson (1987) studied the responses of 35 FH+ and 35 matched FH– men on a host of measures when BAC was maintained at a plateau of approximately 0.10 g/dl for several hours. Contrary to prediction, FH+ subjects had significantly greater self-reported and tester-rated intoxication scores than FH– subjects. However, FH+ subjects also had significantly higher BACs than FH– subjects at some time points, and the significant intoxication comparisons represented 4 of 83 separate t tests.

Finn and Pihl (1987) found no significant differences in self-reported intoxication in 12 FH– men, 12 SOAs, and 12 SOAs with an alcoholic grandparent. However, there was a nonsignificant trend for higher risk subjects to report lower intoxication after drinking a 1.32 ml/kg dose of alcohol.

In Lex et al.'s (1988) pilot study of 6 FH+ and 6 FH– women, there were no significant differences on the SHAS. Moss et al.

(1989) found that SOAs reported lower levels of intoxication in the descending limb of the BAC curve after drinking placebo, low, and high doses of alcohol. After both alcohol doses, SOAs reported nonsignificantly higher levels of intoxication while BAC rose. SOAs also reported greater confusion, less vigor, and more anger than SONAs after the high dose of alcohol. These effects were found in both the ascending and descending limbs of the BAC curves. Kaplan et al. (1988) found in their EEG study that SOAs reported greater intoxication than SONAs immediately after drinking alcohol, although there were no significant differences 30 min after drinking.

It is difficult to summarize the intoxication results because they have been very inconsistent in different laboratories. Resolution of this discrepancy requires consideration of the time in which the measurements were made, an issue discussed later in relation to our integrative model.

Motor or Muscle Responses

Motor or muscle performance has been assessed in several studies. Schuckit, Engstrom, Alpert, and Duby (1981) measured muscle-tension response to ethanol in 20 SOAs and a matched group of 20 SONAs. Electromyographic recordings (EMGs) with frontal placement were made at baseline and regularly for several hours after subjects drank 0.59 g/kg 95% ethanol. Recordings made at rest and during a task did not differ between groups at baseline, but SOAs had significantly lower resting EMGs 15 min after alcohol administration.

Vogel-Sprott and Chipperfield (1987) compared 21 SOAs and 22 SONAs on bead-stringing and hand-steadiness tasks before and after they drank 0.83 ml/kg alcohol. After drinking, SOAs were more impaired on the hand-steadiness measure and on a bead-stringing task during both the rising and falling blood alcohol curves. Nagoshi and Wilson (1987) found essentially no differences between 36 SOAs and 36 SONAs on a large battery of cognitive and motor tasks given following consumption of alcohol.

Chronic Tolerance

Newlin and Thomson (1990) studied the development of chronic tolerance during the rising blood alcohol curve in SOAs and SONAs. In a preliminary study, 9 college-age SOAs and 9 SONAs were selected on the basis of self-report data they provided about their biological fathers. Doses of 0.5 g/kg alcohol were administered on three separate days, and placebo was administered on a fourth day. A range of autonomic measures were recorded continuously before drinking and during the rising blood alcohol curve. Although there were no significant differences between groups in the first session, SOAs tended to develop sensitization (reverse tolerance) across sessions, whereas SONAs showed tolerance. These trends were significant for finger-pulse amplitude, finger temperature, and skin conductance. There were no significant differences in responses to the placebo challenge in the last session. In a replication study, 11 SOAs and 14 SONAs selected through the same procedures received 0.5 g/kg alcohol in four sessions and placebo in the fifth. SOAs became sensitized to alcohol across sessions (as reflected by pulse transit time), and showed greater development of chronic tolerance to alcohol-induced increases in static ataxia (measured with a stabilometer). In the first and second sessions, SOAs showed significantly greater alcohol-induced increases in static ataxia than SONAs, but SOAs showed no increases in static ataxia in the third and fourth sessions. SONAs tended to have a greater decrease in heart rate in response to the placebo. Newlin and Thompson (1990) interpreted the tolerance and sensitization results in terms of potential differences between SOAs' and SONAs' hedonic responses to alcohol during the rising blood alcohol curve.

Stress-Response Dampening

Stress-response dampening refers to the tendency of alcohol to reduce the magnitude of responses to a stressful challenge presented after alcohol has been administered (Levenson, Sher, Grossman, Newman, & Newlin, 1980). If stress-response dampening is greater in SOAs than SONAs, then alcohol has a greater effect on these high-risk individuals, and it can be concluded that SOAs are more sensitive to alcohol in this paradigm.

Levenson, Oyama, and Meek (1987) selected 112 FH+ men and women and 131 FH– men and women for a stress response dampening study with 1.0 g/kg alcohol and either a public speaking or threat of shock stressor. The FH+ group showed a significantly greater decrease in pulse transit time (to the ear) in response to both stressors under alcohol, and FH+ men showed significantly greater decreases in general motor activity in response to the shock stressor under alcohol. In the placebo condition, the response to the stressors did not differ according to familial history.

In a similar study, Finn and Pihl (1987) selected 12 FH– subjects, 12 SOAs with nonalcoholic grandparents, and 12 SOAs with one alcoholic grandparent. Alcohol (1.32 ml/kg) was administered before a signaled shock stressor. SOAs in the highest risk group showed a significantly larger increase in heart rate in response to alcohol and to the stressor without alcohol. Similarly, alcohol significantly decreased digital pulse volume to a greater extent in SOAs with an alcoholic grandparent and digital pulse volume showed a significantly greater decrease to alcohol in this group. More important, the responses of heart rate and digital pulse volume to the stressor were significantly dampened in the SOAs with an alcoholic grandparent in the alcohol condition.

Swartz, Drews, and Cadoret (1987) selected 17 FH+ male and female adoptees and 12 matched FH– adoptees. Epinephrine excretion in urine was measured at baseline, following a videogame stressor, and after subjects drank 0.5 ml/kg alcohol. Resting levels of epinephrine were significantly lower in FH+ individuals, and the stress-induced increase in epinephrine excretion was slightly (nonsignificantly) greater under the effect of alcohol. More important, the stress-induced increase was significantly greater in FH– subjects than in FH+ subjects, though Swartz et al. did not test the interaction reflecting a potentially greater stress-response dampening effect in the FH+ group.

The stress-response dampening studies have been relatively consistent. After consuming alcohol, SOAs show greater reductions in autonomic stress response than do SONAs. Sher and Levenson (1982) and Levenson et al. (1987) found that individ-

uals selected on the basis of personality predictors of alcoholism also showed greater stress-response dampening than subjects without this personality risk.

