As our understanding of alcoholism has advanced, there has been a growing recognition that alcohol misuse and alcoholism are heterogeneous psychopathological conditions with multiple aetiological components (Nurnberger and Gershon, 1984; Gilligan et al., 1987; Cloninger et al., 1989). Research has identified relatively homogeneous subgroups of alcoholics and alcohol-dependent subjects, with each group exhibiting somewhat different psychobiological traits. Cloninger’s neurogenetic, tridimensional theory of personality structure and alcoholism is among the most influential of the current psychobiological models (Cloninger, 1987), although other variations similar to this general classification scheme have been postulated and tested (Babor et al., 1992; Schuckit et al., 1995). Central to these typologies is the finding that impaired impulse control is a CNS trait found in alcoholism and more serious forms of alcohol abuse. Linnoila’s investigations of men with a lower than average cerebrospinal fluid (CSF) concentration of 5-hydroxyindol-3-ylacetic acid (5-HIAA), the major metabolite of serotonin (5-hydroxytryptamine, 5-HT), have been particularly influential in understanding how impulse control deficits contribute to some forms of alcohol abuse and their associated behaviours (e.g. see Linnoila et al., 1994). Studies...
by Linnoila and his colleagues indicated that men with low CSF 5-HIAA concentrations frequently exhibit behavioural problems that may be indicative of impaired impulse control, such as excessive alcohol consumption, polylubstance abuse, suicide attempts, impulsive criminal acts, violence, and criminal recidivism in violent men.

In his model, Cloninger identified two subtypes of alcoholism (Type I and Type II). Type I is characterized by high levels of trait-like anticipatory anxiety. Individuals with Type I alcoholism are postulated to consume alcohol primarily for its anxiolytic properties (Cloninger, 1987, 1988a). The pattern of excessive anxiety and resulting increase in alcohol consumption are typically seen in both men and women and is postulated to result from both genetic background and untoward rearing experiences. Type II alcoholism, on the other hand, is described in its original formulation as male-limited, and characterized by impaired impulse control (Cloninger, 1987). This impairment results in relatively unrestrained alcohol consumption as a consequence of loss of control once alcohol consumption begins. A cluster of unbridled behaviours related to impaired impulse control, similar to those described previously by Linnoila, such as physical aggression, risk taking, and social deficits, distinguishes individuals with Type II alcoholism (Cloninger, 1986, 1987). Each of the two types of alcoholism is proposed to have a different neurogenetic background, with anxiety-mediated Type I alcoholism based primarily on a central nervous system (CNS) noradrenaline excess, and impulse-mediated Type II alcoholism based primarily on a CNS serotonin deficit (Cloninger, 1987).

**WHY STUDY NON-HUMAN PRIMATES?**

A growing number of studies in non-human primates have been used to model some features of alcohol abuse and alcoholism (Crowley et al., 1983; Kraemer and McKinney, 1985; Kraemer et al., 1985; Crowley and Andrews, 1987; Ervin et al., 1990; Higley et al., 1991a). Non-human primates are chosen as subjects primarily because they are our closest relatives phylogenetically and, as a result, share a large percentage of their DNA with humans. Such similarities at the genetic level yield physiological, neuroanatomical, and behavioural similarities, if not actual homologies. These similarities allow researchers to generalize results from the animal model to the human condition more readily than would be possible with results from more phylogenetically distant animal species.

The majority of the alcohol research performed with non-human primates has used macaques (Kraemer and McKinney, 1985; Mello and Mendelson, 1966; Higley and Linnoila, 1997) and other closely related Old World species, such as baboons (Henningfield et al., 1981) and vervet monkeys (Ervin et al., 1990). Like humans, the typical macaque and other Old World species are socially oriented, living in complex societies with frequent social stressors, well-defined social roles, and specific rules concerning social behaviour and reciprocity. As in humans, the social context plays a role in non-human primates’ alcohol consumption (Higley et al., 1996f). Because of these similarities, non-human primates are particularly well suited as subjects for research modelling the antecedents and concomitants of human alcohol problems.

**Difficulties in producing a non-human primate model of alcohol misuse**

Given these advantages, it is perhaps surprising that the use of non-human primates to model alcohol misuse and dependence is a relatively new phenomenon. Difficulty in producing high levels of voluntary alcohol consumption in a typical non-human primate initially posed a substantial problem to researchers interested in developing non-human primate models of alcohol misuse. Until recently, it was widely believed that non-human primates would not consume alcohol (e.g. Mello and Mendelson, 1971; Meisch et al., 1975; Crowley et al., 1983). Newer studies of some non-human primate species have shown, however, that when a palatable alcohol solution is freely available, some (but not all) individuals will readily consume it in quantities sufficient to produce pharmacological effects. In a number of cases, individuals will consume sufficient quantities of alcohol to produce blood levels exceeding the limits of legal intoxication for most states of the USA, resulting in stupor and, at times, unconsciousness (Ervin et al., 1990; Higley et al., 1991a). These recent observations have spurred the use of non-human primates in research on alcohol misuse and alcoholism.
Human and non-human primate parallels in alcohol use

