

An Heuristic Model for the Inherited Predisposition to Alcoholism

R. O. Pihl and Jordan Peterson
McGill University

Peter Finn
Indiana University

A research program studying individuals genetically at high risk for alcoholism is presented. Multigenerational nonproblem-drinking sons of male alcoholics display a pattern of autonomic hyperreactivity to a variety of stimuli. This pattern of reactivity is significantly dampened by high doses of alcohol. These individuals also display difficulty on cognitive tests suggestive of prefrontal lobe dysfunction. This response pattern is not characteristic of controls nor of daughters of multigenerational male alcoholics. A model is presented that hypothesizes a cognitive disturbance underlying the hyperreactivity and posits a problem in the attribution of meaning to novel stimuli and threatening events.

Alcoholism is a pervasive and pernicious disorder. Five to 10% of adults abuse or are dependent upon alcohol (Kamerow, Pincus, & McDonald, 1986). The physical, social, and economic consequences of alcoholism are so severe that, by comparison, detrimental effects of illegal substance abuse pale to relative insignificance. Three very notable facts are that alcohol abuse and its effects pose the third most prevalent health problem in North America after heart disease and cancer, are responsible for approximately one third of general hospital admissions, and are the primary cause of emergency room admissions (Adrian, 1984; Harwood, Napolitano, & Kristiansen, 1984). Given the death, mayhem, and economic loss these facts represent, one might assume that the etiology of the problem would be well delineated and that demonstrated effective treatments would be available. Unfortunately, one would err in forming both assumptions. It has been estimated (Nathan, 1987) that less than 5% of alcoholics are ever treated. If roughly 50% of those treated re-

lapse (Miller & Hester, 1986) and if, as it has been argued (Edwards, 1982), nontreated alcoholics recover to the same degree as those receiving treatment, then clearly we must question our level of understanding of the problem.

The present relative lack of understanding does not exist because the phenomenon has been newly discovered: Alcohol abuse is mentioned in the book of Genesis and is represented in early Egyptian, Babylonian, and Greek writings and drawings (Austin, 1985). Responsibility for the present condition can be attributed, in part, to conflicting philosophical approaches and a poor choice of experimental procedures. One primary viewpoint has been that alcoholism is a moral problem. This definition implicitly defines etiology in a circular manner and thus obviates questioning. The predominant methodological problem has been the all-too-frequent tendency to study seasoned alcoholics and to draw post hoc inferences about etiology from their behavior. This practice can readily confuse cause with consequence. In effect, one is describing the results of the explosion without even identifying remnants of the triggering mechanism. A review of the personality and drug abuse literature completed a few years ago (Pihl & Spiers, 1978) found that 93% of studies used alcoholics in treatment as subjects. The point made most vociferously in that paper was that almost nothing could be said concerning etiology from testing these subjects.

This research was supported by the Medical Research Council of Canada and the McGill-Douglas Hospital Alcohol Study Group.

Correspondence concerning this article should be addressed to R. O. Pihl, Department of Psychology, McGill University, 1205 Ave. Docteur Penfield, Montreal, Quebec, Canada, H3A 1B1.

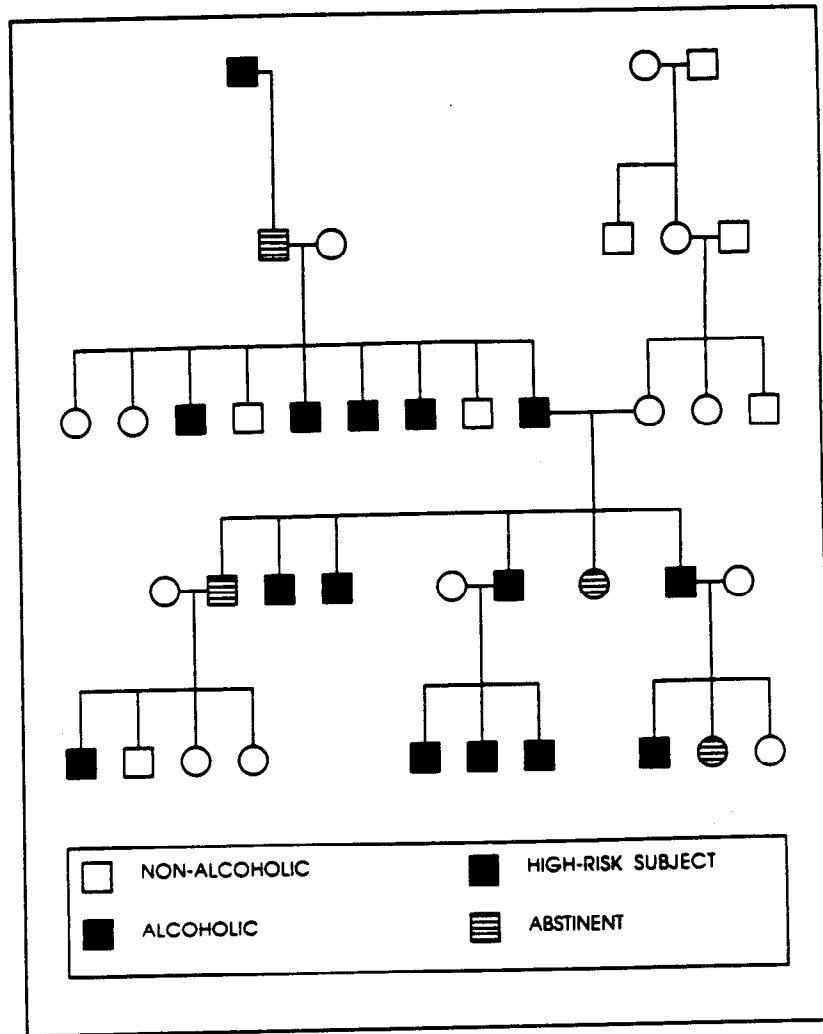


Figure 1. A representative pedigree from which at-risk subjects are selected.

The impact of that argument was demonstrated in a subsequent review for the years 1978-1981, which showed that 92% of studies used alcoholics in treatment as subjects. In spite of this dramatic progress, what remains called for in order to make meaningful statements concerning etiology are at-risk and longitudinal methodologies.

There are numerous groups at risk for problems with alcohol. These include males between the ages of 18 and 24, depressive-psychopathic personality types, individuals with high stress levels, persons in vulnerable occupations, adolescents with histories of drug abuse, acting out,

and/or expectancies of enhancement of social behavior, individuals from alcohol-abusing families, and males from families with a multigenerational history of abuse. It is this last group that encompasses the subject population upon which the following experimental results are predicated. This population was selected for study because of various adoption, family, twin, and experimental studies (reviewed in Pihl, Peterson, & Finn, in press) that suggest these individuals are characterized by a four- to ninefold increased risk. Figure 1 presents a pedigree of a typical family we study. In the one study (Finn & Pihl,

1987) in which we tabulated incidence, 75% of males in the pedigree were diagnosable as alcoholic either directly using DSM III criteria or indirectly using Family History Research Diagnostic Criteria for unavailable family members. (Endicott, Andreasen, & Spitzer, 1975). Typically our experimental subjects are males with a MAST of 6 or less and are between the ages of 18 and 30. Thus all are clearly not problem drinkers but possess a high genetic likelihood for the disorder.

