REVIEW PAPERS

Alcoholism: The Role of Different Motivational Systems

Robert O Pihl, PhD[1], Jordan B Peterson, PhD[2]

[1]Departments of Psychology and Psychiatry, McGill University, Montreal, Quebec, Canada

[2]Department of Psychology, Harvard University, Boston, Massachusetts, USA

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Individuals use and misuse alcohol (and other drugs) because of the pharmacologically mediated effects these substances have on the operation of 4 psychobiological systems, mediating response to motivationally relevant unconditioned and conditioned stimuli. These 4 systems have unique neuroanatomical structure, biochemical modes of operation, association with affect, behavior and cognition, and responsiveness to drugs of abuse. Individual variation in the operation of these systems determines individual susceptibility to initiation and maintenance of drug use and abuse. Sources of such variation differ, in a vitally important fashion, in various specific populations of individuals at heightened risk for drug abuse. Nonalcoholic sons of male alcoholics, with multigenerational family histories of male alcoholism, appear to be at heightened risk for the development of alcohol abuse because alcohol eliminates their heightened response to threat, and because they are hypersensitive to ethanol's psychomotor stimulant effects. Anxiety-sensitive individuals also appear attracted to alcohol for its anxiolytic properties. Many other important sources of idiosyncratic variability exist. Detailed analysis of such sources may lead to the development of more effective prevention and treatment programs.

Key Words: alcoholism, risk factors, etiology, treatment

INTRODUCTION

Alcohol consumption has decreased slightly in recent years (Eliany 1989; Dufour 1995), predictably, because the population is aging, and older people tend to drink less. Prevalence rates for alcohol problems peak between the ages of 18 and 29 (Fillmore and Midanik 1984). However, rates of alcohol-use-related forms of psychopathology (abuse and dependence) have not declined (although fewer people are driving while intoxicated (Hasin et al 1988)), and still constitute the most or second most common form of psychiatric disorder, in terms of lifetime prevalence (Helzer and Pryzbeck 1988; Kessler et al 1994). In light of the high base rate of occurrence, it is surprising that alcoholism, associated critically with the development of many other serious disorders of physical, psychological and interpersonal health, is consistently misdiagnosed — or not diagnosed at all — and left untreated (Nathan 1987; Moore et al 1989). Even Alcoholics Anonymous, ubiquitous in location and brand

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Address reprint requests to: Dr RO Pihl, Department of Psychology, McGill University, 1205 Dr Penfield Avenue, Montreal, Quebec, Canada, H3A 1B1.

recognition, attracts only about 5% of alcoholics (Emrick 1989a).

Excessive alcohol consumption detrimentally affects every physiological and psychological system, which dramatically increases the risk for a surfeit of diseases and disorders, ranging from the trivial to the life-threatening (Eliany 1989; Dufour and FeCaces 1993). Alcohol abuse, pervasive and pernicious, constitutes the third most serious North American health problem (Pattison and Kaufman 1982) and has additional immensely deleterious social effects. Use and misuse of the drug are implicated, for example, in approximately half of all incidents of homicide, suicide, and family violence (Murdoch et al 1990). Direct alcohol-related costs in Canada have been estimated at $5.2 billion a year (Eliany 1989); in the US, in 1990, at $98.6 billion (Rice 1993). Indirect costs are much higher. A perplexing question emerges of its own accord from consideration of this endless litany of pathological effects: why is alcoholism ignored so frequently when it is obviously so destructive? Perhaps it is because everyone, or almost everyone, consumes some alcohol. The mere pervasiveness of a problem sometimes makes it invisible. Perhaps it is because alcoholism tends to co-occur with so many other psychiatric and physiological problems. Diagnostic deference might be given to the personality, affective, or anxiety disorders, more mysterious, instrinsically rewarding, and seductive to the diagnosing professional, as they appear more theoretically explicable, and more clearly amenable to respectable and traditional treatment. Further, such disorders are often viewed as playing a causal role or being primary in the development of alcoholism. Finally, treatment for alcoholism, per se, is typically undertaken by the nonprofessional whose efforts and means of approach are seldom granted medical or psychological legitimacy, often for valid reasons.

Avoidance of diagnosis and specific treatment of alcohol abuse and dependency is likely motivated by any number of value-laden and empirical factors. One such factor, of vital importance to all directly concerned, is lack of specific knowledge of cause. Discernment of cause is difficult, as the propensity to abuse alcohol is complexly determined. A multitude of individual and social factors operate, etiologically, in isolation and combination. In this complex causal context, it is easy to overlook the contribution of the most basic of causal factors: the psychopharmacological properties of alcohol. Knowledge of such fundamental properties — with due consideration given for important individual variability — appears particularly critical to the development of a targeted treatment. Large-scale manipulation of cultural and societal variables, at the level of political intervention, which exists as the only viable alternative, is expensive, ponderous, and ineffective (even counterproductive). Equally problematic are current medical/psychological individual or group treatments, which are generally applied nonspecifically without detailed analysis of individual susceptibility, with questionable success, to a very small percentage of affected individuals (Hester and Miller 1989; Miller and Hester 1986a; Emrick 1989b; Vaillant 1983; Emrick and Hansen 1983). Unfortunately, the type of intervention an individual with an alcohol-related problem is likely to receive seems more dependent on the nature of the office he or she walks into than any personal characteristic, no matter how potentially relevant.

Calls for individualized treatment strategies targeted to relevant agents of cause and maintenance have become increasingly common (Miller and Hester 1986b; Miller 1992; Nace 1993; Garelick 1993; Donovan and Mattson 1994). However, such well-intentioned requests are likely to remain without significant impact until accompanied by a description of demonstrable, readily delineated, potentially alterable, differential, and individualized etiologies. Matching strategies that focus on patient demographics (Azrin et al 1982; Mayer and Myerson 1971) or mere severity of the problem likely do not provide a focus on factors of true etiological significance. Strategies based on analysis of comorbid pathology (McLelland et al 1983; Kadden et al 1990) or personality factors (Annis and Chan 1983) provide more specificity but still appear insufficiently detailed. In consequence, this paper focuses: 1. on the function of 4 psychobiological systems governing general motivation; 2. on the sources of individual variation in such function; and 3. on the psychopharmacological effects of ethanol, considered in the light of general motivation and its sources of variability.

The 4 psychobiological systems which provide the central subject matter of this manuscript allow for response to stimuli of innate or learned motivational significance: unconditioned punishments, which produce hurt and extinguish learned behavior; cues for punishment, or threats, which produce anxiety and inhibit ongoing behavior; unconditioned rewards or satiating agents, which produce contentment or satisfaction and facilitate or reinforce behavior; and, finally, cues for satiation (or incentives), which produce curiosity, hope and pleasure, and activate approach behavior. The central thesis of this paper is that individual difference in the operation of these 4 systems, environmentally and genetically mediated, plays an important determining role in initiation and maintenance of drug and alcohol abuse and dependence, as well as related comorbid behaviors. Each section therefore contains a relatively detailed discussion of the functioning of each system and its involvement in behaviors linked with alcohol problems.

ALCOHOL, PUNISHMENT AND THREAT

Punishment — definition and consequences

Specific behaviors frequently have consequencest that decrease the future likelihood that such behaviors will occur. These consequences are generally termed punishments. Punishments include states of deprivation (like hunger and thirst), sensory overstimulation (loud noise, bright light, tactile pressure), frustration, disappointment and involuntary social isolation. The grouping of such a diverse range of consequences under a single heading may appear surprising, and, therefore,

the rationale for doing so requires elaboration. First, the effects of contingent sensory overload or deprivation on operant behavior are well known as are those of frustration. Behavior which produces sensory overload or frustration tends to decrease in frequency of appearance. Less well understood are the effects of disappointment — defined as the absence of an expected reward — which nonetheless produce modification in affect and behavior analogous to that engendered by simple sensory overload (Gray 1982, 1987). The same can be said for the involuntary restriction of social interaction (Panksepp et al 1985). "Time out" — a behavioral technique used to shape the activity of children (and prison and other institutional inmates) — appears effective because it is punishment. Because human beings are social, they react to enforced loneliness with despair. Deprivation, overstimulation, disappointment, and loneliness all modify behavior in the same manner. It appears that the conservative processes of evolution have determined that a single complex system is responsible, in essence, for the elimination of action patterns whose consequences are counter-productive.

Pain (specifically) or hurt (more generally) constitute one class of specific affective response to punishment, and tend to accompany the punishment-induced extinction of behavior. Pain or hurt exists as the subjective response or felt effect of punishment upon behavior, and serves many functions. Pain prevents the use of damaged tissue and allows it time to heal, undisturbed. Pain serves as an aid to generalization, as a goad to memory: once hurt, twice shy. Pain, expressed in distressed gesture and vocalization, brings social aid to bear upon the individual whose behavioral resources have been exceeded, temporarily or more permanently, particularly in infancy. Punishment and consequent hurt might be considered a necessary precondition to learning: old and no longer adaptive, or new and stupid behavior must be eradicated before appropriate action patterns may be generated in replacement. All such elimination, however, is not necessarily good; inappropriate generalization from punishment, extant as a consequence of the ability to abstract, might be considered to constitute depression, a condition characterized by constant hurt, in which entire classes of behavior, adaptive and maladaptive, disappear.

Anger constitutes a second class of emotional reaction to punishment (Gray 1987), and tends to accompany punishment-induced or defensive expression of aggression, manifested in behavioral patterns designed to punish or threaten. A hurt creature fears and hates the agent that is causing it pain, and inhibits behavior in the presence of that agent. However, too much inhibition is sometimes inappropriate, as a thoroughly cowed creature may be made subject to even more punishment. Anger and aggression are responses to punishment that allow someone who is hurt to rise above his or her fear by lashing out dangerously in order to eliminate potentially the frightening source of pain itself.

The endogenous opioid system appears integrally, although not exclusively, concerned with mediating fundamental affective, cognitive, and behavioral responses to punishment, although other such systems (like those that use epinephrine, serotonin, and dopamine) play important roles. Evidently involved in reaction to sensory overload and food/water deprivation (hence the analgesic and anorexic effects of morphine and heroin), the opioid system also partially governs interpersonal attachment — and the consequence of attachment-disruption (Herman and Panksepp 1978) — as well as responses to frustration and the absence of expected reward (Panskepp et al 1985; Gray 1982, 1987). This odd connection appears to exist, in part, because of the nature of the tactile sense, which simultaneously protects organisms from deadly contact with the dangers of the external world and allows positive human contact to take place. Human affiliation is most fundamentally, although not exclusively, dependent upon touch — maternal, friendly, sexual, reassuring, comforting. The process of affiliation that attaches mother to child (and lovers together as well), for example, serves to protect vulnerable individuals (infants, in particular) from physiological and psychological destruction. The circuitry underlying capacity for affiliation, which allows touch-mediated analgesia to take place, is phylogenetically ancient and relatively mature in the neonate (Valzelli 1981). Hence, the ability of the presence of the mother to soothe the hurts of the child, and for one adult to comfort another. Involuntary withdrawal of such affiliation (i.e., grief) produces affect and behavior strongly reminiscent of those induced by deprivation, frustration, disappointment, sensory overload (and opiate withdrawal (Herman and Panskepp 1978)) and, like other punishers, produces lacrimation (tears), distress vocalization (crying), withdrawal, aggression (Fox and Davidson 1987), and, in more extreme cases, depression (Bowlby 1969).

An appropriate balance of love-related deactivation and social isolation-induced activation of pain circuitry appears vital to healthy maturation (Najam and Panksepp 1989). What precisely constitutes this proper balance appears to be determined by many factors, including the developmental stage of the individual in question, duration of isolation (McKinney 1985), and manner in which separation is initiated (Robertson and Robertson 1971). A delicate interrelationship appears to exist between opiate production in the maternal presence or its functional equivalent, and opiate withdrawal in her absence. Infants whose access to their mother has been involuntarily restricted complain vociferously, at least in the early stages of isolation. If contact is not re-established in some variable critical time period, they cease protesting, and withdraw (Bowlby 1969; Robertson and Robertson 1971). After such withdrawal, infants are often resistant to re-establishment of close contact, as if their trust has been broken. In extreme, desperate cases, they cease seeking conspecific contact, and may die, apparently as a consequence of gastrointestinal failure (Bowlby 1969). This specific pattern of reaction to enforced isolation is not always limited to infants. Adults are evidently similarly susceptible after the death or disappearance of someone close. Destruction of close social ties often precedes the onset of nonbipolar adult-onset depression, a condition to which

individuals who experienced extreme loss in childhood appear particularly vulnerable (McKinney 1985).