There are a number of demographic and epidemiological descriptions of alcohol consumption patterns in human society. Most humans find the initial taste of alcohol aversive. As a result, people rarely consume alcohol in its pure state. Alcohol is instead consumed in solutions with low concentrations, often with its taste disguised by colas, fruit juices, or other flavourings. Despite its aversive taste properties, most people who try alcohol persist in drinking it, either because of social pressure or their expectations concerning its effects, or because they find that they enjoy its pharmacological effects (Gustafson, 1991, 1992, 1993). Most individuals eventually develop a pattern of modest consumption and have minimal alcohol-related problems (Andersson and Magnusson, 1988; Grant et al., 1988). Similarly, in at least some species of non-human primates, when the solution is palatable, and the concentration of alcohol is <15–20%, most subjects will consume alcohol at rates that produce pharmacological effects (Kraemer and McKinney, 1985; Ervin et al., 1990; Higley et al., 1991b). Only ~10–20% of these normally reared subjects will freely consume palatable alcohol solutions at rates that consistently produce blood alcohol levels greater than the legal level of intoxication for most US states (Kraemer and McKinney, 1985; Ervin et al., 1990; Higley et al., 1991b, 1996e, 1999). This low percentage of high alcohol-consuming individuals is one of the primary difficulties in developing non-human primate models of alcoholism, because it means that researchers must have access to a large population of non-human primates in order to identify appropriate subjects for studies of excessive alcohol consumption.

Studies of inter-individual differences

Studies by us and by others have demonstrated that average inter-individual differences in alcohol consumption are markedly stable over time (Higley et al., 1991a), and may therefore reflect an underlying motivation to consume alcohol that is trait-like. This suggests the possibility that, within non-human primate societies, the 10–20% of the population that consumes alcohol at high rates may be homologous to the 10–20% of humans who, at some period of their lives, misuse alcohol (Robins et al., 1984). Researchers studying alcohol consumption in non-human primates have made significant progress in developing a non-human primate model of alcohol misuse by focusing on those subjects that show high rates of alcohol consumption.

REINFORCEMENT, PERSONALITY, AND ALCOHOL CONSUMPTION

In their comprehensive review of alcohol consumption in non-human primates, Meisch and Stewart (1994) concluded that studies conducted since 1980 have provided compelling evidence that alcohol has reinforcing properties that are sufficient to motivate monkeys to self-administer alcohol. Nevertheless, because of alcohol’s aversive gustatory properties, sweetening alcohol solutions serves to promote consumption, even when no extra calories are added because artificial sweeteners are used (Plummer et al., 1997). Some studies, however, suggest that gustatory incentives are primarily important in initiating alcohol consumption and that, once alcohol consumption is established, it will continue even in the absence of sweetening. For example, rodent studies show that once alcohol consumption is initiated and established using a sweetened alcohol solution, alcohol-prefering strains will continue to consume alcohol even when the sugar is removed (Samson et al., 1988). Similarly, non-human primates will self-administer alcohol intravenously, thus responding to its pharmacological reinforcement properties even when the taste-related reinforcing features are absent (Winger and Woods, 1973).

Interestingly, studies in both humans and rodents indicate that a preference for highly concentrated sweet solutions predicts future high alcohol intake, and that preference is high in abstinent alcoholics (Sinclair et al., 1992; Belknap et al., 1993; Overstreet et al., 1993; Kampov-Polevoy et al., 1998). Furthermore, high consumption of a sweetened solution is correlated with personality traits characterizing Babor’s Type B alcoholics, such as high novelty-seeking and anxiety-mediated harm avoidance. Observations of our high alcohol-consuming monkeys led us to postulate a positive correlation between consumption of sweet solutions and subsequent alcohol consumption. In a recently completed study, we tested this possibility by correlating individual consumption rates for sweetened
cranberry juice and for sugar water with future alcohol consumption. Our results showed that monkeys that preferred the sugar water or cranberry juice solutions were likely to consume alcohol to excess (Pushkas et al., 1998).

Although these results provided further support for a link between alcohol-seeking and a preference for sweetened substances, the demonstration also left us with a potential question about our monkeys’ alcohol consumption. In our research paradigms, 8.4% alcohol is typically administered in a sweetened vehicle, with simultaneous access given to the same alcohol-free vehicle, as well as cage water. Because the sweetened alcohol solution has reinforcing gustatory value, might monkeys be drinking alcohol for its gustatory incentive, rather than for its pharmacological reinforcement value? To rule out this possibility, we tested 15 of our high alcohol-consuming monkeys, allowing them to consume sweetened alcohol at a variety of concentrations. Monkeys that consumed the sweetened alcohol solution at relatively high rates continued to do so even when the alcohol solution was unsweetened (J. A. Vivian et al., unpublished work). This finding provided one line of evidence that gustatory factors are not primary in producing high alcohol consumption.

Further comparisons of unsweetened alcohol consumption between NIH alcohol-consuming rhesus monkeys and rhesus monkeys purchased at random showed that the NIH high alcohol-consuming monkeys consume more unsweetened alcohol than monkeys selected at random. Moreover, high consumption of sweetened alcohol in subjects when they were living at the NIH in Poolesville predicted high consumption of sweetened alcohol 1 year later when they were living in Michigan, even though different self-administration procedures were used. Furthermore, this preference for alcohol in NIH monkeys was evident over a wide variety of both sweetened and unsweetened alcohol concentrations (J. A. Vivian et al., unpublished work). The NIH high alcohol-consuming monkeys also exhibited lower CSF 5-HIAA concentrations than monkeys purchased randomly from vendors and, independent of origin, high alcohol-consuming monkeys were more likely to exhibit low CSF 5-HIAA concentrations (J. A. Vivian et al., unpublished work). Interestingly, high alcohol consumption was not correlated with high self-administration of opiates or other reinforcing agents, indicating that preference for alcohol is unique and not a generalized drug preference pattern (J. A. Vivian et al., unpublished work).