Reactivity and Dampening

We have now tested the reactivity of 143 subjects: 64 at high risk and 79 controls. They have been tested while sober and after the consumption of various dosages of alcohol. One control group we have utilized is a "moderate-risk" group in which individuals have an alcoholic father and the concomitant family stresses but do not have the multigenerational history. This attempt at an environmental control is notable in that, in one study on an emotionality factor from self-rating scales, the moderate-risk group was more emotional than was the high-risk group (Finn & Pihl, 1987). The typical paradigm we use involves the presentation of a tone that initiates a countdown from 10 to 1, which is then followed by an electric shock of 1.85 mA for 0.25 s to the forearm of the subject. Various psychophysiological and subjective response measures are taken. Although subjective measures have generally produced very few differences, the psychophysiological responses have been illuminating and consistent.

Figure 2 presents heart rate data for high-, moderate-, and low-risk (no family history of alcoholism) groups. What can be observed is a striking pattern of hyperreactivity when sober, which is dramatically dampened when high-risk subjects are intoxicated with a dose of 1.32 mL/kg of 95% USP alcohol. Both control groups, in comparison, demonstrate little reactivity when sober and more reactivity when intoxicated. This pattern has emerged during three studies (Finn & Pihl, 1988, 1989; Finn, Zeitouni, & Pihl, in press). We have also tested daughters of multigenerational male alcoholics within the paradigm and have determined that they do not respond like their brothers on the heart-rate

measure. Neither daughters nor controls display reactivity, but both dampen when intoxicated.

Alcoholics are known to be hypersensitive to pain (Coopersmith & Woodrow, 1967). It therefore appears possible that the reactivity seen in our at-risk subjects represents a similar sensitivity. In an attempt to test this hypothesis, we compared high- and low-risk men, unexperienced with the shock experiments, to nonaversive tones, which they were told to ignore. Figure 3 illustrates that the GSR of sober high-risk subjects was of a shorter latency, greater amplitude, and took longer to habituate when compared to controls. The opposite pattern occurred when these subjects were drunk (1.00 mL/kg). Consequently, we have concluded that the pattern of hyperreactivity and dampening seen in at-risk subjects does not simply represent hypersensitivity to pain.

We have also completed a dose response study (Stewart, Finn, & Pihl, 1989), which indicates that dampening occurs to intoxicating dosages of 1.32 mL/kg and 1.00 mL/kg, less so to a dose of 0.75 mL/kg, and not at all to a dose of 0.50 mL/kg and a placebo dose. This fact is noteworthy in that many if not most acute alcohol studies in North America utilize insignificant dosages.

Other Electrophysiological and Behavioral Characteristics of High-Risk Males

We have reviewed the characteristics of sons of male alcoholics in detail elsewhere (Pihl et al., in press). Findings that support the notion that hyperreactivity and an atypical response to alcohol characterize high-risk males come from the evoked potential-EEG literature, studies of stimulus augmentation, and studies demonstrating that hyperactivity and conduct disorder are common to such individuals. Briefly, high-risk males display attenuated ERPs when voluntary active attention is required, manifest excess high-frequency beta activity and poorly synchronized EEGs, and are characterized by stimulus augmentation (thought to be a form of perceptual hyperreactivity). In addition, as children, these individuals are often described as conduct disordered/antisocial, and/or as hyperactive and/or impulsive. This conclusion is derived regardless of varying methodologies and measures.

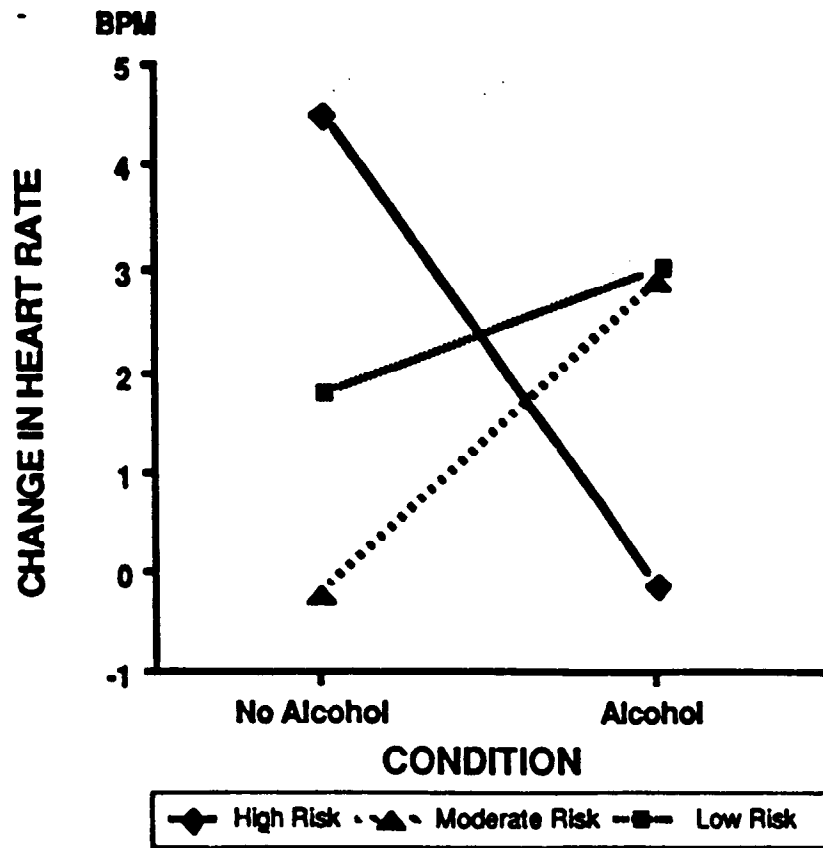


Figure 2. Mean change in heart rate in beats per minute (BPM) from resting baseline for at-risk and control groups under both no-alcohol and alcohol conditions.

Cognitive Characteristics

We tested high-risk and control subjects on a battery of cognitive tests and, in keeping with some 17 other studies (reviewed in Pihl et al., in press), found a rather distinctive pattern of results. At-risk subjects, sober and intoxicated, produced more errors on neuropsychological tests putatively thought to test frontal lobe functioning. Once again daughters of multigenerational male alcoholics did not show this pattern or, in fact, any differential pattern when compared with control subjects. In at-risk males, correlations between test scores and previously assessed reactivity and dampening were dramatic. For example, scores on the Self-Ordered Pointing Test (Petrides & Milner, 1982), which requires the

ability to organize material and on which prefrontally damaged patients consistently manifest deficits, correlated .62 with heart-rate reactivity and .71 with dampening. Scores on the Wisconsin Card Sort Test (Grant & Berg, 1948) which is sensitive to perseveration, correlated .69 with reactivity and .54 with dampening.

