

Etiology

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In labouring to be brief, I become obscure.
— Homer

GENERAL ISSUES

The task of reviewing etiology of drug addiction is herculean. The construct of addiction is not homogeneous in structure. Many diverse processes terminate in addiction. It might be argued that such processes are so complex that attempts to explain them are futile, a priori. Development of effective treatment for and prevention of addiction, however, requires consideration of causality. It is important to consider definition before addressing etiology. The contradiction characteristic of many present theoretical and practical approaches to drug addiction might be reduced if more well-defined populations were considered. Even samples defined by the comparatively rigorous application of modern diagnostic criteria (such as those outlined in the *Diagnostic and Statistical Manual of Mental Disorders* [3rd ed. rev., DSM-III-R; APA, 1987]) are likely to be heterogeneous in composition. A recent broadly based Edemiological Catchment Area survey determined that approximately 30% of men (a minimum of 13% among Taiwanese and a maximum of 43% among Koreans) met lifetime DSM-III-R criteria for alcoholism (Helzer et al., 1990). Extreme sample variability will in all likelihood continue to detrimentally affect ongoing clinical research, since proposed

DSM-IV diagnosis for substance abuse is dependent upon presence of any two items from a long mixed list of diagnostically significant drug use consequences and behaviours (Nathan, 1991).

It is not even easy to determine what constitutes a drug. Many common foods have a direct pharmacological effect on mood (Woods, 1991; Young, Pihl, & Ervin, 1986). It nonetheless appears unreasonable to "just say no" to chocolate. Any discussion of drug addiction etiology must therefore be formally limited. For the purposes of this article, a drug is (a) defined as a substance administered for reasons other than those of nutrition and (b) discussed if its use may lead to addiction and significantly reduces physical, social, and economic well-being. Discussion centers on psychomotor stimulants (cocaine and amphetamine), anxiolytics (benzodiazepines [BDZ], barbiturates, and alcohol), and analgesics (opiates), and is additionally constrained by the necessity of addressing specific issues relevant to the appended papers, chosen by the editors of this volume. These focus primarily upon biological factors affecting alcohol abuse. This article is predicated on the notion, derived mainly from animal research, that a multifactorial developmental process, originating with drug experimentation, maintained in later stages by pharmacological reward, and complicated by development of tolerance, dependence, and withdrawal, culminates in addiction. Each of these developmental stages vary according to a

complex interaction of genetic predisposition and environmental circumstance.

THE ROLE OF GENES

Genetic-biochemical modeling of behavior became common in the 1980s. Waves of relevant information, thundering against intellectual shores, eroding well-fortified psychological views, erected beachheads of formidably impressive, novel information. Discussion surrounding the genetic control of alcoholism provides a representative example. The reprinted editorial review by Merikangas (1990) details this discussion, and presents the family, twin, adoption, and vulnerability studies that provide its basis. Searles (1987, 1990), Littrell (1988), and Lester (1988) determined that authors of the adoption studies (Merikangas, 1990, Table 4) compared poorly defined groups with inappropriate statistical techniques. Merikangas (1990) concludes nonetheless that alcoholism is familial in nature, and that genetic factors in part underly this familial predisposition.

Merikangas (1990) additionally reviewed studies of association and linkage and noted "there is not a single study in which linkage between a known genetic marker and alcoholism has been conclusively demonstrated" (p. 16). Recent events have rendered this observation, in part, dated. Blum et al. (1990) reported identification of a candidate marker for severe alcoholism: increased prevalence of the A1 allele of a Taq 1 polymorphism, close to the dopamine D2 receptor gene. This report set off a flurry of commentary and investigation. Gordis, Tabakoff, Goldman, and Berg (1990) initially highlighted the need for caution in interpreting the findings of Blum et al. (1990), noting (a) the improbability that a single powerful gene controlled the development of alcoholism; (b) that examination of genetic material from individuals with heavily saturated family pedigrees of alcoholism would have to precede final identification of relevant genes; and (c) that the link between the A1 allele and alcoholism might depend upon specific, idiosyncratic characteristics of alcoholics comprising the studied group.

Bolos et al. (1990) failed to replicate Blum's finding, suggesting that Blum's controls were characterized by abnormally low prevalence of the A1 allele, and that his alcoholic subjects were poorly described. Bolos et al. (1990) were subsequently criticized by Smith, Gorelick, O'Hara,

and Uhl (1991) for using "population controls" who may have been or might have become alcoholic. Noble and Blum (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991) then reanalyzed a subset of Bolos' data, claiming that severity of alcoholism in that sample corresponded to increased prevalence of the A1 allele. Parsian et al. (1991) reported that prevalence of the A1 allele was increased among alcoholics with severe medical problems (but could not link presence of this allele to alcoholism in family pedigrees). Comings et al. (1991) determined that patients with a variety of impulsive disorders were all characterized by increased prevalence of the A1 allele and suggested that variants of the dopamine D2 receptor gene might secondarily modify the severity or expression of conditions influenced primarily by other (genetic or nongenetic) factors. Gelernter et al. (1991) simultaneously published a report of failure to demonstrate association between the A1 allele and alcoholism.

Cloninger (1991) subsequently performed a brief analysis of the cumulative study data to date, concluding that differences among studies may be explained (a) by sampling variation expected in relatively small sample investigations, and (b) by Bolos' and Gelernter's exclusion of alcoholics with severe medical problems. Cloninger concluded that the A1 allele is in fact associated with alcoholism in the general population, but is not tightly linked to alcoholism in pedigrees. A recent meta-analysis of relevant studies concluded (in essential accordance with Cloninger) that the A1 allele is approximately 2.5 times more likely to be found in alcoholics than in nonalcoholics (Uhl, Persico, & Smith, in press). Presence of the A1 allele apparently modifies expression of various disorders, like alcoholism, controlled more directly by other genetic factors.

Studies assessing genetic influence on substance abuse and dependence have a number of additional limitations. Variability in the cortical and subcortical systems that respond to the various reinforcing effects of drug experimentation, use, tolerance, dependence, and withdrawal appears controlled by many independent physiological mechanisms, and is therefore logically affected by many independent factors. It seems important to investigate and to separate analysis of genetic contribution by examination of these factors. Was drug use initiated as part of normal or heightened adolescent exploratory behavior? Was such use primarily rewarding, anxiolytic,

or analgesic? At what rate did tolerance develop? How did abuse, mediated theoretically by initial pharmacological reinforcement, transform into dependence? Was subsequent drug use predicated on avoidance of withdrawal? Did the abusing individual have access to other rewarding activities? Did drug use threaten or limit access to these alternatives? Consideration of such issues may necessarily precede useful examination of heritability. It might not be possible to finally determine whether or not addictive processes, as currently defined, are genetically mediated. However, it may be possible to determine whether specific (drug-naive, drug-familiar, or drug-dependent) patterns of reaction to particular classes of related drugs are under genetic influence.

Furthermore, examination of individuals "family-history-positive" for substance abuse or dependence is unlikely to clarify the nature of the genetic contribution to these conditions. The children or lesser kin of the 30% of men who apparently meet DSM-III-R criteria for alcohol abuse/dependence at some time in their life (Helzer et al., 1990) are merely the relatives of one third of men. Studies of vulnerability should be limited to individuals with multigenerational family histories of addiction-prone relatives who meet stringent, homogeneous criteria for specific patterns of drug use and abuse. Care must also be taken to control for the potentially confounding teratogenic effects of the drug in question.

Hesselbrock, Bauer, Hesselbrock, and Gillen (1991) and Newlin and Thomson (1990) described the potential impact of parental drinking prior to or during the course of pregnancy. The (assortative) tendency for daughters of alcoholics or daughters of antisocial men to marry alcoholics means increased likelihood of maternal drinking. Even moderate ethanol consumption during pregnancy might produce fetal alcohol effects that could increase risk (Streissguth et al., 1986). Similarly, elevated paternal consumption rates might detrimentally affect spermatogenesis, seminal fluid, and DNA composition, and alter early pre- and postnatal development. Human infants fathered by regular drinkers weigh less than those fathered by nondrinkers, after control established for maternal alcohol and nicotine use (Little & Sing, 1986). The offspring of male rats who drink heavily prior to and at the point of conception are characterized by lower birth weight (Able & Lee, 1988; Anderson, Baylor, & Zaneveld, 1978); increased susceptibility to in-

fection and stress (Able, Hazlett, Berk, & Mutchnik, 1990); various learning abnormalities (Able & Lee, 1988; Able & Tan, 1988); and alterations in noradrenergic, serotonergic, and m-enkephalergic cortical systems (Nelson, Brighwell, MacKenzie-Taylor, Berg, & Massari, 1988).