It appears possible (although far from established, particularly in detail) that the first stages of loneliness or grief produce a state of neuropharmacological affairs similar to that induced by opiate withdrawal in addicts. Prolonged isolation, by contrast, perhaps reverses the process, overwhelming the organism with endogenous opiates, restricting need for and effect of social contact. The proper amount of voluntary separation enhances development, while excess separation restricts growth. Morphine administration reduces social distress (Knowles et al 1987) which seems to be a positive occurrence, but rat pups regularly administered morphine develop slowly compared to their peers (Najam and Panksepp 1989). Conversely, treatment with naloxone (an opiate antagonist) increases maternal deprivation-induced distress behavior and can induce such distress in nondeprived animals (Knowles et al 1987), but rat pups treated with naloxone develop more quickly (Najam and Panksepp 1989). Furthermore, regular massage (an effective form of tactile stimulation, opiate-mediated in its effects) facilitates weight gain and neurological development among premature babies (Scafidi et al 1986; Scafidi et al 1990), and the pathological effects of maternal deprivation on rat pups can be convincingly duplicated through administration of beta-endorphin (Greer et al 1991). The picture is complicated in detail, but clarified in general, by studies demonstrating brief, 5-minute isolation-induced analgesia in 10-day-old rat pups, and potentiation of morphine-analgesia by such isolation (Kehoe and Blass 1986). The precise dose and time-course effects of isolation and other forms of aversive stimulation on opiate function (and the dose and time-course effects of opiates upon reaction to punishment in general), and the effects of developmental stage or level of maturity on these interactions have not yet been clearly specified. What seems clear, however, is the fact of mediation of response to punishment by the endogeneous opiate system.

The effects of opiates: the relief of pain and negative reinforcement

Animals and humans will work to avoid punishment. Furthermore, the absence of an expected punishment serves as an effective, unconditioned reinforcer — a primary reward. From this fundamental perspective, the reinforcing effects of opiates can be profitably considered. Psychoactive drugs that deactivate the pain system produce learning, which is an enhanced tendency to use the deactivating drug, at least under the conditions where the learning took place. Analgesic drugs — most effectively, opiates — reduce the ability of punishment to extinguish previously rewarded behavior. Drugs which reduce the effects of punishment appear profoundly negatively reinforcing to animals and to people suffering from, or perhaps particularly sensitive to, such effects. Opiates reduce pain, and should therefore prove differentially reinforcing to those in pain.

It is interesting to note, in this regard, that Panksepp et al (1985) have reviewed evidence for correspondence between the psychodynamic and neurochemical processes contributing to social bonding, disruption of such, and opiate addiction; that neurolinguistic analysis has revealed opiate addict substitution of opiate use for normal sources of social gratification (Tokar et al 1975); and that depression is statistically more common among relatives of opiate addicts than among members of the general population (Rounsaville et al 1991). It is also interesting that milk and sugar (most generally administered by mothers to their infants, enhancing social bonding) also have analgesic properties. Rat pups administered milk orally are characterized by reduced postadministration frequency of isolation-induced distress vocalizations, and enhanced resistance to hot-plate pain testing, effects that appear opiate-mediated (Blass and Fitzgerald 1988). Similar results may be produced by corn oil (a fat) and polycose (a polysaccharide (Shide and Blass 1989)). Sucrose appears highly effective as a surgical analgesic for (Blass and Hoffmeyer 1991), and produces rapid behavioral calming of, human infants (Smith et al 1990), as well — effects that have also been attributed to sucrose effects on opiate function, which can be blocked by naltrexone (Blass et al 1987).

The analgesic properties of opiates appear due, in part, to their psychomotor stimulant properties (Wise 1988) and, additionally, to their operation in areas of the brain such as the periaqueductal gray (Panksepp et al 1985), which appears involved in mediation of pain. For example, it is the case that administration of naloxone produces withdrawal symptoms in rats previously exposed to chronic morphine treatment of the periaqueductal gray (Koob and Bloom 1988). These analgesic properties may increase the likelihood to self-administer opiates in the initial stages of drug use, especially for those suffering from the affective and behavioral consequences of exposure to punishment. They almost certainly play a role in maintaining that use, once abstinence-induced withdrawal symptoms have become evident.

Limited, constant, low-level access to endogeneous opioids produces stable patterns of intake among experimental animals. Such animals do not develop tolerance and, once opiate-deprived, do not appear characterized by physical dependence. By contrast, unlimited access inevitably produces high levels of tolerance, leads to increased intake, and to withdrawal upon deprivation. Adaptive changes at relevant opioid receptor sites produce tolerance. Constant long-term adminstration of exogeneous opioid produces reduction in attendant euphoria, reduced desire for social contact, apathy, and interference with gastrointestinal function (Thomason and Dilts 1991) (a symptom pattern strongly reminiscent, once again, of the despair-stage infant). Acute opiate withdrawal, by contrast, produces symptomatology analogous to that produced by punishment: crying and distress vocalization, withdrawal, aggression and depression (Herman and Panksepp 1978), as well as severe muscle pain, gastrointestinal cramps, and diarrhea (Koob and Bloom 1988). The severity of this symptom pattern varies as a function of the speed with which the exogenous opiate agents leave, or are prevented from acting at, the relevant receptor site (Thomason and Dilts 1991). Over a longer period of time,

the now-abstinent addict may suffer from seriously disturbed sleep patterns, preoccupation with physical discomfort and pain, subjective sensations of reduced worth, and intolerance for stress (Thomason and Dilts 1991) — symptomatology markedly reminiscent of severe depression. Re-administration of opiate immediately eliminates withdrawal symptoms. This relief serves, in potential, as a potent source of negative reinforcement, further increasing the likelihood of future use.

Alcohol preference and the opiate system

Some of alcohol's reinforcing effects may be opiate-system mediated, either directly, thus determining alcohol preference and related responses (George et al 1991) as a consequence of alcohol-induced changes in serotonergic function (Blum and Payne 1991), or through the effects of opioid-like ethanol-metabolism byproducts (Altshaler et al 1990; Blum and Payne 1991). Deficient endogenous opioid activity, in general, has been linked to alcohol-preferring in animals (George et al 1991). Gionoulakis and Gupta (1985) have shown that C57BL/6J alcohol-preferring mice are characterized by lower pain threshold than DBA/2 mice. Administration of an opiate agonist increases this threshold within, and decreases voluntary alcohol consumption among, such mice. Similar decreases in consumption can be produced by treatment designed to increase the synaptic half-life of endogenous enkephalins (George et al 1991). In the human population, ethanol intake appears to alter separation-induced despair symptomatology among adults in a dose-dependent manner — moderate doses ameliorate, and higher doses facilitate, such despair (McKinney 1985). This effect is likely blood-alcohol curve-dependent as well, with amelioration during the ascending and facilitation during the descending limb.

Support for the notion of a relationship between alcohol's reinforcing effect and activity in the endogeneous opioid system can also be derived from double-blind, placebo-controlled clinical trials of naltrexone on alcoholics (Volpicelli et al 1993; O'Malley et al 1993). In these studies naltrexone reduced ethanol volume consumed per drinking occasion, ethanol-related craving, and subjective ethanol-induced "high". We have evidence suggesting that nonalcoholic sons of male alcoholics (SOMAs) with multigenerational family histories (MFH) of alcoholism are hyper-reactive to painful stimuli (see Figure 1). We also have preliminary evidence that pain ratings for young adolescent SOMAs and a control group (nonalcoholic age-matched adolescents with no family history of alcoholism in the preceding 2 generations) participating in a session of pressure algometry — a nonanxiety-provoking pain-generating technique involving mild pressure applied to a single digit of each hand — are more pain sensitive. A subpopulation of conduct-disordered boys also appears characterized by abnormalities in response to pain. (Seguin et al, forthcoming). We have also recently reported that SOMAs and controls characterized by ethanol-induced heart-rate acceleration also manifest a highly significant increase at peak BAL of plasma beta-endorphin (Peterson et al, unpublished manuscript). Gianoulakis has previously reported increased production of beta-endorphin, in general, among MFH SOMAs after ethanol consumption (Gianoulakis et al 1989). This has been replicated recently, accompanied by evidence for a correlation of 0.91 between BAL and plasma-endorphin level in such subjects (as compared to 0.26 for FH-controls).

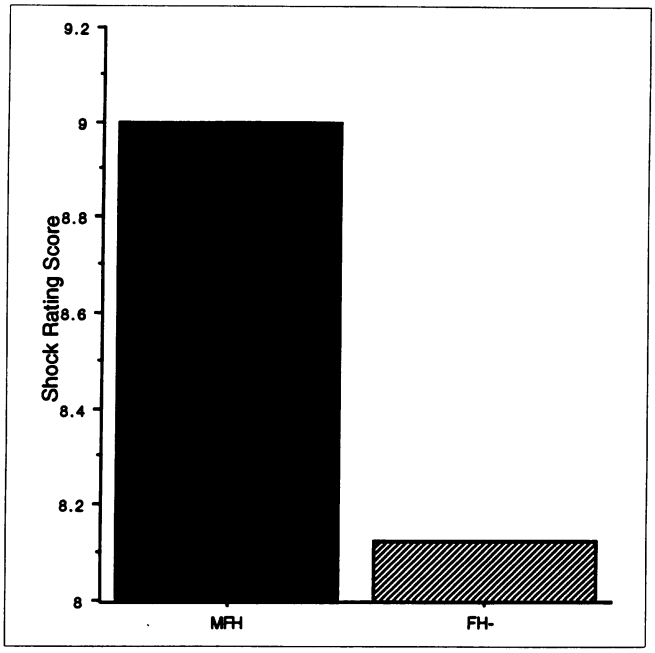

Figure 1. Pain sensitivity ratings to electric shock by multigenerational sons of male alcoholics (MFH) (n = 39) and family history negative subjects (FH-) (n = 42); ($p < 0.01$). (Study reported in Stewart et al 1995.)

Factors potentially affecting the ethanol-opiate connection

Depression is one of the most common psychiatric conditions (McGuffin and Katz 1989a), and frequently co-occurs with alcoholism. Sixteen recently-reviewed studies determined that up to 53% of hospitalized alcoholics qualified for diagnosis of depression (Merikangas and Gelernter 1990). Large-scale epidemiological studies, however, reveal substantially reduced association (Helzer and Pryzbeck 1988). Alcoholics in the general population are twice as likely to be manic and 1.7 times as likely to be severely depressed as nonalcoholics (Helzer and Pryzbeck 1988). The precise nature of the alcoholism-depression relationship has not yet been specified, however, and some authors have hypothesized that the 2 disorders are independent (Schuckit 1986; Merikangas and Gelernter 1990).

The most powerful evidence that depression plays a causal role in alcoholism can perhaps be derived from studies of women. Depression is more common among women than

men (McGuffin and Katz 1989a); in fact, twice as common, according to ECA data (Helzer and Pryzbeck 1988). Hartka et al's (1991) meta-analysis of 8 general population longitudinal studies determined that early depression predicts later alcohol consumption, particularly for women. Similarly, Helzer and Pryzbeck (1988) suggested that 66% of women suffering from alcoholism were depressed prior to becoming alcoholic, whereas alcoholism preceded depression for 78% of affected men.

Depressed females often come from alcoholic or depressed families. Such familial association appears determined in part by genetic factors, particularly in more severe cases (McGuffin and Katz 1989a, 1989b). Kendler et al's (1992) recent study of 1033 female twin pairs who had been interviewed demonstrated that genetic factors appear to play a substantial role in determining risk for depression among women (heritability estimated at 21% to 45%, dependent upon definition of depression). Winokur (1982) described "depression spectrum disease", a co-occurrence of alcoholism, ASP and depression. Males are generally characterized by the first 2 disorders, and females by the third. Recently, Winokur and Coryell (1991) completed a 5-centre collaborative study which examined the familial relationships between depression and alcoholism. These authors interviewed 723 relatives of 326 primarily unipolar depressives and 469 demographically-matched controls. Male alcoholism was significantly more common among relatives of depressed women than relatives of depressed men. However, the authors were unable to determine whether this effect was genetic, environmental or both. The single adoption study examining this issue suggested that the relationship between depression and familial alcoholism in women depended on family environment (Goodwin et al 1977). Berkowitz and Perkins (1988), in a large sample of college students, described children of alcoholics as self-deprecating. Risk for negative self-regard was particularly elevated among women, especially those with an alcoholic father. It is also the case that problems with intimacy appear frequently to account for women's abuse of alcohol — specifically to reduce interpersonal or emotional stress (Frank et al 1990; Zucker 1987; Olenick and Chalmers 1991). It certainly appears possible that the analgesic and/or psychomotor stimulant properties of ethanol may determine its attractiveness to those suffering from the painful states of affect and behavioral immobility central to depression.

Threat — definition and consequences

Specific behaviors often have consequences which indicate increased likelihood of punishment. These consequences might generally be termed threats. Threats are cues of punishment, occurrences which indicate increased probability of ensuing states of deprivation, sensory overstimulation, frustration, disappointment, and social isolation. Unexpected or novel occurrences, per se, also constitute threats because their significance has not yet been determined, and might therefore be punishing. (The unexpected or novel stimulus is complicated, however, because it may signify something positive, and therefore also activates the system governing response to cues for satiating agents, described later).

