Catalase: a Possible Marker for Human Alcohol Consumption.

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ABSTRACT

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Earlier studies have suggested that catalase activity may be a predictor of alcohol intake in animals and in humans. The hypothesis that blood catalase may represent a biological marker for human alcohol intake was tested. An initial study was first designed to rule out the possibility that catalase activity is induced as a function of acute alcohol intake. Subjects (N = 80) were presented with either a control solution, or vodka and orange juice (EtOH 0.5 g/kg of bodyweight), and asked to provide four 100 µl blood and four breath alcohol samples (BAC), which were collected at 0.0, 0.5, 2.0, and 24.0 hours. Results showed no significant differences in catalase activity between individuals who had received alcohol, and controls, even when the effects of previous drinking history were covaried out of the analysis. In addition, results showed that, BAC was higher for the alcohol condition compared to that of controls, and for the alcohol condition, females had significantly higher BAC compared to males. This lack of effect of acute alcohol intake on the possible induction of catalase further supported the notion that catalase may be a viable marker of alcohol intake, rather than the converse. In the second study, the relation between catalase activity and

alcohol intake was investigated in individuals with a family history of alcoholism (FH+), and without a family history of alcoholism (FH-). Subjects (N = 607) were recruited from three treatment centers as well as from newspaper advertising. They were asked to complete the Michigan Alcoholism Screening Questionnaire (MAST), MacAndrew Scale (MAC), and the Concordia University Alcohol Screening Questionnaire (CASQ). They were also asked to answer questions concerning their family history of alcoholism, and to provide a 100 µl blood sample. Results showed that FH+ individuals had higher mean catalase activity compared to FH- individuals. When individuals with FH+ were compared to those with FH- on the above measures, differences in the pattern of relation between catalase activity and alcohol intake were observed. Although a significant relation between catalase activity and alcohol intake was obtained for both FH- and FH+ individuals, this relation was significantly higher ($p<.001$) for individuals with FH+. In order to rule out the possibility that catalase activity in FH+ individuals was a covariate of one or more variables, the data were subjected to multiple regression analysis. Results from the multiple regression analyses suggested that catalase activity in FH+ individuals made the highest contribution to the variance, even after accounting for several additional variables. These results support the contention that catalase activity may be a biological marker of the propensity of FH+ individuals to consume alcohol.

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Alcoholism is the single, most pervasive drug abuse problem in the world (NIAAA, 1990b). Alcohol abuse has serious psychological and physical consequences that affect about 10 to 15 % of adults in North America (Helzer & Prysbeck, 1988; NIAAA, 1990b). Adverse social, psychological, and medical consequences of excessive drinking arise from single bouts of drinking, as well as from the long term effects of alcohol consumption (NIAAA, 1990a, 1990b). A minimum of 3 out of every 100 deaths in the United States alone can be attributed to alcohol-related causes (Van Natta, Malin, Bertolucci, & Kaelber, 1984-85). The main chronic health hazard associated with alcohol abuse, chronic liver disease and cirrhosis associated with alcohol abuse, was ranked as the ninth leading cause of death in the United States in 1986, causing more than 26, 000 deaths in that year alone (NIAAA, 1990b). Proportionally similar numbers have been reported for Canada (Mann, Smart, & Aglin, 1988).

A variety of factors have been proposed to explain individual differences in alcohol drinking patterns in humans. These factors can be classified as being cultural, social, psychological, genetic, and biological in nature (Heath, 1990-91; Lex, 1987; Searles, 1988, 1990; Vaillant, 1983). However, a growing body of evidence (Amit, Brown, Amir, Smith, & Sutherland, 1980; Amit & Smith, 1989; Myers, Ng, Marzuki, Myers, & Singer, 1984; Smith, Spivak, & Amit, 1990; Takayama & Uyeno, 1985) has suggested that acetaldehyde, the primary metabolite of alcohol, may play a role in the

mediation of these individual differences in alcohol consumption patterns.