THE INITIATION OF USE

Drug abuse begins with drug use. Various factors affect propensity to experiment. Individual and social variables each have their effect. Drugs might be considered novel elements in a cognitive field. The rewarding properties of novelty vary considerably between individuals. Zuckerman (1979) formulated the psychological construct of sensation-seeking specifically to assess individual differences in reaction to novelty. A large number of studies have demonstrated that propensity to sensation-seek is linked powerfully and consistently to drug use per se, and to variety of drug use, rather than to use of any particular drug (Andrucci, Archer, Pancoast, & Gordon, 1989; Pedersen, 1991; Pedersen, Clausen, & Lavik, 1989; Zuckerman, 1979). Pedersen et al. (1989) concluded that sensation-seeking was a better predictor than social class, self-esteem, mental health, and various indicators of social bonding. Sensation-seekers find novel experiences particularly rewarding, and therefore are logically driven to experiment with the ingestion of novel substances, perhaps initially for the novel experience.

Most individuals know that illicit and licit drugs exist, prior to initiation of use, but the consequences of such use remain subject to speculation. Familial, societal, and peer opinions determine this speculative context. Drug use is subject to social pressure. North American society is in conflict with regards to licit alcohol and nicotine use, and the social context within which these drugs exist is a combination of contradictory messages, some linking drug use with punishment (automobile accidents, cancer), some linking drug use with reward (enhanced lifestyle, precocious maturity, weight loss or maintenance). Illicit drug use, by contrast, viewed with official suspicion, has been made subject to formal social pressure, in the form of the law. Various cultural subgroups, existing within the more formal system, view particular drugs in various ways, some of which conflict with the official view. Drugs exist in a highly conflicted milieu, and this has complex effects on likelihood

of experimentation and on continued use. Illicit drug use has different personal and social costs and benefits, which vary according to individual predisposition and cultural status.

An excellent review by Dryfoos (1990) concluded that powerful associations exist between drug use, abuse and early initiation, limited expectancy for education, low academic achievement, misconduct, high peer identification and influence, lack of belief that drug use will harm, low church attendance, and lack of parental support. Chassin, Rogosch, & Barrera (1991) examined a large community sample and determined that children of (recently drinking) alcoholics were at particular risk for alcohol and drug use in adolescence. These children were characterized by high levels of "internalizing" (anxious) and "externalizing" (acting-out) symptomatology. Sher, Walitzer, Wood, and Brent (1991) demonstrated similarly that children of alcoholics had more problems with drugs and alcohol, and had particularly strong expectations regarding alcohol effects.

Drug use expectancies have been studied in particular detail. Expectancies predict use (Christiansen, Smith, Roehling, & Goldman, 1989; Leigh, 1989; Stacy, Newcomb, & Bentler, 1991), although debate about what constitutes expectancy continues. Stacey and colleagues' (1991) 9-year longitudinal study of 415 women and 169 men demonstrated that cognitions regarding drug-induced induction of positive and alleviation of negative affect predicted use of marijuana and alcohol in adolescence and adulthood. Expectation of positive effect predicted most powerfully, in accordance with Goldman, Brown, Christiansen, and Smith (1991). Stacey et al. (1991) believe, however, that such cognitions exist and have a powerful effect upon behavior prior to any initiation of use, in contrast to Goldman et al. (1991), who believe that expectancies are affected by drug experience itself.

Individuals who accept formal North American social morality are likely to be deterred from experimentation (and continued use), if society imposes sanctions on experimentation. Sanction links drug use, and experimentation, with punishment. Well-socialized individuals are likely to benefit by, or fall prey, to such an approach. Pope, Ionescu-Pioggia, Aizley, and Varma (1990) investigated drug use among college seniors in 1969, 1978, and 1989. The 1989 students were characterized by "strikingly lower" incidence of illicit drug use (although use of socially

approved alcohol has not declined), and by much decreased rates of self-reported "alienation from American society", a measure that robustly distinguished users from nonusers in 1969. Bachman, Johnston, and O'Malley (1990), in their review of annual nationwide American surveys of drug use, concluded that the significant decline in marijuana and cocaine use during the 1980s could be accounted for by increased perception of danger. These authors conclude that increased provision of reliable and accurate information about the dangers of illicit drug use could further reduce such use. However, formal provision of such information must be considered credible to be effective. Individuals alienated from the formal system doubt its statements; those who are enmeshed within it consider such statements personally applicable and relevant. If drug use is linked with effective punishment (which means that it is considered punishment and considered justified by those so punished), then drug use and experimentation may decline. Formally, such linkage makes drug experimentation and use anxiety-provoking. This induced anxiety is likely to exist in contrast to and limit the intrinsically reinforcing consequences of drug experimentation and use.

The punishments associated with drug experimentation and use, whether applied formally within society, or experienced as a direct consequence of the drug itself, are necessarily experienced within a given context. The negative consequences associated with experimentation and excess substance use depend primarily upon loss of expected reward, at least in the initial stages. Alcohol-induced job loss will not threaten someone who does not find work worthwhile, or who is unemployed. The negative social consequences of drug and alcohol abuse will not appear negative to someone who derives nothing positive from his/her participation in or identification with the formal social milieu. In addition, the direct psychomotor rewards associated with drug experimentation and use may appear particularly rewarding to an individual who has few other modes of eliciting such activation—to someone unsuccessful in the social world or in the course of his/her own personal endeavors.

It is interesting, somewhat surprising, and important to note that adolescents who never experiment with drugs (in particular, marijuana) may be more maladjusted than those who experiment occasionally, and as disturbed as those who abuse drugs (Shedler & Block, 1990). At age

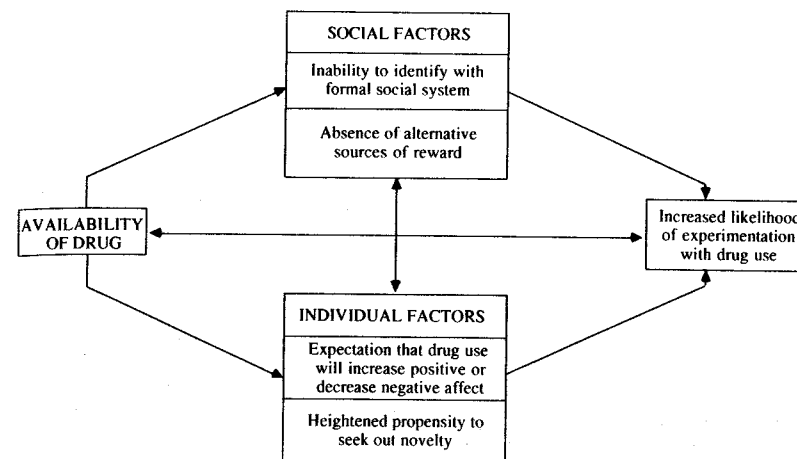


Figure 1. Various factors affecting experimentation with drugs.

11, prior to initiation of drug experimentation among the majority of children, abstainers were "fearful and anxious, inhibited and constricted, immobilized under stress, anxious in unpredictable environments, not curious and open to new experience, not vital or energetic or lively, not confident, not responsive to humor, and not cheerful" (p. 627). Mothers of abstainers and of abusers appeared equally disturbed, quantitatively and qualitatively; unresponsive, critical, lacking warmth and rejecting. Fathers of abstainers, however, were characterized as comparatively authoritarian, autocratic, and domineering. Abusers appeared neither self-confident, nor socialized. Abstainers lack self-confidence, to the same degree, but may have been subjected to punitive socialization, and have lost the ability to separate from or doubt authority. They have perhaps substituted healthy skepticism and self-respect for the tyranny of subjugation. Outside explored territory, as a consequence, they appear lost.

Factors influencing initiation of drug use are schematically presented in Figure 1.

REINFORCEMENT MECHANISMS AND DRUG EFFECTS

Drugs with high abuse/addiction potential fall into three broad categories, in accordance with their effects: directly rewarding psychomotor

stimulation, negatively reinforcing anxiolysis, and negatively reinforcing analgesia. Amphetamines, cocaine, and their chemical analogs are primary psychomotor stimulants (Wise, 1988). Benzodiazepines and barbiturates are primary anxiolytics (Gray, 1982, 1987). Opiates are primary analgesics, but the evidence for their psychomotor stimulant properties is also strong (Wise, 1988). Other commonly abused drugs have less definitely defined or mixed properties. Alcohol, for example, is a psychomotor stimulant (Wise, 1988) and a potent anxiolytic (Gray, 1982, 1987), and may have specific analgesic effects, at doses commonly self-administered for pharmacological effect. Nicotine, caffeine, cannabis, and phencyclidine also activate the psychomotor system (Wise, 1988), and there is evidence that BDZs and barbiturates have some stimulant properties (Wise, 1988), particularly to individuals with histories of substance abuse.

