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# Neurogenetic Adaptive Mechanisms in Alcoholism

C. ROBERT CLONINGER

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Clinical, genetic, and neuropsychopharmacological studies of developmental factors in alcoholism are providing a better understanding of the neurobiological bases of personality and learning. Studies of the adopted-away children of alcoholics show that the predisposition to initiate alcohol-seeking behavior is genetically different from susceptibility to loss of control after drinking begins. Alcohol-seeking behavior is a special case of exploratory appetitive behavior and involves different neurogenetic processes than do susceptibility to behavioral tolerance and dependence on the antianxiety or sedative effects of alcohol. Three dimensions of personality have been described that may reflect individual differences in brain systems modulating the activation, maintenance, and inhibition of behavioral responses to the effects of alcohol and other environmental stimuli. These personality traits distinguish alcoholics with different patterns of behavioral, neurophysiological, and neuropharmacological responses to alcohol.

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THE INTERACTION OF GENETIC AND ENVIRONMENTAL factors in the development of voluntary behaviors, such as the drinking of alcoholic beverages, is an important and challenging field of investigation in the behavioral sciences. The vast majority of people in the United States drink alcoholic beverages, but half of all the alcohol drunk is consumed by only 10% of the population (1). Differences between individuals in the frequency and amount of alcohol that they consume, as well as differences in resulting complications, are determined by many genetic and sociocultural variables. Both consumption and complications have varied widely from one historical era to another and currently vary from country to country, among social classes, among persons of different occupation, and between men and women (2). Children who are reared by alcoholic adoptive parents are no more likely to become alcoholic themselves than other children; however, children of alcoholic biological parents are more likely than other children to misuse alcohol, even when they are separated from their biological parents in infancy and placed in stable adoptive homes (3). Medical complications involving different organs, such as liver, heart, brain, and pancreas, have distinct genetic influences (4).

Since alcohol abuse is so frequent and widespread, it is not surprising that its development should involve the interaction of many different etiological factors (5). Developmental complexity is expected for such common disorders. Nevertheless, investigators who advocate a particular etiological model of alcoholism—psychosocial, psychoanalytic, behavioral learning, or biomedical—have

often questioned or ignored the findings of investigators in other fields and have failed to recognize the compatibility or complementary relationship of both neurobiological and psychosocial factors (6). This has often led to sterile debates about the relative importance of nature versus nurture or instinct versus learning in the development of alcoholism.

Now research on alcoholism is at a watershed in which we can begin to describe the development of the clinical signs and symptoms in terms of its underlying pathophysiological processes. More importantly, the major neurobiological systems involved in alcohol-seeking behavior and acquisition of functional tolerance to and dependence on alcoholism appear to correspond to brain systems involved in an individual's ability to adapt to novel, appetitive, and aversive stimuli in general, not only to alcohol (7). Psychiatric studies of alcoholics have identified clinical subgroups that differ in their patterns of abuse, personality traits, neurophysiological characteristics, and inheritance. These subgroups are not discrete disease entities; rather, recent findings suggest that they result from various combinations of response biases in brain systems that mediate an individual's adaptation to experience, including the effects of alcohol and other drugs. Studies of personality and learning in alcoholic subgroups and in the general population have provided information about structure and function of these neuroadaptive systems. Also neuropsychopharmacological studies in humans and other mammals permit characterization of the functional organization of the brain systems underlying personality and learning in general and susceptibility to alcoholism in particular. In other words, the neurogenetic basis of alcoholism is an important special case in the rapidly advancing study of the neurobiology of motivation and learning.

Many different fields of research in the behavioral and neural sciences contribute important information about developmental factors in alcoholism, and many of the findings that link the results of one field with those of the others remain tentative. Ignorance of the relevance of robust findings in one field often limits the design and interpretation of experiments in another field. For example, personality variation has a highly reproducible tridimensional structure (8, 9), which needs to be considered in both neurobiological and learning experiments on susceptibility to alcoholism. I shall review sturdy findings in several fields and then describe recent observations linking these findings in the hope of stimulating additional integrative research. These links among convergent findings suggest a developmental model that may account for the behavioral features and inheritance patterns observed among alcoholics in terms of underlying neurobiological mechanisms of motivation and learning.

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The author is professor of psychiatry and genetics at Washington University, St. Louis, MO 63110.

## Clinical Subgroups of Alcoholism

Many studies have treated alcoholism as if it were a single discrete entity, but factor analyses show that core symptoms of dependence and loss of control, social problems, family problems, and depressive symptoms are only weakly correlated with one another (10). Jellinek (11) distinguished different subgroups of alcoholics, emphasizing the distinction between individuals who had persistent alcohol-seeking behaviors ("inability to abstain entirely") and others who could abstain from alcohol for long periods but were unable to terminate drinking binges once they had started ("loss of control").

Later work has shown that alcohol-seeking behavior in adolescence and early adulthood is associated with impulsivity, risk-taking, and a tendency to antisocial behavior, such as fighting in bars and arrests for reckless driving when intoxicated (12). In contrast, loss of control is associated with guilt and fear about dependence on alcohol in individuals who are emotionally dependent, rigid, perfectionistic, and introverted (12, 13). Alcoholics with loss of control usually begin to have problems in late adulthood after an extended period of exposure to heavy drinking that is socially encouraged, such as drinking at lunch with co-workers; abusers with an inability to abstain usually begin to experiment with alcohol early, regardless of external circumstances (3).

The distinguishing characteristics of these prototypic groups of alcoholics are summarized in Table 1. These two groups were initially distinguished in terms of alcohol-related symptoms and patterns of inheritance in adoptees (3) and more recently in terms of personality traits (14, 15). These subgroups should not be considered discrete disease entities, because many alcohol abusers have some features of each type. Rather, the different alcohol-related syndromes are associated with the polar extremes of personality traits that vary continuously. The development of loss of control (type 1) is associated with the triad of traits characteristic of individuals with passive-dependent or "anxious" personality: (i) high reward dependence (that is, one who is eager to help others, emotionally dependent, warmly sympathetic, sentimental, sensitive to social cues, and persistent), (ii) high harm avoidance (that is, one who is cautious, apprehensive, pessimistic, inhibited, shy, and susceptible to fatigue), and (iii) low novelty seeking (that is, one who is rigid, reflective, loyal, orderly, and attentive to details).