More specifically, considerable evidence has accumulated suggesting that acetaldehyde may be mediating many of the behavioral, pharmacological, and reinforcing effects of ethanol in animals[1] (Amit & Smith, 1989; Lindros, 1978; Myers et al., 1984; Smith et al., 1990; Takayama & Uyeno, 1985).

Numerous studies, however, have demonstrated that acetaldehyde, when present in peripheral circulation at high concentrations, can also evoke a variety of aversive effects in humans and in laboratory animals (see Kitson, 1989; Lindros, 1978).

In addition to these aversive effects, it has also been demonstrated that rats previously naive to ethanol, will learn to perform an operant task when maintained by response-contingent intracerebroventricular (Brown, Amit, & Rockman, 1979) or by intravenous (Myers, Ng, & Singer, 1982; Myers et al., 1984; Takayama & Uyeno, 1985) infusions of acetaldehyde. These results suggested that acetaldehyde may possess reinforcing properties.

It would appear, therefore, that acetaldehyde may have both aversive and positive reinforcing properties. Given that acetaldehyde is the primary metabolite of ethanol, and that acetaldehyde may be mediating many of the reinforcing properties

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[1] In line with traditional nomenclature, the term 'alcohol' will be used exclusively with regards to humans, while the term 'ethanol' will be used exclusively with regards to animals.

of ethanol (Amit & Smith, 1989; Brown, Amit, & Smith, 1980; Smith et al., 1990), it has been postulated that the enzymes responsible for the formation and degradation of acetaldehyde may play a role in a number of the psychopharmacological effects of ethanol, including voluntary ethanol consumption (Amit & Aragon, 1988; Aragon & Amit, 1985; Aragon, Sternklar, & Amit, 1985c; Lindros, Koivula, & Eriksson, 1975); and, locomotor activity (Spivak, Aragon, & Amit, 1987b). Accordingly, the possible contribution of these enzymes in the mediation of the biobehavioral effects of ethanol, may provide important insights concerning acetaldehyde's role in ethanol's effects. More importantly, it has been suggested that genetic factors which may predispose individuals towards alcoholism, may be related to individual differences in the metabolism of alcohol (Amit, Smith, & Aragon, 1986; Bosron & Li, 1986). The primary reinforcing properties that may mediate the initiation of alcohol consumption and the potential development of alcohol dependence (Amit, Smith, & Sutherland, 1987; Falk & Tang, 1988; Meisch & Beardsley, 1975; Mello & Mendelson, 1972; Myers et al., 1984), may also be modulated by acetaldehyde. Several researchers have in fact gone as far as to suggest that "alcoholism may in fact be acetaldehydism" (Amit et al., 1987; Brien & Loomis, 1983; Raskin & Sokoloff, 1970; Von Wartburg & Buehler, 1984).

Despite the consistency of results from many behavioral studies (Aragon & Amit, 1985, 1988; Aragon et al., 1985c; Lindros

et al., 1975), there has been a reluctance (Erikkson, 1983; Smith et al., 1990) to accept the contention that acetaldehyde has reinforcing properties and that it may play a role in the mediation of voluntary ethanol consumption. This reluctance is attributable to limitations in the current state of analytical technology to reliably measure levels of acetaldehyde in the periphery, or to detect levels of acetaldehyde directly in brain (for a review, see Lindros, 1978, 1989). Nevertheless, evidence for the functional role of acetaldehyde is well documented and substantiated by reliable and previously replicated behavioral data (Aragon & Amit, 1985, 1988; Aragon et al., 1985c; Lindros et al., 1975), which seem to far outweigh the limitations previously outlined. Issues pertaining to the measurement of acetaldehyde are, however, beyond the scope of the present dissertation and will therefore not be discussed beyond the short summary presented below (for a review, see Lindros, 1978, 1989).