THE PSYCHOMOTOR SYSTEM

The neurological system most affected by psychomotor stimulants utilizes dopamine as its primary neurotransmitting chemical. The psychomotor system apparently allows animals to develop and utilize behavioral strategies appropriate to various motivated states. The unconditioned consequence of activating the psychomotor system (specifically, stimulation of the

medial forebrain bundle, an integral part of the dopaminergically mediated psychomotor system) is increased novelty-induced exploration of and interaction with biologically relevant stimuli in the environment (Wise, 1988). It appears that the reward associated with psychomotor activation is akin to the pleasure of involvement in useful activity: the subjective sensation of participating actively in something worthwhile. Artificial stimulation of the psychomotor system is rewarding in the primary sense, unconditioned (unlearned) and innate, accompanied by (human) feelings of euphoria, expansiveness, and increased power and energy. Animals will activate electrodes or self-administer chemicals that stimulate the dopaminergic psychomotor system, and develop conditioned place preference for locations in which such stimulation takes place (Fibiger & Phillips, 1988), although there is considerable variation in human and animal willingness to initiate self-administration, in vulnerability to drug incentive effects, and in rate of development of dependence (Deminiere, Piazza, Le Moal, & Simon, 1989). Gawin (1991) has reported that a variable period of 2-4 years typically separates initiation of cocaine use and addiction.

Drugs that block the action of dopamine receptors, such as the antipsychotic neuroleptics, reduce intracranial self-stimulation (ICS) in a dose-dependent manner, by reducing the rewarding effects of that stimulation. Drugs that destroy dopaminergic neurons, such as 6-hydroxydopamine, reduce ICS and intravenous self-administration, and block amphetamine-induced conditioned place preference. Psychomotor stimulants, by contrast, facilitate ICS, increasing response rate and decreasing current threshold (Fibiger & Phillips, 1988). Use of stimulants may increase the rewarding properties of other forms of reward (Wise, 1988), and initially induces reverse tolerance (sensitization) and cross-sensitization to general stimulant effect (Wise, 1988). This means that use of one stimulant, such as amphetamine, increases the reward induced by independent use of another, such as cocaine, heroin, or alcohol. This stimulant property might explain in part the high rate of overlap between abuse of various classes of drugs. Cross-sensitization also characterizes amphetamine and stress (Deminiere et al., 1989). Repeated stress renders animals more reactive to amphetamine administration, and conversely, repeated injection of amphetamine mimics bio-

chemical and behavioral consequences of stress on dopamine activity (Deminiere et al., 1989).

Cocaine augments dopaminergic neuronal activity by prolonging the effects of released dopamine, by blocking reuptake processes that normally terminate local dopaminergic activity. Amphetamine has a similar effect, but may also release dopamine and norepinephrine (Koob & Bloom, 1988). Ventral tegmental dopamine neurons increase their firing rate after exposure to alcohol, and appear very sensitive to this alcohol effect (Gessa, Muntone, Collu, Vargiu, & Mereu, 1985). These neurons are also considered to mediate the behavioral stimulant effects of the psychomotor stimulants (Gessa et al., 1985). The stimulant effects of alcohol are clearly dose-dependent. Low and moderate doses increase rat motility (grooming, locomotion, and rearing) and increase dopamine release in the nucleus accumbens. Alcohol doses high enough to rapidly induce sedation initially lower dopamine levels in the nucleus accumbens (an integral component of the psychomotor brain reward system). Alcohol also has differential effects during the rising and falling limbs of the blood alcohol curve. Newlin and Thomson (1990) suggest that researchers who have determined that children of alcoholics are sensitized to alcohol, and those who see them as resistant, have tested them at different points on this curve. These authors suggest that such children are hypersensitive during the initial phase but acutely tolerant during the latter phase of ethanol intoxication.

Genetic and environmentally mediated variability in CNS psychomotor/dopaminergic function has been directly and peripherally linked to variability in substance use and abuse propensity. Directly: Damage to this system interferes with maintenance of normal state-relevant motivated locomotor activity (Koob & Swerdlow, 1988). In addition, dopamine D2 receptors appear in the psychomotor activation system pathways, and their drug-induced stimulation appears rewarding. The existence of the A1 allele described previously in some detail may provide a marker for the identification of nervous systems characterized by decreased dopamine D2 receptor function in the brain reward system (Blum et al., 1990) and potential consequent heightened need for pharmacologically induced stimulation. Finally, rats bred or otherwise manipulated for alcohol preference (McBride, Murphy, Lumeng, & Li, 1990, discussed in detail below) and/or other drug preference manifest

various abnormalities in their central sober and drug-intoxicated dopaminergic function (Deminiere et al., 1989).

Indirect evidence linking psychomotor/dopaminergic function to substance use and abuse can be derived from study of sensation-seeking/exploratory humans and animals. Sensation seekers are more likely to initiate use, as described previously. They may also be at increased risk for use maintenance, for a variety of reasons. First, progressive sensitization and cross-sensitization appear to characterize initial psychomotor stimulant use, as described previously. In addition, there is recent evidence that sensation-seekers may be more susceptible to drug-induced reward, per se, and to stimulant sensitization. Rats more exploratory in a novel environment are characterized by increased sensitivity to the rewarding properties of amphetamine and cocaine (Hooks, Jones, Smith, Neill, & Justice, 1991; Piazza, Deminiere, LeMoal, & Simon, 1989) and by more rapid development of sensitization to the rewarding effects of amphetamine (Hooks et al., 1991). Such rats respond to amphetamine much like rats characterized by induced lesions of ventral tegmental area dopamine cell bodies (Deminiere et al., 1989). This is interesting, given that rat pups treated with 6-hydroxydopamine are characterized by juvenile hyperactivity, and by persistent deficits in avoidance learning (Shaywitz, Yager, & Klopfer, 1976).

It is also of interest to note that conduct disorder/antisocial personality (ASP) and psychopathy have been linked to reward (or psychomotor) dominance (Gorenstein & Newman, 1980; Shapiro, Quay, Hogan, & Schwartz, 1988) and/or to failure to inhibit behavior in the face of threat or novelty (Gray, 1982, 1987). Antisocial personality therefore appears associated with sensation seeking, from a theoretical perspective, in that undersocialized sensation seekers may manifest antisocial behavior. These theoretical linkages perhaps account in part for the extremely powerful association between childhood hyperactivity/conduct disorder/ASP and substance abuse (Helzer & Pryzbeck, 1988; Pihl & Peterson, 1990). Sensation seekers/ASP individuals may not inhibit their rule breaking (such as substance abuse) because they are not as threatened by actions that fail to support the socially predicated general cognitive map/expectancy model (described in detail below), which tonically inhibits anxiety. Actions that undermine the general cognitive map might even be perceived as re-

warding, insofar as they introduce novelty into otherwise boring, predictable rule-governed circumstances.

Differences in sensation seeking and ASP may be sex or sex-hormone linked. Administration of the neurotetrapeptide cholecystokinin (CCK) reduces rat exploratory behavior, at nonsedative doses. This reduction can be counteracted by various CCK receptor antagonists (Harro and Vasar, 1991). There is evidence suggesting that postnatal manipulations of androgen level alters CCK responsiveness (Ulibarri, Popper, & Micovych, 1990). Female rats administered testosterone postnatally showed reduced sensitivity to the ability of CCK to inhibit lordosis, an overt display of sexual intent. Gray (1987) has specifically linked inhibition of such sexual behavior to fear. Testosterone level has been associated positively in many social species with level of dominance (Rogers & Astiningsih, 1991; Winslow & Insel, 1991). Dominant males are less inhibited in their behavioral displays (Winslow & Insel, 1991) and are less stressed following social conflict (Huhman, Moore, Ferris, Mougey, & Meyerhoff, 1991). Submissive males administered testosterone tend subsequently to rise in the social dominance hierarchy (Rogers & Astiningsih, 1991), and social defeat often precedes testosterone decrease (Huhman et al., 1991). Higher testosterone levels may also characterize men who were violent criminals (Dabbs, Frady, Carr, & Besch, 1987), victors of sporting events (Booth, Shelley, Mazur, Tharp, & Kitlok, 1989; Elias, 1981), actors, and football players, in contrast to ministers (Dabbs, de La Ruc, & Williams, 1990), and boys displaying low frustration tolerance and physical/verbal aggression (Olweus, Mattsson, Schalling, & Low, 1980). Higher levels of testosterone in general appear to be associated with reduced behavioral inhibition and increased psychomotor activity in the face of novelty and threat.