Methodological Issues

Statistical Power

The statistical power of the high-risk design can be calculated. Statistical power has been calculated for a similar design, the familial–sporadic design in psychiatric epidemiology. Eaves, Kendler, and Schulz (1986) made a series of genetic and statistical assumptions about research designs in which psychiatric patients who do (familial) and do not (sporadic) have affected relatives are studied in relation to potential risk factors. Eaves et al. (1986) found that this design was inherently weak and required extremely large samples to increase the likelihood that risk factors would be detected. The design lacks power in part because sporadic cases are very likely to actually involve a genetic predisposition that simply has not been expressed in relatives. Therefore, the familial and sporadic cases do not differ in genetic makeup to any great degree.

The problem in high-risk designs is the opposite. The control group is not likely to have the genetic predisposition to alcoholism, but many of the experimental subjects (i.e., SOAs) do not have this predisposition either. Therefore, the groups are inherently heterogeneous (genetically, at least), and this greatly reduces the statistical power of the high-risk design (Sher, 1985). This heterogeneity is true only of genetic factors, however, and does not apply to social or familial influences (because, by definition, SOAs grew up in families with alcoholism). In addition, the risk of alcoholism in the general population is much higher than for the types of disorders studied by Eaves et al. (1986).

An initial power analysis run by Eaves (personal communication, November 1987) revealed greater statistical power in the high-risk design than the familial–sporadic design. The sample sizes needed to achieve adequate confidence of detecting a genetic marker are within those typically used in the SOA literature. The power for detecting environmental markers is even greater because the groups (SOAs vs. SONAs) are each homogeneous with regard to familial alcoholism.

To say that the high-risk design is more powerful than the familial–sporadic design does not really say that much, given the extremely low power of the latter. In addition, consideration of the inherently low power of high-risk designs suggests that many reported differences between SOAs and SONAs are actually false positives. This must be weighed against the consistency of results across studies, both within a laboratory and between laboratories, a point to which we return in our discussion of an integrative model.

Representativeness of Samples

We noted previously that SOAs are a heterogeneous group. Some of them will become alcoholics or drug abusers, and some will not. They are also heterogeneous in terms of the degree of family history of alcoholism or the percentage of relatives that are alcoholics. Some researchers (e.g., Finn & Pihl, 1987) have attempted to increase the degree of genetic vulnerability by selecting multigenerational SOAs (individuals who have an alcoholic parent and grandparent). This increases the likelihood that SOAs will themselves display signs of alcoholism before they enter the study.

Interestingly, in most of the studies we reviewed, problem drinkers were screened before subjects were selected. However, problem drinking could easily be prodromal to alcoholism, or a heritable condition, in the typical college-age subject. For example, Sher (1985) inadvertently included problem drinkers in a study of personality traits in SOAs and found significant group differences attributable only to those subjects.

The problem is that if the high-risk sample is to be representative of the high-risk population, then it must necessarily include some individuals who begin to display the psychopathology at an early age. This is particularly problematic for studies of alcohol challenge because the subjects are almost always over the age of 21. The mean age of onset of alcoholism is in the mid-20s (Robins et al., 1984) and is thought to be younger in men who are at the highest risk for a genetically transmitted form of alcoholism (Cloninger, 1983). However, it is possible that SOAs who carry the vulnerability to alcoholism but have not and will not express it are capable of revealing the deviant response to alcohol. This is the case when the phenotypic expression of the genetic vulnerability requires some environmental stressor or other condition for full manifestation of the disorder to occur.

Types of Alcoholism

We suggest that Cloninger's (1983) analysis of the archival data primarily reflects the modulation of the severity of alcoholic behavior by antisocial behavior and that typing may depend more critically on the presence or absence of psychopathy in men or somaticizing disorder in women. It is possible that offspring of alcoholics may differ to a significant degree depending on whether the affected parent, usually the father, has manifested antisocial behavior. In other words, it may be necessary to divide offspring of alcoholics in an alcohol-challenge study into those with an alcoholic parent who is psychopathic and those who do not have psychopathy in the family. We suggest that classification of the fathers as Type 1 (milieu limited) or Type 2 (male limited) may accomplish the same goal. More important, it is entirely possible that alcohol-challenge studies have recruited from different populations, in the sense that some samples are dominated by sons of Type 1 fathers and others by sons of Type 2 fathers. For example, it is likely that subjects sampled from large university samples are primarily sons of Type 1 fathers, whereas subjects recruited from lower socioeconomic communities that have a high rate of criminal behavior might be sons of Type 2 fathers. Research is needed in which SOA samples recruited from university and general populations are typed relative to the form of alcoholism represented in their families. At least in Scandinavia, the proportion of Type 1 alcoholics is much lower than that of Type 2 alcoholics (Cloninger et al., 1981). To the extent that this is the case in the United States, then most samples of SOAs are dominated by sons of Type 1 alcoholics (who are less likely to express antisocial behavior). This is particularly problematic in a search for a

genetic marker if Cloninger's suggestion, that Type 1 alcoholism is less heritable than Type 2 alcoholism, is accurate. This problem may account for the inconsistencies between results from laboratories that recruit SOAs from different populations and may further dilute the genetic linkages often assumed in the high-risk challenge design.

Specificity for Positive Family History

An important question is whether any presumed psychobiological marker that predominates among SOAs is specific for alcoholism. In other words, is an individual who possesses the marker at elevated risk for disorders other than alcoholism? If this were the case, then it would not be valid to suggest that that marker played a direct causal role in the development of alcoholism but only that it was associated with a range of disorders sharing a common diathesis.

There is evidence that SOAs are at heightened risk for drug abuse and antisocial personality. Cadoret, Troughton, O'Gorman, and Heywood (1986) studied 242 male adoptees and 201 female adoptees in terms of their adult psychopathology. Men and women whose biological parent(s) had possible or definite alcohol problems were 4.3 times more likely to abuse drugs, but antisocial personality and other psychiatric disorders in a first-degree biological relative did not significantly increase the likelihood that the proband would abuse drugs. Similarly, probands with familial alcohol problems were 4.8 times as likely to manifest antisocial personality. There was some specificity, however. Familial antisocial personality increased the likelihood of alcohol abuse but not drug abuse.