This inability to detect significant quantities of acetaldehyde in brain, led researchers (Erikkson & Sippel, 1977; Kiianmaa & Virtanen, 1978; Sippel, 1974; Tabakoff, Anderson, & Ritzmann, 1986) to postulate that there may be an enzymatic blood-brain barrier which may limit the entry of peripherally circulating acetaldehyde to the brain. Nevertheless, results from other studies (Hillbom, Lindros, & Larsen, 1981; Kiianmaa & Virtanen, 1978; Pertersson & Kiessling, 1977; Westcott, Weiner, Shultz, & Myers, 1980) have suggested that, because acetaldehyde has been

identified in cerebrospinal fluid (CSF) of rats injected with ethanol, that acetaldehyde may indeed cross the blood-brain barrier. Thus, the presence of acetaldehyde in CSF would seem to suggest that acetaldehyde may in fact also be present in the interstitial fluid of the brain. It would appear, however, that current limitations in the state of analytical technology may preclude the direct measurement of the acetaldehyde present in brain tissue following ethanol exposure. It has also been suggested that acetaldehyde, reversibly bound to erythrocytes, may be transported via hepatocytes to the brain (Baraona, DiPavoda, Tabasco, & Lieber, 1987; DiPavoda, Alderman, & Lieber, 1986). It seems unlikely, however, that acetaldehyde may reach the brain from the periphery (Deitrich, 1987; Eriksson & Sippel, 1977; Sippel, 1974) because hepatic aldehyde dehydrogenase (ALDH), an enzyme involved in the elimination of acetaldehyde, is extremely metabolically efficient (Lindros, 1978).

The metabolic degradation of acetaldehyde is largely controlled by the NAD-dependent enzyme ALDH which metabolizes acetaldehyde to acetic acid (Lundquist, 1971; Von Wartburg, 1980). The presence of ALDH has been confirmed in the liver, kidney, small intestine, and even in the brain (Petterson & Tottmar, 1982). Thus the brain may possess the oxidative capacity for the removal of acetaldehyde. ALDH has been proposed to be the most likely

candidate, as it has a high affinity for this substrate (Duncan & Tipton, 1971; Erwin & Deitrich, 1966; Mukherji, Kashiki, Ohyanagi & Sloviter, 1975).

Furthermore, additional evidence confirming a role for acetaldehyde in the mediation of the reinforcing properties of ethanol has been suggested from results of behavioral studies (Amir, 1977, 1978; Amir & Stern, 1978; Sinclair & Lindros, 1981) on the role of ALDH in mediating ethanol-oriented behavior. These studies established that a positive relationship exists between brain ALDH and ethanol consumption in rats (Amir, 1977, 1978; Amir & Stern, 1978; Sinclair & Lindros, 1981). In addition to correlational evidence implicating ALDH in ethanol consumption in animals, experimental results pertaining to the inhibition of ALDH in both animals (Spivak & Amit, 1987; Spivak, Aragon, & Amit, 1987a, 1987b) and in humans (Behar, Berg, Rapoport, Nelson, Linnoila, Cohen, Bozevich, & Marshall, 1983; Brown, Amit, Smith, Sutherland, & Selvaggi, 1983; Kitson, 1989; Peachey, 1989) have suggested that ALDH and acetaldehyde may be involved, either independently or mutually, in the mediation of some of the reinforcing effects of alcohol. Given that the focus of the present dissertation is the presumed formation of acetaldehyde, the involvement of ALDH in the mediation of the reinforcing effects of acetaldehyde will not be discussed further (see Amit et al., 1987; Smith et al., 1990)

Alcoholism in general, and voluntary alcohol consumption in particular, are by definition behavioral phenomena, controlled by

brain function as any other motivational phenomena; and, given that it seemed unlikely, based on previous research (Deitrich, 1987; Eriksson & Sippel, 1977; Sippel, 1974) that acetaldehyde may reach the brain via the periphery; in the past, researchers working on the possibility that acetaldehyde mediated ethanol-induced behavior were always left with the question of how acetaldehyde reached the brain. Thus, it was proposed that acetaldehyde might be formed directly in the brain itself (Cohen, Sinet, & Heikkila, 1980).