There are profound cross-culturally validated sex differences in rate of antisocial behavior and associated, overlapping rates of substance abuse (Helzer & Pryzbeck, 1988). Men are 5 times more likely than women to display DSM-III-R diagnosable ASP characteristics during their life span and, by contrast, are about half as likely to develop anxiety disorders or depression. Men are also 5 times as likely as women to be diagnosed alcoholic. Alcoholics are 21 times more likely than nonalcoholics to suffer from comorbid ASP. Lifetime prevalence rates for ASP range from

10% for female alcoholics (compared to 0.81% of female nonalcoholics) to 15% for male alcoholics (compared to 4% of male nonalcoholics). Alcoholics with ASP are also characterized by earlier mean onset of alcoholism (20 years of age) compared to alcoholics without ASP (24 years), have a higher lifetime alcoholism symptom count, and stay alcoholic longer. The severity of the two disorders, by symptom count, is correlated at .37 for women, and .57 for men. Furthermore, the rate of comorbid ASP among alcoholics over the age of 45 doubles (40 times population rate), in comparison to that which characterizes younger alcoholics (16 times population rate) (Helzer & Pryzbeck, 1988). These latter figures are particularly interesting, given that a large number of males drink heavily in adolescence and early adulthood, but control their intake upon the adoption of formal adult responsibilities: marriage and career, in the mid to late twenties, as described in the reprinted article by Frank, Tuer, and Jacobson (1990) and by Zucker (1987). Frank et al. (1990) do not discuss abuse directly, but describe mildly antisocial patterns of behavior associated with increased male drinking.

Equally interesting is the degree to which drug use and alcoholism overlap (Helzer & Pryzbeck, 1988). Nineteen percent of alcoholic men (compared to 7% of nonalcoholic men) and 31% of alcoholic women (compared to 5% of nonalcoholic women) abuse or depend upon one or more other drugs. Lifetime alcoholism prevalence for those using THC, the active ingredient in marijuana and related preparations, is 36%. Amphetamine and cocaine abusers, profoundly at risk, have alcoholism prevalence rates of 62% and 84%, respectively. It seems apparent that anyone seeking drug-induced reward, willing to ignore the social threat inherent in illegal use, is almost impervious to the milder social control imposed upon alcohol consumption. Furthermore, the issue of multidrug titration has also been underexplored. Cocaine and amphetamine users often report that alcohol dampens the negative effects of such use. Alcohol's pronounced ability to potentiate GABA-mediated inhibition of neuronal hyperexcitability (described below) might account in part for its mixed administration with psychomotor stimulants.

Sons of male alcoholics (SOMAs) are at 4-9 times higher risk for the development of alcoholism (Cloninger, 1987), especially if further characterized by dense multigenerational family his-

tory of male alcoholism. SOMAs appear particularly sensitive to what may be the direct, positively reinforcing effects of acute alcohol intoxication, often display childhood hyperactivity and conduct disorder, and often come from families with high rates of male antisocial personality (reviewed in Pihl, Peterson, & Finn, 1990). Pollock et al. (1983) noted that alcohol-intoxicated SOMAs were characterized by increased production of electroencephalogram waveforms associated with states of well-being and pleasure. This may be particularly relevant, given that Gabrielli et al. (1982) noted previously that SOMAs produce more high frequency waveforms when sober, like alcoholics (Mendelson & Mello, 1979), and that this (beta) production has been associated with subjective feelings of tension and anxiety (Kiloh & Osselt, 1961). Finn and Pihl (1987, 1988); Finn, Zeitouni, and Pihl (1990); and Peterson, Giancola, and Pihl (1990) demonstrated that the baseline heart rate of SOMAs with multigenerational family histories of male alcoholism increases significantly, when compared to controls, within 20 min of relatively high dose alcohol ingestion. This baseline rise could be indicative of positive affect, as drug-induced increases in heart rate have been linked, in some situations, with reward (Fowles, 1983; Wise & Bozarth, 1987). Recent research conducted by Peterson, Pihl, Seguin, Stewart, and Finn (in press) suggests that this alcohol-induced increase is highly correlated with weekly rates of voluntary alcohol consumption, among SOMAs and controls. SOMAs could conceivably be characterized by heightened sensitivity to the psychomotor stimulant properties of alcohol, by rapid development of sensitization to these effects, or by some combination of both factors. SOMAs may also be more sensitive to the detrimental effects of alcohol withdrawal (Newlin & Thompson, 1990).

The consequences of withdrawal from psychomotor stimulants are likely to contribute to their abuse. Tolerance to psychomotor stimulant euphoric properties develops rapidly (Gawin, 1991; Karan, Haller, & Schnell, 1991). Long-term binge use of cocaine results in neurotransmitter depletion, and behavioral sequelae of depression, fatigue, poor concentration, loss of self-esteem, decreased libido, increased motor tremor, paranoia, and insomnia. Acute cocaine withdrawal consists of strong craving, EEG abnormalities, depression, sleep pattern alteration,

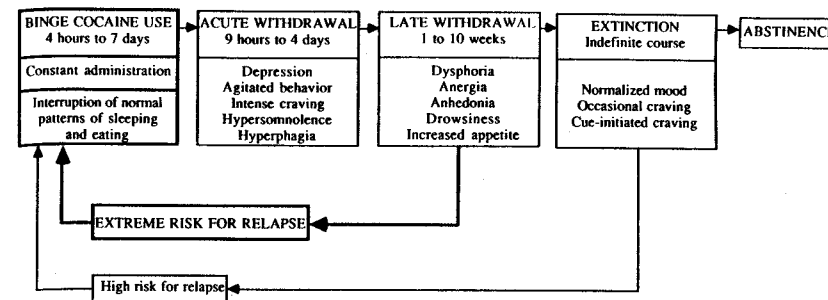


Figure 2. Schematic of the cocaine binge withdrawal syndrome. From "Cocaine Addiction: Psychology and Neurophysiology" by F. H. Gawin, 1991, *Science*, 251, pp. 1580-1586. Copyright 1991 by the American Association for the Advancement of Science. Adapted by permission.

hypersomnolence, and hyperphagia (Gawin, 1991; Karan et al., 1991). Chronic dysphoria, anergia, anhedonia, drowsiness, increased appetite, and decreased initiative (Koob & Bloom, 1988) predominate for a 1- to 10-week period following cessation of use, and gradually remit (Karan et al., 1991). During this period, the memory of cocaine euphoria is particularly pronounced. Later, conditioned cocaine craving tends to reappear in situations associated with cocaine use, for an indefinite period (Koob & Bloom, 1987). Similar symptomatology accompanies withdrawal from other primary psychomotor stimulants (Mirin, Weiss, Griffin, & Michael, 1991). Relapse, of course, induces rapid but temporary symptom remission. The cocaine withdrawal syndrome is illustrated graphically in Figure 2.

Psychomotor stimulant abusers set the stage for further abuse by indulging in drug binges. The typical binge, averaging 12 h, may last as long as 7 consecutive days (Karan et al., 1991). The binge-using drug-seeking pattern of behavior increasingly dominates the stimulant abuser's life, devouring financial resources and interfering with social and economic responsibilities. Food, rest, and health care are increasingly irrelevant (Karan et al., 1991). The stimulant abuser, like many drug users, is in a precarious situation, even when detoxified, and during the stages of acute withdrawal. Chronic or conditioned craving-induced risk for relapse may be further complicated by what has become known as behavioral or associative tolerance (Poulous

& Cappell, 1991). Stewart, de Wit, and Eikelboom (1984) concluded that stimuli contiguously paired with psychomotor stimulant administration become capable of independently engendering neural states similar to those induced by the drug itself. Such states might serve as partial basis for conditioning craving. In addition, addicts have often limited their access to alternative conventional sources of social and economic stability and pleasure by indulging in erratic drug-driven behavior, or have replaced such sources with social and economic networks dependent solely on drug use. Destruction of normal lifestyle is likely to intensify anxiety and depression, and additionally limits opportunity for participation in non-drug-induced rewarding activity.