**SEROTONIN AND TYPE II ALCOHOLISM**

Non-human primates have recently been used to model features of Type II alcoholism. These studies used group-living adolescent and adult rhesus monkeys to investigate high alcohol consumption in subjects with reduced CNS serotonin function (King et al., 1993; Higley et al., 1994a, 1996d,e). As noted earlier, a distinguishing neurobiological feature of Type II alcoholism is impaired impulse control, which is believed to result in part from reduced CNS serotonin function (see review in Linnoila et al., 1994). The theory underlying Cloninger’s model of Type II alcoholism postulates that initial alcohol consumption among vulnerable individuals is primarily motivated by the euphorogenic effects of alcohol, but that once consumption is initiated, loss of controlled drinking occurs as a result of impulse control deficits. In his original formulation and other publications, Cloninger discussed an overall behavioural style that characterizes individuals with Type II alcohol problems as having a pattern of behaviours related to impaired impulse control, including physically aggressive behaviours, antisocial traits, excessive risk-taking, and difficulties in social relationships (Cloninger, 1986, 1987). Unlike the risk for expressing Type I alcoholism, the risk for expressing Type II alcoholism appears to be primarily genetically transmitted and relatively unaffected by early experiences. Non-human primate studies suggest that the neurobiology underlying Type II alcoholism may be based on long-term, stable inter-individual differences in the serotonin system.

**CSF 5-HIAA concentrations as an enduring trait**

A principal neurobiological feature of Type II alcoholism is a CNS serotonin deficit as measured by low cisternal CSF 5-HIAA concentrations. This deficit has been shown in a number of human and non-human primate studies that used different methodologies (Linnoila et al., 1994; Higley et al., 1996c,d,e). To the degree that individual differences in personality styles that characterize alcoholism and excessive alcohol intake are stable across
time and between situations, one should find similar inter-individual stability in the neurobiological systems postulated to underlie stable personality traits.

Perhaps the most replicated finding from our laboratory is that inter-individual differences in cisternal CSF 5-HIAA concentrations are trait-like, showing stability across time and between situations, with day-to-day individual differences in CSF 5-HIAA concentrations showing positive correlations. Longitudinal studies of non-human primates have shown that inter-individual differences in CSF 5-HIAA concentrations are stable over time (Kraemer et al., 1989; Higley et al., 1992b, 1993). Even when the settings and situations change, at least under some conditions, inter-individual differences remain stable. For example, when CSF 5-HIAA is sampled in two different settings: first, when the subjects live alone in single cages, and then again after they are placed into novel social groups, inter-individual differences in CSF 5-HIAA concentrations are positively correlated (Higley et al., 1996a). Furthermore, when 14 CSF samples were obtained from the same adult female subjects over a 1-year period, inter-individual stability was high, with the average correlation coefficient $r > 0.50$ (Higley et al., 1996a).

Evidence for stability in this measure of CNS 5-HT function is found in other non-human primate species as well. When Raleigh and colleagues obtained repeated CSF samples from adult males of a closely related species of an Old World primate, they also found a high degree of inter-individual stability in CSF 5-HIAA concentrations (Raleigh et al., 1992; Raleigh and McGuire, 1994).

This degree of inter-individual stability is not limited to the closely controlled laboratory setting. In a naturalistic setting, male macaques migrate from their natal group at adolescence to join new social groups (Higley et al., 1994b). This is a period of high social stress, as the young males must form new relationships and face social challenges where trauma and premature mortality are relatively frequent outcomes (Higley et al., 1994b). Despite these changes, inter-individual differences in CSF 5-HIAA concentrations during the year preceding migration to a new social group are positively correlated with inter-individual differences in CSF 5-HIAA concentrations following migration, with the between-year correlation coefficient $r > 0.50$.

Inter-individual differences in CNS 5-HT turnover appear to stabilize, beginning early in life. When CSF 5-HIAA was obtained from neonatal monkeys on postnatal days 14, 30, 60, 90, 120, and 150, inter-individual differences were stable across time (average $r = 0.50$; Shannon et al., 1995). These early differences remain stable, with mean interindividual concentrations of CSF 5-HIAA taken in late infancy (6 months of age) predicting interindividual concentrations a year later in middle childhood (Higley et al., 1992b), and into adulthood as well (Higley et al., 1996d,e). The presence and early developmental emergence of stability in CSF 5-HIAA concentrations have important clinical implications. Primary among them are the growing number of studies that identify low CSF 5-HIAA concentrations as a potential risk factor for alcohol misuse, alcoholism, and impulse control disorders.

**Reduced CNS serotonin functioning and high alcohol consumption**

Animal studies show excessive or high rates of alcohol consumption among subjects with reduced central serotonin function (see e.g. LeMarquand et al., 1994b for a recent review). In humans, reduced central serotonin function is frequently found in subjects who are at risk for, or who exhibit, alcohol misuse and alcoholism (see LeMarquand et al., 1994a for a recent review). For example, relative to healthy volunteers, young abstinent alcoholic men and women exhibit low CSF 5-HIAA concentrations (Ballenger et al., 1979; Banki, 1981; Borg et al., 1985). Depressed patients with first-degree alcoholic relatives have significantly lower CSF 5-HIAA and 3-methoxy-4-hydroxyphenylglycol (MHPG) concentrations than depressed patients without alcoholic relatives (Rosenthal et al., 1980).