The system which responds to threat can be defined neither as primarily affective nor primarily cognitive. The process of identifying something previously paired with a punishment as dangerous or threatening involves reactivation of previously inhibited apprehension, as much as learning that one thing now signifies another. LeDoux (1992), for example, has recently stated: "It is well established that emotionally neutral stimuli can acquire the capacity to evoke striking emotional reaction following temporal pairing with an aversive event. Conditioning does not create new emotional responses but instead simply allows new stimuli to serve as triggers capable of activating existing, often hard-wired, species-specific emotional reactions." The same relation between cognition and emotion applies to reaction to the unexpected: what is unpredictable depends integrally on what is predictable. The unknown presupposes the known.

The system that responds to threat functions to preserve us from serious disruptions in psychophysiological homeostasis, without the necessity of temporary or longer term subjugation to such disruptions. Anxiety replaces pain as an agent of learning in the course of phylogenetic and ontogenetic development. The threat system inhibits ongoing behavior when a cue for punishment or something unknown appears. Such inhibition stops us from getting hurt. Fear (specifically) or anxiety (more generally) constitutes a single class of affective response to threat. Fear or anxiety exists as the subjective response to or felt effect of cues of punishment (or novelty) upon behavior, and serves a variety of functions. Fear protects us from things that have hurt us before, and helps ensure the continuation of pain-free survival in the future. Anxiety makes us wary in the presence of physical dangers or the unknown, and makes us cautious in social situations where our future social adaptation — and, therefore, our security — may be at risk if we make a social blunder. Anxiety and fear help us avoid involuntary social isolation by making us careful in the presence of others, and help us avoid disappointment and punishment by providing motivational impetus to plan and to act with intelligence and insight. Anxiety tells us, as well, when we have been wrong. When something unexpected occurs in our daily lives, it means that our plans were at fault and that our model of reality was insufficient and in need of update. Anxiety may be regarded, in many instances, as a signal for the necessity of adaptive change. Unfortunately, however, this intrinsically useful response to threat can become a problem if we are temperamentally fearful and unable to deal with that, or if we have disinhibited fear responses to a plethora of formerly irrelevant stimuli.

The idea of an independent system governing response to cues of punishment may (once again) seem somewhat of a conceptual leap. However, evidence exists at the functional, neuroanatomical, and psychopharmacological levels of analyses, indicating that such a system exists. The amygdala

and hippocampus, deep in the phylogenetically ancient limbic system, in concert with the prefrontal cortex and cortical memory stores, appear integrally involved in programming response to threat (the unknown and specific cues of punishment). The anxiety system appears to work something like this: the amygdala presumes, generally speaking, that everything unknown is dangerous and promising. Therefore, it adds category-appropriate affect to experience, producing both behavioral tendency to approach and explore (Aggleton 1992) (experienced, theoretically, as pleasure and hope (Fox and Davidson 1988; Gray 1982)), and equivalent conflicting tendency to inhibit such approach (experienced as anxiety). Approach to the unknown, punctuated by cautious inhibition, constitutes exploration. Exploration may be undertaken as a consequence of motor activity, in which case the feared and promising object is actually approached, manipulated, observed; or as a consequence of observation of someone else's exploration; or by means of abstraction, imagination and verbal thinking. Exploration allows for the categorization, in permanent memory (mediated by hippocampal function), of the heretofore unknown object for determination of its significance: does it punish? does it satiate? does it signal punishment or satiation? or (most likely) does it do nothing — is it irrelevant? If the explored object punishes or threatens upon initial exploration, it will remain categorized as threatening and will be responded to with inhibition of behavior (or with anxiety, from the subjective viewpoint) upon next encounter. The same is true if it remains unexplored — although in this case, it will also still invoke a certain amount of curiosity. The amygdala essentially appears to label sensory experience as relevant (Kling and Brothers 1992) (as threatening and promising) unless otherwise explicitly commanded by the higher cortical structures involved in episodic (imaginative) and semantic (verbally-mediated) memory, generated as a consequence of exploratory behavior.

Voluntary exposure to (exploration of) novel phenomenon — and, under some conditions, to more specific cues of punishment — produces habituation. Habituation is negatively reinforcing and appears mediated, at least in part, by neuroanatomical systems that employ GABAergic neurotransmission. Endogenous (naturally occurring) anxiolytics (Sangameswaran et al 1986) and anxiogenics (Bodnoff et al 1989) (which reduce or heighten anxiety, respectively) have been identified and affect GABA transmission. Production of endogenous anxiolytics likely accompanies repeated voluntary exposure to a feared but nonpunishing situation. In contrast, anxiogenics are perhaps generated when fear must be re-activated. It is of central interest to note that ethanol, benzodiazepines, and barbiturates are highly effective exogeneous anxiolytics (at least at doses commonly ingested for use or abuse). Ingestion of one or more of these chemical agents (which are characterized by production of cross-tolerance (Gray 1987)) mimics the natural process of habituation, and artificially inhibits anxiety (Bodnoff et al 1989).

Alcohol, benzodiazepines, and barbiturates share one important mechanism of action in the central nervous system, directly related to their anxiolytic properties (Zorumski and Isenberg 1991): they potentiate GABA-mediated chloride (Cl) ion influx at the $GABA_A$ receptor complex, and increase cellular resistance to excitation (Warneke 1991). Alcohol and barbiturates, more potent than the rather benign benzodiazepines, may additionally potentiate such influx independently of GABA (Mehta and Ticku 1988; Zorumski and Isenberg 1991). Alcohol's Cl- flux effect has been linked genetically to alcohol-intoxication sensitivity (Harris and Allan 1989). The Cl/GABA-mediated anxiolytic effect of alcohol, benzodiazepines, and barbiturates appears as a consequence of increased direct inhibition, or potentiation of indirect inhibition, of anxiogenic structures such as the amygdala (Thomas 1988). Such effects should prove particularly reinforcing to anyone suffering from anxiety for any reason — familial, social, economic, personal, cognitive, or as a consequence of anything that destabilizes environmental predictability and allows previously controlled anxiety to re-emerge, or that interferes with the establishment of initial control (Pihl and Peterson 1992a).

Sons of male alcoholics from families with multi-generational histories of alcoholism (MFH SOMAs) and the cue for punishment system

Hyper-reactivity of the threat system appears typical of nonalcoholic young males from families characterized by high prevalence of male-limited alcoholism (Finn and Pihl 1987, 1988; Peterson et al 1993). This hyper-reactivity is graphically portrayed in Figure 2, which contrasts the cardiac response, first of 8- to13-year-old MFH SOMAs and family-history-negative (FH-) controls exposed to a task involving impossible math problems; and second, of 18- to 30-year-old MFH SOMAs and FH- controls receiving a brief signalled electric shock. A like pattern of hyper-reactivity has also been described in individuals at risk for disorders like hypertension (Ditto et al 1986; France et al 1991) and heart disease (Krantz and Manuk 1984). However, these putatively hypertension-sensitive individuals do not appear characterized by what is perhaps a more specifically relevant reaction: susceptibility to elimination of this reactivity by ethanol (Conrod et al 1995). This effect, which has been labelled dampening, is portrayed graphically in Figure 3, which also reveals its highly dose-dependent nature. Failure to explicitly consider these dose (and time-course) dependent effects accounts for much of the otherwise inexplicable variability in the relevant literature.

The fact of differential sensitivity to ethanol's capacity to dampen activity in the anxiety system has been well established in studies conducted on samples of genetically differentiable rodents. Animals who differ in sensitivity to ethanol-induced anxiety-dampening also tend to manifest unique behavioral and biochemical characteristics. Crabbe et al (1994) recently reviewed the relevant literature and described 22 different strains where high and low variants differ predictably in their initial sensitivity to alcohol and other drugs, tolerance to and dependence on alcohol, and preference for 10% alcohol versus water solution. Strains such as the HAS (high alcohol sensitive) rat and LS (long

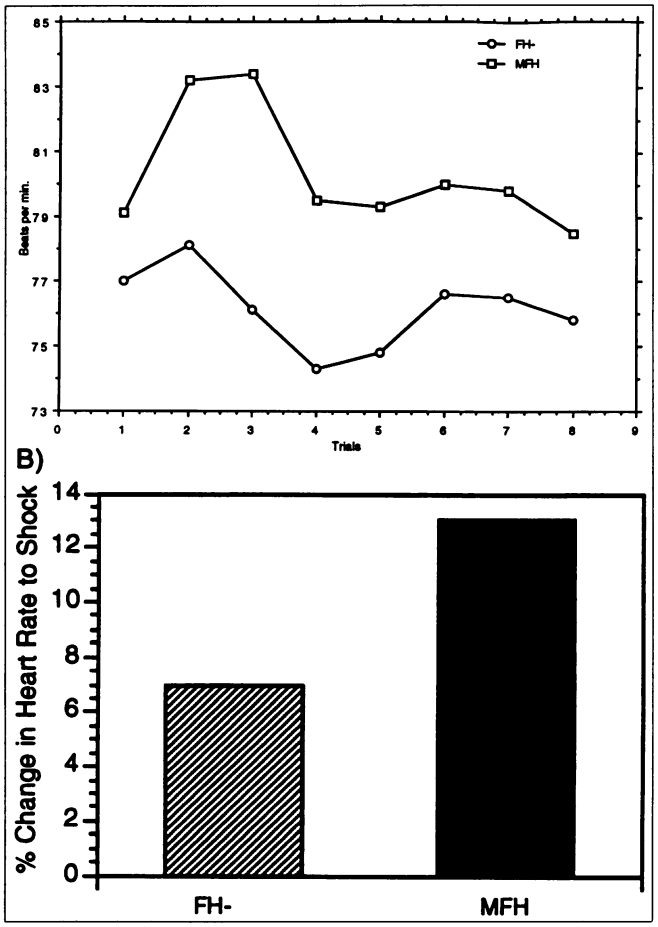

Figure 2. **Heart rate reactivity to: 1. a math stress test in 8- to 15-year-old multigenerational sons of male alcoholics (MFH) (n = 14) and family history negative subjects (FH-) (n = 14) ($p < 0.04$); and 2. an electric shock in 18- to 30-year-old MFH (n = 36) and FH- (n = 33) subjects; ($p < 0.01$). (Studies reported in Harden and Pihl 1995; Peterson et al 1993.)**

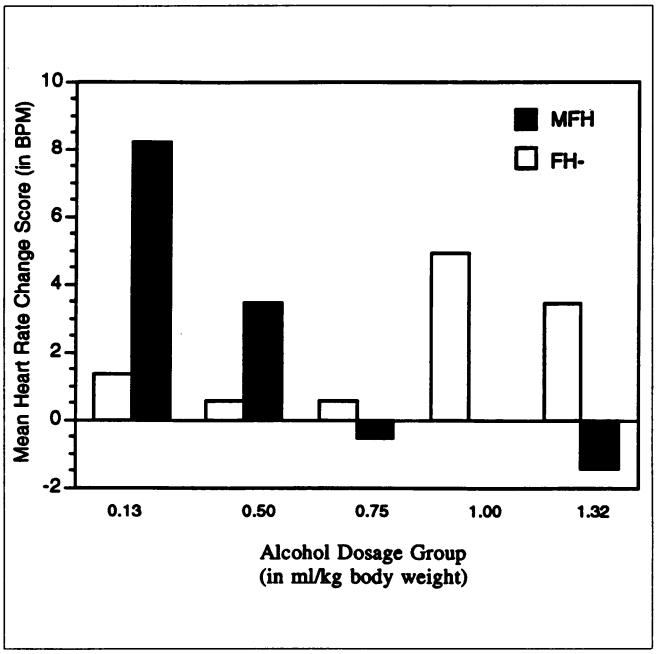

Figure 3. **Heart rate response to electric shock in multigenerational sons of male alcoholics (MFH) (n = 51) and family history negative subjects (FH-) (n = 54) under various dosages of alcohol; ($p < 0.01$). (Study reported in Stewart et al 1992.)**

sleep) mouse are hypersensitive to the sedative/hypnotic effects of alcohol. When compared to LAS (low-alcohol-sensitive) or SS (short sleep) animals, they display heightened sensitivity to alcohol-induced loss of righting reflex (Crabbe 1989), quicker response to lethal overdose (Baker et al 1987), increased sensitivity to ethanol-potentiated muscimol-stimulated chloride ion (Cl-) influx at $GABA_A$ receptors, and increased sensitivity to barbiturates and benzodiazepine. It is also notable that LS mice display high operant responses to alcohol reinforcement, but are not characterized by spontaneous alcohol preference (George 1990). This finding implies, at least in principle, that tendency to initiate use may be separable from sensitivity to ethanol-induced reinforcement, at least among mice.