It is possible that SOAs are at risk for an even broader spectrum of psychiatric disorders. However, it is also possible that the psychobiological marker itself is specific to alcoholism even when familial alcoholism is not. In other words, individuals who possess some distinct marker may be at greatly elevated risk only for alcoholism. In any case, the specificity of any potential psychobiological marker is an empirical question, and the specificity of that marker should be tested rather than assumed.

Specificity of Alcohol Response

A similar issue is whether the response to alcohol is specific to alcohol or is manifest with any drug or, indeed, any intense stimulus. No studies have been reported in which SOAs or FH+ individuals have been challenged with a drug other than alcohol. Therefore, there is no basis on which to suggest that any potentially deviant response to alcohol is specific to that particular drug.

The response may not even be specific to drugs as a particular class of stimuli. Finn and Pihl (1987) reported that multigenerational SOAs had enhanced responses to a shock stressor in the absence of alcohol. Newlin (1985) found that SOAs responded differently than SONAs to alcohol placebo. The heart rate decrease following placebo was greater in SOAs than in SONAs, which Newlin attributed to drug conditioning processes. Newlin and Thomson (1990) also found differences in placebo response between SOAs and SONAs, although in the opposite direction. In the latter study, subjects were given alcohol on four separate occasions prior to receiving the placebo, whereas Newlin (1985) administered placebo in the first session. Newlin and Thomson (1990) also found that SOAs became sensitized to the laboratory itself, as indicated by increasing baselines across sessions in this group.

It is entirely possible that SOAs have deviant responses to any intense stimulus, whether pharmacological, biological, or psychological. Again, specificity must be verified empirically rather than assumed. Potential nonspecificity of response to stimuli may suggest a conceptual link between deviant responses to alcohol challenge and various cognitive and personality differences between SOAs and SONAs. In other words, deviant responses to a wide range of stimuli (in addition to alcohol) could reflect underlying differences in the organization of the nervous system that would also result in personality and cognitive differences between groups. The presumed psychobiological marker could be manifest in deviant responses to alcohol and a range of other responses that are not specific to alcohol.

Follow-Up

To date, no alcohol-challenge studies with FH+ and FH– subjects have included a long-term follow-up to determine whether those subjects (whether FH+ or FH–) that manifested the deviant response to alcohol later developed alcoholic behavior. This is a serious gap in the literature that is likely to be corrected in the future.

Laboratory Specificity

Schuckit and his colleagues (Schuckit, 1980a, 1980b, 1982b, 1982c, 1985b) have contributed the majority of data concerning alcohol challenges to FH+ and FH– men. Their methodology has been relatively constant across studies (in fact, many separate publications from this group represent results from the same experiment), and elements of their methodology have been adopted by other researchers in this field. Therefore, it may be useful to examine their methodology to determine in what ways it advances or undermines the alcohol-challenge paradigm. Also, it may be valuable to determine whether this methodology merits emulation.

Subject selection procedures. Schuckit's subjects have been routinely recruited from the undergraduate student population of the University of California at San Diego (UCSD). They are White and non-Jewish. Because of the relative affluence and high social functioning of these families, this population probably represents individuals whose relatives have less severe forms of alcoholism that are not associated with antisocial behavior (e.g., Type 1). Although there is some evidence that these individuals are at elevated risk for alcoholism, the risk is not great and it may be modulated strongly by environmental factors (Cloninger, 1987). It is also likely that UCSD students have primarily positive, nurturant home environments that would not encourage alcoholic behavior. Therefore, it is particularly important in this population to determine eventual risk for alcoholic behavior. Other researchers (e.g., Newlin, 1985; Newlin & Thomson, 1990) have also used university samples and are subject to the same criticism.

The only alcohol-challenge study to further divide SOAs was a stress-response dampening experiment by Finn and Pihl (1987). They used single- and multigeneration SOAs, which were interpreted roughly as environmental and genetic risk groups, respectively. Although we would not agree that single-generation SOAs are only at heightened environmental risk for alcoholism, Finn and Pihl found clear differences between the two groups. This suggests that further subdivision of SOAs, particularly into groups with and without familial psychopathy, is a potentially fruitful research strategy.

Finally, direct clinical and psychometric evaluation of family members could provide more definitive diagnoses for classifying family members in terms of antisociality and drug abuse. There is evidence that FH+ individuals' self-reports about their family members have some validity. Sher and Descutner (1986) found that siblings' reports of their biological father's drinking behavior were concordant when they answered questions from the Michigan Alcoholism Screening Test (Selzer, 1971; Selzer, Vinokur, & van Rooijen, 1975) phrased in terms of their father's drinking rather than their own. This was particularly true of items that were relatively observable, such as attendance at Alcoholics Anonymous and arrests for public intoxication and driving under the influence of alcohol. In addition, Levenson et al. (1987) found that responses to questionnaires mailed to the parents of their subjects were in good agreement with the offsprings' reports of their parents' drinking behavior. O'Malley, Carey, and Maisto (1986) also reported significant agreement between university students' reports of their parents' drinking practices and the reports of the actual parents. However, even though it may be possible to validly diagnose alcoholism by using offspring reports, it is unlikely that these reports would allow subtyping of the parent's alcoholic behavior (e.g., into Type 1 or Type 2 alcoholism).

Placebo. Early studies by Schuckit's laboratory were not placebo controlled. This is a potentially serious problem given evidence that SOAs and SONAs may differ in their responses to a placebo challenge (Newlin, 1985; Newlin & Thomson, 1990) and to a laboratory stressor in the absence of alcohol (Finn & Pihl, 1987). Later studies by Schuckitt's laboratory included a placebo challenge and both low and high doses of alcohol challenge. In these reports, FH+ and FH– groups did not differ in terms of their placebo response, and their responses were generally minimal. However, Schuckit's placebo manipulation does not have the rigor of those employed in balanced-placebo studies (Rohsenow & Marlatt, 1981). Therefore, it is likely that subjects could determine that they were drinking a placebo beverage on the basis of taste and other cues. Schuckit did not include a validity check on the placebo manipulation to determine whether it was successful.

The exact wording of the instructions in the placebo condition may be important for obtaining a robust placebo response (Kirsch & Weixel, 1988). The standard instructions in double-blind placebo studies involve telling the subjects that they will receive either placebo or alcohol and that they will not know and the experimenter will not know which is being administered. Alternatively, in deceptive-administration studies, subjects are told that they will receive alcohol in both conditions, but in fact, they receive alcohol in one condition and placebo in the other.