An Heuristic Model

Figure 4 contains aspects of a model that focuses on the hyperreactivity and dampening displayed by high-risk individuals. The model is based on the assumption that dampening is negatively reinforcing. Thus, any drug use or behavior pattern that reduces this response, will, we believe, increase in frequency. Clearly, choice

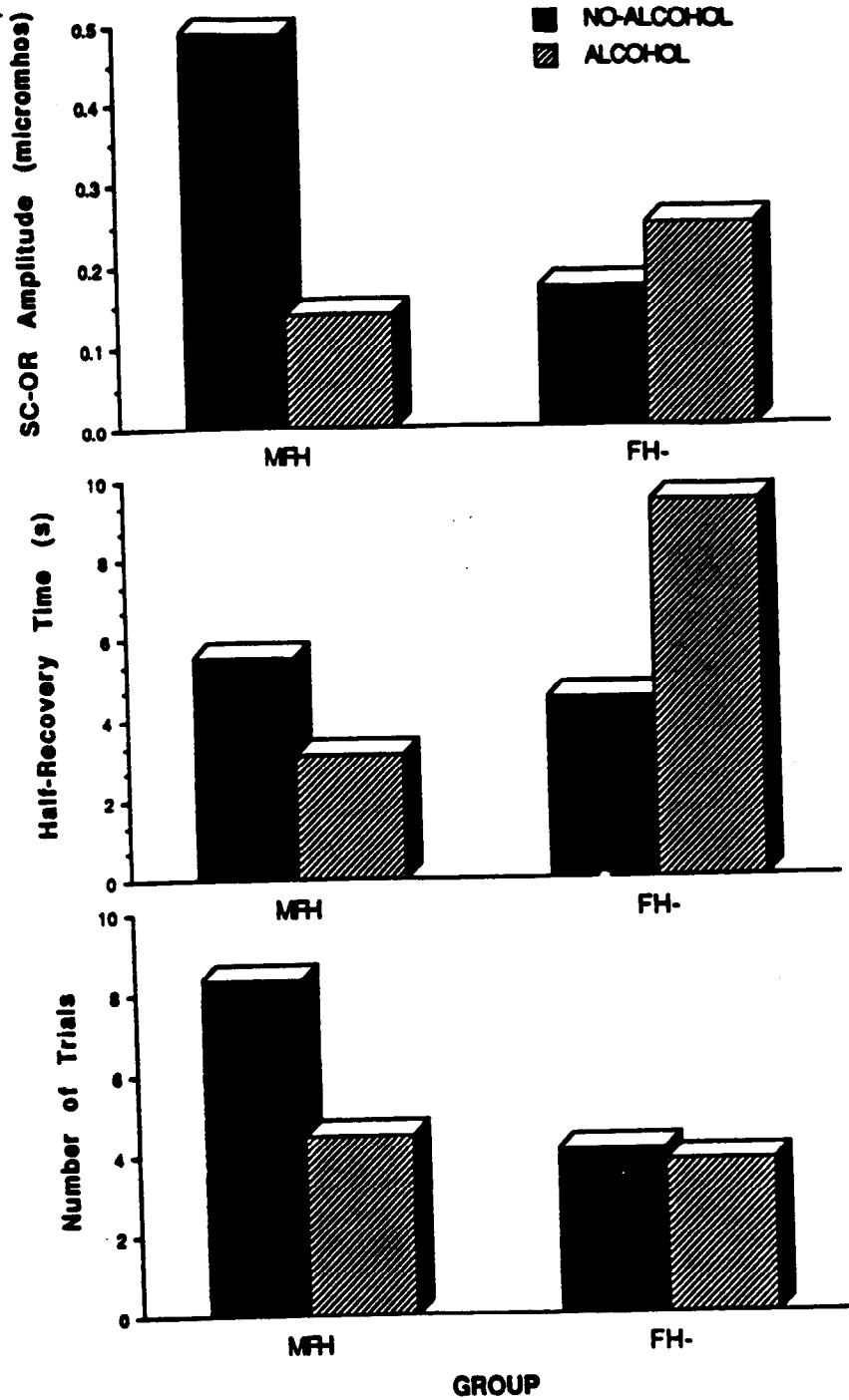


Figure 3. Skin conductance response to 1 kHz tones showing mean amplitude (top), half-recovery time (middle), and habituation rate (bottom) for multigenerational (MFH) and family history negative (FH-) subjects for both no-alcohol and alcohol conditions.

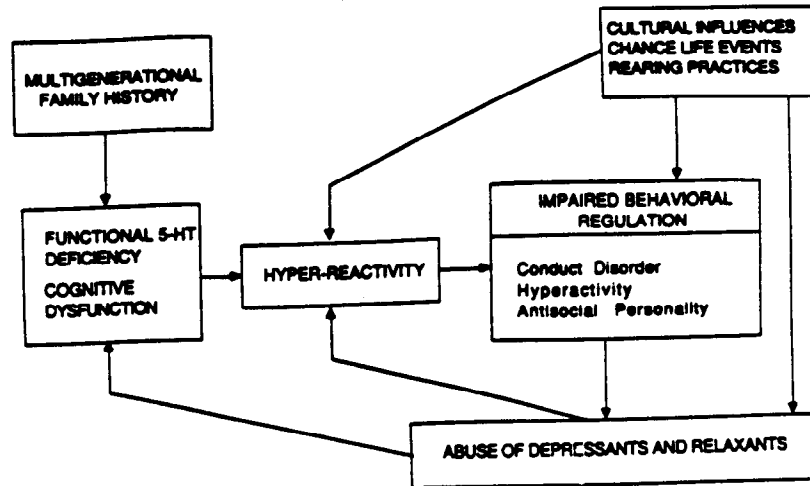


Figure 4. A schematic model of the predisposition to alcoholism in multigeneration high-risk males.

of drug or behavior will depend on availability, sanction, and a surfeit of experiences. Equally susceptible to chance variation and other circumstances is the likelihood of developing problematic behavior patterns, such as conduct disorder, hyperactivity, and others. The model posits that these forms of behavior in high-risk males are consequences of the same process responsible for the hyperreactivity and are thus frequently associated with drug abuse. The term "impaired behavioral regulation" is offered as a description of this common response pattern. Previously presented evidence and additional studies reviewed below suggest two not necessarily mutually exclusive explanations. The first explanation posits a disturbance in central serotonin function; the second a neuropsychological dysfunction that affects the processing of internal and external events.