We have studied 2 mechanisms in human populations whereby anxiety-system function may be potentiated. Both might be termed "cognitive" in nature. However, the first involves a problem in cognitive ability; the second, a problem in cognitive output, or content. Figure 4 graphically displays the separate but related nature of these 2 mechanisms, their (putative) effects on anxiety, and their ability to heighten the negatively reinforcing or anxiety-reducing consequences of acute ethanol intoxication. Given persistence of these trait-like precipitators and attendant increased likelihood of ethanol-use-related anxiety reduction, likelihood of problematic ethanol use is theoretically increased.

A processing problem?

Sons of male alcoholics (SOMAs) appear characterized, in general, by a 4- to 9-fold increased risk for developing alcoholism (Goodwin et al 1974). The population we have been studying, characterized by prevalence of severe familial alcoholism beyond the paternal, is almost certainly at higher risk (Dawson et al 1992). SOMAs, in general, are very likely to be conduct-disordered, characterized by attention problems and academic difficulties. They also frequently produce a particular response pattern during evoked response potential (ERP) studies, and show deficits measurable by certain neuropsychological tests (Pihl et al 1990a). Various studies of ERP (Hill et al 1990; Peterson and Pihl 1990) have

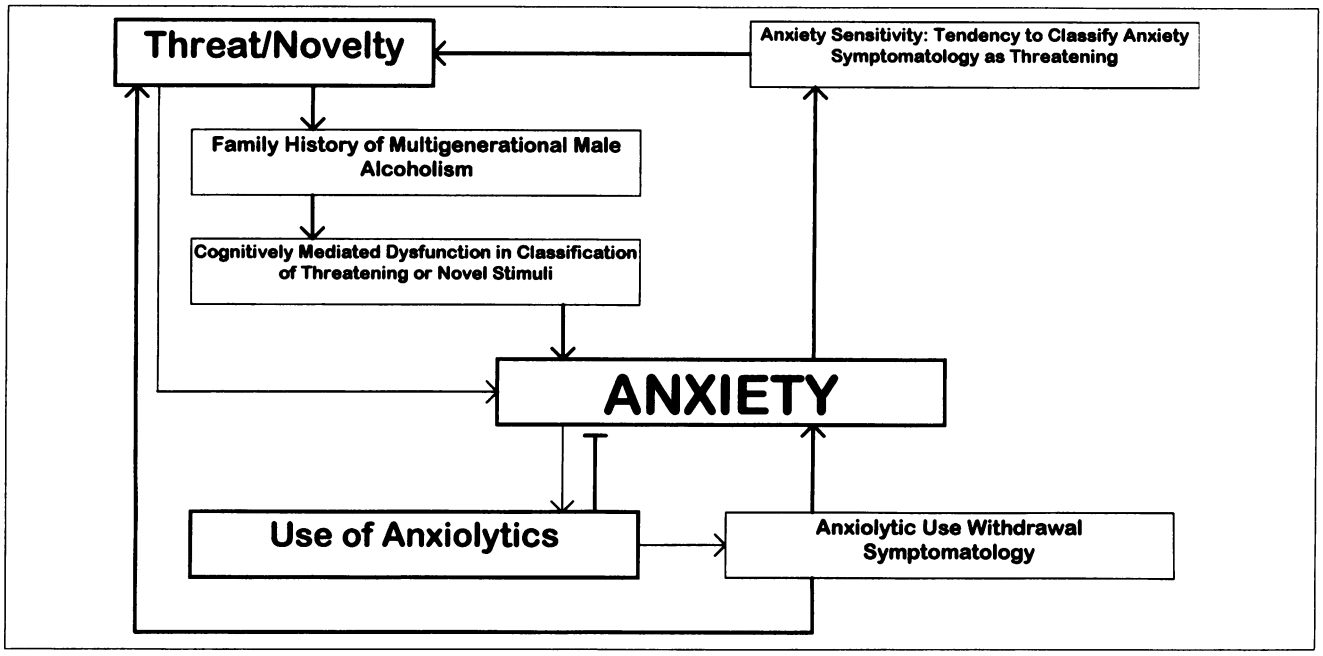

Figure 4. **A partial schematic model for the predispositional risk of alcoholism in multigenerational sons of male alcoholics and anxiety-sensitive individuals. (Light arrows indicate normal path: threat causes anxiety and heightens tendency to use and appreciate anxiolytics. Heavier arrows indicate manner in which this normal process can be pathologized: cognitive dysfunction, attendant upon familial history of alcoholism, makes classification of threat and novelty more difficult; anxiolytic withdrawal symptomatology produces anxiety and is threatening as well; anxiety sensitivity makes anxiety symptoms themselves threats. Bar indicates inhibition.)**

concluded, for example, that SOMAs are characterized by abnormally low amplitude and longer latencies of the P300 waveform to predictable occurrences, and abnormally high amplitude to unpredictable occurrences. The P300 is an indicator of subjective significance; the results indicate that SOMAs have a difficult time attributing significance to events merely because they are told to, and, conversely, inhibiting or restricting the significance of relatively novel events which they are instructed to ignore. The psychophysiological abnormalities characteristic of SOMAs have been associated (Peterson and Pihl 1990) with reduction in classification-oriented cognitive processing (Pihl and Peterson 1992a; Peterson et al 1992). Figure 5 presents data from MFH SOMAs between the ages of 18 and 30 (Peterson et al 1992) and from ages 8 to 15 (Harden and Pihl 1995), and graphically portrays a pattern of deficient performance on tests thought to assess cognitive abilities mediated by the prefrontal cortex. Most of these tests have been shown to be differentially affected by surgical or disease processes in various parts of the frontal lobes, or found to induce increased activity in this area in PET studies (Petrides 1990; Petrides et al 1993a, 1993b; Milner et al 1985; Parks et al 1988; Frith et al 1991).

Figure 6 provides schematic representation of a model for processing of sensory information. This model portrays relevant neurological systems and their putative function, displays deficits in operation characteristic of SOMAs, and indicates where ethanol might produce its dampening effect. The cognitive functions of the prefrontal cortex appear fundamental to maintenance of voluntary attention, particularly under conditions of social demand; to regulation of psychophysiological response to threat and novelty; and to the ability to engage in exploratory behavior and classification including verbal reasoning, abstraction and problem solving. Deficits or dysfunctions in prefrontal ability as assessed by neuropsychological test could render MFH SOMAs less able to attend to nonintrinsically relevant stimuli (like ideas presented in the abstract, by a teacher) and more likely to respond with affective activation when confronted by novelty and threat because of difficulty in abstract classification and difficulty in reduction of general affective relevance to the particular or irrelevant. Ethanol theoretically dampens such affective activation, eliminating the cognitive deficit-induced hyper-reactivity in a negatively reinforcing manner, perhaps by potentiating inhibition of anxiety-producing psychobiological systems. Alcohol crosses the blood brain barrier with impunity and bathes the entire brain. However, a substantial body of recent research supports the proposition that limbic structures involved in anxiogenesis and its control — including the amygdala and hippocampus — are particularly sensitive to ethanol-induced alteration in function. These structures appear integrally involved in signalling the presence of the novel (or otherwise dangerous) in governing behavioral response to that danger, and, interestingly, in moving information from short-term attention to long-term

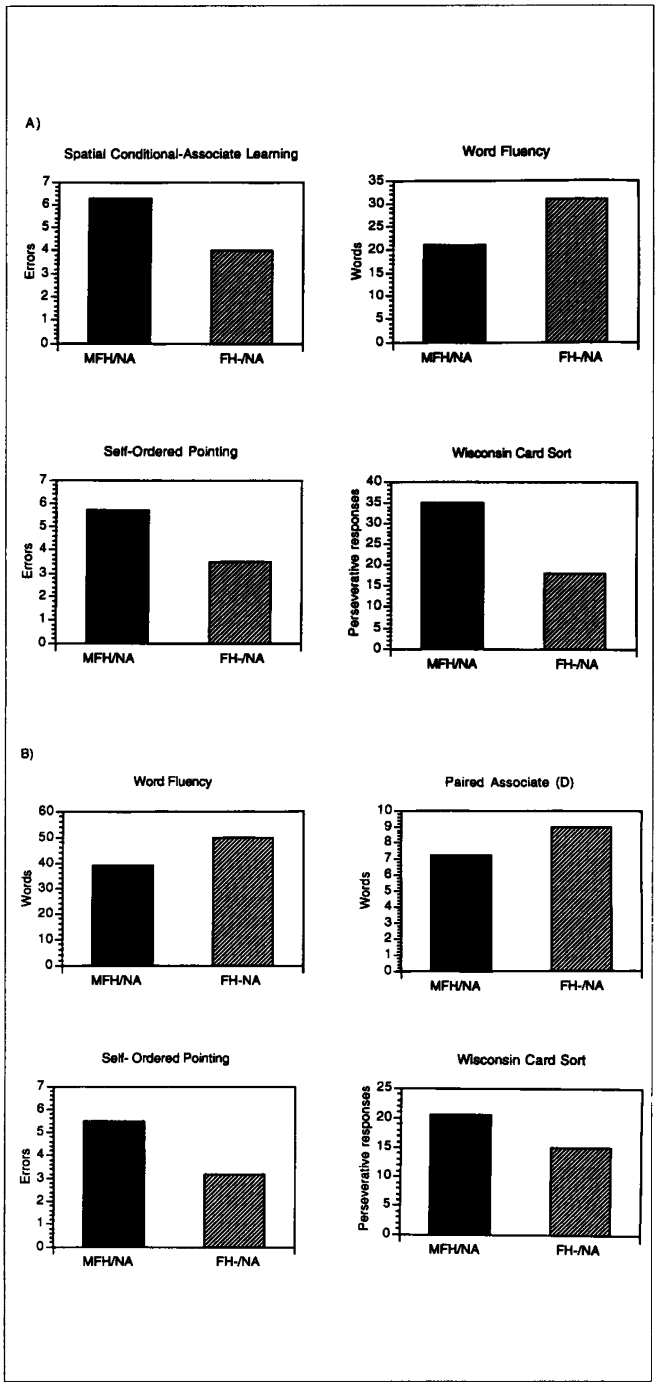

Figure 5. Performance on cognitive tests by: 1. multigenerational 8- to 15-year-old sons of male alcoholics (MFH) (n = 14) and family history negative subjects (FH-) (n = 14) without alcohol (NA); (all p's < 0.05); and 2. 18- to 30-year-olds, (MFH, n = 22; FH-, n = 22); (all p's < 0.05). (Studies reported in Harden and Pihl 1995; Peterson et al 1992.)

storage. For example, it might be noted that the P300 component of the cortical evoked-response potential (ERP), which is produced by the hippocampus/amygdala (Okada et al 1983) in response to novelty (Duncan-Johnson and Donchin 1977), is dampened by alcohol among SOMAs and controls (Elmasian et al 1982). Recently, Ryabinin et al (1994) demonstrated that ethanol selectively reduced restraint stress-induced C-fos expression in rat hippocampus. Numerous more general studies have demonstrated that the hippocampus and amygdala are particularly sensitive to the acute and chronic effects of alcohol (Gray 1987; Lovinger et al 1989; Freund and Ballenger 1989; Peterson et al 1990).

Anxiety sensitivity: the etiological role of specific cognitions

Numerous studies have linked pathological anxiety — particularly panic disorder — with alcohol abuse and dependence (Cox et al 1990; George et al 1990; Kushner et al 1990; Otto et al 1992). The overlap between alcoholism and panic disorder is largely accounted for by female panic patients (Norton et al 1993). Most of these patients' panic attacks preceded their alcohol abuse (Bibb and Chambless 1986; Chambless et al 1987). Furthermore, such patients report that they use alcohol explicitly to self-medicate — to help them cope with or otherwise lessen their anxiety symptoms. A trait characteristic, anxiety sensitivity has been linked with anxiety and panic disorders, and appears importantly related to drug and alcohol abuse. The construct of anxiety sensitivity has been more narrowly defined than that of trait anxiety, and refers specifically to the tendency to define as unbearable the subjective experience of anxiety and its accompanying bodily sensations themselves (Reiss 1987; Reiss and McNally 1985). The anxiety-sensitive appear, perhaps, to use cortically mediated, exploration-derived labelling paradoxically. Such paradoxical labelling, which should decrease fear by appropriate categorization, actually enhances, by defining the novel as life, status or sanity-threatening. The highest levels of anxiety sensitivity have been observed in those individuals suffering from panic disorder with and without agoraphobia (Taylor et al 1992). Predictably, therefore, successful treatment of agoraphobia has been shown to be associated with marked decline in anxiety sensitivity (McNally and Lorenz 1987).