In contrast, the development of spontaneous alcohol-seeking behavior or inability to abstain (type 2) is associated with the triad of traits characteristic of individuals with an antisocial personality, which is the reverse of the traits seen in passive-dependent personalities: (i) high novelty seeking (that is, one who is impulsive, exploratory, excitable, disorderly, and distractible), (ii) low harm avoidance (that is, one who is confident, relaxed, optimistic, uninhibited, carefree, and energetic), and (iii) low reward dependence (that is, one who is socially detached, emotionally cool, practical, tough-minded, and independently self-willed). Novelty seeking, harm avoidance, and reward dependence are quantifiable traits that vary independently (14), and so alcoholics have widely varying combinations of personality traits. Alcoholics also have variable patterns of predisposition to seek out alcohol and to become tolerant to and dependent on it. Consequently, various combinations of these personality traits have been supposed to reflect differences in brain systems that determine individual liabilities to seek behavioral reinforcement from alcohol and to become tolerant and dependent on it after exposure (15). This hypothesis will be examined in later sections.

Women develop loss of control (type 1) alcoholism predominantly, with a later onset and more rapid progression of complications associated with guilt, depression, and medical complications from sustained high blood levels of alcohol, such as cirrhosis and other

**Table 1.** Distinguishing characteristics of two types of alcoholism.

Characteristic features	Type of alcoholism	
	Type 1	Type 2
<i>Alcohol-related problems</i>		
Usual age of onset (years)	After 25	Before 25
Spontaneous alcohol-seeking (inability to abstain)	Infrequent	Frequent
Fighting and arrests when drinking	Infrequent	Frequent
Psychological dependence (loss of control)	Frequent	Infrequent
Guilt and fear about alcohol dependence	Frequent	Infrequent
<i>Personality traits</i>		
Novelty seeking	Low	High
Harm avoidance	High	Low
Reward dependence	High	Low

liver abnormalities (3, 16, 17). Both types of alcoholism are common in men, but type 2 alcoholism is characteristic of most men in hospital treatment samples (3, 16, 17).

Recently, male relatives of hospitalized alcoholic women have been distinguished with 80% accuracy from male relatives of hospitalized alcoholic men by a discriminant function made up of the alcohol-related symptoms summarized in Table 1 (18). The type 1 alcoholism syndrome, characteristic of male relatives of alcoholic women, was indicated by onset of prolonged binges, behavioral tolerance to alcohol, guilt feelings, and trouble limiting or controlling alcohol intake after the age of 25 years. The type 2 syndrome, characteristic of male relatives of alcoholic men, was indicated by onset of fighting when drinking, auto accidents and arrests for reckless driving when intoxicated, hospitalization for alcoholism, and inability to abstain entirely before the age of 25 years. Because men in the families of male and female alcoholics differ in this way, the association between loss of control and female sex seems to be based on variables such as personality traits that have a sex-influenced expression but are heritable regardless of the sex of the parent or child.

The importance of distinguishing these subgroups of alcoholics is shown by findings that they also differ in neurophysiological and neurochemical characteristics. Abstinent type 1 alcoholics at rest are hypervigilant and apprehensive with much anticipatory worrying; their resting electroencephalogram (EEG) shows minimal brain-wave activity in the slow alpha frequency range, excessive beta activity, and poor synchrony (16, 19). In response to alcohol, individuals with such EEG patterns show a marked increase in alpha activity and subjectively report a sense of calm alertness that they regard as a pleasant relief of tension (20).

In contrast, abstinent type 2 alcoholics at rest are hypovigilant, distractible, impulsive, and easily bored. Alcoholics and others with impulsive-aggressive behavior have low cerebrospinal fluid levels of serotonin, dopamine, and their metabolites (8, 21). They also show increasing amplitudes of EEG potentials evoked by visual stimuli of increasing intensity (22). In other words, type 2 alcoholics have an "augmenting perceptual reactance" instead of the more frequent "reducing" pattern. Short-term ingestion of alcohol leads to either less augmentation or a reducing perceptual reactance. In addition, abstinent type 2 alcoholic men and their male children who are at high risk for later alcoholism have a reduced amplitude of the late positive component (P3) of the event-related EEG potential, even though their reaction time and number of errors do not differ from those of other alcoholics or controls (23). This pattern suggests that individuals at high risk for type 2 alcoholism are deficient in their ability to allocate significance to targeted stimuli.

Many clinical and developmental studies of alcoholics have not distinguished between such clinical subgroups or quantified associated personality and cognitive traits. It is difficult to interpret findings about heterogeneous samples of alcoholics with confidence or to integrate such findings with the growing body of genetic and neurobiological studies. Reliable and brief methods for distinguishing the two syndromes and quantifying relevant personality traits are now available, so this limitation can be avoided in future studies (14).

## Genetic Epidemiology of Alcoholism

One of the most rapidly advancing fields of research on alcoholism is genetic epidemiology—the study of the interaction of biological and social risk factors influencing the inheritance and development of familial disorders. The strong familial aggregation of alcohol abuse is one of the most robust observations in medical research. Over the past 80 years, more than 100 studies have shown that alcoholism is three to five times as frequent in the parents, siblings, and children of alcoholics as in the general population (24). However, alcoholism seems not to be inherited in a simple Mendelian manner, and such familial aggregation may be due to genetic influences, familial environmental influences, or both.