Kirsch and Weixel (1988) found that subjects were more likely to be deceived by deceptive administration than by a double-blind placebo and that the placebo responses were different in the two conditions. Kirsch and Weixel challenged the validity of the double-blind placebo design because it does not produce as robust a placebo effect. The rationale for telling subjects that they will receive either drug or placebo stems from ethical issues in treatment research (i.e., subjects might wish to seek alternative treatment if they knew that they might receive a placebo). The same concern does not apply in the present deceptive administration design, and the only ethical issue is deception relative to the placebo administration.

Schuckit and others have used double-blind placebo rather than deceptive administration and have generally not found a placebo effect of any significant magnitude. In contrast, Newlin (1985; Newlin & Thomson, 1990) used deceptive administration and found a robust placebo response, as well as differences in placebo response between SOAs and SONAs. Adoption of the balanced-placebo design (Hull & Bond, 1986; Marlatt & Rohsenow, 1980) in SOA challenge studies, as advocated in the preceding paragraphs, would also involve deceptive administration.

Alcohol administration. Schuckit's subjects come into the laboratory at 7:00 a.m. and are administered alcohol at approximately 9:00 a.m. The alcohol is served in the form of 95% laboratory alcohol mixed in a 20% by volume solution with "sugar-free, noncaffeinated, carbonated beverage served at room temperature." It is not difficult to imagine that a significant number of subjects would become ill when drinking this beverage at 9:00 in the morning. Most social drinkers imbibe in the late afternoon and evening rather than in the morning. Jones (1974) found that the response to alcohol was greater in the morning than the evening hours, potentially reflecting conditioned tolerance at times when alcohol is normally consumed. Laboratory-grade alcohol is easily tasted in a 20% by volume beverage, and more palatable forms of alcohol are available.

Therefore, it is entirely possible that Schuckit's procedure of giving substantial quantities of alcohol in the early morning leads to illness and "terrible feelings" from alcohol. A major portion of the SHAS (Judd et al., 1977), adapted by Schuckit, includes such items as "nausea," "discomfort," and "feeling terrible," which Schuckit has grouped together on a terrible-feelings scale. This scale was the best single discriminator between SOAs and SONAs in a recent study (Schuckit & Gold, 1988) of multiple markers of alcohol challenge. This suggests that a very basic aspect of Schuckit's procedure may involve inducing illness that is greater in SONAs.

If it is true that a significant portion of Schuckit's subjects become ill or experience nausea because of the alcohol administration procedure, then this casts a different light on the biochemical measures he has used to measure the effect of alcohol. In other words, the differences in serum cortisol and PRL that Schuckit and his colleagues have found may be due to nausea and illness rather than to alcohol per se. Cortisol and PRL are stress hormones that are increased by a wide variety of stressors in both humans and animals (Martin & Reichin, 1987). Schuckitt found that increases in these hormones were accompanied by increased terrible feelings and that the differences in hormones were greatest from 1 to 3 hours following alcohol, when

headache, nausea, and other negative side effects are most prevalent.

This analysis suggests that differences between SOAs and SONAs in subjective intoxication (as measured by the terrible-feelings scale of the SHAS), serum cortisol, and PRL may actually have been due to nausea rather than the effect of alcohol. This would suggest that SONAs are more sensitive to these negative side effects of alcohol than are SOAs. This conclusion is of considerable theoretical importance if it is assumed that negative side effects tend to inhibit drinking behavior, but it is a very different conclusion from that of Schuckit and Gold (1988).

Novelty. Schuckit's procedure involves a highly novel laboratory environment to which subjects have not habituated. Newlin and Pretorius (in press) found that the response to alcohol challenge was suppressed in a novel environment, compared with response in the same environment when it was familiar to subjects. Newlin and Pretorius suggested that groups may differ in the rates and degree to which they habituate to a novel environment. In this case, SOAs may be more reactive to a novel laboratory environment (as they are to a laboratory stressor; Finn & Pihl, 1987) than are SONAs, so that SOAs show greater inhibition of the response to alcohol in the novel laboratory. This might account, in part, for Schuckit's finding that SOAs are less sensitive to alcohol than SONAs in a single session in the laboratory.

The simplest solution to this problem is to habituate subjects to the laboratory before giving them alcohol. Another solution is to give alcohol more than once, which also allows the measurement of chronic tolerance or sensitization to the drug. These procedures would tend to minimize the effect of laboratory novelty on the response to alcohol and the potential interaction of this factor with familial alcoholism.

Multiple alcohol challenges. Newlin and Thomson (1990) argued that there are many problems with using a single alcohol challenge in the high-risk paradigm and many advantages to administering alcohol on several different occasions (i.e., multiple alcohol challenges). A single alcohol challenge confounds sensitivity to the drug with acute tolerance (i.e., tolerance within a session), chronic tolerance (i.e., tolerance across multiple sessions), and inhibition caused by the novelty of the laboratory. Acute tolerance requires consideration of different responses in the rising and falling limbs of the blood alcohol curve. Schuckit's procedure often does not involve any measurement during the rising curve; his first measurement period is typically 30 or 60 min after alcohol has been consumed, which is beyond the peak BAC produced with his alcohol administration procedures. Therefore, it is not possible to compare responses in the rising and falling curves.

Clearly, the measurement of chronic tolerance requires multiple sessions. If there are adaptational trends (such as chronic tolerance or chronic sensitization) that occur over sessions with alcohol, these trends may be more important clinically than the response to the first challenge. Second, adaptational trends across sessions with multiple alcohol challenges may become apparent in responses that do not differ, or differ only to a limited degree, in the first session (Newlin & Thomson, 1990).

Finally, adaptation to the laboratory may be superimposed on the response to alcohol (Newlin & Pretorius, in press). It is difficult to predict the effect of this process on differences in the response to alcohol of SOAs and SONAs.

Dose dependency. Schuckit's laboratory has been one of the few to use two alcohol doses. However, in most cases the difference between SOAs and SONAs has not been dose dependent. In some cases, the higher dose has shown differences between high- and low-risk groups, and in others, the low dose has shown effects. This raises the question of the extent to which the effect follows traditional pharmacological characteristics, such as dose dependency. Evidence that alcohol itself was the causative factor in these studies would be greatest if the highest dose produced the largest difference between groups.

It is possible, however, that a low dose allows the greatest manifestation of individual differences in drug response. If all subjects are heavily intoxicated, then few differences between groups may be apparent. In contrast, with a low dose, individual differences between groups could be expressed without ceiling effects. This question deserves further experimental research because it has direct implications for the choice of dose in individual-difference studies.