The bulk of evidence to date demonstrates that women are characterized by significantly higher ratings of anxiety sensitivity than men. This finding stands in marked contrast to results obtained with traditional measures of trait anxiety, on which men and women tend not to differ (Speilberger et al 1983). A growing literature suggests an important link between anxiety sensitivity and the abuse of alcohol (Peterson and Reiss 1992; Stewart and Pihl 1995; Telch et al 1993). It has become evident that self- reported weekly alcohol consumption rate is highly correlated with anxiety sensitivity in both clinical (Cox et al 1993) and nonclinical samples (Stewart al 1994). Figure 7 graphically portrays differences in the rating of how alcohol affects coping in low, moderately and highly anxiety-sensitive individuals, and provides an

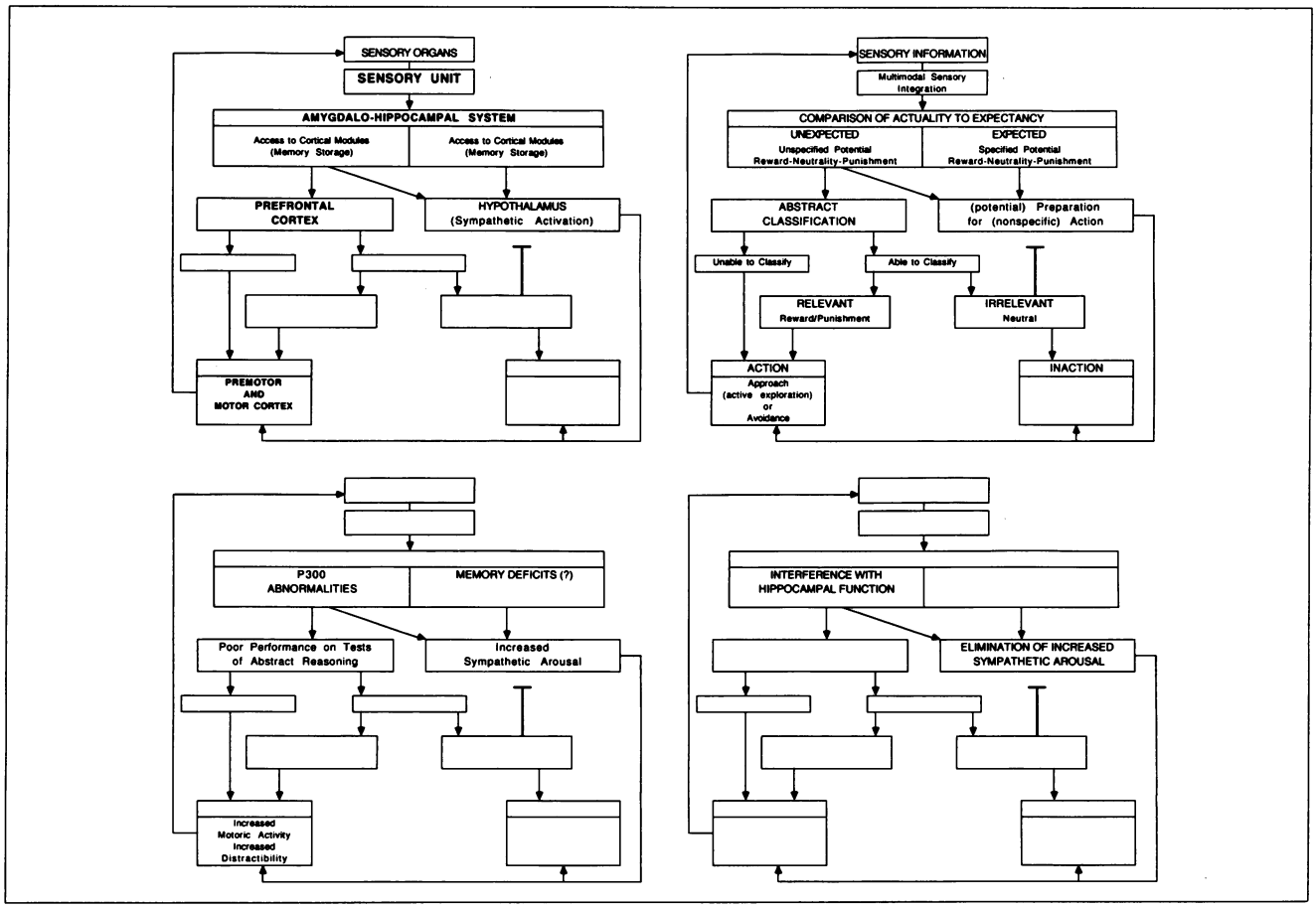

Figure 6. Schematic model of: 1. the classification of sensory information; 2. hypothesized underlying structures; 3. putative abnormalities of sons of male alcoholics; 4. localization of the alcohol effect.

illustration of the relationship between reactivity and dampening in skin conductance response among such individuals. This dampening of response appears analogous to that experienced by MFH SOMAs.

Conclusion

A powerful body of evidence suggests that the cognitive/neurological systems that respond to punishment and threat are involved in governing individual response to alcohol consumption. These systems appear primarily involved in mediating ethanol's capacity to reinforce consumption through the mechanisms of negative reinforcement. Alcohol has direct and indirect effects on behavioral, affective and cognitive response to punishment and to cues of punishment. MFH SOMAs are characterized, perhaps, by sensitivity to ethanol's ability to enhance endogenous opiate production and to decrease anxiety. The latter characteristic appears shared by anxiety-sensitive individuals. The negative-reinforcement model of susceptibility to alcoholism is limited, however, by its failure to take into account the clear evidence for the role positive reinforcement plays in initiation and maintenance of ethanol (and other drug) use and abuse. The remainder of the paper, therefore, focuses on the positive effects, so to speak, of alcohol use.

ALCOHOL, SATIATION AND PROMISE

Satiation — definition and consequences

Specific behaviors often have consequences that increase the future likelihood of such behaviors. These consequences have been traditionally termed rewards or positive reinforcements. Rewards include stimuli that eliminate states of deprivation, reduce sensory overstimulation, and ease frustration, disappointment or loneliness. Water is rewarding to a water-deprived individual; food is rewarding in states of food deprivation; social contact is reinforcing to those who are lonely, and so on. The problem with the term "reward", however, or even "positive reinforcement", is that the effect of a reward (or a positive reinforcement) can easily be

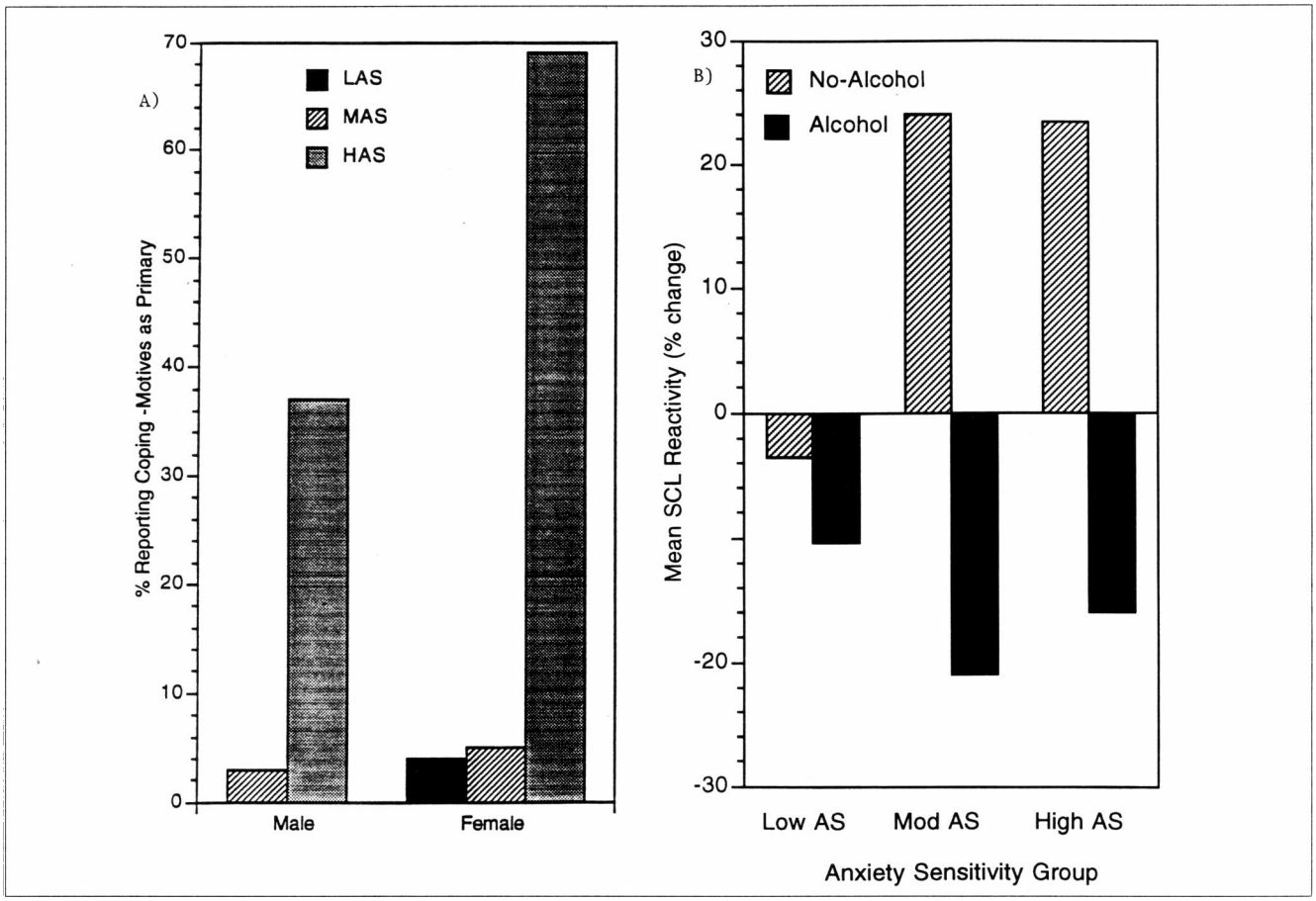

Figure 7. **Scores of high (HAS) (n = 27), moderate (MAS) (n = 145) and low (LAS) (n = 47) anxiety-sensitive subjects on: 1. self-report of the coping use of alcohol ($p < 0.01$); 2. electrodermal response to aversive stimulation sober and intoxicated ($p < 0.05$) (HAS, n = 10; MAS, n = 10; LAS, n = 10). (Study reported in Stewart et al 1993; Stewart and Pihl 1994.)**

confused with the effect of cues indicating that such rewards are forthcoming. This is a nontrivial problem, because the behavioral effects of rewards and their cues are not identical. Animals respond to food, in sufficient quantities, with the cessation of food intake; to water, upon slaking of thirst, with cessation of drinking. Sufficient unconditioned positive reinforcement is associated with invulnerability to previously positively reinforcing agents. Enough food, enough water, enough sex — sufficient basic needs — produce satiation. Application of satiating agents, in deprivation states, reinforces behavior but results in the overall cessation of behavior (in satisfaction) in sufficient quantity. Cues of reward, by contrast, produce approach behavior, and their presence is generally accompanied by intense subjective pleasure. The depth electrodes that a rat will constantly activate do not produce satiation — they produce constant approach behavior, even unto death. It is a peculiarity of the mammalian brain that it produces more pleasure to cues of rewards than to the rewards themselves, at least under most normal circumstances. This is perhaps because, while you can have too much of a good thing, it is not so easy to have too much of something indicating increased likelihood that good things are coming.

Neural systems that employ 5-HT or serotonin appear integrally involved in mediating satiation (and in many other important processes). These systems are exceedingly ancient, from an evolutionary viewpoint, and employ a large number of differentiated receptor subtypes (Peroutka et al 1990). During the early stages of nervous system development, the 5-HT system guides and influences neuronal development, differentiation and organization throughout the brain. In adult life, 5-HT plays a similar role, altering and shaping brain structure at the microanatomical level (Whitaker-Azmitia et al 1990). As a classical neurotransmitter and neuromodulator,

serotonin helps regulate circadian rhythm, food and water intake, sexual behavior, locomotor activity, and response to pain, and aids in the control of various additional complex vital functions (Whitaker-Azmitia and Peroutka 1990). Diverse forms of psychopathology including depression and alcoholism (which share mood disturbance, alterations in appetitive function, sleep disruption, and pathologized aggression) appear associated with reductions in central 5-HT concentrations. Reduced central serotonergic function may also characterize impulsive individuals, as well as those afflicted with obsessive-compulsive disorder and anorexia (Whitaker-Azmitia and Peroutka 1990). The important role 5-HT plays in governing psychological processes is logically associated with its equally pervasive physical presence.

General conclusions

A number of recent reviews have described the potential role played by serotonin in governing cognitive, affective and behavioral response to environmental stimuli (Spoont 1992; Soubrie 1986; Whitaker-Azmitia and Peroutka 1990; Depue and Spoont 1986; Van Praag 1993).