The most objective means of evaluating gene-environment interaction for non-Mendelian disorders is to study the biological and adoptive families of adoptees who have been separated from their biological parents at an early age. The sample sizes in early adoption studies were too small to distinguish among subgroups of alcoholics and the results were inconsistent. In the United States, Roe and Burks found that good foster placement was associated with no alcohol abuse in all but one of 27 children of alcoholic biological parentage and in all but one of 22 children of normal biological parentage (25). They found that none of 21 adopted-out sons of alcoholics had drinking problems as adults. In contrast, Goodwin and co-workers observed that chronic alcoholism was four times as common in 55 adopted-out sons of Danish alcoholics as in 78 such sons of nonalcoholics; however, alcoholism in adopted-out daughters of Danish alcoholics was not significantly increased above the incidence in adopted controls (26).

These different findings were difficult to compare because of differences in the clinical characteristics of alcohol abuse in the parents and differences in the adoptive placements. Goodwin and co-workers studied children whose biological parents had been hospitalized for alcoholism, but none of the parents studied by Roe and Burks had been treated. Also the children of alcoholics studied by Roe and Burks were more often placed in rural areas (where drinking was infrequent) than were the children of alcoholics.

In view of these discrepancies, Bohman and co-workers undertook a large-scale adoption study of alcoholism in Sweden (3). The

subjects included all 862 men and 913 women of known paternity who were born to single women in Stockholm, Sweden, from 1930 to 1949 and adopted by nonrelatives at an early age. Most of the subjects were separated from their biological relatives in the first months of life (average, 4 months), and all had their final placement in the adoptive home before the age of 3 years (average, 8 months). Information about alcohol abuse, psychopathology, and medical treatment was available for the entire lifetimes of the adoptees and their parents from hospitals, clinics, and several registers that are systematically maintained in Sweden. Identification of alcohol abuse from these sources can identify about 70% of alcoholics; those so identified are representative of alcoholics in general, with no appreciable bias for either type 1 or type 2 alcoholics (27). Such detailed information permitted a population-based study large enough that the adoptees could be divided into subgroups related to type 1 and type 2 alcoholism.

The two types of alcohol abuse were distinguished on the basis of the pattern of alcohol abuse in the biological parents of the adoptees. Adoptees whose biological fathers or mothers had an adult onset of alcohol abuse and no criminality requiring prolonged incarceration were considered to have a type 1 genetic background. In contrast, adoptees whose biological fathers had extensive treatment for alcohol abuse and serious criminality beginning in their adolescence or early adulthood were considered to have a type 2 genetic background. Too few biological mothers with type 2 characteristics were identified for separate analysis.

Alcohol abuse in the adoptive parents was not associated with an increased risk of abuse in the children they reared, so there was no evidence that alcoholism is familial because children imitate their rearing parents (3). However, both genetic predisposition and postnatal provocation were found to be necessary if the adopted-away sons were to express susceptibility to loss of control (type 1) alcoholism (Table 2). If the adoptee was likely to be exposed to a pattern of heavy recreational drinking, as expected in the homes of adoptive fathers with unskilled occupations, the risk of severe alcoholism was greater. More specifically, if there was either a genetic predisposition or a provocative postnatal environment, but not both, the risk of alcohol abuse was lower than in the general population. However, if both occurred in the same person, the risk of severe alcohol abuse was more than doubled. Consequently, type 1 alcoholism has been described as “milieu-limited.”

In contrast, in adopted-away sons of fathers with spontaneous alcohol-seeking (type 2), the risk of alcoholism increased regardless of environmental background (Table 3). In these families the risk of alcohol abuse in the adopted-away sons of type 2 alcoholic fathers was nine times that in the sons of all other fathers.

To evaluate this apparent genetic heterogeneity further, predictions were tested in the adopted-away daughters of type 1 and type 2 alcoholics. The background of the daughter's biological parent was classified as it was in the study of the men. The daughters of type 1 alcoholics were predicted to be at increased risk for alcohol abuse because the mothers in these families were often alcohol abusers; the daughters at high risk for type 1 alcoholism were three times as likely to abuse alcohol as those at low risk. The daughters of type 1 alcoholics were not at high risk for other psychopathology. In contrast, the adopted-away daughters of type 2 alcoholic fathers were found to be at higher risk only for somatic anxiety (that is, somatization or frequent disabling physical complaints), which is associated with high novelty seeking (28). Consequently type 2 alcoholism has been called “male-limited.” In a related Swedish study, abstinent type 2 alcoholic men were found to have higher scores than men or women with type 1 alcoholism on personality tests indicating impulsivity and novelty seeking (29).

It has also been possible to identify individuals at high risk for

**Table 2.** Cross-fostering analysis of severe type 1 alcohol abuse in men in the Stockholm adoption study.

Type 1 genetic back- ground	Severe environ- mental back- ground	Male adoptees observed	
		Total <i>n</i>	Severe abuse (%)
No	No	376	4.3
No	Yes	72	4.2
Yes	No	328	6.7
Yes	Yes	86	11.6*

\*Risk is significantly increased compared with all others ( $\chi^2 = 5.6$ ,  $P < 0.02$ ) (3).

**Table 3.** Cross-fostering analysis of type 2 alcohol abuse in men in the Stockholm adoption study.

Type 2 genetic background	Type 2 environmental background	Male adoptees observed	
		Total <i>n</i>	Type 2 abuse (%)
No	No	567	1.9
No	Yes	196	4.1
Yes	No	71	16.9*
Yes	Yes	28	17.9*

\*Risk is significantly increased in those with type 2 genetic background compared with others ( $P < 0.01$ ) (3).

alcoholism by selection of subjects with different forms of anxiety or somatization. Cognitive anxiety or frequent anticipatory worrying is associated with the personality trait of high harm avoidance, particularly when reward dependence is high and novelty seeking is low (28); this pattern is similar to that associated with loss of control or type 1 alcoholism. In contrast, individuals with high somatic anxiety have the personality traits of high novelty seeking and low harm avoidance, which is associated with spontaneous alcohol-seeking behavior or type 2 alcoholism. This categorization was supported by the finding of increased risk for alcoholism in individuals with either somatic or cognitive anxiety (30). However, cognitive anxiety was associated with fewer criminal biological parents than in the general population, whereas somatic anxiety in adoptees was associated with more criminal biological parents (30).