Like humans, non-human primates with low CSF 5-HIAA concentrations are more likely to exhibit behaviours characteristic of impaired impulse control, such as spontaneous long leaps at dangerous heights and repeated jumping into baited traps where they are captured and restrained (Mehlman et al., 1994; Higley et al., 1996c). Because they are impaired in controlling their impulses, we postulated that monkeys with low CSF 5-HIAA would exhibit high rates of alcohol consumption. This hypothesis is consistent with one of the postulates of Cloninger’s tridimensional model of alcoholism,
namely that Type II alcoholism is mediated by central serotonin and noradrenaline deficits (Cloninger, 1987, 1988b). In what is to our knowledge the first study of this hypothesis in non-human primates, we found that alcohol consumption was related to reduced CNS serotonergic and noradrenergic function (Higley et al., 1991a, 1996e). High rates of alcohol consumption during the stressful conditions of a social separation were correlated with low CSF 5-HIAA (Higley et al., 1996e) and MHPG (Higley et al., 1991a, 1996e) concentrations obtained during the social separation stress. MHPG obtained during social separation was also negatively correlated with alcohol consumption during non-stressful conditions (Higley et al., 1996e). To the degree that non-human primate findings can be extrapolated to the human condition, our results suggest that excessive alcohol consumption associated with serotonin deficit may be particularly evident in stressful conditions. Reduced noradrenaline, on the other hand, was correlated with high alcohol consumption under both stressful and non-stressful conditions. This finding suggests that the level of stress a subject is undergoing should be taken into consideration when obtaining CSF 5-HIAA to use as a biological marker to predict alcohol consumption, although in a subsequent study we found that, independent of stress, CSF 5-HIAA concentrations were negatively correlated with alcohol consumption (Higley et al., 1999).

CNS SEROTONIN AND PERSONALITY

Some studies have suggested that low CSF 5-HIAA concentrations are a marker for a wide array of psychopathological problems, and that the common variable in subjects exhibiting these difficulties is impaired impulse control. For example, lower than average baseline CSF 5-HIAA concentrations have been found in individuals who engage in impulsive fire setting or frequent violent criminal behaviours (Virkkunen et al., 1987), as well as excessive alcohol intake and alcohol dependence (Ballenger et al., 1979; Banki, 1981; Borg et al., 1985; Moss, 1987; Roy and Linnoila, 1989). Parallel-ling these biochemical findings, Type II alcoholics, sons of alcoholic fathers (Schulsinger et al., 1986; Limson et al., 1991; Sher et al., 1991; Giancola et al., 1993) and, in some studies, daughters of alcoholic fathers (Sher et al., 1991) have been rated as high in impulsivity and other measures of behavioural dyscontrol.

Consistent with these findings, low CSF 5-HIAA concentrations are often found in individuals exhibiting other psychopathological syndromes that are characterized by impaired impulse control: Gilles de la Tourette’s syndrome (Cohen et al., 1978; Butler et al., 1979; Cohen et al., 1979), bulimia (Jimerson et al., 1990, 1992), criminal recidivism in violent, male offenders (Virkkunen and Linnoila, 1990), inappropriate or excessive aggression in adolescence (Kruesi, 1989; Kruesi et al., 1990, 1992), and unplanned violence or higher than average lifetime rates of aggression (Brown et al., 1979, 1982; Linnoila et al., 1983; Lidberg et al., 1985; Limson et al., 1991). By contrast, increased concentrations of CSF 5-HIAA have been found in individuals whose psychopathology is characterized by overly inhibited and obsessive symptoms. For example, long-term, weight-recovered anorexic women have higher than average baseline CSF 5-HIAA concentrations (Kaye et al., 1984, 1991). Similarly, in some studies, individuals with obsessive–compulsive disorder have shown increased CSF 5-HIAA concentrations (Insel et al., 1985), and the higher their concentrations of CSF 5-HIAA, the more likely patients are to improve when treated with a pharmacotherapy that modulates serotonin activity (Thorén et al., 1980; Åsberg et al., 1982; Swedo et al., 1992). Similarly, pharmacological treatments that affect the serotonin system have been reported to have efficacy in the treatment of some of the syndromes mentioned above. For example, serotonin reuptake inhibitors decrease alcohol preference and consumption (Naranjo and Sellers, 1989; Naranjo et al., 1990), although the effect is at times short-lasting (Gorelick, 1989), and fluoxetine has been used to treat bulimia (Freeman and Hampson, 1987). Serotonin-enhancing pharmaceutical interventions have been used recently to reduce violent outbursts and aggression among borderline patients (Cornelius et al., 1990, 1991).

Research using animals has provided further evidence that serotonin may play an aetiological role in disorders of impulse control and aggression. Analysis of CNS biochemistry in animals selectively bred for domestication show that, as the programme of selective breeding progressively produces animals with more docile and less aggressive temperaments, there is a concomitant increase
in CNS serotonin and 5-HIAA concentrations (Naumenko et al., 1989; Popova et al., 1991a,b). In rodents, pharmacologically increasing serotonin activity decreases aggression, while decreasing serotonin activity increases aggression (Miczek and Donat, 1990; Olivier and Mos, 1990; Olivier et al., 1990; Nikulina et al., 1992).

Non-human primate studies lend additional convergent evidence for the relationship between low CNS serotonin function and high impulsivity. In rhesus monkeys, low CSF 5-HIAA concentrations are not simply correlated with rates of aggression, but only with aggression that is impulsive and unrestrained (Higley et al., 1996c). Moreover, high rates of impulsive behaviour are positively correlated with severe, unrestrained aggression, but not with the competitive, restrained aggression that is used to maintain status, a type of aggression that seldom escalates out of control (Higley et al., 1996c). The generalizability of this finding is supported by a cross-species comparison of serotonin–behaviour relationships in females of two closely related macaque species with known differences in sociality and aggression: rhesus (Macaca mulatta) and pigtailed macaques (Macaca nemestrina). By using two closely related species with known behavioural differences, we were able to test the hypothesis that macaque species with friendly, less aggressive relationships (pigtailed macaques) would have higher CSF 5-HIAA concentrations than the less friendly, more aggressive rhesus macaques. In a recently submitted manuscript, we reported that the female pigtailed macaques exhibited higher CSF 5-HIAA concentrations, more friendly relations, and less aggression than the rhesus macaques. In a replication and extension of our work with rhesus macaques, within-species analyses indicated that CSF 5-HIAA concentrations were inversely correlated with escalated aggression and positively correlated with social dominance rank (G. C. Westergaard et al., unpublished work).