Social interaction. The standard procedure of having an experimenter in the same room as the subject during studies of alcohol challenge may represent a methodological problem. Social interaction between the subject and the experimenter is an inevitable result of this procedure, particularly with measures that require verbal and nonverbal interaction for their completion. These researchers may be studying the effect of alcohol on social interaction rather than the effect of alcohol itself. Some measures, such as cortisol, PRL, and autonomic measures, may be particularly sensitive to the social atmosphere of the laboratory. This factor could interact with the novelty of the laboratory because the subject is required to deal with a new person in addition to a new laboratory. To minimize the confounding of social contact with the effect of alcohol, it may be necessary to place the subject alone in a subject chamber.

A Differentiator Model

As noted previously, the issue of whether SOAs are more or less sensitive to alcohol has been a central focus of alcohol-challenge studies. The psychobiological response to alcohol during the rising and falling limbs of the blood alcohol curve has been idealized in the set of curves at the top of Figure 1. Sensitivity to the drug is represented by the area under this curve. If two curves are of the same shape or are identical, as they may be for SOAs and SONAs, then the areas under the curve will be the same, and the curves can be compared by using the mean response over time. If alcohol is administered on several occasions (Newlin, 1989; Newlin & Thomson, 1990), then sensitivity may be conceptualized as the mean response across occasions, aside from any trends toward increasing responses (chronic sensitization) or declining responses (chronic tolerance).

Acute Tolerance

Schuckit's results showing reduced sensitivity to alcohol have been found during the declining blood alcohol curve, from 60 min to as much as 300 min after alcohol is consumed. For example, P300 latency in FH+ men declined toward baseline

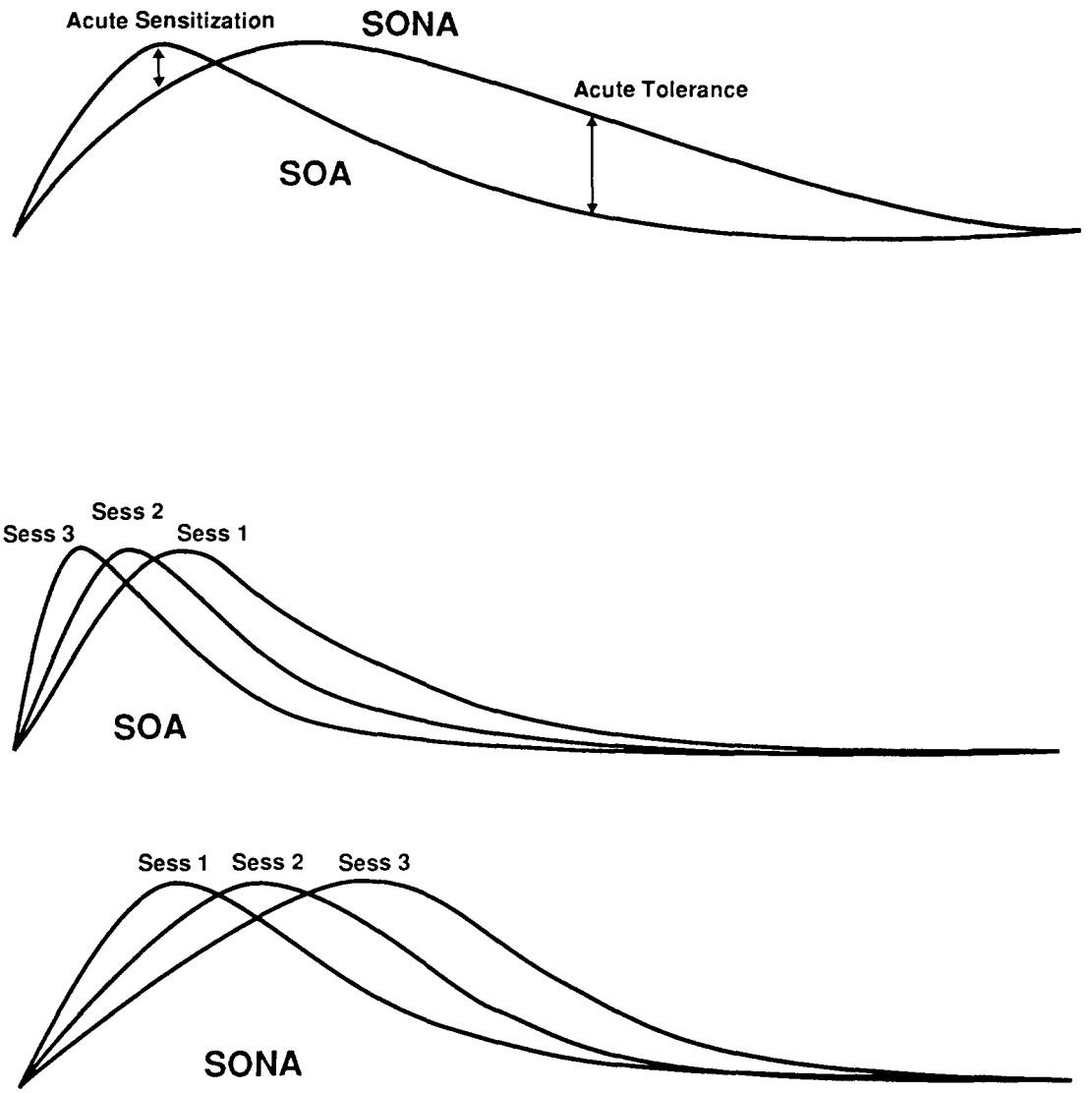

Figure 1. Schematic diagram of differentiator model. (In the first set of curves, note the greater acute sensitization during the ascending limb of the blood alcohol curve in sons of alcoholics [SOAs] and the greater acute tolerance in SOAs during the falling limb of the curve. This is indicated by a more rapid and robust onset of the effect of alcohol and more rapid return to baseline of the falling blood alcohol curve. In the second and third sets of curves, the accentuation of acute sensitization and acute tolerance across sessions in SOAs is illustrated. SONA = sons of nonalchoholic parents.)

more quickly than for FH– men 240 min after alcohol consumption, but not at baseline or 70 min following alcohol consumption (Schuckit, Gold, et al., 1988). As measured by serum PRL, SONAs had a larger response to alcohol at 60 min with the low dose and at 120 min with the high dose (Schuckit et al., 1987a); in another study, reduced PRL response was found in SOAs 150 min after alcohol consumption. Curves for serum cortisol diverged with the high dose at 90 min and thereafter (Schuckit et al., 1987b); in another study using analysis of covariance, the curves diverged at 240 min and beyond. Similarly, SONAs showed greater body sway than SOAs 135 min after the low dose (Schuckit, 1985a).