Serotonin dysfunction. Direct evidence suggesting a biochemical dysfunction in high-risk individuals is scant and/or difficult to interpret. Previous reviews (Tarter, Alterman, & Edwards, 1985; Tarter, Hegedus, Goldstein, Shelly, & Alterman, 1984) have proposed the presence of a neurochemical dysfunction based primarily on evidence suggesting lower platelet monoamine oxidase (MAO) in family history positive subjects. These data are problematic in that the relationship between platelet MAO activity and central nervous system MAO activity or genetic factors is unclear. Although many neurochemical sys-

tems are undoubtedly involved in the predisposition to alcoholism (Cloninger, 1987) the evidence is nonetheless strongest in support of the notion of a functional deficit of serotonin (5-HT) activity in multigeneration high-risk males. In support of this hypothesis, we draw on biochemical evidence obtained from studies of factors such as stimulus augmenting, increased pain sensitivity, and behavioral disinhibition, all characteristic of our subjects. Stimulus augmenting, which is also partially under genetic control (Buchsbbaum, 1974), appears to be related to a functional deficiency in central 5-HT activity (von Knorring & Perris, 1981). For example, treatment with Zimelidine, a specific 5-HT reuptake inhibitor, results in a shift from augmenting to reducing in chronic pain patients (von Knorring & Johansson, 1980) and in healthy volunteers (von Knorring, 1982). CSF samples taken concurrently with the Zimelidine treatment indicated a concomitant reduction in 5-HIAA levels (a 5-HT metabolite) with no change in dopamine or norepinephrine metabolite levels. Deficiencies in 5-HT functioning have also been linked to increased pain sensitivity. This effect has been noted by lowering brain 5-HT in rats pharmacologically (Harvey & Yager, 1972; Telner, Lepore, & Guillemot, 1979), surgically (Tenen, 1967), and via dietary manipulation (Kantak, Hegstrand, Whitman, & Eichelman, 1980; Messing, Fisher, Phebus, & Lytle, 1976). In one study with humans (Johansson & von Knorring, 1979),

Zimelidine was found to be more effective in reducing the pain of chronic pain patients than placebo. In another, significantly higher pain tolerance levels were induced by the administration of tryptophan (Seltzer, Stoch, Marcus, & Jackson, 1982), the 5-HT precursor.

Additional supportive evidence can be derived from the literature on personality and biochemistry. High-risk males are frequently described as impulsive or as behaviorally disinhibited. An increased incidence of disinhibited-aggressive behaviors is correlated with low CSF 5-HIAA, suggesting a functional deficiency in central serotonergic activity (G. L. Brown, Ballenger, Minichiello, & Goodwin, 1979; G. L. Brown, Goodwin, Ballenger, Goyer, & Major, 1979; G. L. Brown et al., 1982). Ballenger, Goodwin, Major, and Brown (1979) found that CSF levels of 5-HIAA were significantly lower in alcoholics abstinent for at least 4 weeks than such levels in controls and in alcoholics in the immediate post-intoxication phase. Low CSF 5-HIAA has been associated with other indicators of disinhibitory psychopathology such as increased monotony avoidance, impulsivity, and psychoticism (Schalling, Asberg, & Edman, 1985). In addition, tryptophan-depleted humans and monkeys have been shown to be more reactive to provoking stimuli and to display mood variations (Young, Pihl, & Ervin, 1986).

One final indirect area of evidence comes from animal self-selection of alcohol studies. The P strain rats are predisposed to drink alcohol to intoxication on a daily basis under conditions of free choice, to work for alcohol, to consume alcohol for its postingestion effects, and to develop alcohol tolerance. These animals are also characterized by low levels of central serotonergic activity (Li, Lumeng, McBride, Waller, & Murphy, 1986; Murphy, McBride, Gatto, Lumeng, & Li, 1988; Murphy, McBride, Lumeng, & Li, 1982, 1987) as are other strains of alcohol-preferring rats (Daoust et al., 1985; Zhukov, Varkov, & Burov, 1985). Recent evidence also suggests that alcohol consumption per se may increase central functional serotonergic activity in rats (Hyatt & Tyce, 1985; Kuriyama, Kanmori, & Yoneda, 1984; McBride, Murphy, Lumeng, & Li, 1986; Murphy et al., 1988). Although few similar studies have been carried out on human subjects, significant positive correlation between CSF 5-HIAA and blood alcohol

levels in alcoholics, suggesting that alcohol consumption produces an increase in human serotonergic activity, has been found (Borg, Kvande, Liljeberg, & Valverius, 1985). In addition, treatment with serotonin reuptake inhibitors, such as Zimelidine and Citalopram, significantly decreases the voluntary ethanol intake of rats (Amit, Sutherland, Gill, & Ogren, 1984; Naranjo, Sellers, & Lawrin, 1986) and of heavy-drinking humans (Naranjo et al., 1984, 1986, 1987).

Neuropsychological Dysfunctions

Studies of high-risk males have consistently demonstrated abnormalities in their ability to use language and to control their behavior, to modulate their level of arousal and maintain attention and to engage in complex goal-specific activities. Deficits in perceptual-motor capacity and memory have been identified with somewhat less regularity (Pihl et al., in press). The maintenance of these abilities may be dependent primarily on the function of an integrated cortical unit that includes the limbic system and the structures connected with it—the mediobasal division of the prefrontal cortex (Brodmann's Area 9, 10, 11, and 46, in particular) and the hypothalamus. A detailed description of the function of this area and its relevance to the control of behavior can be found in Luria (1980). Luria has noted that these prefrontal areas are phylogenetically among the most recent parts of the brain, possess a fine, relatively undifferentiated structure, and are particularly vulnerable to functional disruption. These prefrontal sites can be distinguished from other areas of the brain by certain peculiarities in their function. They attain a considerable level of development only in the primates, and some of their sections can be considered as specifically human (Luria, 1980; Nauta, 1971). Their manner of performance is environmentally determined; whether or not they can perform may be genetically determined (Luria, 1980). They are integrally involved in control of the speech system and in the regulation of activation processes that are under the complete or partial control of that system. Finally, they synthesize information about the outside and the inside world and provide the means whereby behavior is regulated in conformity with its consequences.

Impairments in these prefrontal subsystems disinhibit activity in certain phylogenetically ancient structures, including those commonly described as limbic, and may consequently lead to discernible autonomic hyperreactivity, mediated hypothalamically. Gray's (1982) description of the "behavioral inhibition system" is particularly instructive in this regard. Gray defines this system, a priori, as susceptible to the actions of the antianxiety drugs (barbiturates, benzodiazepines, and alcohol). Its functions, which are to respond to secondary punishing, secondary rewarding, innate fear stimuli, and to novelty, are subsumed primarily by the septal-hippocampal structures. These structures theoretically compare actuality with expectancy. As long as actuality and expectancy coincide, the behavioral inhibition system merely monitors activity; but when the unexpected occurs, it takes control. In animals, this control takes the form of behavioral inhibition, increased levels of attention, and an increment in arousal, and is theoretically associated with the animal equivalent of anxiety. This state of subcortical dominance does not cease until valid plans are substituted for those that led to the unexpected sequence of events. In animals, these new plans are drawn primarily from the animal's repertoire of learned and instinctual behavior. In human beings, the case is similar, but more complex. It is likely that the prefrontal lobes play an increasing role in the operation of this system at the higher phylogenetic levels. For example, patients with extensive prefrontal lesions have difficulty in modulating their emotional responses, may alternate rapidly between mood states characterized by facetiousness and boasting, apathy and indifference, and may demonstrate bursts of anger (Eslinger & Damasio, 1985).