A number of proposals concerning the mechanism by which acetaldehyde may be formed in brain have been proposed (Aragon, Rogan, & Amit, 1992; Cohen et al., 1980; Gill, Menez, Lucas, & Deitrich, 1992). It is well established that ethanol is readily absorbed into brain tissue (Ritchie, 1970) and, in fact, several metabolic pathways for ethanol in the brain have been suggested (Aragon et al., 1992; Cohen et al., 1980; DeMaster, Redfern, Shirota, & Nagasawa, 1986; Gill et al., 1992; Hawkins & Kalant, 1972; Lieber, 1977,1983; Lieber & DeCarli, 1971; Sinet, Heikkila, & Cohen,1980; Thurman, Glassman, Handler, & Forman, 1989). These pathways included the oxidation of ethanol via alcohol dehydrogenase (ADH) (Hawkins & Kalant, 1972); the hydrogen peroxide dependent ethanol conversion by catalase (Aragon et al., 1992; Cohen et al., 1980; DeMaster et al., 1986; Gill et al., 1992; Sinet et al., 1980; Thurman et al., 1989); and, the NADPH- and O2-dependent microsomal ethanol oxidation pathways (MEOS) (Lieber,

1977, 1983; Lieber & DeCarli, 1971). The evidence for the metabolic processes mentioned above will be briefly examined below.

I. The Formation of Acetaldehyde

A. Role of Alcohol Dehydrogenase

There is a general consensus that formation of acetaldehyde through the oxidation of ethanol, is primarily controlled by the enzyme ADH (see Hawkins & Kalant, 1972) in the liver. Aside from the liver, where large quantities of ADH have been measured, smaller quantities have also been found in the kidney, and in endocrine organs (Raskin & Sokoloff, 1970). Although trace amounts of ADH have also been found in various areas of the brain (Buehler, Pestalozzi, Hess & Von Wartburg, 1983; Giri, Linnoila, O'Neil, & Goldman, 1989), ADH is considered essentially unreactive in the brain (Raskin & Sokoloff, 1970; Tabokoff & Von Wartburg, 1975). In addition, evidence from behavioral studies examining the role of ADH in ethanol consumption, have generally yielded equivocal results (Carr, Brown, Rockman, & Amit, 1980; Sinclair & Lindros, 1979).

Aside from ADH, however, the role of other enzymes in ethanol metabolism has also been investigated. In the brain, three alternative pathways for the formation of acetaldehyde have been proposed. The first pathway involves the formation of hydroxyl radicals during the auto-oxidation of ascorbate (Cohen, 1977); and, the second is via the enzyme cytochrome P-450, whose presence

has been established in the brain (Paul, Axelrod, & Diliberto, 1977). The existence of these pathways has, however, only been shown in vitro. Therefore to date, there is no direct evidence to support the role of these two pathways in the metabolism of ethanol in brain. The third pathway proposed for the formation of acetaldehyde from ethanol has been shown, both in vitro and in vivo, to be the hydrogen peroxide dependant catalase system (Cohen et al., 1980; Thurman et al., 1989). Since this third pathway was the only pathway to receive validation from in vivo studies (Aragon et al., 1992; Cohen et al., 1980; Gill et al., 1992), the examination of the possible involvement of catalase in the mediation of ethanol-relevant motivated (in vivo) behaviors has become a central field of investigation within the alcohol research area.

B. The Role of Catalase

The presence of the enzyme catalase throughout the body, including the liver, has been well established. Thurman and Handler (1989) showed that catalase oxidized ethanol in perfused rat liver by using fatty acids as a source of hydrogen peroxide. Earlier findings (Thurman, Oshino & Chance, 1975) suggested that the rate-limiting step in the peroxidatic conversion of ethanol to acetaldehyde via catalase, is the generation of hydrogen peroxide. These results supported the notion that catalase represented a possible metabolic pathway for the conversion of ethanol to

acetaldehyde in the liver (Thurman et al., 1989; Thurman et al., 1975).