THE ANXIETY SYSTEM

Individuals apparently vary in their susceptibility to direct pharmacological reward, and to the development of sensitivity to such reward. By the same token, people also vary in their susceptibility to indirect pharmacological reward, to the alleviation of anxiety and physical or emotional pain. The basic rewarding properties of stimuli vary according to the motivational state of the organism encountering the stimuli. Anxiolytics are likely to be particularly (negatively) reinforcing to those who are anxious. Anxiety appears to protect organisms from punishment—from pain and the absence of expected reward (Gray, 1982, 1987)—by inhibiting ongoing behavior in the presence of novel stimuli and stim-

uli previously associated with punishment. Anxiety can nonetheless become a source of serious distress in and of itself. Anxiolytic drugs—BDZs, barbiturates, and alcohol—appear capable of alleviating this distress, regardless of its etiology.

Novelty-induced psychomotor activation, in the form of exploratory behavior, allows animals and humans to build complex memory-based viewer-independent (Squire & Cave, 1991) cognitive maps (Nadel, 1991) or expectancy models (Luria, 1980; Sokolov, 1969; Vinogradova, 1975) of their territory. Expectancy models are also dependent in their development upon complex processes of socialization (Luria, 1980). Ongoing integrated sensory experiences are constantly compared to this model of reality, which is updated in memory through exploratory and other information-seeking activity, when incomplete (Peterson & Pihl, 1990). Expectation allows for prediction—for determination of future events based upon the dynamic configuration of present events. The predictability of the future is necessarily associated with security, and associated freedom from anxiety. An intact cortically based cognitive map, or expectancy model, permanently established through hippocampally mediated activity, during the course of novelty-induced exploratory behavior tonically inhibits anxiety, in a familiar environment. In addition, the expectancy model provides a framework within which individuals can participate in socially sanctioned modes and socially developed patterns of rewarding psychomotor activity.

The process by which novelty-induced anxiety or curiosity is tonically or actively inhibited (through the processes of socialization or through active exploration) appears to become pathological when behavioral or cognitive patterns designed to control stimuli that induce anxiety are extremely rigid and inflexible in structure, when they fail and cannot be reconstituted, or when they cannot be designed in the first place. Processes as diverse as familial dysfunction, socio-cultural disintegration, economic uncertainty, and cognitive dysfunction appear to destabilize or interfere with development of the general expectancy model, and have as necessary consequences reemergence of previously controlled or initial failure to inhibit anxiety.

Field (1962) subjected a data set containing information on the alcohol use of 120 societies to extensive analysis, and concluded that inebriation increased with increased structural and functional instability of formal kin relationship.

Structural instability, especially within the context of more traditional, family-oriented societies, means destabilization of anxiety-inhibiting belief structure. Functional instability means reduced opportunity for participation in socially-sanctioned rewarding psychomotor behavioral patterns. Members of traditional cultures, whose integrity has been destroyed by rapid experiential transformation, have perhaps therefore been rendered extremely vulnerable to various forms of substance abuse. This is particularly obvious in the case of the devastated aboriginal people, whose situation has been further worsened by their cultural inexperience with alcohol.

Barry, Bacon, and Child (1965), examining the same data set, emphasized the consequences of child-rearing practices that stressed childhood dependence, in societies that paradoxically required adult independence. Childhood rearing practices that stress dependence fail to promote the sophisticated ability to create individual behavioral patterns, or context-independent belief systems. Dependent individuals are trained to rely on the advice of others when confronted by the unexpected, or, conversely, may be punished or remain unrewarded for self-initiated exploratory activity. This appears to render such individuals extremely susceptible to the development of pathological anxiety in those situations where conventional authority disappears or loses its validity.

More primary cognitive factors may also play a role. There appear to be cognitive/information-processing deficits, which make the initial classification of novel or threatening information difficult, and therefore heighten susceptibility to cued anxiety. A subset of SOMAs may be characterized by such a deficit. Evidence suggesting that SOMAs may manifest abnormalities in the function of the system that compares actuality with expectancy can be derived most directly from studies that concentrate on the cortical event-related potential (ERP) and/or upon general psychophysiological response to specific stimuli.

The cortical ERP, a waveform of approximately 0.5-s duration, derived from the EEG, is produced by the electrical response of the brain to brief stimulus of any modality, when active attention is devoted towards discrimination or when the specified target occurs unpredictably (Porjesz & Begleiter, 1981). P300 latency appears to depend upon processing speed (Donchin, Ritter, & McCallum, 1978), and P300 am-

plitude upon subjective event meaning (Halgren et al., 1980). Unpredictable/novel events elicit large P300 amplitudes (Duncan-Johnson & Donchin, 1977). The P300 component has been described as an electrophysiological manifestation of the orienting response (Donchin, 1981; Porjesz & Begleiter, 1985), with its probable origin in the hippocampus and amygdala (Halgren et al., 1980; Okada, Kaufman, & Williamson, 1983). SOMAs are generally characterized by reduced P300 amplitude and/or by increased P300 latency, averaged over the course of a large number of trials (Peterson & Pihl, 1990). This general conclusion is probably too simplistic, however, because P300 response varies with predictability and novelty.

Hill, Steinhauer, Park, & Zubin (1990), as reported in another reprinted article, conducted their analyses carefully enough to control for these confounding factors. These authors analyzed the ERP reactions of children (male and female) of alcoholics with positive family histories of alcoholism (FH+) and controls according to the conditional probability of target stimulus appearance. Children of FH+ alcoholics were characterized by larger mean P300 amplitudes and shorter latencies than children of controls, when exposed to the most unpredictable target stimuli, and produced smaller P300 amplitudes with longer latency to the more predictable targets.

Non-university-educated children of alcoholics (particularly the SOMAs) with well-defined and extensive histories of severe paternal-lineage familial alcoholism are apparently characterized by attenuated amplitude or delayed latency of P300 response to stimulus presentation requiring voluntary, directed attention and/or higher order cognitive or linguistic processing (stimuli that are predictable, and therefore boring), and by enhanced P300 production to stimuli that are novel or threatening. The motivational significance of a task undertaken in accordance with social (experimenter) demand appears to deteriorate more rapidly among SOMAs because of decreases in novelty or increases in predictability than among matched controls. When SOMAs are faced with involuntarily or intrinsically motivating stimuli, by contrast, the situation appears reversed.

Finn and Pihl (1987, 1988) demonstrated that sober young adult nonalcoholic SOMAs with extensive multigenerational family histories (MFH) of paternal-lineage alcoholism mani-

festated increased heart rate and decreased digital blood volume amplitude when anticipating and receiving mild electrical shock. Finn et al. (1990) reported a similar pattern of cardiovascular hyperreactivity among SOMAs faced with and receiving avoidable and unavoidable signalled electric shock, and demonstrated that SOMAs were further characterized by larger amplitude and shorter latency electrodermal orienting responses, and slower rates of habituation to a series of novel nonaversive tones. Harden and Pihl (1992) demonstrated that early adolescent MFH SOMAs manifested heightened heart rate and decreased digital blood volume amplitude (DBVA) during a mental arithmetic task. It is interesting to note, given this work, that Lovullo, Pincomb, Brackett, and Wilson (1990) demonstrated that individuals who react with heightened heart rate increase to the cold pressor test are characterized by similar responses to other stressors, and by elevated norepinephrine production.

The physiological hyperreactivity typical of SOMAs has been linked to reduction in classification-oriented cognitive processing (Peterson & Pihl, 1990). These authors combined analyses of the P300 and associated psychophysiological studies discussed previously, with evidence from over 17 studies suggesting that non-university-educated sons of severe male alcoholics are characterized by reduced performance academically, and on tests of linguistic ability, abstraction, and problem-solving. The subcortical centers responsible for the integration of physiological preparation-for-activity (such as heart rate increase and digital blood volume amplitude decrease), and for integrating such preparation within the context of stimulus-relevant behavior, are partially under the inhibitory control of the hippocampal system and the prefrontal cortex. Many of the 17 studies referred to previously used tests of cognitive performance drawn from the neuropsychological literature. This approach allows for the formulation of inferences about the relationship between brain function and behavior (Tarter, Alterman, & Edwards, 1985, 1988). Many of the cognitive functions tested in this literature depend on the proper functioning of the prefrontal cortex. This cortical subunit is primarily responsible for the abstract classification of sensory stimuli and organization of behavior (Luria, 1980). Tarter et al. (1985, 1988), Peterson and Pihl (1990), and Gorenstein (1987) have all noted that the pattern of cognitive impairment

typical of males at increased risk for alcoholism is reminiscent of that characteristic of adults with mild prefrontal cortical trauma. The non-cognitive characteristics of SOMAs and such individuals also share certain features in common (Peterson & Pihl, 1990), including abnormalities of the orienting response, heightened sympathetic reactivity to novelty, and reduced ability to engage in goal-directed behavior. Peterson, Finn, & Pihl (1991) have demonstrated highly significant correlations between MFH SOMAs' performance on two (putative) tests of prefrontal function and susceptibility to cardiovascular hyperreactivity. Harden and Pihl (1992) found similar patterns of cognitive deficit and cardiovascular hyperreactivity among young adolescent MFH SOMAs, matched with controls for IQ. Whipple, Parker, and Noble (1988) showed that the performance of SOMAs and their fathers on various tests of visuospatial performance correlated with the ERP production to a (non-novel) target stimuli. Parsons, Sinha, and Williams (1990) have replicated the latter finding in a population of FH+ male alcoholics.