5-HT appears to play a constraining or governing role in activity within the central nervous system (Spoont 1992). The ascending serotonergic projections might be compared to the conductor in an orchestra, whose responsibility is the organization and control over the orchestra's constituent parts; fractious instrumental sections, composed potentially of talented but individualistic soloists who must, for the purposes of the music, be melded into a harmonious unit. In general, it appears that normal or slightly elevated levels of 5-HT function appear associated with the coupling of neuronal activity with integration of affect, cognition, and behavior (Spoont 1992). Central 5-HT facilitates the formation of neural synchrony, associated with higher thresholds to outside influences. 5-HT depletion, by contrast, is associated with EEG dysynchronization (Spoont 1992). Lack of such synchrony implies dissociated neural activity — competition between brain centers or systems responsible for specific subroutines (for the production of anxiety as affect, for example, as opposed to use of anxiety for behavioral inhibition), and consequent psychic disharmony and behavioral dysregulation impulsivity (Spoont 1992).

Reduction in 5-HT activity apparently allows not only for dissociation between behavioral inhibition and affective state, as well as in increased propensity for affective instability (i.e., greater stress reactivity), but also for disintegration of operation within and between diverse neural systems. Low 5-HT, therefore, simultaneously (and paradoxically) might produce disinhibition of behavior and heightened sensitivity to various stressful stimuli, including cues of punishment (threat). Anxiety, the affective response to threat, accompanies inhibition of ongoing behavior when 5-HT function is normal. When such function is decreased, however, anxiety may lose its inhibitory effect without decreasing in intensity, from the affective perspective. The anxiety felt by an individual characterized by low concentrations of 5-HT could, therefore, be intense but nonetheless remain entirely dissociated from behavior.

The net consequence of these effects of 5-HT-deficiency is increased duration and amplitude of behavioral response: more sexual behavior, more food and water intake, more aggression, higher startle response, increased sensitivity to painful stimulation, and more novelty-induced exploration (Spoont 1992; Whitaker-Azmitia and Peroutka 1990). Such response-enhancement is not spontaneous as much as it is motivated, dependent on internal or external stimulus cueing. Normal or enhanced 5-HT concentrations, by contrast, appear associated with satiety, with relief from need for reward, with enhanced resistance to punishment, and with the ability to use threat cues to govern behavior. It might be said that decreased 5-HT function decreases the inhibitory control of secondary reinforcers over response to primary reinforcers. Consummatory and approach behaviors emerge in response to satiating agents and their cues, aggressive and depressive behaviors, and in response to punishment. Threat, the learned association between behavioral manifestation and receipt of punishment, controls both. Decreases in 5-HT increase saliency of behavioral activation induced by punishment and reward, and simultaneously decrease anxiety-related control of behavior.

The 5-HT-depleted individual is, therefore, likely to be irritable (affectively, cognitively and behaviorally reactive to sensory input), stimulus-driven (hyper-responsive to reward, cues of reward and punishment), and unable to use anxiety, which may be substantially heightened, to govern stimulus-driven behavior. This individual will thus appear more depressed and aggressive (more affected by punishment), more appetite-driven (more motivated by food, water, sex, and drugs of abuse, which share psychomotor-stimulant properties) and more impulsive (less able to control behavior in the face of threat). It may be difficult for the person to stop engaging in a behavior once started unless actually faced with alternative sources of reward, cues for reward or punishment. He or she may also be more likely to initiate alcohol consumption and be less likely to disengage.

Ethanol, in part, is a true satiating agent. It has caloric properties, and its short-term effects on the serotonergic system — at least during the ascending limb of the BAL curve — appear, additionally, to mimic pharmacologically the effect of real satiating agents. After reviewing the relevant literature, LeMarquand et al (1994a, 1994b) recently concluded, that increases in serotonergic function decrease ethanol intake, and that, conversely, decreased serotonergic function predisposes to heightened alcohol use. In keeping with this notion, studies assessing the effects of serotonergic reuptake inhibitors (zimelindine, citalopram, viqualine, fluxetine) administration have consistently demonstrated associated reduction in alcohol intake among members of variously selected human subject groups: male social drinkers (Amit et al 1985), males characterized by mild dependence (Naranjo et al 1989), and more seriously alcohol-dependent males (Gorelick and Parades 1992).

Promise — definition and consequences

Specific behaviors often have consequences that indicate increased likelihood of satiation. These consequences are rewarding, in the classic behavioral sense, in that their appearance increases the chance that the behavior which preceded them will re-occur. However, unlike satiating agents (which are unconditioned rewards), cues for satiation produce pleasurable approach behavior (as described previously). What stimuli activate the cue for the satiation system? Anything previously paired with something satiating or with something that produced the cessation of punishment or threat, or anything novel. Novel stimuli, of course, are unique cues for satiation because, as explained earlier, they also activate the cue for the punishment system. Application of satiating agents in sufficient quantity produce satisfaction, contentment, calm, and quell anger, anxiety, and curiosity. Appearance of cues for satiating agents, by contrast, produce excitement, curiosity, pleasure and hope. Animals (and people) will work for both, but they are not the same. Money serves as a classic example. You can't eat it, or drink it, and it will not quell loneliness. However, because it is exchangeable for virtually any satiating agent, it is the (abstract) ultimate in promise, and its ability to motivate behavior obviously remains beyond debate.

Dissimilarity in response to satiating agents and to their cues is reflected in the makeup of the psychobiological systems whose operations underlie response to the 2 classes of motivationally relevant events. The serotonergic system appears integrally (although not uniquely or exclusively) involved in mediating the effects of satiating agents. By contrast, the dopaminergic system appears to mediate the effects of cues of satiating agents. This system, like the threat system, can neither be considered primarily affective nor cognitive. The process of reacting to something previously paired with something rewarding — like the process of anxiety — involves reactivation of previously inhibited excitement, as much as learning that some previously irrelevant thing signifies the appearance of something good. The same applies to response to novelty: what is unknown, once again, depends absolutely for its identification and effect on what is known. The system that responds to cues of satiation serves to force us near what is potentially necessary to us, and it uses pleasure, hope, curiosity and excitement as enticement. The dopaminergic system activates behavior when something tells us something useful is nearby, and promotes exploration in the face of the novel, eternally threatening and promising. Hope, excitement and curiosity — the subjective responses or felt effects of these cues — are analgesic, allowing us to continue behaving in the face of adversity and pain. This analgesia allows us to move forward when we might otherwise retreat, and forces us to investigate what we do not understand. It underlies our tendency to expand constantly our general competence. Our response to cues of satiating agents makes breaking rules — a procedure which results in production of the unexpected — exciting, and propels us out of a natural, and perhaps useful, but stultifying conservatism. However, pathologized — which means manifested in the absence of sufficient sensitivity to threat and punishment — the approach system produces intra- and inter-personally dangerous asocial and disruptive behavior.

The dopaminergic psychomotor system, integrally involved in the control of motor behavior, appears primarily responsive to cues of satiating agents. The unconditioned consequence of activating this system (specifically, of stimulating the medial forebrain bundle) is increased novelty-induced exploration of and interaction with biologically relevant stimuli in the environment (Wise 1988). Such activation is intrinsically motivating, such that animals with electrodes implanted in this system will ignore satiating agents themselves, even when they are in severe states of deprivation, in favor of self-stimulation of such electrodes, and will develop potent place-preference for locations in which such stimulation takes place (Fibiger and Phillips 1988). The rate of such self-stimulation appears dependent on density of DA neurons, where the electrical current has its effect. By contrast, drugs (like the antipsychotic neuroleptics) that block the action of DA receptors reduce intracranial self-stimulation in a dose-dependent manner, intravenous stimulant self-administration, and amphetamine-induced conditioned place preference (Fibiger and Phillips 1988).

The psychomotor stimulants, which include most drugs of severe abuse potential such as cocaine and amphetamine, share a capacity to activate the dopaminergically-mediated cue for satiating agents system. Cocaine does this by prolonging the effects of released dopamine by interfering with reuptake processes. Amphetamine acts similarly but may also release dopamine and norepinephrine (Koob and Bloom 1988). Psychomotor stimulant administration tends to facilitate intracranial self-stimulation among animals (Fibiger and Phillips 1988). It appears that such drugs heighten sensitivity to the cues of satiation, as well as directly activate the system that governs such sensitivity (Wise 1988).

Use of such stimulants results, initially, in reverse tolerance (or sensitization) and reverse cross-tolerance, which means that initial use of one stimulant makes that drug — and all others that share its pharmacological properties — that much more intrinsically attractive (Wise 1988). Such development might account, in part, for the fact that most drug-abusers are polydrug abusers. For example, up to 84% of cocaine abusers abuse alcohol (Helzer and Pryzbeck 1988). It is also relevant and important that the action of stress, generally defined, appears to potentiate sensitivity to the effects of psychomotor stimulants (Deminiere et al 1989).

Ventral tegmental area (VTA) dopaminergic neurons that accelerate firing rate after contact with alcohol are, in fact, very susceptible to this ethanol effect (Gessa et al 1985). These neurons also appear to mediate facilitation of approach behavior by more primary psychomotor stimulants such as cocaine and amphetamine (Gessa et al 1985). Ethanol's stimulant effects are evidently dose- and rate-dependent. Low to moderate doses heighten rat mobility and increase dopaminergic release in the nucleus accumbens. Alcohol doses of sufficient magnitude to rapidly sedate, by contrast,

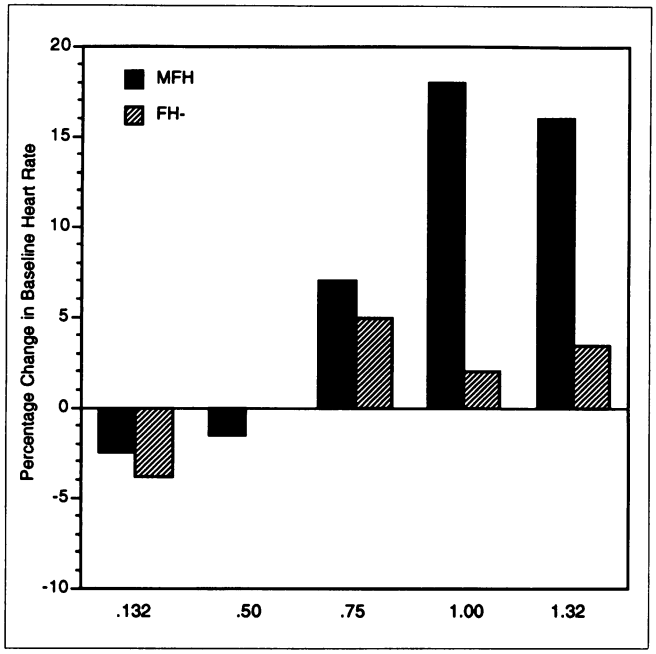

Figure 8. Heart rate response to various doses of alcohol in multigenerational sons of male alcoholics (MFH, n = 51) and family history negative (FH-, n = 54) subjects; ($p < 0.01$). (Study reported in Stewart et al 1992.)

decrease such release. Ethanol also acts differently at different stages of the blood alcohol curve. Various investigators claim that children of alcoholics are sensitive to ethanol; others see them as resistant. Newlin and Thomson (1990) suggest that testing at different places on the BAL curve accounts for the difference, and claim that such children are hypersensitive during the initial phase but acutely tolerant during the latter phase of ethanol intoxication.

Psychomotor stimulants might be considered innately interesting (hope-inspiring, exciting), but there is still considerable variability in human and animal tendency to begin stimulant self-administration, in susceptibility to drug stimulant effect, and in proclivity to develop dependence (Deminiere et al 1989). Genetic/environmental variation in central nervous system function has been linked to such differences in use and abuse propensity. Damage to the dopaminergic system interferes with maintenance of normal state-relevant motivated locomotor activity (Koob and Swerdlow 1988). In addition, dopamine D_2 receptors appear in the psychomotor activation system pathways, and their drug-induced stimulation appears rewarding. The existence of the A1 allele may provide a marker for the identification of nervous systems characterized by decreased dopamine D_2 receptor function in the brain reward system (Blum et al 1990), and potential consequent-heightened need for pharmacologically induced stimulation. Rat breeds selected or trained for ethanol preference are characterized by various idiosyncracies in sober and intoxicated dopaminergic function (Deminiere et al 1989) or in other systems that mediate such function (McBride et al 1988; Hwang et al 1990). HAD (high alcohol drinking) and P (alcohol-preferring) rats are theoretically characterized by a variety of the behaviors of the human alcoholic. These rats have unnaturally dense GABA-innervation of the dopaminergic system. This increased innervation, which serves an inhibitory function and may decrease dopaminergic release, is apparently associated with heightened ethanol preference (McBride et al 1990; Hwang et al 1990). P rats also manifest more locomotor activity and higher sleeping EEG spectral power after ethanol and nicotine administration (Gordon et al 1993), and appear more sensitive to the anxiolytic effects of alcohol (Baldwin et al 1991). In addition, P rats will differentially maintain bar-pressing, reinforced by ethanol administration, under a variety of conditions (Schwartz-Stevens et al 1991), and are more resistant to alcohol-induced sedation (Gordon and Schechter 1991). HAD rats are also more sensitive to the locomotor-activity enhancing effects of ethanol (Krimmer and Schechter 1992).