In brain, preliminary findings by Cohen et al. (1980) showed that ethanol was converted to acetaldehyde in brain homogenates via the peroxidatic activity of the enzyme catalase. The necessary presence of hydrogen peroxide in brain tissue has also been established (DeMaster et al., 1986; Patole, Swaroop, & Ramasarna, 1986; Sinet et al., 1980). These preliminary findings were later confirmed independently by others (e.g. Aragon et al., 1992).

The presence of catalase in the brain has been verified both biochemically (Brannan, Maker, & Raes, 1981; Gaunt & DeDuve, 1976; Tampier & Mardones, 1979) and histochemically (McKenna, Arnold, & Holzman, 1976). It was found (Branan et al., 1981; Gaunt & DeDuve, 1976; McKenna et al., 1976) that the activity of catalase was related to the presence of small subcellular particles known as microperoxisomes. Areas of the brain reported to contain the highest distribution of catalase-reactive neurons include the locus coeruleus, nucleus A_1 of the medulla, and the substantia nigra (Brannan et al., 1981, McKenna et al., 1976), with small numbers of microperoxisomes also present in the cortex and the cerebellum (McKenna et al., 1976). Examinations of the rates of oxidation of ethanol in brain have revealed that rates of oxidation differ across various brain regions, with the cortex-diencephalon showing the highest rates of oxidation (Tampier & Mardones, 1979; Tampier, Quintanilla, & Mardones, 1980). Given that catalase has been found

in the brain and that catalase has thus, been implicated in the mediation of motivated behaviors (Amit & Aragon, 1988), a direct behavioral examination of the role of catalase in ethanol-mediated behavior was undertaken (Amit & Aragon, 1988; Aragon et al., 1985c; Quintanilla, Tampier, & Mardones, 1980).

1. Role of Catalase in Voluntary Ethanol Consumption

A direct examination of the behavioral role of catalase in ethanol-mediated behavior was carried out. Recently Aragon et al. (1985c) found a positive correlation between brain catalase activity and voluntary ethanol consumption in rats. They also found that mean brain catalase activity measured across a 25 day period did not differ between groups of animals exposed to ethanol, and those exposed to water. This finding implied, since voluntary ethanol consumption did not affect catalase activity over a 3 to 4 week period, that it was actually the inherent catalase activity that was correlated with the amount of ethanol consumed. This conclusion has also been supported by Aragon et al. (1985c) who showed that brain catalase activity was not affected when animals were given ethanol over a 25 day period, as their exclusive source of fluid.

Further evidence for a relationship, through its possible role in the metabolism of ethanol to acetaldehyde, between catalase activity and voluntary ethanol consumption, was obtained by Amit and Aragon (1988). Rats, initially naive to ethanol, were presented with a choice between a 10% ethanol solution or water over a 30 day period. Catalase activity was measured in tail blood prior to

the experiment, and again in blood and brain 10 days after ethanol withdrawal. Blood catalase activity remained unchanged as a result of exposure to ethanol, and there was a strong positive correlation between blood and brain catalase activity.

Furthermore, in support of earlier findings (Aragon et al., 1985c), voluntary ethanol consumption was positively correlated with brain catalase activity.

Another line of evidence for the involvement of catalase in ethanol consumption comes from studies utilizing inbred strains of mice such as the C57BL/6 and DBA/2. The large differences in sensitivity to ethanol between the C57BL/6 and DBA/2 mice have been well documented (Holmes, Mether, & Duley, 1985; Kakihana, Nable & Butte, 1968; Kiianmaa, Hoffman, & Tabakoff, 1983; Tabakoff & Kiianmaa, 1982). In particular, the C57BL/6 mice, as compared to the DBA/2 mice, have been shown to consume larger amounts of ethanol (Belknap, 1980; Belknap, Belknap, Berg, & Coleman, 1977; Schneider, Evans, Chenoweth, & Benman, 1973).