Not only are natural levels of serotonin associated with aggression in non-human primates, but pharmacological studies also demonstrate that manipulation of the serotonin system affects behaviour in a predictable manner. In the laboratory, non-human primates that engage in spontaneous self-injurious behaviours cease such behaviours after administration of the serotonin precursor tryptophan (Weld et al., 1998). Similarly, consumption of experimental diets high in the serotonin precursor tryptophan reduces aggression in monkeys that are provoked, whereas diets low in tryptophan increase aggression, with these effects greater at times among males than females (Raleigh et al., 1985, 1991; Chamberlain et al., 1987). Similar changes in aggression have been demonstrated with other serotonin treatments, including decreases in aggression with short-term administration of serotonin reuptake inhibitors (Raleigh et al., 1985; Raleigh and McGuire, 1986), and increases in aggression after administration of the serotonin synthesis inhibitor p-chlorophenylalanine (Raleigh et al., 1980; Raleigh and McGuire, 1986). Likewise, long-term treatment with fenfluramine, which decreases CSF 5-HIAA concentrations, increases aggression among non-human primates (Raleigh et al., 1983, 1986).

As noted earlier, beyond the social context, monkeys with low CSF 5-HIAA concentrations are more likely to exhibit behaviours that are characteristic of impaired impulse control (Mehlman et al., 1994; Higley et al., 1996c). Data from other animal studies further implicate serotonin in the control of impulses outside the expression of aggressive tendencies. For example, pharmacologically reducing CNS serotonin activity in rodents increases the frequency of performing a response, despite the threat of punishment for responding (Gleeson et al., 1989; Miczek et al., 1989; see also Soubrié, 1986 for a review). Such studies suggest the hypothesis that serotonin may serve to inhibit a variety of urges, and may not be limited to the inhibition of suicide, aggression, or alcohol consumption.

OTHER TRAITS ASSOCIATED WITH EXCESSIVE ALCOHOL CONSUMPTION

While impulsivity and aggression are characterized associated with Type II alcoholism, high anxiety is the central personality characteristic of Type I alcoholism. One frequently used measure of anxiety and fear is excessive hypothalamic–pituitary–adrenal (HPA) axis activity. HPA activity in primates is typically measured by plasma or serum levels of two hormones, cortisol and adrenocorticotropic hormone (ACTH). Consistent with Cloninger’s predictions for Type I alcoholics, in one study of alcohol-consuming non-human primates, high ACTH predicted future excessive alcohol
consumption, independent of other variables that affect cortisol output, such as early rearing background (Higley et al., 1991a). In humans, fenfluramine-stimulated cortisol levels are higher in boys at risk for future alcoholism (Schulz et al., 1998). In monkeys, high cortisol levels in infancy were predictive of high cortisol levels in the juvenile and adolescent periods (Higley et al., 1991a, 1992b).

Taken together, these findings led us to postulate that high plasma cortisol concentrations in infants could be used as biological markers to predict future alcohol consumption. Assessments of 150 infant monkeys supported this hypothesis, showing that plasma cortisol obtained in infancy under stressful conditions was predictive of excessive alcohol consumption three-and-a-half years later when the subjects were adolescents and young adults. As noted earlier, inter-individual differences in cortisol concentrations were stable over development, with a correlation between concentrations obtained in infancy and adulthood. This finding is important, because it suggests a biological marker that may be used in young subjects prospectively to identify those prone to excessive alcohol consumption. Replicating earlier studies, we also found that peer-reared subjects (who show low CSF 5-HIAA concentrations and inappropriate aggression) exhibited high levels of anxiety and cortisol (Higley et al., 1991a), consistent with Cloninger’s Type I, but not Type II, alcohol misuse. This later finding suggests that there may be some overlap between Type I and Type II alcohol-related physiological and behavioural profiles in monkeys. This overlap is consistent with the Babor model, where Type B alcohol problems are characterized by impairments in both impulsivity and anxiety. These studies and those cited earlier also point to the responsibility of the HPA axis as a potential area in which to investigate aetiological mechanisms and novel treatment interventions for excessive alcohol intake.

In a study of abstinent human alcoholics with low CSF 5-HIAA concentrations (Virkkunen et al., 1994) it was observed that they exhibited dysregulated diurnal activity patterns. Higher levels of night-time activity and more frequent daytime naps occurred in the abstinent alcoholics than the healthy volunteers, pointing to a general disruption of diurnal activity patterns in the alcoholics with low CSF 5-HIAA concentrations. The alcoholics with low CSF 5-HIAA also showed evidence of hyperactivity during the daytime hours. These findings led us to postulate that monkeys with low CSF 5-HIAA concentrations would exhibit similar dysregulated diurnal activity patterns. To address this hypothesis, adult male macaques living in field settings were collared with radio transmitters designed to detect motion, and 24-h activity samples were obtained while they were freely ranging. When they were compared to their counterparts with high CSF 5-HIAA concentrations, males with low CSF 5-HIAA concentrations had more frequent and longer periods of night-time activity, and more frequent naps during the daytime hours (G. C. Westergaard et al., unpublished work). They also exhibited more activity during the daytime than their counterparts with high CSF 5-HIAA concentrations. We followed up these findings in the more controlled laboratory environment, where we found that, in a large group of young monkeys, subjects with low CSF 5-HIAA concentrations were the last to fall asleep (Zajicek et al., 1997). These findings suggest that monkeys with low CSF 5-HIAA concentrations possess dysregulated circadian activity patterns, with high daytime activity, patterns that parallel those seen in male human alcoholics with low CSF 5-HIAA concentrations.