Heart-rate increase has been frequently associated with activation of the cue for satiation system (Fowles 1983; Wise and Bozarth 1987; Gray 1982), among other things. Alcoholics characterized by accelerated resting baseline heart-rate after ethanol consumption tend to drink more when given the opportunity, and suffer more intense cravings in the absence of ethanol (Laberg and Ellertson 1987; Kaplan et al 1985). It appears possible that this heart-rate increase is associated with ethanol-induced dopaminergic activation. Figure 8 graphically portrays a dose-response curve of resting heart-rate activation to an intoxicating dose of alcohol in a population of MFH SOMAs and FH- controls. We have data on over 300 subjects demonstrating that nonalcoholic MFH SOMAs (mean 6 drinks per week) and alcoholics (mean 65 drinks per week), on whom we ran an alcohol challenge, were specifically characterized by this heightened heart-rate increase (in comparison to FH- controls, sons and daughters of unigenerational male alcoholics, and daughters of multigenerational male alcoholics) (Peterson et al, unpublished manuscript). Such increase predicts voluntary laboratory alcohol consumption in the course of a laboratory taste test, and number of alcoholic drinks self-reported consumed per week among MFH SOMAs. This information is portrayed in Figure 9. We have also recently demonstrated that heavy-drinking MFH SOMAs peak faster in their blood alcohol level curve than heavy-drinking FH- subjects (Conrad et al, unpublished manuscript), and are characterized by significantly higher heart rates during the initial part of the BAL curve. MFH subjects, however, did not report different subjective evaluation of intoxication, but were more depressed and tired (and had lower resting heart-rates) 2 and 3 hours post-drinking offset.

Pollock et al (1983) similarly demonstrated that alcohol-intoxicated SOMAs were characterized by increased production of electroencephalogram waveforms associated with states of well-being and pleasure. This may be particularly

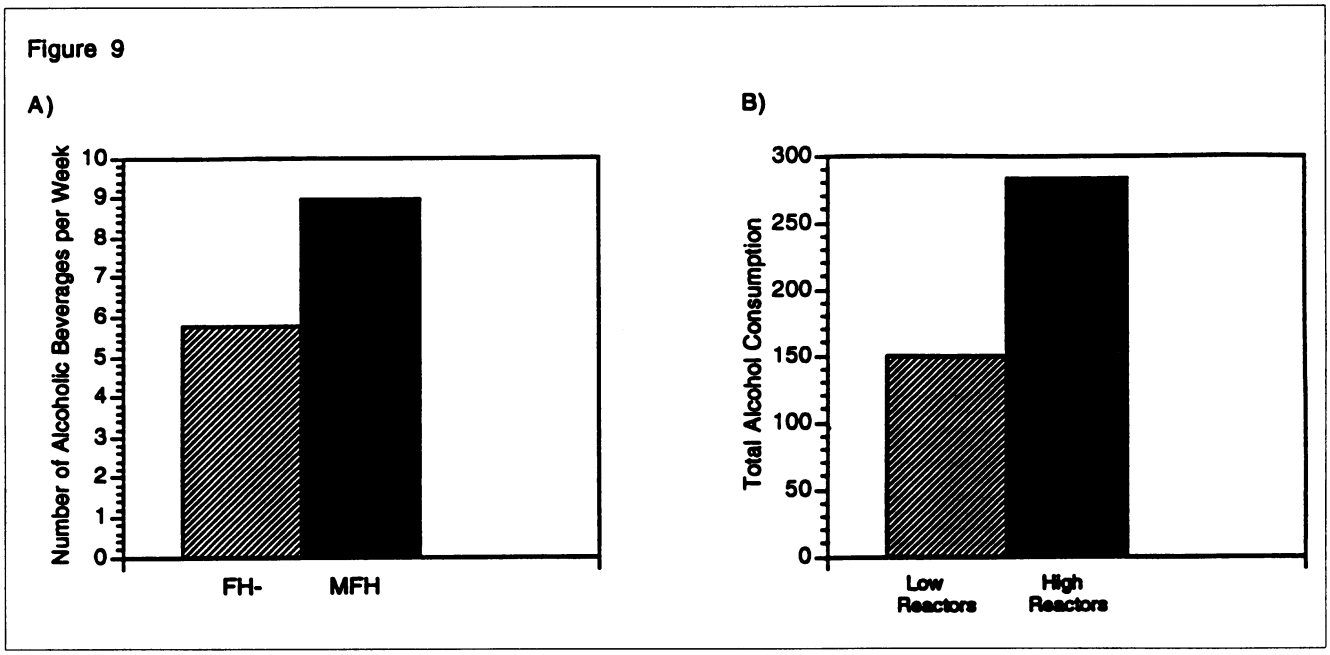

Figure 9. A: Alcohol consumption of multigenerational sons of male alcoholics (MFH, n = 36) and family history negative (FH-, n = 33) subjects; ($p < 0.01$); and B: amount of alcohol consumed in a laboratory taste task by high heart rate reactors (n = 9); ($p < 0.01$). (Studies reported in Peterson et al 1993; Pihl et al 1994.)

relevant, given that Gabrielli et al (1982) found that SOMAs produced more high frequency waveforms when sober (like alcoholics (Mendelson and Mello 1979)), and that these wave forms have been associated with subjective feelings of tension and anxiety (Kiloh and Osselton 1961). It would be of exceptional interest to determine whether or not these EEG waveforms were hemispherically localized, given Davidson's reports (1984a, 1984b) and replications thereof (Fox and Davidson 1987, 1988) attributing positive affect to relative left-sided activation.

Conclusion

A compelling body of evidence suggests that separate psychobiological systems governing response to satiating agents (unconditioned or consummatory rewards) and to cues of such agents (conditioned or incentive rewards) are critically involved in mediating individual response to ethanol intake. These systems are responsible for ethanol's ability to psychopharmacologically reinforce consumption through positive reinforcement. Alcohol has direct and secondary effects on behavior, affect and cognition manifested in response to satiating agents and to their secondary cues. MFH SOMAs appear characterized by heightened sensitivity to ethanol's effects on opiate function, and by increased heart-rate after alcohol consumption (a potential marker, in our view, for activation of the cue-for-satiation system). The model, as currently stated, is now limited primarily by its failure to take into account interactions between modes of positive and negative reinforcement. The rest of the paper, therefore, focuses on the description of such interrelationships.

INTERACTIONS OF THE SYSTEMS

Sensation-seeking, resistance to anxiety, and initiation and enjoyment of drug use

A great deal of energy has been invested in discovering what combination of factors determines initial use, since such knowledge is thought quintessential to prevention efforts. Expenditure of this energy has resulted in determination of an interesting fact: reasons for initiating drug use are separable in principle and actuality from those that maintain abuse and dependence. Consideration of this generally useful proposition might lead to development of useful prevention programs if more attention were paid to several critically important details. First, it is important to determine what drugs, or what classes of drugs, are being used or misused by a given individual or class of individuals, and at what age. Second, it is important to consider whether or not the factors that influence can be realistically influenced as a result of application of a given theoretically or ideologically attractive intervention or prevention program. With regard to the latter point, for example, community-sponsored messages promoting the delay or absolute elimination of drug use are typically unintelligible, unbelievable, or viewed accurately as

hypocritical, from the adolescent perspective, particularly in the case of cigarettes and alcohol, which are widely advertised and modelled for use by more effective agents of promotion. Social sanction of illegal substance use is perhaps somewhat more readily understood, although the effect of such sanction is likely to vary with subculture. Threat of and punishment for illegal substance use (including use of ethanol for underage individuals) are likely to prove rather useless when applied to individuals who believe, perhaps with some justification, that they have nothing important to lose in the long run, and everything to gain — status, power, financial advantage, and interesting experience — in the short run. Furthermore, it has been shown (Shedler and Block 1990) — and this is of vital importance, from the perspective of policy and prevention — that adolescents who never experiment with drugs (not even marijuana) tend to be as maladjusted as (although somewhat differently from) actual drug abusers; that is, significantly more maladjusted than occasional users. Nonexperimenters tend to be fearful, highly anxious, behaviorally constricted individuals. It appears as though it takes a certain level of adjustment and self-confidence to try an illegal drug — at least in the confines of our present culture — and also to restrain deeper involvement.

Age of initiation is important and diagnostically relevant. Everything else being equal, the younger the age of initiation, the more deviant the individual; the wider variety of drugs taken, the more associated, generally antisocial pathology, and the more likely that substance abuse or dependence will develop. The typical early-onset drug-abusing individual is characteristically male, of low educational achievement and expectation, nonconforming (except within self-selected peer group), conduct-disordered or antisocial in behavior and attitude, free of religious belief and paternal support, and replete with positive expectation concerning drug effects (Bucholz 1990; Dryfoos 1990; Chassen et al 1991; Goldman et al 1991; Newcomb et al 1986). Bates (1993) has recently reviewed the personality literature relevant to abuse predisposition. Characteristics such as low ego control, poor emotional regulation (including impulsiveness, aggression, sensation-seeking, fearlessness, heightened activity level) and inability to delay gratification are frequently reported. The same pattern of factors and characteristics place individuals at multiple risk: higher rates of school dropout, delinquency and early promiscuity (for males and females) and, logically, enhanced risk of teenage pregnancy (for females) (Dryfoos 1990; Hawkins et al 1992). This description, which provides an outline of the conduct-disordered personality, is of intense theoretical interest, but often appears of little practical value. Classification does not translate directly into means of alteration. Application of diagnostic labels devoid of etiologic knowledge (like "conduct disorder") means explanation of one mystery with another. Attention must shift toward detailed delineation of more specific mechanisms which lead to and maintain abuse and dependency.

Detailed consideration of sensitivity to anxiety and sensitivity to cues of satiating agents as predisposing factors illuminates the nature of 2 key phenomena. The first is the tendency to initiate drug use — to explore drug effects, perhaps at an early age. The second, which is related intrinsically to the first, is the tendency of conduct disorder, antisocial personality, and criminality to co-occur with alcohol abuse and dependence. Simply stated, individuals high in sensitivity to cues of satiating agents and low in sensitivity to cues of punishment are very likely to try new (and forbidden) things, to break rules (just to see what might happen, and to revel in the novelty) and to truly appreciate the pharmacologically mediated psychobiological effects of psychomotor stimulants. SOMAs tend to be at increased risk for manifestation of attention deficit and conduct disorder. Conduct disorder/ASP, aggression and psychopathology have all been linked to reward dominance (Gorenstein and Newman 1980), which, in this context, means heightened sensitivity to cues of satiating agents. Furthermore, they have been linked to reduced reactivity to threat and novelty (Gray 1982, 1987; Pihl and Peterson 1992b). Antisocial personality disorder, which might be described as rule-breaking behavior (Pihl and Peterson 1992b), may be compared to undersocialized sensation-seeking; that is, means behavior driven by cues of satiation not brought under appropriate, inhibitory control of threat. Zuckerman (1979) formulated the psychological construct of sensation-seeking specifically to determine how intrinsically attractive the exploration of novelty is to a given individual. Variability in sensation-seeking appears influenced substantially by genetic factors (Martin et al 1979). Drugs are novel elements in the cognitive field of drug-naive individuals. Various studies have demonstrated that sensation-seeking is linked to drug use per se, and to a variety of drug use, rather than to the use of any particular drug (Zuckerman 1979; Pedersen 1991; Pedersen et al 1989; Andrucci et al 1989). Pedersen et al (1989) concluded that sensation-seeking was, in fact, a better predictor of drug use than social class, self-esteem, mental health, and various indicators of social bonding. Sensation-seekers find novel experience highly rewarding, and are, therefore, likely to experiment with novel drugs, initially for the experience. Sensation-seekers may also be more likely to continue such use for at least 2 related reasons. First, progressive sensitization and cross-sensitization appear to characterize use of psychomotor stimulants (as described previously). Second, recent evidence suggests that sensation-seekers may be more susceptible to drug-induced psychomotor stimulation, and that they may sensitize more rapidly than more inhibited individuals. Rats, highly exploratory in a novel environment, are more sensitive to cocaine- and amphetamine-induced reward (Hooks et al 1991; Piazza et al 1989), and sensitize more rapidly to such effects (Hooks et al 1991). These rats respond to amphetamine like rats with ventral tegmental DA cell body lesions (Deminiere et al 1989). FAST mice, characterized by increased post-alcohol-consumption open-field activity, also drink up to 50% more than SLOW mice, and manifest rapid sensitization to ethanol's locomotor stimulant properties (Crabbe and Phillips 1990).