Several mechanisms have been proposed to explain the differences in ethanol sensitivity of these two strains. These proposed mechanisms included differences in neurosensitivity (Belknap et al., 1977; Schneider et al., 1973); development of tolerance (Crabbe, Johnson, & Gray, 1982; LaDroitte, Lamboeuf, & De Saint Blanquat, 1984; Schneider, Trzil, & D'Andrea, 1974; Tabokoff & Kiianamaa, 1982); liver metabolism of ethanol and acetaldehyde (Hjelle & Petterson, 1981; Holmes, 1985; Schneider et

al., 1973); and, membrane fatty acid composition (LaDroitte et al., 1984).

Of particular interest, in this context, however, was the finding that, compared to DBA/2 mice, the C57BL/6 mice have lower catalase activity in the liver (Ganschow & Shimke, 1969, 1970) and brain (Aragon & Amit, 1987). In other words, these differences have been detected between C57BL/6 mice which have been shown to consume larger amounts of ethanol, and DBA/2 mice who tend to avoid ethanol (Belknap, 1980; Belknap et al., 1977; Schneider et al., 1973). These findings tended not to support other studies (Amit & Aragon, 1988; Aragon et al., 1985c), which found a correlation between voluntary ethanol consumption and catalase activity in standard strains of laboratory rats.

In summary, considerable evidence has accumulated in support of the contention that catalase activity is related to voluntary ethanol consumption in rodents. The possible mediation by catalase of other ethanol-induced effects has also been investigated, and will be discussed in the next section.

2. The Effect of Catalase Inhibition on Ethanol-Mediated Behaviors

There is also evidence (Aragon & Amit, 1992a, 1992b; Aragon, Spivak, & Amit, 1985a, 1985b, 1989, 1991; Koechling & Amit, in press; Rotzinger, Smith, & Amit, 1993) to suggest that the inhibition of the activity of catalase would result in the

modification or inhibition of some ethanol-mediated behaviors.

The compound 3-amino-1,2,4-triazole (AT), a specific irreversible catalase inhibitor (Darr & Fridovich, 1986; Heim, Appleman, & Pyfrom, 1955), has been widely used in studies to inhibit catalase activity (Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1989, 1991; Koechling & Amit, in press; Rotzinger et al., 1993). AT, administered via intraperitoneal injections, has been shown to inhibit both the catalytic and peroxidatic activity of catalase (Cohen et al., 1980), and further, (Cohen et al., 1980) that the irreversible inhibition of catalase by AT could be prevented by the prior administration of ethanol. In addition, it was demonstrated (Aragon et al., 1992) that AT produced a dose-dependent reduction of acetaldehyde in brain homogenates, and that this reduction was not observed while using pyrazole, an alcohol dehydrogenase inhibitor, or metyrapone, a cytochrome P-450 inhibitor. Similar results were obtained by Gill et al. (1992) who found that while the catalase inhibitors AT, sodium azide, and cyanamide all reduced the production of acetaldehyde in brain homogenates, pyrazole and metyrapone did not produce a similar reduction in acetaldehyde production in brain homogenates.

The effects of AT on voluntary ethanol consumption have been examined in both rats and in mice (Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1989, 1991; Koechling & Amit, in press; Rotzinger et al., 1993). Aragon and Amit (1992a) found

that, in rats, AT produced a dose-dependent reduction in the maintenance of voluntary ethanol intake without having an effect on total fluid consumption. Furthermore, daily administrations of AT induced a dose-dependent inhibition of brain catalase activity which was maintained for the duration of the five day treatment period (Aragon & Amit, 1992a). The effects of AT on the acquisition of ethanol intake in rats have also been examined (Rotzinger et al., 1993). It was found that AT reduced ethanol intake, without affecting total fluid intake during the acquisition period. When treatment with AT was terminated, the same animals continued to consume a reduced amount of ethanol during the rest of the ethanol maintenance period. However, when a second acquisition period without AT treatment was initiated in these same animals, no effect of the previous drug treatment was found (Rotzinger et al., 1993). That is to say, ethanol consumption rates of these animals were not different from pretreatment consumption rates.