These observations are particularly relevant to the topic at hand given that individuals at high risk for the development of alcoholism have consistently demonstrated assumed impairments in prefrontal function. The ability to plan and maintain complex forms of behavior and to inhibit irrelevant associations seems to be dependent on the intact functioning of the prefrontal cortex (Luria, 1980). This is true in the short term, when task demands are temporarily limited and new short-lived behavioral schemata must be designed, or when new combinations of old schemata must be implemented (Walsh,

1978). It is equally true in the long term (Damasio, 1985). Although adults with mild verified prefrontal lesions do not generally demonstrate deficiencies in measured intelligence and do not lose their knowledge of social skills, the effect of a genetically mediated childhood prefrontal dysfunction on the learning and implementation of social rules has not been explored. Disruptions in such learning could account for the inability of hyperactive and conduct-disordered individuals and children at high risk for the development of alcoholism to regulate their behavior in accordance with social norms, and may account for various descriptions of the personality of those individuals: highly active and disinhibited, with a tendency towards risk-taking and antisocial behavior. Animals without a frontal cortex manifest disturbances in orienting and investigative behavior, particularly in the form of increased reactivity to novelty (Luria, 1980).

The role of the prefrontal cortex in man deserves more explicit consideration, given the dramatic behavioral consequences of disruption in its activity. We propose that the neuropsychological dysfunction in the prefrontal cortex of those males with an extensive family history of alcoholism impairs their ability to place potentially relevant stimuli into a meaningful context. This impairment leads to heightened autonomic and limbic reactivity to a variety of events within their field of experience. This dysfunction is likely mediated genetically, and the susceptibility to alcoholism that accompanies it is incidental to the sequence of ontogenetic development that underlies the neuropsychological impairment itself. Figure 5 diagrammatically presents this view.

We suggest that information can be classified according to its motivational significance along two dimensions (knowledge and relevance) and in four categories (known and unknown irrelevant, and known and unknown relevant). Known irrelevant stimuli provide information categorized previously as meaningless. These are events that have previously been habituated to and integrated into a system of meaning, and that neither provide nor signal reward or punishment of any kind. They have little motivational significance. Unknown irrelevant stimuli provide information that can be immediately classified as meaningless because they fall within the bounds of generalization (in that they are either perceived as identical to known irrelevant stimuli

man, & Williamson, 1983). The process underlying its manifestation is initiated only whenever the stimuli presented to the individual as "motivationally significant" (Begleiter, Porjesz, Chou, & Aunon, 1983). The amplitude of the P300 component is low in anhedonic individuals (Simons, 1982) and in those with aberrant levels of motivation (Porjesz, Begleiter, & Samuely, 1980; Roth, Pfefferbaum, Horvath, Berger, & Koppell, 1980). Finally, unexpected or uncertain events elicit large P300 amplitudes (Duncan-Johnson & Donchin, 1977; Teuting, Sutton, & Zubin, 1971). Increased reticular activity, which may potentiate responses of the behavioral inhibition system (Gray, 1982), has been associated with increases in EEG beta activity (Caspers, 1958; Propping, 1977), which have in turn been associated with unpleasant affective states (Kiloh & Osselton, 1961). The fact that the reticular activating system is quite sensitive to the inhibitory effects of alcohol is interesting in this regard (Caspers, 1958; Ohega, 1962; Perrin, Hockman, Kalant, & Livingston, 1974).

The model offered in this discussion predicts variable cortical and/or autonomic response to different forms of stimuli. High-risk males are likely to demonstrate augmented response to novel stimuli—to the unexpected—but attenuated response to stimuli whose recognition requires directed, sustained voluntary attention. To posit hyperreactivity to "stress" is no longer sufficient in terms of experimental design. Individuals with various forms of autonomic and cortical response to certain types of stimuli will vary under very narrowly defined circumstances. The predicted response, the nature of the stimuli, and the circumstances under which it is to be encountered must be specified prior to development of any new experiments in this area and should be considered in interpretation of previous research. The fact that the central nervous system tends to process information garnered as signal to noise, rather than in terms of absolute intensity of stimulation, also must be considered. This means that degree of environmental activity *per se* may not necessarily be the determining factor in producing hyperreactivity; rather that change in such activity may play the deciding role. The fact that high-risk subjects and hyperactive and conduct-disordered children do not generally manifest disturbances in basal levels of arousal offers support for this conclusion (Finn

& Pihl, 1987; Grings & Dawson, 1978; Hastings & Barkley, 1978).

Alcohol consumption may dampen the effect of arousing stimuli by interfering (directly and/or indirectly) with the function of the hippocampus and the septum, structures that are particularly sensitive to its effects. This interference potentially relieves the anxiety associated with overactivity in the behavioral inhibition system. Gray's (1982) theory is built upon the premise that alcohol as well as other antianxiety drugs impair the functioning of this system, at least in animals. Recent research carried out by Peterson, Rothfleisch, Zelazo, and Pihl (in press) demonstrates a pronounced transient alcohol-induced memory impairment of the type usually associated with hippocampal damage.

The action of alcohol on the EEGs of high-risk males (Pollock et al., 1983) reflects both positive and negative reinforcement. The increase in slow alpha associated with positive psychological states (Kiloh & Osselton, 1961) and alcohol-induced euphoria (Lukas, Mendelson, Benedikt, & Jones, 1986) may be positively reinforcing, and the decrease in high-frequency EEG energy associated with unpleasant psychological states negatively reinforcing. A potentially powerful negatively reinforcing effect of alcohol in multigenerational high-risk males is also apparent in the studies of reactivity dampening. The fact that these subjects tend to be hyperreactive may increase the potential for such reinforcement. We have found a correlation of .82 between reactivity and sensitivity to alcohol's reactivity dampening effect in high-risk males. Consistent with these studies is the significant reduction in autonomic reactivity (Coopersmith & Woodrow, 1967; Garfield & McBrearty, 1970) and pain reactivity (R. A. Brown & Cutter, 1977) demonstrated by alcoholics after drinking alcohol. Alcohol consumption also results in a shift from stimulus augmentation to reduction in alcoholics (Buchsbaum & Ludwig, 1978; Petrie, 1978). These results suggest that alcohol consumption may be particularly negatively reinforcing to alcoholics and their sons by reducing perceptual reactivity, stimulus augmentation, muscle tension, and ANS hyperreactivity. It appears that consumption of alcohol may be adaptive for these individuals at least in the short term. Ludwig, Cain, and Wikler (1977) found that alcoholics who were augmenters worked harder for alcohol than those who

were normalizers or reducers, and there is evidence that cognitive functioning may also be positively affected (S. A. Brown, Creamer, & Stetson, 1987). Brown et al. also demonstrated that adolescents with positive family histories for alcoholism expect enhanced cognitive and motor functioning from alcohol to a significantly greater degree than alcohol-abusing adolescents without a positive family history. Finally, at-risk individuals appear to be less sensitive to the debilitating short-term effects of alcohol ingestion, including decreased subjective levels of intoxication.