This tendency toward more rapid return to baseline in SOAs has been a very consistent finding under Schuckit's methodology. This trend is reflected in the top set of curves in Figure 1 as a reduced response to alcohol during the declining blood alcohol curve. We argue that this represents SOAs' greater acute tolerance for alcohol, compared with SONAs.

Acute tolerance is defined as the development of tolerance for a drug within a session in which the drug is administered. Acute tolerance may be measured several different ways. First, using steady-state pharmacokinetic procedures, the amount of the drug in the blood may be maintained at a constant level for long periods of time; because drug levels are constant, any decrease in response to the drug represents the development of acute tolerance. A second method is to assess the drug effect at

equivalent blood drug levels on the rising and falling blood drug curves; acute tolerance is indicated when subjects show greater response to the drug during the rising curve than during the falling curve. A final method is to measure recovery rates from the drug. One group of subjects may be said to show greater development of acute tolerance if they recover more quickly from the effects of the drug. With all these measurement procedures, acute tolerance is indicated when response to the drug is less than that expected on the basis of the blood drug curve. For our example, we would suggest that SOAs show greater development of acute tolerance when they show less response during the declining blood alcohol curve than do SONAs. Acute sensitization is then defined as greater drug action than that expected on the basis of the blood drug curve.

However, Schuckit's procedure has also yielded results suggesting that SOAs are more sensitive to alcohol than SONAs. For example, Schuckit, Engstrom, et al. (1981) found that frontal muscle tension was lower in SOAs than SONAs only 15 min after alcohol was consumed. Elmasian et al. (1982) recorded event-related potentials immediately after alcohol consumption and 30 min later; the results indicated greater decreases in P300 latency among SOAs, although this effect was also found with placebo. In addition, Savoie, Emory, and Moody-Thomas (1988) found that FH+ men reported lower anxiety than FH− men during the ascending blood alcohol curve. These effects occurred during the rising blood alcohol curve, and they indicated that SOAs were more sensitive to alcohol than SONAs. These relationships are summarized in Figure 2.

Other researchers have also found that SOAs are more sensitive to alcohol during the rising blood alcohol curve. Newlin and Thomson (1990) reported that SOAs showed greater increases than SONAs in finger-pulse amplitude, skin temperature, and skin conductance during the rising blood alcohol curve in the third session with alcohol but not in the first session; similar nonsignificant trends were found for heart rate and general motor activity. Newlin and Thomson (1990) also found in a second experiment that SOAs had greater increases in pulse transit time in the fourth session with alcohol during the rising blood alcohol curve and greater increases in static ataxia in the first and second sessions. Unfortunately, Newlin and Thomson (1990) did not record these measures during the falling blood alcohol curve to determine whether SONAs would show smaller effects at the later time points. Nagoshi and Wilson (1987) found that SOAs reported greater intoxication following the first "topping" dose of alcohol when BAC was increasing, and Kaplan et al. (1988) found that SOAs reported greater intoxication immediately after drinking two beers. O'Malley and Maisto (1985) reported that SOAs had greater impairment on some perceptual-motor tasks 10 and 35 min after drinking alcohol. This effect represents acute sensitization because the psychological response to the drug increases more rapidly than expected on the basis of the blood alcohol curve.

This effect is illustrated by the top set of curves in Figure 1, in which the psychological effects during the rising blood alcohol curve occur more rapidly for SOAs than SONAs, whereas the reverse is true during the falling blood alcohol curve. These relationships suggest an active Newtonian differentiator in SOAs that responds to the first differential or slope of the blood alcohol curve rather than to its level. In other words, the response to alcohol is accentuated when the slope is positive (during the rising blood alcohol curve) and attenuated when the slope is negative (during the falling blood alcohol curve). The former is acute sensitization and the latter is acute tolerance. This differentiator function is indicated in the top set of curves in Figure 1 by a curve for SOAs that represents the first differential of the curve for SONAs.

This differentiator model is hampered by the fact that there are no instances in which both acute sensitization and acute tolerance have been found in the same experiment. Moss et al. (1989) displayed self-reported intoxication curves that strongly support the differentiator model, but only acute tolerance on the falling curve was significant. The standard-error bars indicate that even though acute sensitization in SOAs was actually of greater magnitude than the statistically significant acute tolerance, the former was not significant because of greater variability. Moss et al. (1989) had 10 subjects per group; the two effects might both have been significant in a larger sample. Research that directly tests the model presented in Figure 1 is needed to establish that both effects can be found in the same subjects.

Many of the measures listed in Figure 2 were used by the same researchers (presumably using similar procedures). Moreover, many measures appear in both the left- and right-hand panels (e.g., self-reported intoxication and static ataxia). This indicates that the time-dependent pattern we noted does not appear to be due solely to different procedures or to specific measures. Therefore, this pattern does show some degree of generality despite the fact that greater acute sensitization and acute tolerance have not been reported in the same study.

The differentiator model goes a long way toward resolving the many discrepancies between results in the alcohol-challenge literature. As shown in Table 1, about as many studies have found that SOAs are more sensitive to alcohol as have reported the opposite. Consideration of the time factor reduces these inconsistencies markedly. It is clear that researchers need to consider the temporal factor in relation to the sensitivity issue.

Relation to Mood Effects

The differentiator model corresponds in interesting ways to reports of the differential mood and subjective responses to alcohol in normal social drinkers during the rising and falling blood alcohol curves. Babor, Berglas, Mendelson, Ellingboe, and Miller (1983) reported that "subjects tested while blood alcohol levels [BAL] were ascending. . . described themselves as more elated, friendly, and vigorous. As BAL declined, subjects described themselves as more angry, depressed, and fatigued" (p. 53).