**TREATMENT STUDIES**

A large number of animal studies have demonstrated high or excessive rates of alcohol consumption among rodents with reduced central serotonin functioning (e.g. see LeMarquand et al., 1994b for a recent review), and in non-human primates with low CSF 5-HIAA concentrations, high alcohol intake is frequent (Higley et al., 1991a, 1996e), but not universal (Ervin et al., 1990). Among humans, clinical studies show evidence of reduced central serotonin function in subjects who exhibit alcohol misuse and alcoholism, or who are at risk for alcohol-related problems (see LeMarquand et al., 1994a for a recent review). Some studies in humans and rodents suggest that serotonin-enhancing pharmacological treatments decrease alcohol consumption (Gill and Amit, 1989; McBride et al., 1989; Higley et al., 1998; however, see Palmour et al., 1998). To test its effectiveness in treating alcohol consumption in non-human primates, rhesus monkeys were treated with 20 mg/kg/24 h
of sertraline and allowed unfettered access to an 8.4% ethanol solution in three conditions: a baseline home-cage setting, during a social separation stressor, and during reunion with cage-mates. Although there was no immediate effect, sertraline reduced alcohol consumption at the beginning of the second week of baseline treatment and did not reduce water intake, but this treatment effect only occurred in subjects that consumed large amounts of alcohol. Modest alcohol intake was unaltered by sertraline treatment. Thus the sertraline treatment effect was specific to over-consumption of alcohol, and was not a result of a generalized reduction in consumption or overall reduction in moderate alcohol intake.

Social separation stress initially caused the sertraline-treated subjects’ alcohol consumption rates to return to their high baseline levels, but when the stress became chronic, alcohol consumption again fell below baseline and placebo levels. Sertraline treatment was ineffective in reducing alcohol consumption during the stressful period of home-cage reunion, a period also characterized by high levels of aggressive behaviour. These findings indicate that sertraline may be an effective pharmacological treatment for excessive alcohol consumption, but that stress during treatment may reduce its effectiveness. We also found in this study that long-term, but not acute, sertraline treatment reduced aggression and anxiety in rhesus monkeys (Higley et al., 1998).

Other studies in non-human primates show that sertraline is effective for treating excessive alcohol consumption and severe aggression. Weld et al. (1998) treated male monkeys chronically with sertraline and then tested them 1 day a week in a paradigm designed to elicit aggression. Aggression and alcohol consumption were recorded when previously singly-caged adult males were paired in a novel environment, returned to their single cage, and allowed to consume alcohol. Sertraline reduced CSF 5-HIAA concentrations, aggression, and alcohol consumption under these conditions. In view of these findings, we postulated that treatments with other serotonin-enhancing pharmacological agents would reduce aggression. Monkeys that engaged in serious self-biting were treated with the serotonin precursor tryptophan (100 mg/kg, twice a day). Tryptophan increased CNS serotonin function in these animals and eliminated self-injurious behaviour.

TOLERANCE, SEROTONIN, AND EXCESSIVE ALCOHOL CONSUMPTION

Schuckit’s identification of biological markers for alcoholism risk shows that alcoholics’ offspring are less responsive to the intoxicating effects of alcohol. Moreover, even when family history is controlled, a reduced response to the intoxicating effects of alcohol is a predictor of future alcohol misuse (Schuckit and Smith, 1996; Schuckit et al., 1996). One limitation of such studies is that in humans, previous history of alcohol use is a potential factor producing a low response to alcohol. Although retrospective histories indicated that a reduced response to alcohol was not correlated with previous history of alcohol use, the effect of previous alcohol consumption as a factor in this dampened response can only be ruled out by performing longitudinal studies that begin before alcohol consumption is initiated. Non-human primates are ideally suited to test whether inherent tolerance to alcohol is a biological marker for excessive alcohol intake.

While current knowledge concerning the neurobiological mechanisms that underlie intrinsic tolerance is rather rudimentary, some evidence suggests that CNS serotonin may be involved. Kalant (1996) recently reviewed the neurobiological influences on acute alcohol tolerance and concluded that serotonin is likely to play an important role. Findings with monkeys led us to design a series of studies to investigate the relationship between serotonin and inherent tolerance. In a positron-emission tomography (PET) study, we found that non-human primates with low CSF 5-HIAA concentrations were intrinsically tolerant to drugs such as pentobarbital, which, like alcohol, are functional GABA A receptor agonists and show cross-tolerance with alcohol. These findings led us to postulate that alcohol-naïve monkeys with low CSF 5-HIAA concentrations would show less intoxication following a standard dosage of alcohol, and that low intoxication after alcohol administration would predict future high alcohol consumption.