Differences in criminal proclivity, defined as reduced sensitivity to cues of punishment and heightened sensitivity

to cues of satiating agents, may be gender-linked. Rates of ASP and substance abuse certainly vary profoundly with gender (Helzer and Pryzbeck 1988). Lifetime prevalence rates of DSM-IV diagnosable ASP and alcoholism (abuse or dependence) among men are 5 times those of women, but men are only half as likely to develop anxiety disorders or to become clinically depressed. Alcoholics are 21 times more likely than nonalcoholics to be diagnosable as ASP. ASP lifetime prevalence rates range from 10% for female alcoholics (compared to 0.81% for female nonalcoholics) to 15% for male alcoholics (compared to 4% of male nonalcoholics). ASP alcoholics begin drinking earlier than non-ASP alcoholics, manifest more symptoms of alcoholism, and remain alcoholics longer. Severity of the 2 disorders is correlated: for women, 0.37; for men, 0.57 (by symptom count). Rate of ASP among alcoholics over 45 doubles to 40 times the population rate compared to alcoholics in general (16 times the population rate) (Helzer and Pryzbeck 1988). Drug use and abuse and alcoholism overlap substantially, as (Helzer and Pryzbeck 1988) 19% of male alcoholics (in contrast to 7% of nonalcoholic men) and 31% of female alcoholics (in contrast to 5% of nonalcoholic women) abuse or depend on more than a single drug.

There is consistent, relatively strong evidence that antisocial tendencies are influenced by genetic factors (Centerwall and Robinnette 1989). In addition, sensitivity to threat among animals can be manipulated effectively through programs of selective breeding (Gray 1987). ASP (i.e., heightened sensitivity to cues of satiation; reduced sensitivity to cues of punishment) may well serve as a marker or a risk factor for alcoholism, as its onset often precedes that of problem drinking. Pre-adolescent and adolescent SOMAs have been consistently described as conduct-disordered and hyperactive, or purely as conduct-disordered, and as impulsive, even in those studies controlling for environmental influence. Male and female children of alcoholics have also frequently been described as conduct-disordered, and are commonly characterized by attention deficits, hypersensitivity to sensory stimulation, and difficulty in regulating emotion (Tarter et al 1985,1988; Pihl et al 1990a). Tarter et al (1990) have demonstrated that SOMAs are impaired in behavioral and affective regulation, and that the degree of such impairment is positively correlated with magnitude of psychiatric, psychosocial, behavioral, and physical health problems. Sher et al (1991) found that children of alcoholics were more behaviorally undercontrolled and more neurotic than controls. Similarly, Harden and Pihl (1995) demonstrated that early adolescent MFH SOMAs had more behavioral problems according to parent ratings. Further, in another study with older subjects (Finn et al 1992), sensation-seeking, stress reactivity and alcohol dampening were found to be linked in an MFH SOMA population and not in controls. Longitudinal studies of pre- and post-pubescent individuals who develop alcoholism later in life generally present similar conclusions. A relatively large proportion of these susceptible individuals have one or more alcoholic parents. Familial alcoholism has long been associated with male sociopathy (Pihl et al 1990a). Furthermore, the relationship between the predisposition to alcoholism and attention deficit disorder or hyperactivity seems to be mediated primarily by aggression (Pihl and Peterson 1992b). Finn et al (1994) have recently shown via cluster analyses 3 subtypes of familial alcoholism, antisocial and mood disorder both with high densities of alcoholism and one low in frequency of both alcoholism and other psychopathology.

A subset of sons of severe male alcoholics, particularly those with extensive family histories of alcoholism, may manifest impairments in the ability to control their motor behavior, to pay attention and concentrate when required (particularly in formally structured situations) and to control aggression in social situations (Pihl et al 1990). Such SOMAs apparently often break rules, and, although they may appear or even be gregarious, are often in conflict with others. These tendencies may well be worsened in severity by parental divorce and neglect, frequently associated with familial alcoholism and its comorbid partner — antisocial personality disorder (Pihl et al 1990).

We have recently studied a conduct-disordered population of boys and have found commonalities and dissimilarities between this population and that composed of MFH SOMAs. The conduct-disordered boys are part of the University of Montreal longitudinal study and have been extensively assessed since kindergarten (Tremblay et al 1991). Physically aggressive behavior was rated by teachers at ages 6, 10, 11 and 12. Figure 10 reflects performance of boys selected from this population categorized according to stability of fighting (stable: consistent at fighting at all 4 ages; unstable: sporadic fighting at all 4 ages; and stable nonfighting: absence of fighting at all 4 ages) on the same neuropsychological tests presented previously for SOMAs. The putative frontal dysfunction displayed by SOMAs is also found in this population of boys with histories of aggression. A factor analysis of an extensive battery of neuropsychological tests administered to this population resulted in derivation of 4 factors. Stable fighters were characterized by deficits on the verbal and executive functioning factors. When each of these factors was co-varied against each other, the executive functioning factor maintained predictive power and was unassociated with a measure assessing degree of family adversity (Seguin et al, forthcoming). In addition, in another study, these boys were characterized by increased autonomic reactivity to the loss of rewards in comparison to nonaggressive subjects. Further, the aggressive population splits into those who are high and low in anxiety (Harden et al, unpublished manuscript). A recent evaluation of the predictive value of the characteristics displayed by these boys in kindergarten to delinquent behavior between the ages of 10 and 13 (Tremblay et al 1994) proved significant. The characteristics of impulsivity (high), anxiety (low) and reward dependence (or prosociality) (low), in that specific order, proved germaine. It is notable how these characteristics correspond to Cloninger's (1987) conclusion of the characteristics of high novelty seeking, low harm avoidance, and low reward dependence as typifying type-II male-limited early-onset alcoholics.

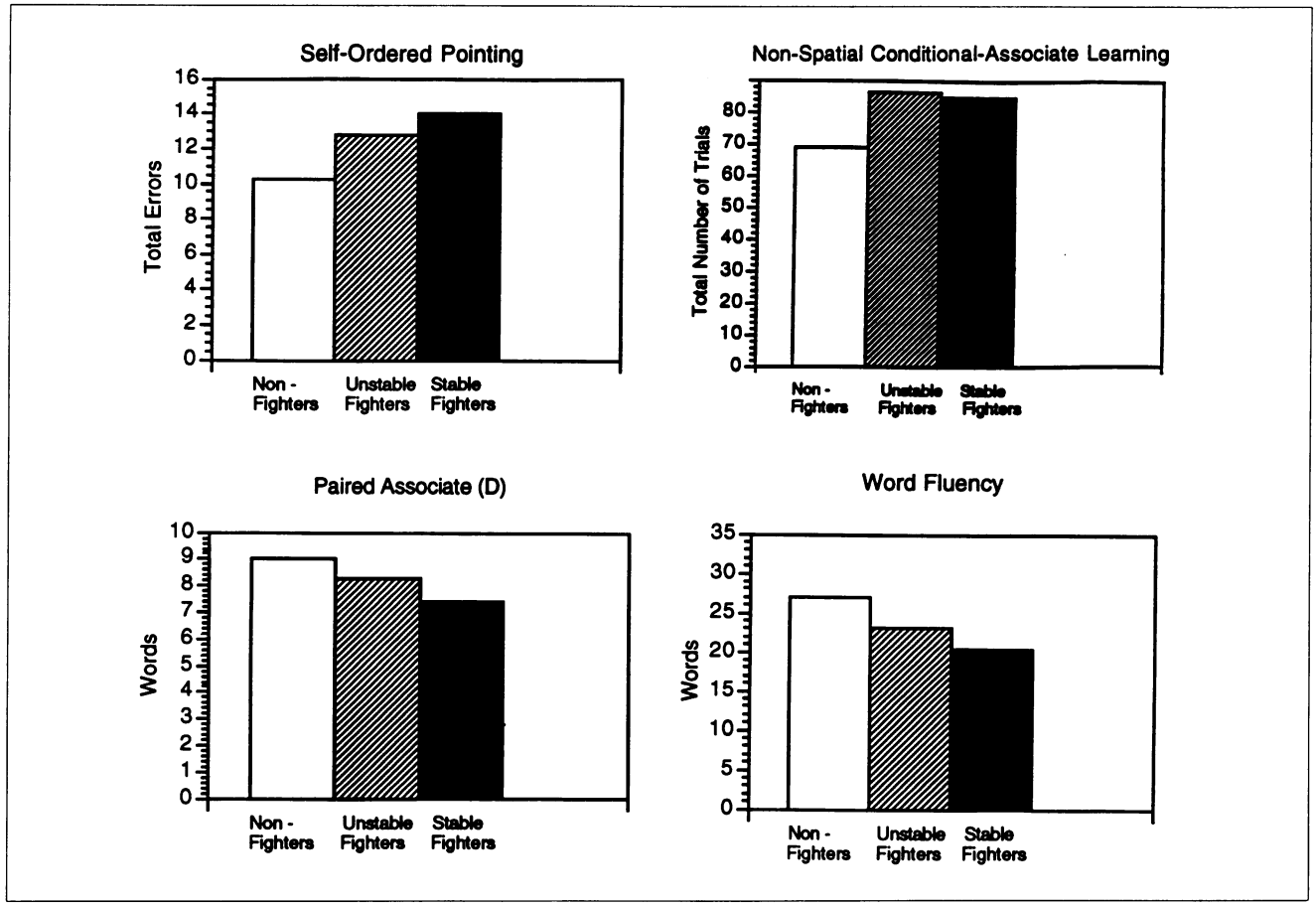

Figure 10. Scores on 4 cognitive tests for boys with stable (n = 63), unstable (n = 55), and no histories (n = 59) of fighting behavior. (Over all group F's significant at $p < 0.01$.) (Study reported in Séguin et al, forthcoming).

CONCLUSION

It has become increasingly apparent, in recent years, that the relevant question with regard to drug abuse and even dependence is not why? but why not? Most psychopharmacological agents ingested voluntarily by human beings for their noncaloric properties are also very attractive to nonhuman animals. This is particularly true in the case of the primary psychomotor stimulants like cocaine and amphetamine. Heroin and morphine are also very rewarding in the unconditioned sense. It is more difficult to get animals to take ethanol, probably because of the taste, but there is little doubt that ethanol shares a psychomotor stimulant property with other primary drugs of abuse. The issue is more complex with the anxiolytics, benzodiazepines and barbiturates, but their intrinsically negatively reinforcing properties are well established. Perhaps if nonhuman animals were capable of worrying as much as human beings, they would like anxiolytics more. The point most fundamentally is this: we have good reason to use drugs, from the perspective of short-term motivation. They are intensely pleasurable, even to those absolutely free of psychopathology. They are also capable of providing intense relief to those oppressed by pain and anxiety. Nonetheless, their long-term effects, with frequent use, are clearly negative, and provide grounds for dire concern. The issue for prevention then becomes this: how can those long-term negative consequences be made sufficiently germane to inhibit excess initial experimentation — presuming that elimination of such experimentation is impossible in a free society? This issue is of particular complexity when consideration is given to the fact that those most likely to abuse drugs — the low anxiety sensation-seekers — are also least likely to respond with behavioral inhibition to a distant threat of punishment.

We have attempted to isolate patterns of individual difference in susceptibility to ethanol-induced reinforcement. Some people appear more sensitive because they are victims of fear. Sons of male alcoholics with multigenerational family histories of male alcoholism appear more fear reactive to threat and novelty because they cannot inhibit their response to such stimuli as rapidly or efficiently as individuals with no family history of alcoholism. Anxiety-sensitive individuals

appear to categorize psychophysiological responses to threat as threatening in and of themselves, and catch themselves in a vicious circle as a consequence. Alcohol serves both these groups well, at least in the short term, because it inhibits anxiety (mimics habituation) regardless of its cause. Other people appear more sensitive because they are particularly attracted by cues indicating something good is likely to happen. Ethanol pharmacologically activates the system that mediates reaction to such cues. Certain individuals appear more sensitive to such activation. We have evidence suggesting that MFH SOMAs are likely to be such people. Perhaps those with antisocial tendencies are as well.

We hope that focus on individual difference of this sort will eventually provide information that will allow for the development of effective prevention and treatment programs. We think that our tentative evidence suggesting that familial alcoholism might be opiate-mediated constitutes one such piece of information. Treatment of alcoholism with opiate antagonists appears promising. What would happen if such treatment were targeted to those who showed initial sensitivity to ethanol opiate effects? Would treatment efficacy improve? What if the clearly anxious were treated for their anxiety, as well as for their ethanol misuse or dependence? Would this be of use? Could the sensation-seeker be encouraged to find other sources of excitement? Could the depressed be encouraged to heighten their activity levels and expand their networks of social interaction? These are optimistic thoughts. Perhaps they might be realized someday in effective action.

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