## A Neurobiological Learning Model

The evidence of clinical and genetic heterogeneity suggested the importance of personality variables in understanding susceptibility to alcohol-seeking behavior and loss of control. To pursue this clue further, recent efforts have focused on specifying the causal structure of personality and related neural mechanisms. One of the most robust findings in personality research comes from factor analytic studies: three major dimensions consistently account for most observed variability in a wide variety of self-report inventories and observer rating schedules (8, 9, 28). However, factor analysis can determine only the number of dimensions, not their underlying causal structure, as evidenced by the conflicting tridimensional structures that have been proposed (8, 9). Furthermore, the architecture of the underlying genetic variation does not correspond well to observed behavioral variation, which involves gene-environment interaction (31). The heritabilities of adaptive personality traits have consistently been estimated to be between 40 and 60%, so genetic

and environmental factors have roughly equal importance in determining behavioral responses (32).

Four lines of evidence have provided a basis for specifying a general causal model of the neuroadaptive systems involved in personality development and susceptibility to alcoholism: (i) family studies evaluating the genetic and environmental architecture of personality; (ii) neuropsychopharmacological studies evaluating the systems that may influence learning and adaptation to various kinds of environmental stimuli; (iii) ethological studies of learning ability in animals, which provide evidence that systems for behavioral inhibition, activation, and maintenance have evolved in separate steps and are dissociated in lower animals; and (iv) descriptive, conditioning, and psychophysiological studies in human subjects, which provide evidence that variation in each of the same three brain systems is independent and dissociated in various clinical groups (28, 33). Many limitations and gaps exist in each one of these lines of evidence, but together they provided the basis for a testable, unified model to guide future research.

On the basis of a synthesis of this information, I hypothesized three dimensions of personality that are genetically independent and that have predictable patterns of interaction in their adaptive responses to novel, aversive, and appetitive stimuli. The stimulus-response characteristics of three putative brain systems for behavioral inhibition, activation, and maintenance are summarized in Table 4. These brain systems are proposed to underlie heritable individual differences in the three personality dimensions described earlier: harm avoidance, novelty seeking, and reward dependence. Each system is complex, involving multiple brain structures and neurotransmitters, as described elsewhere in relation to the development of anxiety states and personality disorders (28). Only aspects relevant to alcoholism are summarized here.

**Behavioral activation system.** Novelty seeking refers to a heritable tendency toward frequent exploratory activity and intense exhilaration in response to novel or appetitive stimuli. It may reflect variation in the brain's "incentive" or behavioral activation system. Dopaminergic cell bodies in the midbrain receive inputs from several sources and then project impulses to the forebrain, thereby possibly acting as a final common pathway for behavioral activation (34). Spontaneous exploratory behavior by mammals in a novel environment depends on integrity of mesolimbic dopaminergic projections, particularly from the ventral tegmental area to the nucleus accumbens (35). That low doses of ethanol have an excitatory effect on neurons of the ventral tegmental area suggests that this action of ethanol may provide a pharmacological "reward" that would facilitate alcohol-seeking behavior (36). Dopamine agonists, such as amphetamines and cocaine (as well as alcohol, opiates, and opioid neuropeptides), facilitate dopaminergic transmission and behavioral activation; dopamine blockers, such as haloperidol, reduce exploratory behavior and lead to anhedonia

**Table 4.** Three major brain systems influencing stimulus-response characteristics.

Brain system (related personality dimension)	Principal monoamine neuromodulator	Relevant stimuli	Behavioral response
Behavioral activation (novelty seeking)	Dopamine	Novelty Potential rewards or their conditioned signals Potential relief of: Punishment or Monotony or their conditioned signals	Exploratory pursuit Appetitive approach  Escape Active avoidance
Behavioral inhibition (harm avoidance)	Serotonin	Conditioned signals for: Punishment, novelty, or Frustrative nonreward	Passive avoidance Extinction
Behavioral maintenance (reward dependence)	Norepinephrine	Conditioned signals for reward or relief of punishment	Resistance to extinction

(reduced responsiveness to positive reinforcement) (35). Self-stimulation with electrodes at sites of dopaminergic neurons is rapid; it is also accompanied by marked locomotor activation and positive reinforcement of eliciting behavior in mammals and by reports of the subjective experience of pleasure and satisfaction in humans (34, 35, 37). Low basal firing rates of dopaminergic neurons are thought to be associated with greater postsynaptic sensitivity to dopamine when it is released, lower turnover of dopamine as measured by cerebrospinal fluid concentrations, and greater novelty seeking.

Alcohol-seeking behavior may be considered a special kind of exploratory appetitive behavior. Rodent strains that show high exploratory activity and low fearfulness behaviorally, such as C57BL mice, show greater alcohol-seeking behavior than other animals. Rodent strains that show little spontaneous exploratory or alcohol-seeking activity, such as BALB/c and DBA/2 mice, have a biphasic response to alcohol with greater suppression of dopamine release with lower doses of ethanol and smaller increases at higher doses than C57BL/6 mice (38). Alcohol-preferring rats, which have low basal dopamine concentrations in the cortex and nucleus accumbens, show greater locomotor activation and greater increases in dopamine turnover after low doses of alcohol than alcohol-nonpreferring rats do (39). Long-term ethanol intake produces behavioral tolerance to the high-dose depressant effects of ethanol, but not to these low-dose activating effects (38).

The inhibition of prolactin release by dopamine has provided a means of studying the effects of dopamine release in human subjects. Schuckit and co-workers (40) measured serum prolactin concentrations after moderate ethanol intake by 44 nonalcoholic young men who had an alcoholic first-degree relative and by 44 controls without a family history of alcoholism. Prolactin increased by 30 minutes and returned to baseline by 90 minutes for the controls, but continued to decline until 150 minutes for the men with a family history of alcoholism. This result is consistent with the suggestion that individuals with a predisposition to alcohol-seeking have a greater dopaminergic response to alcohol, but it needs to be replicated together with personality measurements.