To test the relationship between impaired CNS serotonin function and intrinsic tolerance to the intoxicating effects of alcohol, CSF was obtained from alcohol-naïve, adolescent macaque subjects and assayed for CSF 5-HIAA concentrations. The monkeys were subsequently administered identical doses of alcohol intravenously and rated for their
degree of intoxication. Two to three months later, they were allowed to freely consume a palatable alcohol solution. Subjects with low CSF 5-HIAA concentrations were rated as less intoxicated than monkeys with high CSF 5-HIAA concentrations (Higley et al., 1999). When they were allowed to consume alcohol, the monkeys that previously showed minimal signs of intoxication in response to the intravenously administered alcohol were more likely to voluntarily consume alcohol to excess than monkeys previously rated as high in intoxication (Higley et al., 1999). Monkeys with low CSF 5-HIAA concentrations were shown to consume alcohol in excess. Such findings in subjects with low CSF 5-HIAA concentrations suggest an interesting possibility that could lead to a better understanding of excessive alcohol consumption: subjects with low CSF 5-HIAA concentrations are intrinsically tolerant to alcohol, and drink more to experience a pharmacological effect. Once they begin to drink, they may be more likely to continue in an unrestrained fashion because of their impaired impulse control, suffering loss of control in their drinking patterns. In a recent follow-up of this study, we anaesthetized subjects with identical dosages of ketamine and measured how long it took them to wake up. Inter-individual differences in CSF 5-HIAA concentrations were also shown to correlate positively with time to recover from ketamine anaesthesia (Shannon et al., 1997).

Human studies show a high co-occurrence between alcohol intake and violent behaviour. In the above study, previous lifetime rates of severe aggression, and low CSF 5-HIAA concentrations measured prior to alcohol exposure predicted high rates of aggression during intoxication (Higley et al., 1999). These findings suggest that high rates of aggression during intoxication are an extension of a life-long pattern of severe aggression, rather than a special form of aggression.

AETIOLOGICAL MECHANISMS: GENETIC AND ENVIRONMENTAL INFLUENCES

One area where the primate model has been most useful is in partaillying genetic and environmental influences on CNS serotonin function. Genetic and environmental influences on CSF monoamine metabolite concentrations were investigated in non-human primate infants reared in different social environments. Paternal genetic effects were assessed by rearing infants apart from their fathers and performing a paternal half-sibling analysis. Maternal genetic influences were studied by rearing infants with their biological mothers, unrelated lactating females, or in peer-only groups. At 6 months of age, CSF was obtained before and during a series of social separations. When the results were statistically pooled according to the biological father, CSF 5-HIAA showed significant heritable effects ($h^2 > 0.5$) for both sons and daughters. In addition, there were substantial maternal genetic influences on the young offsprings’ 5-HIAA ($h^2 > 0.5$). Although they did not study maternal contributions, the finding of a paternal genetic contribution to CSF 5-HIAA concentrations was replicated in a study of non-human primates by Clarke et al. (1995). Taken together, these findings suggest that a significant portion of the variance in the turnover of CNS serotonin is determined by genetic mechanisms. While somewhat speculative, these findings may suggest a mode of genetic transmission of Type II alcoholism. It predicts that low serotonin function is genetically transmitted, which may lead to deficits in impulse control and ultimately to increased risk for excessive alcohol consumption once alcohol consumption begins. It is of note that this pattern does not fit Cloninger’s predictions and findings, since those studies have shown that Type II alcohol problems are transmitted from fathers to sons only (Cloninger et al., 1985), and our studies show that low serotonin function is genetically transmitted by both mothers and fathers.

In a smaller study, a similar analysis was performed to assess alcohol consumption. Although the sample size was too small to assess maternal contributions, paternal contributions accounted for a significant portion of inter-individual differences in alcohol consumption (Higley, 1996).

Animal studies have shown that appropriate environmental input during proper developmental periods is essential for the normative development of the CNS (Greenough, 1987; Black et al., 1989). Primate societies are explicitly structured to ensure that the infant receives such input. Among most Old World monkey societies, neonatal monkeys initially develop their social skills under the watchful tutelage of their biological mother. Mothers are especially important social agents through which infant and juvenile monkeys develop the capacity to properly inhibit and express emotions, including
aggression (Harlow and Harlow, 1965; Harlow, 1969; Bernstein and Ehardt, 1986; Higley and Suomi, 1986, 1989). Mothers are the first to punish unrestrained and impulsive behaviour, and it is in the context of mother–infant interactions that infants first learn to inhibit inappropriate and exhibit appropriate behaviours. Infants and young monkeys deprived of opportunities to interact with their mothers are likely as adolescents and adults to exhibit unrestrained emotional responses, such as hyperaggression and anxiety. They also exhibit impoverished social interactions, and have difficulties maintaining social relationships (Coelho and Bramblett, 1984). Their initial interactions with peers are characterized by less frequent and less skilled use of aggression or the expression of excessive aggression in social interactions (Coelho and Bramblett, 1981; Capitanio, 1986; Higley et al., 1994b, 1996b).

One manipulation that has been widely used to study the effects of early experiences among monkeys is peer-only rearing. In this rearing condition, subjects are removed from their mothers at birth and reared with other age-matched infants, where they develop in the absence of adult influence. Like infants reared by their mothers, peer-reared monkeys develop strong bonds with their agemates and use them as a secure base from which to explore (Higley et al., 1992a). Nevertheless, when they are compared to their mother-reared counterparts, peer-reared subjects exhibit evidence of non-secure attachment bonds, higher levels of anxiety, and less exploration in novel settings when their attachment sources are present (Higley et al., 1992a). As peer-reared monkeys mature, with the exception of infantile clinging, they exhibit fewer overall social interactions and, when they do interact, their interactions are immature and infant-like (Higley et al., 1996d,e). Perhaps as a result of these deficits, they are more likely to ultimately rank low in social dominance, a measure of social competence in a non-human primate (Higley et al., 1996d,e).