The effects of AT have also been examined in Swiss Webster mice (Koechling & Amit, in press). Their findings showed that AT significantly reduced ethanol intake and preference across treatment days, without affecting total fluid intake.

In addition, it has been found that a strain of acatalasemic mice (Eide & Syverse, 1982; Feinstein, Howard, Braun, & Seaholm, 1966; Srivastava & Ansari, 1980) developed in Oak Ridge National Laboratories through x-ray irradiation and the resultant induction

of a catalase deficient mutation, have differential ethanol consumption patterns (Aragon & Amit, 1992a). More specifically, it was found that acatalasemic mice (C3H-A), compared to inbred animals of the same strain (C3H-N) , consumed significantly higher amounts of ethanol when presented with ethanol concentrations ranging from 12% to 18%. The tendency of acatalasemic mice to drink more ethanol than their normal controls, seemed to be the reverse of what had been observed with regards to ethanol intake in rats treated with AT. With respect to this anomaly, it may be important to note that that this difference between acatalasemic mice and their normal controls, seemed identical to the difference found between the high ethanol consuming C57BL/6 mice and the ethanol avoiding DBA/2 mice (Belknap, 1980; Belknap et al., 1977; Schneider et al., 1973). The C57BL/6 mice were found to be significantly lower in brain catalase activity than the DBA/2 mice (Aragon & Amit, 1987). However, despite the fact that the C57BL/6 mice drink more ethanol, and have lower brain catalase activity when compared to DBA/2 mice, in all other measures of ethanol-induced behaviors with the exception of voluntary ethanol consumption the former resembled that of both rats and mice treated with AT and acatalasemic mice (Aragon & Amit, 1992b; Aragon et al., 1985a, 1985b, 1989, 1991; Koechling & Amit, in press; Rotzinger et al., 1993).

These results suggested a role for brain catalase in determining patterns of ethanol intake in a variety of strains of

mice (Aragon & Amit, 1992a; Koechling & Amit, in press), and of rats (Aragon et al., 1992b; Rotzinger et al., 1993). Investigations of the effects of AT have included a variety of ethanol-mediated behaviors in rats. In one experiment, the role of catalase in ethanol-induced conditioned taste aversion (CTA) to a saccharin solution was examined (Aragon, et al., 1985b). AT was found to attenuate an ethanol-induced CTA, and at the same time, it was found not to affect a CTA induced by either morphine or by lithium chloride. This suggested that the effects of AT were specific to ethanol (Aragon et al., 1985b). Furthermore, the fact that AT did not affect peripheral blood levels of ethanol, implies that the observed effects were centrally mediated (Aragon et al., 1985b).

Further investigations of the involvement of catalase in ethanol-mediated behaviors have included examinations of the durations of ethanol-induced narcosis and of ethanol-induced lethality. In a series of experiments, Tampier and Mardones and their associates showed that AT produced a significant reduction in the narcotic actions of ethanol in two inbred strains of rat (Quintanilla et al., 1980; Tampier, Quintanilla, Letelier, & Mardones, 1988; Tampier & Mardones, 1979, 1983). In contrast, AT had no effect on the narcotic effects of paraldehyde or of pentobarbitol (Quintanilla et al., 1980). Since AT had no effect on blood ethanol elimination rates, the reduction produced by AT in the narcotic actions of ethanol were attributed to a central effect of AT (Tampier & Mardones, 1986). More recently, Aragon et al. (1991) confirmed

that pretreatment with AT in standard laboratory rats produced a reduction in ethanol-induced narcosis and lethality.