Euphoria and accompanying EEG alpha activity have been reported only during the rising blood alcohol curve. Lukas, Mendelson, Benedikt, and Jones (1986) measured EEG, "euphoria" on a joystick, and plasma ethanol levels in 18 young men as they drank 0.35 or 0.70 g/kg alcohol. Reports of euphoria on the joystick and transient episodes of alpha activity occurred at the same times on the rising blood alcohol curve. Reports of euphoria were reduced during the falling curve, and there was relatively little alpha activity at later time points. In

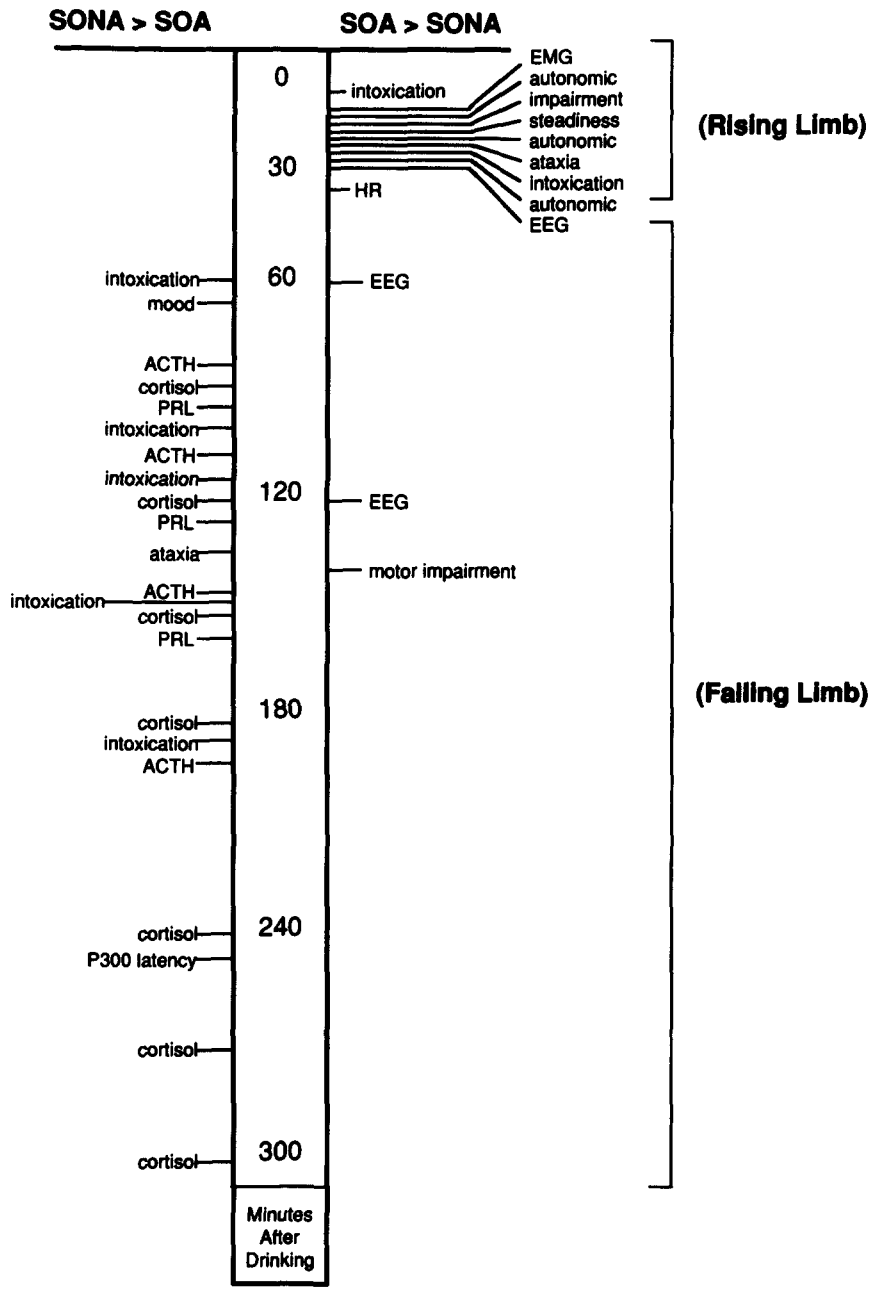

Figure 2. Summary of studies of sons of alcoholics (SOAs) and sons of nonalcoholics (SONAs) in terms of the timing of the effect. (The dependent measures that were greater in SOAs than in SONAs are illustrated to the right of the time line [time in minutes since consuming alcohol], and the measures that were greater in SONAs than in SOAs are illustrated to the left of the time line. The rising blood alcohol curve is represented by approximately the first 30 min after drinking [depending on dose and rate of drinking], and the falling blood alcohol curve is reflected by the remaining time. The effects for which SOAs showed greater responsivity than SONAs tended to occur during the rising blood alcohol curve, and effects for which SONAs showed greater responsivity than SOAs tended to occur during the falling curve. This pattern supports the differentiator model. EMG = electromyograph; EEG = electroencephalograph; PRL = prolactin; ACTH = adrenocorticotropic hormone; HR = heart rate.)

contrast, following alcohol consumption, theta activity was increased during the entire recording session and closely matched the blood alcohol curve. Lukas, Mendelson, and Benedikt (1986) found similar results for euphoria during the rising blood alcohol curve.

There are also parallels to subjective responses to drugs other

than alcohol. The "rush" or intense subjective high felt immediately after injection of cocaine or opiates can be differentiated from the less intense pleasurable feelings experienced during prolonged responses to these drugs (Kumor, Sherer, & Cascella, in press). Rush is most often experienced when drugs are injected intravenously or when a drug is inhaled, and both routes of drug administration are associated with very rapidly rising blood drug curves. In contrast, the high associated with the falling blood drug curve, or with slower routes of administration, such as by mouth or by "snorting," is both qualitatively and quantitatively different from that of rush. These observations also suggest that the slope of the rising blood drug curve may be an important determinant of the psychological response to drugs and that the subjective responses to these drugs are different in the rising and falling limbs of the blood drug curve.

These observations suggest that subjective responses to alcohol and to other drugs may be more sensitive to the slope of the blood drug curve than to its absolute level. It is as if the transition in state induced by the drug is more important than the state itself. This also suggests a differentiator model of the psychobiological response to drugs of abuse.

More important, it suggests that SOAs may be more sensitive to the drug during the rising blood alcohol curve, when euphoria is greatest, and less sensitive during the falling curve, when anxiety and depression are greatest. This would suggest that alcohol is more reinforcing for SOAs than for SONAs during both the rising and falling curves. SOAs may experience greater euphoria during the rising blood alcohol curve and experience less dysphoria during the falling curve. This double benefit may produce greater motivation to drink alcohol and thereby place SOAs at greater risk for alcoholism. We feel that this interpretation is more consistent with the available data than simple consideration of sensitivity to alcohol and more compelling as an interpretation of the relationship between these psychobiological markers and final manifestation of the disorder.