Damage to the prefrontal cortex in adulthood can cause "acquired sociopathy" (Eslinger & Damasio, 1985)—impulsivity and inability to regulate behavior in accordance with social demands (Damasio, 1986; Luria, 1980). Such damage sustained early in life can lead to the development of a "pervasive developmental abnormality of social and affective behaviors" (Eslinger & Damasio, 1986) or a "primary social defect"—the inability to integrate "social impulses into the total personality structure" (Ackerly & Benton, 1948). Sons of severe male alcoholics (particularly those with extensive family histories of alcoholism) manifest impairments in the ability to control their behavior when required to (particularly in formally structured situations), concentrate and pay attention relatively poorly, and appear comparatively quick to resort to aggression in social situations (Pihl, Peterson, & Finn, 1990). Peterson and Pihl (1990) have theorized that SOMAs are characterized by increased impulsivity and motoric activity because their psychomotor systems tend to become overactivated by novelty and threat. Instead of relying on their comparatively poor ability to abstract and verbally classify, SOMAs may tend towards implementation of search or avoidance strategies, or to resort to aggression. A general model for the increased risk accompanying these characteristics is presented in Figure 3.

Finn and Pihl (1987, 1988) and Finn et al. (1990) also demonstrated that acute administration of a relatively high dose of ethanol to SOMAs essentially eliminated this pattern of cardiovascular hyperreactivity. Levenson, Oyama, and Meek (1987) similarly determined that alcohol intoxication reduced certain aspects of cardiovascular reactivity and general somatic reactivity to self-disclosing speech among SOMAs. A male control group, composed of "outgoing, aggressive, impulsive and antisocial individuals" (Sher & Levenson, 1982), was also characterized by decreased stressor-induced heart rate acceleration after alcohol consumption (and by increased baseline heart rate). A comparable pattern of "stress-response dampening" appears typical of alcoholics (reviewed in Sher, 1987, and Peterson & Pihl, 1990). It may be that alcohol-induced anxiolysis and cardiovascular reactivity-dampening takes place because acute alcohol intoxication interferes with the function of the subcortical unit that governs the orienting response and produces the acute psychophysiological response to threat and/or novelty (Gray, 1982). The hippocampus, part of that subcortical unit, is very responsive to novel stimuli (Vinogradova, 1975), has a high density of BDZ receptors (Braestrup & Squires, 1977; Williamson, Paul, & Skolnick, 1978), and appears particularly sensitive to the acute and chronic effects of alcohol intoxication (Freund & Ballinger, 1989; Gray, 1982, 1987; Lovinger, White, & Weight, 1989; Peterson et al., 1990) and to the action of the other anxiolytics (BDZs and barbiturates) as well (Gray, 1982, 1987). Alcohol intoxication reduces the amplitude of the P300 response, which is produced at least in part by the hippocampus, in SOMAs and controls (Elmasian, Neville, Woods, Schuckit, & Bloom, 1982). Generalized alcohol-induced reduction of hippocampal response could be negatively and positively reinforcing to SOMAs (and to others at heightened risk for cued anxiety), given that increased activity in the hippocampal region has been associated with anxiety and negative affect (Gray, 1982; Reiman, Fusselman, Fox, & Raichle, 1989), especially when it accompanies threat and novelty, and that such activity inhibits the operation of other limbic centers (like those utilizing dopamine) that provide the physiological basis for the sensations of pleasure, euphoria, and well-being (Heath, 1986). Anxiolytic-induced elimination of threat and/or novelty-induced hippocampal activity (above a cer-

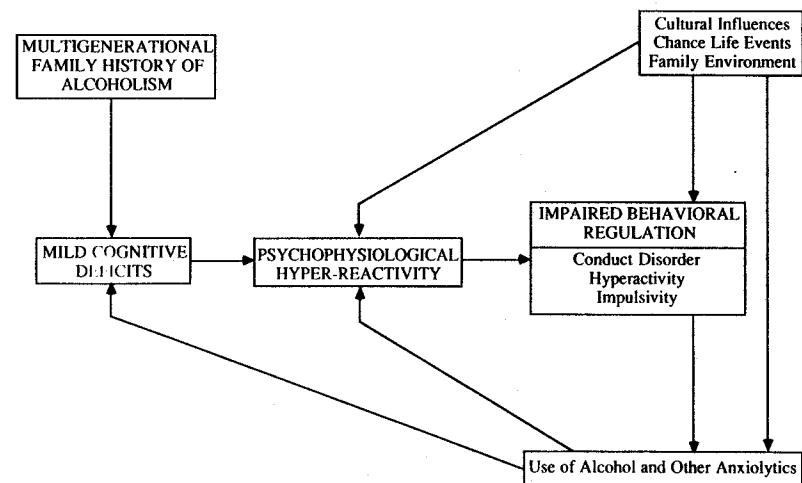


Figure 3. A general schematic model for the increased risk for alcoholism characteristic of sons of male alcoholics, from families with multigenerational histories of alcoholism.

tain threshold) should therefore prove negatively reinforcing, in direct proportion to the degree of such activity. This idea serves as specific replacement for the tension-reduction hypothesis, which is "no longer adequate" (Pohorecky, 1991), primarily because of its excess generality.

Evidence suggesting that pathological sensitivity to anxiety is linked to alcoholism, and perhaps to BDZ and barbiturate abuse as well, has been reviewed by Weissman, 1988; George, Nutt, Dwyer, and Linnoila (1990); Kushner, Sher, and Beitman (1990); and Pohorecky (1991). Phobias are at 2.5 times, and panickers 4 times normal risk for alcoholism (Weissman, 1988). Alcoholism and anxiety disorders cosegregate in families. Symptoms of panic and of acute alcohol withdrawal overlap, with regards to tremor, tachycardia, increased perspiration, anxiety, and dizziness or orthostatic hypotension. Alcoholics, by the same token, are frequently characterized by anxiety disorder (Cox, Norton, Dorward, & Fergusson, 1989), which may precede development of alcoholism (review by Barlow, 1988). Elevated scores on measures of anxiety sensitivity, such as the Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986), have been linked to alcohol dependence, alcoholic family history, use of alcohol

for anxiogenic purposes, and self-reported alcohol consumption among women (Stewart, Peterson, & Pihl, 1992). Fifteen per cent of alcoholic men have an anxiety disorder (contrasted with 10% of male nonalcoholics), compared to 38% of alcoholic (and 18% of nonalcoholic) women (Helzer & Pryzbeck, 1988). Stewart, Achille, Dubois-Nguyen, and Pihl (in press) have also determined that anxiety-sensitive women are characterized by heightened reactivity to threatening words, when sober, and that this reactivity is significantly reduced by alcohol intoxication. Anxiety and depression (discussed in detail later) appear to be common pathways to female alcoholism, a condition which is more uncommon, associated with more pathology (Helzer & Pryzbeck, 1988), and more physiologically dangerous (Frezza et al., 1990) than male alcoholism.

At normal doses, the anxiolytics act to potentiate the action of inhibitory neurons utilizing the neurotransmitter GABA (Warneke, 1991). GABA promotes the direct opening of chloride (CL⁻) selective ion channels (at GABA-A BDZ chloride receptors, the major site of action for sedatives and anxiolytic agents) (Zorumski & Isenberg, 1991). Intake of CL⁻ by a given neuron makes it less likely to fire (Warneke, 1991).