**Behavioral inhibition system.** Harm avoidance refers to a heritable tendency to respond intensely to aversive stimuli and their conditioned signals, thereby facilitating learning to inhibit behavior in order to avoid punishment, novelty, and frustrative omission of expected rewards. Harm avoidance may involve variation in the behavioral inhibition system, which includes the septo-hippocampal system, serotonergic projections from the raphe nuclei in the brainstem, and cholinergic projections to frontal neocortex from the midbrain reticular formation near the ventral tegmental area and from the basal nucleus of the amygdala. Ascending serotonergic neurons from the raphe nuclei project to the limbic system, including the septum and hippocampus, as well as to the prefrontal cortex. The septo-hippocampal system is thought to function as a comparator, checking predicted against actual events, and then interrupting behavior when the unexpected is encountered (41). Ascending serotonergic projections from the dorsal raphe nuclei to the substantia nigra inhibit nigro-striatal dopaminergic neurons and are essential for conditioned inhibition of activity by signals of punishment and frustrative nonreward (42). In response to novel stimuli, ascending cholinergic projections excite the frontal cortex and stimulate release of stress hormones, such as cortisol (41). In turn, fronto-striatal projections reduce exploratory activity by inhibiting dopaminergic neurons in the caudate nucleus (35).

Ethanol, benzodiazepines, and other antianxiety drugs block the expression of behavioral inhibition acquired by operant conditioning in which a particular behavioral response is learned to predict punishment or omission of rewards. The effects of antianxiety drugs in human subjects are strongly correlated with their effects on such

passive avoidance learning in rodents (43). These antianxiety effects are thought to be a consequence of inhibition by  $\gamma$ -aminobutyric acid of serotonergic neurons originating in the dorsal raphe nuclei (43). In any case, the reduction of anxiety is positively reinforcing, and serotonergic projections from the raphe nuclei have been strongly implicated in the development of behavioral tolerance to the sedative effects of alcohol. In rodents, the development of tolerance is accelerated (and, conversely, loss of tolerance is slowed) by procedures that increase serotonergic activity or sensitivity, whereas it is slowed (and loss is accelerated) by procedures that reduce serotonin effects (7).

In human subjects, serotonergic activity, as measured by cerebrospinal fluid concentrations of its metabolites, is strongly correlated with harm avoidance (8, 21, 44). Increased serotonergic activity also inhibits dopaminergic activity, so that dopamine and serotonin turnover are strongly correlated in human subjects and other mammals (45). Consequently, high harm avoidance is expected to inhibit alcohol-seeking behavior and to accelerate the development of behavioral tolerance and psychological dependence on alcohol. This expectation is consistent with the findings in clinical and family studies that low harm avoidance is associated with alcohol-seeking behavior, and high harm avoidance is associated with susceptibility to loss of control.

**Behavioral maintenance system.** Reward dependence is hypothesized to involve variation in behavioral maintenance or resistance to extinction of previously rewarded behavior. This resistance to extinction is hypothesized to result from facilitation of paired-associate learning by a brain system that is activated primarily at the onset of reward or the offset of punishment, thereby facilitating formation of conditioned signals of reward or relief from punishment. Norepinephrine seems to satisfy the characteristics required of the major neuromodulator for this system and may play a critical role in the learning of new paired associations (46). The major ascending noradrenergic pathways arise from the locus coeruleus in the pons and project to the hypothalamus, limbic structures including the amygdala, septum, and hippocampus, and then branch throughout the entire cerebral cortex. Norepinephrine seems to modulate the general level or "tone" of neuronal activity or response to other inputs. More specifically, stimulation of the locus coeruleus or its dorsal bundle, or direct application of norepinephrine, has two effects on a target area: the spontaneous firing rate of affected neurons is inhibited, but their response to other afferents is increased (47). Thus the signal-to-noise ratio is increased, allowing relevant or important stimuli to stand out from irrelevant stimuli.

In human subjects, short-term reduction of norepinephrine release by acute infusion of the  $\alpha_2$  presynaptic agonist clonidine selectively impairs paired-associate learning, particularly the acquisition of novel associations (46). This deficit in learning is similar to the circumscribed learning deficit characteristic of patients with destructive lesions of the locus coeruleus that occur in many subjects with Korsakoff's amnesic syndrome. Arginine vasopressin and norepinephrine metabolites are reduced in the cerebrospinal fluid of patients with such lesions (48). Vasopressin enhances memory when injected immediately after learning trials, but this enhancement depends on an intact dorsal noradrenergic bundle (49). The locus coeruleus is inhibited by increased serotonergic activity at the onset of punishment or the offset of rewards (50), so under natural conditions the enhancement of paired-associate learning by norepinephrine release is expected to occur mainly at the onset of rewards or the offset of punishment.

As a result of the conditional inhibition of noradrenergic activity, individuals with low basal firing rates of the locus coeruleus (and hence greater postsynaptic sensitivity to norepinephrine) are expected to respond to signals of reward, such as social approval, and to

persist in reward-seeking behavior even when frustrated; whereas, those with higher basal noradrenergic activity (and hence lower postsynaptic sensitivity to norepinephrine) are more practical and quickly stop activities that are no longer tangibly gratifying (8, 15, 28). These expectations are directly supported by studies in rhesus monkeys: individuals with low basal noradrenergic activity at rest show more severe depressive-like responses to separation and have greater increases in norepinephrine release after receiving low doses of ethanol (51). Furthermore, acquisition of behavioral tolerance to the sedative effects of ethanol is not possible after destruction of noradrenergic projections in mice or after destruction of both serotonergic and noradrenergic projections in the rat (7). Daily vasopressin injections can maintain acquired behavioral tolerance beyond the time it is usually lost, but only if the projections of the dorsal noradrenergic bundle are intact (52).

These findings support the suggestion from clinical and genetic studies that high reward dependence reflects individual differences in a brain system modulated by norepinephrine. Furthermore, the findings provide preliminary support for the hypothesis that reward dependence reflects neuroadaptive processes that are critical in the acquisition of behavioral tolerance to the sedative effects of ethanol and in susceptibility to loss of control of ethanol intake.