Peer-only-reared monkeys appear to exhibit deficits in impulse control. For example, during aggressive episodes, minor episodes of aggression are more likely to escalate into severe aggression (Higley et al., 1994b). When they are provoked, peer-reared subjects are likely to express aggression at inappropriate targets or in unexpected settings, and they are particularly prone to violently aggressive behaviours (Mitchell, 1970; Suomi, 1982a,b; Capitanio, 1986; Higley et al., 1994b, 1996b). There is evidence of impulse control problems that are also found in humans who are likely to have suffered parental deprivation. In humans, parental loss from divorce early in life predicts future excessive alcohol consumption in adults (Kendler et al., 1996; Hope et al., 1998). Under baseline, non-stressful conditions, adolescent and adult parentally deprived peer-reared monkeys consume alcohol in excess (Higley et al., 1991a), but when stress is induced using a social separation stressor, mother-reared monkeys increase their consumption to equal that of the peer-reared (Higley et al., 1991a). Peer-reared subjects’ low rates of social interactions are also predictive of excessive alcohol intake (Higley et al., 1996d,e). It is noteworthy that whereas peer-only-reared monkeys are typically more likely to consume alcohol in excess and exhibit severe aggression, administration of the serotonin reuptake inhibitor sertraline reverses these aberrant behaviours by reducing alcohol consumption, anxiety, and aggression (Higley et al., 1998). Moreover, inter-individual differences in CSF 5-HIAA concentrations predict subjects’ response to sertraline, and thus suggest an underlying serotonin deficit.

Interactions of parents with offspring not only affect the acquisition and development of the observed behaviour, they also play a crucial role in the organization and proper development of the CNS. For example, a number of studies using non-human primates have shown that prior experiences affect serotonin function during infancy and childhood (Kraemer et al., 1989; Higley et al., 1992b, 1993). These studies have shown that adult influences, particularly maternal input, are critical to govern the development of the CNS serotonin system. In the absence of adult influence, the development of serotonin functioning is impaired. When CSF 5-HIAA was obtained from neonatal peer-only-reared and mother-reared monkeys on postnatal days 14, 30, 60, 90, 120 and 150, parentally neglected peer-reared subjects exhibited lower CSF 5-HIAA concentrations than mother-reared subjects (Shannon et al., 1995). One study with a limited sample size suggested that the effect of early rearing experiences on CSF 5-HIAA may disappear by adolescence (Higley et al., 1991b). In a study in which peer- and mother-reared subjects were longitudinally studied from infancy
into adulthood, peer-reared subjects exhibited lower CSF 5-HIAA concentrations than motherreared subjects both in infancy and adulthood (Higley et al., 1996e).

SUMMARY AND CONCLUSIONS

Our findings show that there is a non-human primate phenotype of low CSF 5-HIAA concentrations. Subjects with this phenotype exhibit high rates of alcohol consumption, and many personality traits that are similar to those described by Cloninger in his typology of Type I and Type II alcoholism. Reduced central serotonin and noradrenaline function, impaired impulse control, excessive violence, decreased social affiliation, and less competent social functioning are risk factors in both non-human primates and in humans with Type II alcohol problems. Behaviour patterns and biological indices that characterize high anxiety, whether constitutionally or stress-induced, were correlated with high rates of alcohol consumption, consistent with predictions drawn from descriptions of Type I alcoholism. While these findings indicate many similarities to Cloninger’s model, our pattern of results also shows several differences from the predictions of the neurogenetic models. As noted earlier, in the monkeys, there is some overlap between Type I- and Type II-like alcohol problems, with Type II-like traits present in both male and female macaques. This is not predicted by the original neurogenetic model, where Type II alcohol problems were male-limited. Levels of anxiety were also high in the peer-reared monkeys, who exhibited Type II-like traits, such as low CSF 5-HIAA concentrations, impulse control and social deficits, and high rates of aggression. Moreover, Type II-like features in peer-reared monkeys are a direct consequence of early rearing experiences. This pattern is different from Cloninger’s predictions and findings since, in the neurogenetic model, Type II alcoholism is environmentally independent, and in the non-human primates environmental influences accounted for a large percentage of the variance in CSF 5-HIAA concentrations and alcohol consumption. Whether these differences between human and non-human primate studies are species-related remains to be verified. Studies in humans have produced some updates to the original neurogenetic model and indicate, for example, that early experiences shape and account for antisocial behaviour among adolescents and young adults (Cador et al., 1995), and other studies performed in humans indicate that Type II features may be present in females with alcohol problems (Heath et al., 1994).

Perhaps our most important finding is that low CSF 5-HIAA concentration appears to be a lifelong pattern that may underlie many of the long-term deficits seen in humans with Type II alcoholism. CSF 5-HIAA concentrations, and probably excessive alcohol consumption, are genetically influenced, but parental neglect during infancy and early childhood contributes to long-term reduced central serotonin function. Early rearing experiences that reduce serotonin function appear to exaggerate inherited predispositions for alcohol consumption. Our non-human primate subjects with low CSF 5-HIAA concentrations show impaired impulse control resulting in frequent violence, infrequent and less competent social behaviours, and low social dominance status. They are shunned as companions, forced to leave their social groups at an early age, and, as a consequence, are likely to suffer from early mortality, frequently as an adjunct consequence of violent behaviour. These findings suggest the potential utility of this non-human primate model for understanding the neurobiology of impulse control deficits leading to excessive alcohol consumption, disruptive social behaviours, and excessive aggression.

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