The model also predicts that hyperactive and conduct-disordered individuals who express hyperactivity are at risk for alcoholism and for the abuse of depressant drugs. Follow-up studies in the late adolescence or early adulthood of individuals diagnosed in childhood as hyperactive generally reflect an increased prevalence of substance abuse, antisocial behavior, and conduct disorder that is independent of stimulant treatment effects (Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Hoy, Weiss, Minde, & Cohen, 1978; Milich & Loney, 1979). One study (Blouin, Bornstein, & Trites, 1978) and the conclusion of a review on the topic (Kramer & Loney, 1982) have indicated these individuals are more likely to use alcohol. Interestingly, these individuals are also significantly less likely to use hallucinogens (Weiss, Hechtman, Perlman, Hopkins, & Wener, 1979). However, such research requires the use of psychiatric rather than normal control groups (Thorley, 1984) and results of studies that employ such a strategy suggest that there may be a general increase in the likelihood of drug and conduct problems in many children of diagnosed psychiatric populations (White, Barratt, & Adams, 1979).

In all likelihood our model does not account for the long-term effects of heavy alcohol consumption, which may in fact potentiate the patterns of cognitive dysfunction and psychophysiological hyperactivity that lead high-risk subjects to use alcohol to begin with. Alcohol abuse has a myriad of negative social and physiological consequences. The former may add to the problems of potential alcoholics by alienating them from personal and social systems that aid in the maintenance of adaptive behavior, and the latter may lead to further difficulties in the regulation of behavior. Harper, Kril, and Daly (1987) have

provided documentation supporting a phenomenon previously suspected by clinicians. Their quantitative neuropathological tests showed that the brains of alcoholics had significantly fewer cortical neurons in the superior frontal cortex than did the brains of controls, although the number of neurons in the motor cortex did not differ significantly. Alcohol abuse may cause this pattern of deterioration. Alternatively, this cortical deficiency may precede the development of alcoholism and may be etiologically significant.

In summary, the model proposed in this paper seems to fit the facts, as they are presently known, about the inherited predisposition to the development of alcoholism. However, the facts themselves are meager in quantity and are often difficult to synthesize. Little is known in detail about the proper function of neurochemical and neurophysiological systems, or about the interrelationship of these systems and their causal interaction with personality and temperament or with behavior in general. In addition, there is no incontrovertible evidence at the structural level of analysis for the existence of neurological abnormalities in the high-risk population. Finally, our statements about the relationship between prefrontal function and the role of culture in governing behavior in the individual are still conjectural, and the structures underlying verbal behavior and behavioral inhibition have not been identified with certainty. Nonetheless, the model is plausible, is somewhat general, and deserves to be disproved.

References

- Adrian, M. (1984). *Statistics on alcohol and drug use in Canada and other countries* (Vols. 1 and 2). Toronto: Addiction Research Foundation.
- Amit, Z., Sutherland, E. A., Gill, K., & Ogren, S. O. (1984). Zimelidine: A review of its effects on ethanol consumption. *Neuroscience & Biobehavioral Reviews*, 8, 35-54.
- Austin, G. A. (1985). *Alcohol in western society from antiquity to 1800*. Oxford, England: Clio Press.
- Ballenger, J. C., Goodwin, F. K., Major, L. F., & Brown, G. L. (1979). Alcohol and central serotonin metabolism in man. *Archives of General Psychiatry*, 36, 224-227.
- Begleiter, H., Porjesz, B., Chou, C. L., & Aunon, J. I. (1983). P3 and stimulus incentive value. *Psychophysiology*, 20, 95-101.
- Blouin, A. G., Bornstein, R. A., & Trites, R. L. (1978). Teenage alcohol use among hyperactive children: A

- five year follow-up study. *Journal of Pediatric Psychology*, 3, 188-194.
- Borg, S., Kvande, H., Liljeberg, P., Mossberg, D., & Valverius, P. (1985). 5-Hydroxyindoleacetic acid in cerebrospinal fluid in alcoholic patients under different clinical conditions. *Alcohol*, 2, 415-418.
- Brown, G. L., Ballenger, J. C., Minichiello, M. D., & Goodwin, F. K. (1979). Human aggression and its relationship to cerebrospinal fluid 5-hydroxyindoleacetic acid, 3 methoxy-4-hydroxyphenylglycol, and homovanillic acid. In M. Sandler (Ed.), *Psychopharmacology of aggression* (pp. 131-148). New York: Raven Press.
- Brown, G. L., Goodwin, F. L., Ballenger, J. C., Goyer, P. F., & Major, L. F. (1979). Aggression in humans: Correlates with cerebrospinal fluid amine metabolites. *Psychiatry Research*, 1, 131-410.
- Brown, G. L., Ebert, M. H., Goyer, P. F., Jimerson, D. C., Klein, W. J., Bunney, W. E., & Goodwin, F. K. (1982). Aggression, suicide, and serotonin: Relationship to CSF amine metabolites. *American Journal of Psychiatry*, 139, 741-746.
- Brown, R. A., & Cutter, H. S. G. (1977). Alcohol, customary drinking behavior and pain. *Journal of Abnormal Psychology*, 86, 179-188.
- Brown, S. A., Creamer, V. A., & Stetson, B. A. (1987). Adolescent and alcohol expectancies in relation to personal and parental drinking patterns. *Journal of Abnormal Psychology*, 96, 117-121.
- Buchsbaum, M. S. (1974). Average evoked responses and stimulus intensity in identical and fraternal twins. *Physiology and Psychology*, 2, 365-370.
- Buchsbaum, M. S., & Ludwig, A. M. (1978). Effects of sensory input and alcohol administration on visual evoked potentials in normal subjects and alcoholics. In H. Begleiter (Ed.), *Biological effects of alcohol* (pp. 561-571). Proceedings of the International Symposium on Biological Research in Alcoholism, Zurich, Switzerland. New York: Plenum Press.
- Caspers, H. (1958). Die beeinflussung der corticalen krempfesregarkein durchdas aufsteigende Reticularsystem des Hirnstammes. II Narkose-wirkungen. *Zeitschrift fur die Gesamte Experimentelle Medizin* *Enschliesslich Experimentelle Chirurgie*, 129, 582-600.
- Cloninger, C. R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science*, 23, 410-415.
- Coopersmith, S., & Woodrow, K. (1967). Basal conductance levels of alcoholics and alcoholics. *Quarterly Journal of Studies on Alcohol*, 28, 27-32.
- Damasio, A. R. (1985). The frontal lobes. In K. Hellman & E. Valenstein (Eds.), *Clinical neuropsychology* (2nd ed.) (pp. 339-375). New York: Oxford University Press.
- Daoust, M., Chretien, P., Moore, N., Saligaut, C., Lhuintre, J. P., & Boismare, F. (1985). Isolation and striatal (3H) serotonin uptake: Role in the voluntary intake of ethanol by rats. *Pharmacology Biochemistry & Behavior*, 22, 205-208.
- Duncan-Johnson, C. C., & Donchin, E. (1977). Quantifying surprise: The variation of event-related potentials with subjective probability. *Psychophysiology*, 14, 456-467.
- Edwards, G. (1982). *The treatment of drinking problems*. New York: McGraw-Hill.
- Endicott, J., Andreasen, N., & Spitzer, R. L. (1975). *Family history research diagnostic criteria*. New York: Biometrics Research, New York State Psychiatric Institute.
- Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbances of higher cognition after bilateral frontal lobes ablation: Patient E.V.R. *Neurology*, 35, 1731-1741.
- Finn, P. R., Martin, J. B., & Pihl, R. O. (1987). Alexithymia in males at high genetic risk for alcoholism. *Psychotherapy and Psychosomatic Illness*, 47, 18-21.
- Finn, P. R., & Pihl, R. O. (1987). Men at high risk for alcoholism: The effects of alcohol on cardiovascular response to unavoidable shock. *Journal of Abnormal Psychology*, 96, 230-236.
- Finn, P. R., & Pihl, R. O. (1988). Risk for alcoholism: A comparison between two different groups of sons of alcoholics on cardiovascular reactivity and sensitivity to alcohol. *Alcoholism: Clinical and Experimental Research*, 12, 742-747.
- Finn, P. R., Zeitouni, N. C., & Pihl, R. O. (in press). The effects of alcohol on psychophysiological hyperreactivity to non-aversive and aversive stimuli in men at high risk for alcoholism. *Journal of Abnormal Psychology*.
- Garfield, Z. H., & McBrearty, J. F. (1970). Arousal level and stimulus response in alcoholics after drinking. *Quarterly Journal of Studies on Alcohol*, 31, 832-838.
- Gittelman, R., Mannuzza, S., Shenker, R., & Bonagura, N. (1985). Hyperactive boys almost grown up: I. Psychiatric status. *Archives of General Psychiatry*, 42, 937-947.
- Grant, A. D., & Berg, E. A. (1948). A behavioural analysis of degree of reinforcement and ease of shifting to new responses in a weigl-type card-sort. *Journal of Experimental Psychology*, 38, 404-411.
- Gray, J. A. (1982). *The neuropsychology of anxiety: An enquiry into the junction of the septal-hippocampal system*. Oxford: Oxford University Press.
- Grings, W. W., & Dawson, M. E. (1978). *Emotions and bodily responses*. New York: Academic Press.
- Halgren, E., Squires, N. K., Wilson, C. L., Rohrbaugh, J. W., Babb, T. L., & Crandell, P. H. (1980). Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science*, 210, 803-805.
- Harper, D., Kri, J., & Daly, J. (1987). Alcoholic brain degeneration. *British Medical Journal*, 294, 534-536.
- Harvey, J. A., & Yager, L. (1972). Relationship be-