In other words, sensitivity to the drug must be related to the time and circumstances under which the response is measured. Sensitivity to the drug probably is a key component of the rewarding aspect of the response to alcohol, but that sensitivity must be understood in relation to the transition in blood alcohol rather than its absolute level. Most important, adaptational trends that occur over time are critically important and might be better measured with multiple alcohol challenges.

It is possible that this differentiator model has a pharmacokinetic substrate, even though SOAs and SONAs do not differ in peak blood alcohol levels or curves. First, it may be that SOAs and SONAs differ in the levels of psychoactive metabolites of alcohol, although the data on acetaldehyde are very weak. Second, Noe and Kumor (1983) suggested that small, low-flux compartments may have different absorption characteristics than larger central compartments. For this to account for the results of alcohol-challenge studies, a small, low-flux compartment critical to the response measures used in such studies would have to have faster absorption characteristics in SOAs and more rapid clearance during the falling blood alcohol curve. Noe and Kumor's (1983) analysis assumes that the area under the low-flux compartment's curve that is higher during the rising blood drug curve must be equal to the area between the small compartment's falling curve and that of the larger compartment. In other words, the total area under the curves of the two compartments must be equal. This analysis may be unlikely given alcohol's propensity to circulate throughout the body in relatively equal amounts but is worth considering because it leads to testable predictions.

Chronic Tolerance and Sensitization

This differentiator model has implications for chronic in addition to acute tolerance and sensitization. Chronic tolerance is defined as attenuation in the effect of a drug with repeated administrations across sessions rather than within a session. Conversely, chronic sensitization represents increasingly greater responses to a drug across sessions. There is no necessary assumption that acute and chronic tolerance reflect operation of the same mechanism.

If it is assumed that the differentiator is accentuated by repetition of the alcohol stimulus across sessions with alcohol, then the model predicts both greater chronic sensitization and chronic tolerance in SOAs compared with SONAs, depending on whether the response to alcohol is measured in the rising or falling blood alcohol curves. This is depicted by the two sets of curves at the bottom of Figure 2. As the differentiator in SOAs is accentuated, it leads to a more rapidly rising psychological response to the drug, and, at the same time, to a more rapidly decaying response after BAC has peaked. Newlin and Thomson (1990) found results consistent with greater chronic sensitization to alcohol in SOAs during the rising blood alcohol curve across three or four sessions with alcohol (Newlin, 1987). With stimulant measures (i.e., autonomic measures that were affected in an arousal-like manner), chronic sensitization was found in SOAs compared with SONAs; these measures were finger-pulse amplitude, finger temperature, and skin conductance in the first study and pulse transit time in the replication study. With a depressant measure, static ataxia, the reverse was found; SOAs showed greater increases in body sway only in the first and second sessions. There is a conceptual analogy between Schuckit's (1985a) body-sway results in a single session with alcohol, in which he found SOAs to have greater acute tolerance than SONAs, and Newlin and Thomson's (1990) results with body sway, in which they found greater chronic tolerance across four sessions with alcohol.

Greater acute tolerance has also been found with rats that were genetically selected for preference for oral alcohol (Gatto, Murphy, Waller, McBride, Lumeng, & Li, 1986). Gatto et al. found that alcohol-preferring rats (P rats) showed greater acute tolerance than alcohol-nonpreferring (NP) rats in their first exposure to the drug. This was found on a dynamic ataxia measure for which P rats showed more rapid recovery from alcohol compared with NP rats. In addition, P rats retained this acute tolerance for 10 days, whereas NP rats lost their acute tolerance.

These results suggest interesting parallels between rats that are genetically selected for alcohol preference and SOAs. Further research is needed to test the limits of this analogy. This would involve more research with P and NP rats to determine

whether they show other effects similar to SOAs (e.g., chronic sensitization on stimulant measures), and with SOAs and SONAs to determine whether they show greater retention of acute tolerance (in addition to the findings already mentioned concerning initial display of acute tolerance). This could lead to a potentially very powerful boot-strapping line of research in which parallels between particular strains of animals and familial alcoholism in people are investigated.

Implications

If this analogy to a differentiator in SOAs is accurate, it has implications for a variety of responses other than alcohol. The model may explain presumed personality differences between those at high and low risk for alcoholism (Hennecke, 1984; Morrison & Schuckit, 1983; Saunders & Schuckit, 1981; Schuckit, 1982a, 1983; Tarter, Hegedus, Goldstein, Shelly, & Alterman, 1984). Sons of alcoholics may be particularly sensitive to the leading edge of psychological stimuli, such that their responses are accentuated early in the response to a stimulus and are blunted or habituated quickly when the response is repeated. This analysis might be profitably extended to habituation paradigms and personality measures that are related to the temporal dimensions of arousal to a wide range of different stimuli.

Summary and Conclusions

Many of the procedures in alcohol-challenge research have become de facto standards, even though they may tend to minimize the potential differences between SOAs and SONAs and may lead to alcohol-induced illness on the part of the subjects. Few researchers have acclimated their subjects to the novel laboratory environment or given alcohol more than once to study chronic tolerance or sensitization in these individuals. In addition, very few researchers have measured alcohol effects in SOAs and SONAs during both the rising and falling limbs of the blood alcohol curve. We argue that this is essential to resolve the issue of differences in sensitivity to alcohol as a function of familial alcoholism.

We have made a number of proposals for methodological improvements in alcohol-challenge research. We particularly stress that it is important to avoid making subjects ill during the procedure by giving them alcohol in impure form early in the morning in a very unpalatable mixture. There are sound empirical reasons for administering alcohol in a form and at a time that is similar to the usual drinking practices of normal social drinkers. This prevents both the confounding effects of illness and increases the generalizability of the results.

We have proposed a differentiator model of the response to alcohol, in which SOAs show both greater acute sensitization to and greater acute tolerance for alcohol than SONAs depending on whether the effect of alcohol is measured during the rising or falling limbs of the blood alcohol curve. This is a testable model that has many implications for research.

Despite problems with the alcohol-challenge literature, the early results are promising and easily justify continued research in this area. Alcoholism is a serious social problem that is difficult to prevent or treat in part, because practitioners do not yet understand the various etiologies of the disorder. It is clear that alcohol-challenge studies of SOAs and SONAs may further understanding of the etiology of alcoholism.

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