## Overview

The convergence of findings about clinical and genetic heterogeneity with findings about the neuropsychopharmacology of ethanol suggests important links between research in several different fields. Many gaps in knowledge remain, but we can finally begin to account for the signs and symptoms of alcoholism and related personality traits in terms of underlying pathophysiological mechanisms. The ability to quantify personality traits that may correspond to the underlying biogenetic structure of brain systems regulating behavioral inhibition, activation, and maintenance may have wide application in the study of the neurobiology of motivation and learning. In particular, quantification of individual differences in personality may provide a powerful means of characterizing the heterogeneity observed in alcoholism and related disorders.

Available information about the neurochemical systems regulating behavioral responses to alcohol and other stimuli remains fragmentary and difficult to interpret despite remarkable recent progress (53). Early hypotheses about individual neural centers or transmitters that control specific behavioral responses proved to be simplistic. Recent work emphasized that neural pathways are not merely links between control centers, but essential parts of a dynamic system or interacting set of systems. The tridimensional structure of personality suggests the existence of three major systems that are genetically regulated independently, even though they interact with one another. Attention to this tridimensional structure should help in the design and interpretation of future neurobiological studies. Each specific monoamine seems to have a major neuromodulatory role in only one system, but each one of these higher order systems seems to be complex, involving the interplay of multiple neurotransmitters. More fine-grained accounts of behavioral mechanisms should become possible as we learn more about the relevant neurochemical networks.

Neither the development of metabolic tolerance to alcohol nor susceptibility to specific medical complications from chronic alcohol use have been discussed here. These phenomena involve mechanisms different from those involved in alcohol-seeking, behavioral tolerance, or loss of control, and they will need to be considered in understanding chronic effects of alcohol (4, 54).

In view of the major public health costs of alcoholism, it is

fortunate that relevant etiological research in several fields has converged in such a complementary manner. Advances in our understanding of developmental factors in alcoholism may be expected to have immediate relevance to the neurobiology of motivation and learning in general. Although the neurobiological learning model described here may have heuristic value, it will certainly undergo change as our knowledge increases. The model is primarily intended to facilitate the interdisciplinary research that is needed for a comprehensive perspective of the adaptive organization of behavior.

## REFERENCES AND NOTES

1. M. M. Heckler, *Fifth Special Report to the U.S. Congress on Alcohol and Health* (Government Printing Office, Washington, DC, 1983).
2. D. Cahalan, *Problem Drinkers: A National Survey* (Jossey-Bass, San Francisco, 1970); D. Goodwin, *Is Alcoholism Hereditary?* (Oxford Univ. Press, New York, 1976).
3. C. R. Cloninger, M. Bohman, S. Sigvardsson, *Arch. Gen. Psychiatry* **38**, 861 (1981); M. Bohman, S. Sigvardsson, C. R. Cloninger, *ibid.*, p. 965; C. R. Cloninger, M. Bohman, S. Sigvardsson, A.-L. von Knorring, *Recent Dev. Alcohol.* **3**, 37 (1985).
4. Z. Hrubecc and G. S. Omenn, *Alcohol. Clin. Exp. Res.* **5**, 207 (1981); Editorial, *Lancet* **1985-I**, 1427 (1985); E. A. Laposata and L. G. Lange, *Science* **231**, 497 (1986).
5. C. R. Cloninger, *J. Psychiatr. Treat. Eval.* **5**, 487 (1983); ———, T. Reich, S. Sigvardsson, A.-L. von Knorring, M. Bohman, in *Alcoholism: A Medical Disorder*, R. Rose, Ed. (Raven, New York, in press).
6. See reviews by S. Peele, *J. Stud. Alcohol* **47**, 63 (1986); J. M. Donovan, *Am. J. Psychiatry* **143**, 1 (1986).
7. J. M. Khanna, H. Kalant, A. D. Le, A. E. LeBlanc, *Acta Psychiatr. Scand. Suppl.* **286**, 161 (1980); H. Kalant, *Can. J. Physiol. Pharmacol.* **63**, 1485 (1985); A. D. Le, J. M. Khanna, H. Kalant, A. E. LeBlanc, *Psychopharmacology* **75**, 231 (1981); C. L. Melchior and B. Tabakoff, *J. Pharmacol. Exp. Ther.* **219**, 175 (1981); *Recent Dev. Alcohol.* **2**, 5 (1984).
8. C. R. Cloninger, *Psychiatr. Dev.* **3**, 167 (1986).
9. A. Tellegen, in *Anxiety and the Anxiety Disorders*, A. H. Tuma and J. Maser, Eds. (Erlbaum, Hillsdale, NJ, 1985), pp. 681–706; R. C. Nichols and R. R. Schnell, *J. Consult. Psychol.* **27**, 228 (1963); H. J. Eysenck and S. B. Eysenck, *Manual of the Eysenck Personality Inventory* (Educational and Industrial Testing Service, San Diego, 1976).
10. P. Park and P. C. Whitehead, *Q. J. Stud. Alcohol* **34**, 887 (1973); C. R. Cloninger, T. Reich, R. Wetzel, in *Alcoholism and Affective Disorders*, D. W. Goodwin and C. K. Erickson, Eds. (SP Medical & Scientific Books, Jamaica, NY, 1979), pp. 57–86; C. R. Cloninger and T. Reich, in *Genetics of Neurological and Psychiatric Disorders*, S. S. Kety *et al.*, Eds. (Raven, New York, 1983), pp. 145–166.
11. E. M. Jellinek, *The Disease Concept of Alcoholism* (Hillhouse, New Haven, CT, 1960); *Can. Med. Assn. J.* **83**, 1341 (1960).
12. H. J. Walton, *Br. J. Psychiatry* **114**, 761 (1968); J. Knop, T. W. Teasdale, F. Schulsinger, D. W. Goodwin, *J. Stud. Alcohol* **46**, 273 (1985); R. E. Tarter, A. I. Alterman, K. L. Edwards, *ibid.*, p. 329; A.-L. von Knorring, M. Bohman, L. von Knorring, L. Orelund, *Acta Psychol. Scand.* **72**, 51 (1985); O. Hagnell, J. Lanke, B. Rorsman, R. Ohman, *Eur. Arch. Psychiatr. Neurol. Sci.* **235**, 192 (1986).
13. H. A. Witkin, S. A. Karp, D. R. Goodenough, *Q. J. Stud. Alcohol* **20**, 493 (1959); A. A. Sugerman and D. U. Schneider, in *Alcoholism: Interdisciplinary Approaches to an Enduring Problem*, R. E. Tarter and A. A. Sugerman, Eds. (Addison-Wesley, Reading, MA, 1976), pp. 395–433.
14. These distinguishing personality traits can be reliably measured by a brief 100-item self-report inventory, called the Tridimensional Personality Questionnaire, available from the author. [Also see (8, 15).] These traits, measured at 11 years of age, distinguish boys who vary in their risk of later alcohol abuse in adulthood from 4 to 75%: C. R. Cloninger, S. Sigvardsson, M. Bohman, *Alcoholism: Clin. Exp. Res.*, in press.
15. C. R. Cloninger, *Arch. Gen. Psychiatry*, in press.
16. P. Propping, J. Kruger, N. Mark, *Hum. Genet.* **59**, 51 (1981).
17. S. B. Blume, *J. Am. Med. Assn.* **256**, 1467 (1986).
18. Interviewed male relatives ( $n = 176$ ) of alcoholic men were distinguished from interviewed male relatives ( $n = 67$ ) of alcoholic women by a discriminant function of alcohol-related symptoms including four items characteristic of type 1 alcoholics and five items characteristic of type 2 alcoholics. After adjustments are made for the total number of symptoms reported, the number of type 1 symptoms in men is negatively correlated ( $r = -0.23$ ,  $P < 0.01$ ) with the number of type 2 symptoms (S. Gilligan, C. R. Cloninger, T. Reich, in preparation).
19. The alcoholic probands with minimal alpha EEG activity were women with characteristic type 1 alcoholic features.
20. P. Propping, J. Kruger, A. Janah, *Psychiatry Res.* **2**, 85 (1980); P. Propping, *Hum. Genet.* **35**, 309 (1977); H. Begleiter and A. Platz, in *The Biology of Alcoholism*, B. Kissin and H. Begleiter, Eds. (Plenum, New York, 1972), pp. 293–343.
21. J. C. Ballenger, F. K. Goodwin, L. F. Major, G. L. Brown, *Arch. Gen. Psychiatry* **36**, 224 (1979); M. Linnoila *et al.*, *Life Sci.* **33**, 2609 (1983).
22. L. von Knorring, *Neuropsychobiology* **2**, 233 (1976); ———, K. Monakhov, C. Perris, *ibid.* **4**, 150 (1978).
23. H. Begleiter, B. Porjesz, B. Bihari, B. Kissin, *Science* **225**, 1493 (1984); S. O'Connor, V. Hesselbrock, A. Tasman, *Prog. Neuropsychopharmacol. Biol. Psychiatry* **10**, 211 (1986). The sons with low P3 amplitude had fathers with early onset of antisocial behavior characteristic of type 2 alcoholics (H. Begleiter, B. Porjesz, R. Rawlings, M. Eckardt, *Alcohol*, in press).
24. N. S. Cotton, *J. Stud. Alcohol* **40**, 89 (1979).