- tween telencephalic content and pain sensitivity in the rat. *Pharmacology Biochemistry & Behavior*, 10, 657-661.
- Harwood, H. J., Napolitano, D. M., & Kristiansen, H. (1984). *Economic cost to society of alcohol and drug abuse and mental illness: 1980*. Triangle Park, NC: Research Triangle Institute.
- Hastings, J. E., & Barkley, R. A. (1978). A review of psychophysiological research with hyperkinetic children. *Journal of Abnormal Child Psychology*, 6, 413-447.
- Hoy, E., Weiss, G., Minde, K., & Cohen, N. (1978). The hyperactive child at adolescence: Cognitive, emotional and social functioning. *Journal of Abnormal Child Psychology*, 6, 311-324.
- Hyatt, M. C., & Tyce, G. M. (1985). The effects of ethanol on the efflux and release of norepinephrine and 5-hydroxytryptamine from slices of rat hypothalamus. *Brain Research*, 337, 255-262.
- Johansson, F., & von Knorring, L. (1979). A double-blind controlled study of a serotonin uptake inhibitor (Zimelidine) versus placebo in chronic pain patients. *Pain*, 7, 69-78.
- Kamerow, D. B., Pincus, H. A., & Mac Donald, D. J. (1986). Alcohol abuse, other drug abuse, and mental disorders in medical practice. *Journal of the American Medical Association*, 255, 4-7.
- Kantak, K. M., Hegstrand, L. R., Whitman, J., & Eichelman, B. (1980). Effects of dietary supplements and a tryptophan-free diet on aggressive behavior in rats. *Pharmacology Biochemistry & Behavior*, 12, 173-180.
- Kiloh, L. G., & Osselton, J. W. (1961). *Clinical electroencephalography*. London: Butterworths.
- Kramer, J., & Loney, J. (1982). Childhood hyperactivity and substance abuse: A review of the literature. *Advances in Learning and Behavioral Disabilities*, 1, 225-259.
- Kuriyama, K., Kanmori, K., & Yoneda, Y. (1984). Preventive effect of alcohol against stress-induced alteration in content of monoamines in brain and adrenal gland. *Neuropharmacology*, 23, 649-654.
- Li, T. K., Lumeng, L., McBride, W. J., Waller, M. B., & Murphy, J. M. (1986). Studies on an animal model of alcoholism. *National Institute of Drug Abuse Research Monograph Series*, 66, 41-49.
- Ludwig, A. M., Cain, R. B., & Wikler, A. (1977). Stimulus intensity modulation and alcohol consumption. *Journal of Studies on Alcohol*, 38, 2049-2056.
- Lukas, S. E., Mendelson, J. H., Benedikt, R. A., & Jones, B. (1986). EEG alpha activity increases during transient episodes of ethanol-induced euphoria. *Pharmacology Biochemistry & Behavior*, 25, 889-895.
- Luria, A. R. (1980). *Higher cortical functions in man*. Moscow: Moscow University Press.
- Martin, J. B., & Pihl, R. O. (1986). Influence of alexithymic characteristics on physiological and subjective stress responses in normal individuals. *Psychotherapy and Psychosomatic Illness*, 45, 66-77.
- McBride, W. J., Murphy, J. M., Lumeng, L., & Li, T. K. (1986). Effects of ethanol on monoamine and amino acid release from cerebral cortical slices of the alcohol-preferring P line of rats. *Alcoholism: Clinical and Experimental Research*, 10, 205-208.
- Messing, R. B., Fisher, L. A., Phebus, L., & Lytle, L. D. (1976). Interaction of diet and drugs in the regulation of brain 5-hydroxyindoles and the response to painful electric shock. *Life Sciences*, 18, 707-714.
- Milich, R., & Loney, J. (1979). The role of hyperactive and aggressive symptomatology in predicting adolescent outcome among hyperactive children. *Journal of Pediatric Psychology*, 4, 93-112.
- Miller, W. R., & Hester, R. K. (1986). Inpatient alcoholism treatment: Who benefits? *American Psychologist*, 41, 794-805.
- Murphy, W. J., McBride, W. J., Gatto, L., Lumeng, L., & Li, T. K. (1988). Effects of acute ethanol administration on monoamine and metabolite content in forebrain regions of ethanol-tolerant and -nontolerant alcohol-preferring (P) rats. *Pharmacology Biochemistry & Behavior*, 29, 169-174.
- Murphy, J. M., McBride, W. J., Lumeng, L., & Li, T. K. (1982). Regional brain levels of monoamines in alcohol-preferring and nonpreferring lines of rats. *Pharmacology Biochemistry & Behavior*, 16, 145-149.
- Murphy, J. M., McBride, W. J., Lumeng, L., & Li, T. K. (1987). Contents of monoamines in forebrain regions of alcohol-preferring (P) and nonpreferring (NP) lines of rats. *Pharmacology Biochemistry & Behavior*, 26, 389-392.
- Naranjo, C. A., Sellers, E. M., & Lawrin, M. O. (1986). Modulation of ethanol intake by serotonin uptake inhibitors. *Journal of Clinical Psychiatry*, 47 (Suppl. 4), 16-22.
- Naranjo, C. A., Sellers, E. M., Roach, C. A., Woodley, D. V., Sanchez-Craig, M., & Sykora, K. (1984). Zimelidine-induced variations in alcohol intake by non-pressed heavy drinkers. *Clinical Pharmacological Therapy*, 35, 374-381.
- Naranjo, C. A., Sellers, E. M., Sullivan, J. T., Woodley, D. V., Kaldec, K., & Sykora, K. (1987). The serotonin uptake inhibitor Citalopram attenuates ethanol intake. *Clinical Pharmacological Therapy*, 41, 266-274.
- Nathan, P. (1987). *Prevention and early intervention: Current research*. Paper delivered at the Fourth International Conference on Treatment of Addictive Behaviors, Oslo, Norway.
- Nauta, W. J. H. (1971). The problem of the frontal lobe: A reinterpretation. *Psychiatric Research*, 8, 167-187.