Benzodiazepine administration mimics the effects of habituation, while BDZ inverse agonist administration increases anxiety and fear (Bodnoff, Suranyi-Cadotte, Quirion, & Meaney, 1989). BDZ inverse agonists occur endogenously (Bodnoff et al., 1989; Sangameswaran, Fales, Friedrich, & De Blas, 1986), and may be produced after repeated exposure to novelty, or to increase fear, respectively. Benzodiazepines acting at receptor sites distinct from those of barbiturates and GABA merely potentiate GABA inhibition, enhancing the ability of GABA to open the CL- channel (Zorumski & Isenberg, 1991), and they work most effectively when synaptic concentration of GABA is low. Barbiturates and alcohol, by contrast, work like BDZ, and additionally directly potentiate CL- ion intake (Mehta & Ticku, 1988; Morrow, Suzdak, Karanian, & Paul, 1988; Warneke, 1991; Zorumski & Isenberg, 1991). This direct effect may account for their increased danger, in comparison to the relatively safe benzodiazepines (Warneke, 1991).

Several reports have documented differences in sensitivity to BZD-, barbiturate-, and alcohol-induced increase in GABA-activated uptake of CL- among genetically inbred strains of animals characterized by differential vulnerability to various intoxicating effects of alcohol (Harris & Allan, 1989; Zorumski & Isenberg, 1991). McBride, Murphy, Lumeng, and Li (1990), in their reprinted article, claim (a) that alcohol-preferring (P) rats have abnormally dense GABA innervation of the nucleus accumbens (NA); (b) that the action of this GABA system tonically inhibits the action of the reward system at the NA in P rats, (c) that alcohol is inhibiting the action of this GABA inhibitory system, through its action at the GABA-BDZ-CL- receptor complex; and (d) that this inhibitory action is accounting for the reward P rats receive from alcohol. This is difficult to understand, given that alcohol is usually considered capable of enhancing the inhibitory activity of GABA (Warneke, 1991), in terms of its anxiolytic and sedative effects. However, Imperato and Di Chiara (1986) have suggested that the biphasic effects of alcohol on dopamine neurons might be a consequence of an identical cellular effect, at different neurological targets.

The anxiolytic effects of alcohol are apparently mediated by potentiation of GABAergic transmission. Dopamine neurons in the ventral mesencephalon (VM) are under the inhibitory

control of substantia nigra pars reticulata (SNPR) GABAergic neurons. These SNPR neurons, in turn, are under the inhibitory control of massive striatonigral GABAergic projections. Perhaps at lower, stimulating doses (or during the initial stimulant phase of the blood alcohol curve) ethanol might potentiate striatonigral inhibitory input onto SNPR GABAergic neurons. The net consequence of this effect would be disinhibition of VM dopamine neurons, and enhanced reward. At higher, sedative doses, alcohol might directly potentiate inhibition of DA neurons (Imperato & Di Chiara, 1986). An ethanol effect, similar to that proposed in this post hoc theory, might account for the apparently rewarding properties of alcohol intake for the P rat. It may be that the P and HAD rats consume alcohol purely for its directly rewarding effects, and that its anxiolytic properties are irrelevant.

McBride et al. (1990) have also suggested that lower levels of serotonergic function characterize the P rat. There is a vast literature on the role of serotonin in determining acute response to and withdrawal from alcohol. Research conducted upon humans has primarily associated low serotonin level with susceptibility to depression and various forms of impulsive behavior (Coccaro et al., 1989). Tabakoff and Hoffman (1991) have recently proposed that alcohol may be consumed by alcoholics to self-medicate serotonergic hypofunction.

Development of tolerance to alcohol, and the relationship between such tolerance and withdrawal, is an exceedingly complex matter (reviewed in Tabakoff & Hoffman, 1991). Tolerance to ethanol, and to the psychomotor stimulant properties of BDZs, develops quickly, although anxiolytic BDZ properties apparently remain powerful among people who do not abuse (DuPont & Saylor, 1991). Withdrawal from acute alcohol intoxication is generally a mildly unpleasant experience, involving heightened anxiety, depression, irritability, insomnia, motor tremor, and elevated blood pressure and pulse rate (Miller, Betkin, & Gold, 1991). Withdrawal from chronic alcoholism, by contrast, is very unpleasant, and potentially life-threatening. Symptoms begin 4 to 6 h after the last drink, increase to their maximum at 24 to 48 h, and may last 5 days (Nace & Isbell, 1991). Alcoholics in withdrawal may experience exacerbation of the previously listed symptoms, and are also at risk for seizure and alcohol withdrawal delirium. If untreated, the latter condition has a mor-

ality rate of approximately 10-15% (Nace & Isbell, 1991).

Benzodiazepine, barbiturate, and alcohol tolerance and withdrawal symptomatology are all likely mediated at least in part through changes in the flow of ions through GABA-A channels. These changes only occur at doses that produce withdrawal upon abstinence, and reverse after withdrawal disappears. Subsensitivity of the GABA-BDZ-CL- receptor complex after chronic ethanol treatment may contribute to ethanol tolerance and the ethanol withdrawal syndrome (Morrow et al., 1988). Chronic alcohol administration appears to produce cellular desensitization of the GABA-A receptor-coupled CL- ion channel. Similar functional changes in chloride ion flux have been reported following chronic administration of BZD (Zorumski & Isenberg, 1991).

Withdrawal from short-acting BDZs produces a more severe syndrome than the long-acting BDZs. Symptoms are similar to those of acute alcohol withdrawal. It is also important to note that BDZs and barbiturates ameliorate alcohol withdrawal, and that cross-tolerance for all three drugs develops (Morrow et al., 1988). Benzodiazepines are often used, in fact, to ameliorate the effects of withdrawal from the more dangerous barbiturates and alcohol, and BDZ inverse agonists and antagonists reverse signs of alcohol intoxication in animals (Zorumski & Isenberg, 1991). It is of course the case that each anxiolytic works well to ameliorate the effects of withdrawal engendered by acute or chronic alcohol, barbiturate, or BDZ administration.

THE PAIN/LOSS/ DISAPPOINTMENT SYSTEM

Finally, the effects of opiates might be considered. Opiates are potent psychomotor stimulants (Wise, 1988), and their stimulant properties, like those of cocaine or amphetamines, are capable of inducing analgesia in and of themselves (Franklin, 1989). However, opiates have additional analgesic properties, perhaps due to their operation in areas of the brain that are not directly involved in psychomotor activation, such as the periaqueductal gray (Panksepp, Sivity, & Normansell, 1985; Wise, 1988). Opiates reduce pain, and should therefore prove differentially reinforcing to those in pain. But what exactly is pain? The pain system serves to shield complex organisms from physical damage. Pain serves as

an unconditioned punishment or aversive stimulus. Relief of pain is rewarding. Tactile stimulation, above a certain variable threshold, evidently produces pain, and elicits defensive aggression or escape behavior (Gray, 1982, 1987)—typical reactions to punishment. There appear, in addition, to be other less obvious forms of pain- or punishment-like response, mediated by the same or similar neurochemical systems, operative in the absence of aversive tactile stimulation.

Gray (1982, 1987) has described the absence of an expected reward, disappointment, as behaviorally equivalent to pain. Animals and human beings generally learn to modify their behavior, in the face of the absence of an expected reward, very much like they learn from pain. This "expected reward" might be food, water, or any unconditioned reinforcer, including social reward. The absence of social reward appears very similar to pain, in terms of its effects upon spontaneously generated and manipulated behavior (Panksepp et al., 1985). The endogenous opiate system has apparently come to govern more than reaction to aversive sensory stimulus in the course of mammalian evolution. It appears integrally involved in mediating interpersonal attachment, or love (Herman & Panksepp, 1978), and responds to the absence of an expected reward (Panksepp et al., 1985). The interpersonal bonding that underlies love is mediated in large part through stimulation of the tactile system, perhaps through maternal, affiliative, or sexual touch, and may involve more abstract cues, such as adult gaze and infantile facial configuration, olfactory stimulation, and gustatory instincts. Behaviors exhibited as a consequence of pain, withdrawal of love, and opiate withdrawal share many features in common, including lacrimation (crying) and distress vocalization, withdrawal, aggression, and depression (Herman & Panksepp, 1978). Some of these behaviors are common across many species. It appears possible that the opiate system mediates love attachment, and that destruction of close social bonds might result initially in the development of a condition resembling heroin or morphine withdrawal.

The social affiliative process has as one of its primary goals protection against physical destruction, particularly in infancy. The circuitry that underlies affiliation is phylogenetically ancient, and mature at birth (Valzelli, 1981) (as opposed to the circuitry that mediates anxiety,

which matures much later (Gray, 1982, 1987). A complex interplay between affiliation-induced deactivation of pain circuitry and isolation-induced pain appears to be critically important to further development (Najam & Panksepp, 1989). What is proper interplay depends on the maturity of the animal, possibility for social interaction with other conspecifics, the duration of isolation (reviewed in McKinney, 1985), and on who initiates the separation (Robertson & Robertson, 1971). It is possible that a necessary balance exists between endogenous opiate production, in the presence of mother, and opiate withdrawal. Infants deprived of close contact first protest, and then give up (Bowlby, 1969; Robertson & Robertson, 1971). Once they give up, it is difficult for them to reestablish bond, and death is a common consequence. In the despair stage, they stop seeking conspecific contact. This pattern of reaction to separation is not necessarily limited to infancy, and such separation often precedes development of nonbipolar depression in humans (McKinney, 1985).