25. A. Roe and B. Burks, *Memoirs of Section on Alcohol Studies* (Yale Univ. Press, New Haven, CT, 1945), no. 3.
26. D. W. Goodwin et al., *Arch. Gen. Psychiatry* **28**, 238 (1973); D. W. Goodwin et al., *ibid.* **34**, 751 (1977).
27. L. Ojesjo, *Soc. Psychiatry* **15**, 81 (1980); L. Kaij, *ibid.* **5**, 216 (1970).
28. For a detailed description of the theory and supporting data, see (8, 15); C. R. Cloninger, in *Human Genetics: Proceedings of the 7th International Congress* (Springer-Verlag, Berlin, in press).
29. A.-L. von Knorring, M. Bohman, L. von Knorring, L. Orelund, *Acta Psychiatr. Scand.* **72**, 51 (1985).
30. C. R. Cloninger, A.-L. von Knorring, S. Sigvardsson, M. Bohman, *Genet. Epidemiol.* **3**, 171 (1986).
31. L. Eaves and H. J. Eysenck, *J. Pers. Soc. Psychol.* **31**, 102 (1975); D. W. Fulker, in *A Model for Personality*, H. J. Eysenck, Ed. (Springer-Verlag, New York, 1981).
32. J. C. Loehlin, *Behav. Genet.* **12**, 417 (1982).
33. C. R. Cloninger and S. B. Gilligan, *J. Psychiatr. Res.*, in press.
34. J. R. Stellar and E. Stellar, *The Neurobiology of Motivation and Reward* (Springer-Verlag, New York, 1985); R. A. Wise, *Pharmacol. Biochem. Behav.* **13**, 213 (1980); A. Routtenberg, *Sci. Am.* **239**, 154 (November 1978).
35. A. Kelley and L. Stinus, in *Affective Development: A Psychobiological Perspective*, N. A. Fox and R. J. Davidson, Eds. (Erlbaum, Hillsdale, NJ, 1984), pp. 1-75; S. D. Iversen, in *Handbook of Psychopharmacology*, L. L. Iversen, S. D. Iversen, S. H. Snyder, Eds. (Plenum, New York, 1977), vol. 8, pp. 333-374.
36. G. L. Gessa, G. Muntoni, M. Collu, L. Vargiu, G. Mereu, *Brain Res.* **348**, 201 (1985).
37. R. G. Heath, *The Role of Pleasure in Behavior* (Harper & Row, New York, 1964).
38. J. R. Nichols, *Ann. N.Y. Acad. Sci.* **197**, 60 (1972); K. Kiianmaa and B. Tabakoff, *Pharmacol. Biochem. Behav.* **18** (suppl. 1), 383 (1983); B. Tabakoff and R. F. Ritzmann, *Drug Alcohol Depend.* **4**, 87 (1979).
39. M. B. Waller, J. M. Murphy, W. J. McBride, L. Lumeng, T. K. Li, *Pharmacol. Biochem. Behav.* **24**, 617 (1986); J. M. Murphy, W. J. McBride, L. Lumeng, T. K. Li, *ibid.* **19**, 849 (1983); T. K. Li, in *Causes and Consequences of Alcohol-Related Problems: An Agenda for Research* (Institute of Medicine, Washington, DC, in press).
40. M. A. Schuckit, D. C. Parker, L. R. Rossman, *Biol. Psychiatry* **18**, 1153 (1983). However, prolonged suppression of prolactin is not observed in daughters or some sons of alcoholics [H. B. Moss, S. Guthrie, M. Linnoila, *Arch. Gen. Psychiatry* **43**, 1137 (1986)].
41. D. M. Warburton, in *Handbook of Psychopharmacology*, L. L. Iversen, S. D. Iversen, S. H. Snyder, Eds. (Plenum, New York, 1977), vol. 8, pp. 385-432; J. A. Gray, *The Neuropsychology of Anxiety* (Oxford Univ. Press, New York, 1982).
42. M.-H. Thiebot, M. Hamon, P. Soubrie, in *Psychopharmacology of the Limbic System*, M. R. Trimble and E. Zarifian, Eds. (Oxford Univ. Press, New York, 1984), pp. 164-174.
43. J. Sepinwall and L. Cook, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **39**, 3021 (1980); L. Stein, in *Anxiety: New Research and Changing Concepts*, D. F. Klein and J. Rabkin, Eds. (Raven, New York, 1981), pp. 201-214.
44. C. M. Banki and M. Arato, *Psychiatry Res.* **10**, 253 (1983); M. Asberg, L. Bertilsson, B. Martensson, *Adv. Biochem. Psychopharmacol.* **39**, 87 (1984); G. L. Brown et al., *Am. J. Psychiatry* **139**, 741 (1982).
45. H. Agren, I. N. Mefford, M. V. Rudorfer, M. Linnoila, W. Z. Potter, *J. Psychiatr. Res.* **20**, 175 (1986).
46. C. D. Frith, J. Dowdy, I. N. Ferrier, T. J. Crow, *Psychopharmacology* **87**, 490 (1985).
47. M. Segal and F. E. Bloom, *Brain Res.* **107**, 513 (1976).
48. R. G. Mair and W. J. McEntee, *Psychopharmacology* **88**, 274 (1986); W. J. McEntee, R. G. Mair, P. J. Langlais, *Neurology* **31**, 648 (1984); R. G. Mair et al., *Life Sci.*, in press.
49. D. DeWeid and B. Bohus, in *Brain Mechanisms in Memory and Learning: From the Single Neuron to Man* (Raven, New York, 1979), pp. 139-149; G. L. Kovacs, B. Bohus, D. H. G. Versteeg, *Brain Res.* **172**, 73 (1979).
50. T. J. Crow and J. F. W. Deakin, in *Handbook of Psychiatry*, M. Shepherd, Ed. (Cambridge Univ. Press, Cambridge, 1985), vol. 5, pp. 137-182.
51. G. W. Kraemer, C. R. Lake, M. H. Ebert, W. T. McKinney, *Psychopharmacology* **85**, 444 (1985); G. W. Kraemer, M. H. Ebert, C. R. Lake, W. T. McKinney, *Psychiatry Res.* **11**, 303 (1984).
52. P. L. Hoffman, C. L. Melchior, B. Tabakoff, *Life Sci.* **32**, 1065 (1983).
53. D. M. Warburton, *Br. Med. Bull.* **37**, 105 (1981); R. F. Thompson, *Science* **233**, 941 (1986).
54. H. Rigter and J. C. Crabbe, Eds., *Alcohol Tolerance and Dependence* (Elsevier/North-Holland, Amsterdam, 1980).
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## Research Articles