- Ohga, N. (1962). Electroencephalographic studies on alcoholic intoxication in rabbits. *Japanese Journal of Legal Medicine*, 16, 196-213.
- Okada, Y. C., Kaufman, L., & Williamson, S. J. (1983). The hippocampal formation as a source of the slow endogenous potentials. *Electroencephalography and Clinical Neurophysiology*, 55, 417-426.
- Perrin, R. G., Hockman, C. H., Kalant, H., & Livingston, K. E. (1974). Acute effects of ethanol on spontaneous and auditory evoked electrical activity in cat brain. *Electroencephalography and Clinical Neurophysiology*, 36, 19-31.
- Peterson, J., Rothfleisch, J., Zelazo, P., & Pihl, R. O. (in press). Acute alcohol intoxication and cognitive functioning. *Journal of Studies on Alcohol*.
- Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal and temporal lobe lesions in man. *Neuropsychologica*, 20, 249-262.
- Petrie, A. (1978). *Individuality in pain and suffering* (2nd ed.). Chicago: University of Chicago Press.
- Pihl, R. O., Peterson, J., & Finn, P. (in press). The inherited predisposition to alcoholism: Characteristics of sons of male alcoholics. *Journal of Abnormal Psychology*.
- Pihl, R. O., & Spiers, P. (1978). Individual characteristics in the etiology of drug abuse. *Progress in Experimental Personality Research*, 8, 93-195.
- Pollock, V. E., Volavka, J., Goodwin, D. W., Mednick, S. A., Gabrielli, W. F., Knop, J., & Schulsinger, F. (1983). The EEG after alcohol administration in men at risk for alcoholism. *Archives of General Psychiatry*, 40, 857-861.
- Porjesz, B., Begleiter, H., & Samuelly, I. (1980). Cognitive deficits in chronic alcoholics and elderly subjects assessed by evoked brain potentials. *Acta Psychiatrica Scandinavia*, 62(Suppl. 286), 15-29.
- Propping, P. (1977). Genetic control of ethanol action of the central nervous system: An EEG study in twins. *Human Genetics*, 35, 309-334.
- Roth, W. T., Pfefferbaum, A., Horvath, T. B., Berger, P. A., & Koppel, B. S. (1980). P3 reduction in auditory evoked potentials of schizophrenics. *Electroencephalography and Clinical Neurophysiology*, 49, 497-520.
- Schalling, D., Asberg, M., & Edman, G. (1985). *Personality and neurochemical risk factors for disinhibiting psychopathology*. Paper presented at the IV International Congress of Biological Psychiatry, Philadelphia, PA.
- Seltzer, S., Stoch, R., Marcus, R., & Jackson, E. (1982). Alteration of human pain thresholds by nutritional manipulation and L-tryptophan supplementation. *Pain*, 13, 385-393.
- Simons, R. F. (1982). Physical anhedonia and future psychopathology: An electrocortical continuity? *Psychophysiology*, 19, 433-441.
- Stewart, S. H., Finn, P. R., & Pihl, R. O. (1989). *The effects of alcohol on the cardiovascular stress in men at high genetic risk for alcoholism: A dose response study*. Paper presented at the Canadian Psychological Association, Halifax, Nova Scotia.
- Tarter, R. E., Alterman, A. O., & Edwards, K. L. (1985). Vulnerability to alcoholism in men: A behavior-genetic perspective. *Journal of Studies on Alcohol*, 46, 329-356.
- Tarter, R. E., Hegedus, A. M., Goldstein, G., Shelly, C., & Alterman, A. I. (1984). Adolescent sons of alcoholics: Neuropsychological and personality characteristics. *Alcoholism: Clinical and Experimental Research*, 8, 216-222.
- Telner, J., Lepore, F., & Guillemot, J. P. (1979). Effects of serotonin content on pain sensitivity in the rat. *Pharmacology Biochemistry & Behavior*, 10, 657-661.
- Tenen, S. S. (1967). The effects of P-chlorophenylalanine, a serotonin depletor on avoidance acquisition, pain sensitivity, and related behavior in rats. *Psychopharmacologia*, 10, 204-219.
- Thorley, G. (1984). Hyperkinetic syndrome of childhood: Clinical characteristics. *British Journal of Psychiatry*, 144, 16-24.
- Tueting, P., Sutton, S., & Zubin, J. (1971). Quantitative evoked potential correlates of the probability of events. *Psychophysiology*, 7, 385-394.
- von Knorring, L. (1982). Effect of imipramine and zimelidine on the augmenting-reducing response of visual evoked potentials in healthy volunteers. *Advances in Biological Psychiatry*, 9, 81-86.
- von Knorring, L., & Johansson, F. (1980). Changes in the augments-reducer tendency and in pain measures as a result of treatment with a serotonin reuptake inhibitor—Zimelidine. *Neuropsychobiology*, 6, 313-318.
- von Knorring, L., & Ferris, C. (1981). Biochemistry of the augmenting-reducing response in visual evoked potentials. *Neuropsychobiology*, 7, 1-8.
- Walsh, K. W. (1978). *Neuropsychology: A clinical approach*. London: Churchill, Livingstone.
- Weiss, G., Hechtman, L., Perlman, T., Hopkins, J., & Wener, A. (1979). Hyperactives as young adults: A controlled, prospective ten year follow-up of 75 children. *Archives of General Psychiatry*, 6, 675-681.
- White, J., Barratt, E., & Adams, P. (1979). The hyperactive child in adolescence. *Journal of the American Academy of Child Psychiatry*, 18, 154-159.
- Young, S. N., Pihl, R. O., & Ervin, F. R. (1986). The effect of altered tryptophan levels on mood and behavior in normal human males. *Clinical Neuropharmacology*, 9(Suppl. 4), 516-518.
- Zhukov, V. N., Varkov, A., & Burov, I. V. (1985). Effect of the destruction of the brain serotonergic system on the alcohol consumption by rats in the early periods of alcoholism. *Bulletin Eksperimentalnoi Biologii i Meditsiny*, 99, 576-577.