It appears that initial social isolation produces a state similar to opiate withdrawal, but that prolonged social isolation perhaps reverses this process, flooding the organism with endogenous opiates, eliminating need for social contact. It may be that a certain amount of controlled separation promotes development, but that too much severely retards growth. Rat pups chronically treated with morphine develop slower than normal rats, in terms of physical development and motor coordination, and normal rats develop slower than rats treated with the opiate antagonist naloxone (Najam & Panksepp, 1989). Administration of the opiate antagonist naloxone, which blocks the reinforcing effects of opiates, can increase development, but increases social deprivation-induced distress behavior and can induce distress in nondeprived animals (Knowles, Conner, & Panksepp, 1987). Morphine administration, by contrast, can reduce social distress (Knowles et al., 1987), but slow and retard development (Najam & Panksepp, 1989). Recent experiments have demonstrated that enhanced interpersonal tactile substantially increases thriving (weight gain and neurological development) among premature babies, but also that the detrimental developmental effects of maternal deprivation in rats can be mimicked by artificial administration of beta-endorphin (Greer, Bartolome, & Schanberg, 1991). This latter effect seems to be similar

to the consequences of long-term, despair-stage deprivation.

It appears likely that in the course of normal development, experience is first dominated by the pain-mediated social-affiliation system and then by the threat- and novelty-mediated anxiety and dopaminergic exploratory systems. In other words, a developing individual moves from a world characterized by passive subjection to pain, and maternal blockade of that pain (from direct subjugation to punishment or physical harm), to a world governed by reaction to cues of punishment or pain, mediated by the late maturing threat/novelty system, which both inhibits ongoing psychomotor processes in the face of certain danger or excess novelty, and motivates rewarding active exploration, undertaken under conditions of relative security. It appears likely that there exist numerous events that can disturb transition from the pain system to the anxiety/exploration systems, and as well, that numerous events might pathologize operation of the pain system.

There is evidence that exposure to interpersonal loss in childhood, and later in life, predisposes to development of depression (McKinney, 1985). This may be particularly relevant to women. This is an extremely interesting possibility, given (a) that social bonding mechanisms obviously play an important role in establishing a vital and effective maternal-child relationship in infancy (Kraemer, 1985); (b) that depression is more than twice as common in women as men (Helzer & Pryzbeck, 1988); (c) that female depression tends to precede the development of alcoholism (in 66% of cases—Helzer & Pryzbeck, 1988) and comorbid substance abuse, whereas male depression more commonly follows extended abuse (in 78% of cases—Helzer & Pryzbeck, 1988); (d) that depressed women, especially those with histories of marital and social disruption, tend to be characterized by elevated rates of familial alcoholism (Winokur & Coryell, 1991); and (e) that problems with intimacy tend to account for women's differential use of alcohol to reduce interpersonal stress as described in the (Frank, Jacobson, & Tuer, 1990; Zucker, 1987).

There is evidence that some of alcohol's reinforcing effects may be mediated through the opiate system, either directly, through secondary effects on the serotonergic system, or through the action of opiate-like by-products of ethanol metabolism (Altschuler, Phillips, & Feinhandler,

1990). Deficient endogenous opioid activity has been linked to alcohol-preference in animals (George, Roldan, Lui, & Naranjo, 1991). Effects of alcohol on separation-induced despair seem to be dose-dependent; moderate doses ameliorate, and higher doses increase such despair (McKinney, 1985). Depression (in addition to antisocial personality and alcohol/drug abuse) is relatively common among relatives of opiate addicts (Rounsaville et al., 1991). There is also a certain correspondence between the psychodynamic and neurochemical processes underlying opiate addiction as such, and social bonding (reviewed in Panksepp et al., 1985). Neurolinguistic analyses have highlighted opiate addiction substitution for sources of normal social gratification (Tokar, Brunse, Steffle, Sodergren, & Napior, 1975). Addicted opiate users high on opiates show many of the same symptoms as detachment-stage isolated infants—reduced desire for social contact, apathy, and gastrointestinal failure (Thomason & Dilts, 1991).

Limited access opioid and psychostimulant administration produces stable level and patterns of intake. Animals deprived of this stable level and pattern do not manifest tolerance nor physical dependence. Unlimited access, by contrast, invariably produces profound tolerance, leading to heightened intake and severe withdrawal. Tolerance develops because of adaptive changes at the opioid receptor site. Repeated opioid administration results in decreased opiate-induced euphoria, and decreased sensitivity to myosis, constipation, and feelings of urinary urgency (Thomason & Dilts, 1991). Abstinence results in withdrawal, and varies in severity with the speed at which the exogenous opioid is blocked from acting at or is withdrawn from the opiate receptor site (Thomason & Dilts, 1991). Acute opiate withdrawal produces lacrimation (crying) and distress vocalization, withdrawal, aggression, and depression (Herman & Panksepp, 1978), as well as severe muscle pain, gastrointestinal cramps, and diarrhea (Koob & Bloom, 1988), over 5–21 days, depending on the drug. Over the longer term, for many months, abstinent opiate addicts may be characterized by disturbed sleep, preoccupation with physical discomfort, feelings of reduced self-worth, and decreased ability to tolerate stress (Thomason & Dilts, 1991).

Non-morphine-dependent rats will self-administer morphine directly into the ventral tegmental area (VTA), with no signs of with-

drawal upon abstinence (Wise & Bozarth, 1987). However, constant administration of morphine into the periaqueductal grey (which seems involved in the pain system) causes withdrawal symptoms after administration of the opiate antagonist naloxone (Koob & Bloom, 1987). Withdrawal syndromes, associated with cravings, can be elicited by exposing detoxified opiate users to stimuli associated with previous use (Koob & Bloom, 1987). This process appears to have its analog in the conditioned place preference characteristic of animals. It goes without saying that administration of opiates temporarily eliminates withdrawal symptomatology.

CONCLUSIONS

Drugs with psychomotor stimulant properties appear to have the highest potential for abuse. These drugs are primarily rewarding. A substantial number of perfectly normal animals (and perfectly normal humans), will self-administer drugs like cocaine, amphetamine, morphine, and heroin, and ignore food, water, and appropriate powerful sexual cues. Most psychoactive drugs have some psychomotor stimulant property, but there may be other reasons why drugs are abused. Anxiolytics reduce the negative consequences of threat, and analgesics reduce the negative affective consequences of pain. Consideration of these distinctions makes analysis of the etiology of drug abuse more particular, and perhaps more useful. Pleasure, power, and euphoria almost universally accompany use of psychomotor stimulants. Anxiolytics provide relief from the unpleasant sensations of anxiety. Analgesics reduce pain and loneliness. Even though feelings of boredom, anxiety, and pain are common, even chronic, in human experience, most people do not abuse drugs, or become addicted. Why not?

Genetic and environmentally mediated temperamental variability appear to determine susceptibility. Some people, perhaps those who are more exploratory in nature (with antisocial tendencies as associated pathology), might be more susceptible to experimentation, and to the effects of psychomotor stimulants. Anxiety-sensitive people may be vulnerable to anxiolytics, and individuals characterized by propensity to social-isolation distress, or loneliness, might differentially prefer analgesics. Even those who experiment, or who use moderately, might be protected from escalating use and dependence if

their lives are in order; if they are shielded from physical and emotional pain by strong family bonds and friendships; if they are not threatened and made anxious by unpredictable personal, social, and economic events; and if they live in a community that provides a rationale for living and allows for the exercise of interesting, constructive, prosocial behavior.

P propensity for drug abuse does not end with the cessation of withdrawal. People need protection from their own vulnerability, within the confines of a close social network, and must have the opportunity to engage in productive work. Drug use temporarily provides powerful security, confidence, and euphoria. Drug users and addicts in treatment must nonetheless come to replace pharmacological dependence with real experience. Psychological, psychiatric, and medical authorities interested in individual treatment must aid the recovering individual in building or rebuilding a productive and rewarding life, as well as ensuring that the process of withdrawal takes place in safety. Social policy planners truly interested in limiting drug use must concentrate on ensuring that such real life is possible, rather than waging war against "evil" illicit drug abusers.

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