# Direct Evidence for DNA Bending at the Lambda Replication Origin

KENNETH ZAHN AND FREDERICK R. BLATTNER

Replication initiation in bacteriophage lambda appears to require wrapping of origin DNA on an approximately 50 angstrom radius in or around the complex with the initiator protein O. Since short lengths of DNA are not that flexible, it may be that runs of coherently spaced deoxyadenylate residues constitute bend sites in the ori sequence that facilitate the process. Earlier data showed that ori DNA has electrophoretic anomalies characteristic of bend sites and that these are augmented by initiator protein binding. Here origin bending is examined by direct measurement of the ability of polymerized ori sequences to form small circles. The smallest circles observed (84 residues) are compatible with the required radius of curvature. Bend sites within the O protein binding sites, bend sites in the spacers between them, plus the inherent flexibility of non-bent DNA in the origin may all contribute to origin bending. The data also show that a bend site is required for O protein binding to DNA.

BACTERIOPHAGE LAMBDA DNA REPLICATION IS INITIATED bidirectionally at a unique origin site (ori) (1), which contains four binding sites (iterons) to which the initiator protein O binds (2, 3). Origin DNA exhibits a pronounced curvature in solution (4) as indicated by electrophoretic mobility anomalies and O protein binding enhances bending of origin DNA (5). Binding of O protein to the origin results in a condensed structure (O-some) (6) whose appearance in the electron microscope suggests that DNA is folded or wrapped around protein. Curvature of ori DNA may therefore play a role in O-some formation and ori function.

The mechanism leading to DNA curvature is not understood in detail (7, 8). But in a number of cases (9, 10), for example the kinetoplast DNA of *Leishmania tarentolae* (11-13), clusters of deoxyadenylate (dA) residues punctuating the sequence coherently with the helical pitch induce significant curvature. There are seven

The authors are in the Department of Genetics, University of Wisconsin, Madison, WI 53706.