The effects of AT on ethanol-induced locomotor changes have also been investigated. Ethanol has been reported to have a biphasic effect on locomotor activity in some species: high doses producing a decrease in motor activity, and low doses producing an increase in motor activity (Frye & Breese, 1981). Although ethanol-induced motor excitation has been well documented in mice, this effect is less frequently observed in genetically unselected strains of rats (Frye & Breese, 1981). When Aragon et al. (1989) injected Long-Evans rats intraperitoneally with either 1.0 or 2.0 g/kg of ethanol, the highest dose produced a depression of motor activity, while the lower dose had no effect. AT, at a dose which by itself had no effect on motor activity produced no change in activity at the lower dose of ethanol, but this dose significantly attenuated the depression in motor activity observed for the higher ethanol dose. This dose of AT was also found to significantly reduce mean brain catalase activity (Aragon et al., 1992; Gill et al., 1992; Quintanilla et al., 1980; Sinet et al., 1980). Thus, since AT blocks brain catalase activity, it is probable that the modulation of ethanol-related behaviors by AT is mediated via some action on the central nervous system.

The role of catalase in ethanol-induced hypothermia has also been examined (Aragon et al., 1991). Although it has been established that high doses of ethanol induce hypothermia (Kalant & Le, 1984; Lomax, Bajorek, Bajorek, & Chaffee, 1981), there is little

consensus as to the mechanism underlying this phenomenon (Crowell, Hinson, & Siegel, 1981; Myers & Ruwe, 1982; Ymawaski, Nishiguchi, Miyamoto, Ogita, & Kakanishi, 1983). AT, however, was found to have no effect on ethanol-induced hypothermia (Aragon et al., 1991). These findings led Aragon et al. (1991) to suggest that hypothermia was mediated directly by ethanol rather than by its metabolites. This contention was supported by others (Eriksson & Sarviharju, 1984; Linakis & Cunningham, 1979), who found the genetic mechanism of ethanol-induced hypothermia to be different from the one mediating ethanol-induced motor activity. In this respect, the results obtained by Aragon et al. (1991) indirectly supported the previously mentioned contention (Eriksson & Sarviharju, 1984; Linakis & Cunningham, 1979) since Aragon et al. (1991) suggested a role for catalase in motor activity but not in hypothermia.

The last in this series of investigations examining the role of catalase in ethanol-induced phenomena, focused on ethanol-induced corticosterone release. Considerable data support the notion that acute administration of ethanol results in an increase in corticosterone release (e.g. Aragon & Amit, 1987; Kakihana et al., 1968). An examination of the involvement of catalase in the ethanol-induced corticosterone response was conducted by Aragon and Amit (1987) in selectively bred mice. C57BL/6 and DBA/2 mice were treated with AT prior to injections with ethanol. It was found that AT pretreatment significantly attenuated the ethanol-induced release of corticosterone in both strains of mice,

even though blood ethanol levels of mice pretreated with AT were not different from those of controls. Furthermore, AT pretreatment resulted in a significant decrease in brain catalase activity in both strains of mice. These results (Aragon & Amit, 1987) suggested that inhibition of brain catalase via AT, resulted in an attenuation of ethanol-induced corticosterone release.

In summary, there is considerable evidence that the enzyme catalase plays a role in the mediation of voluntary ethanol consumption, as well as in a variety of other ethanol-mediated effects (Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1989, 1991; Koechling & Amit, in press; Rotzinger et al., 1993; Tampier & Mardones, 1980).

3. Catalase as a Potential Predictor of Alcohol Consumption

Taken together, evidence from many animal experiments has suggested that catalase is involved in the mediation of some of ethanol's psychopharmacological effects (Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1987, 1989; Rotzinger et al., 1993; Tampier & Mardones, 1983). In particular, individual differences in catalase activity have been shown to predict, in part, levels of ethanol consumption in animals (Amit & Aragon, 1988; Aragon et al., 1985c). Thus, it was found that the activity of catalase in brain was positively correlated with levels of ethanol intake in rats (Amit & Aragon, 1988; Aragon et al., 1985c). Furthermore, it was reported that catalase activity in blood of

ethanol-naive rats was positively related to subsequent levels of ethanol consumption, as well as to catalase activity in brain (Aragon & Amit, 1988). Based on these findings, Amit and Aragon (1988) suggested that catalase may represent a biological marker for the propensity of an organism to ingest alcohol.

Under present day technological limitations, it is not possible to measure catalase activity directly in the brains of humans to assess its relation to alcohol intake. Less invasive and more indirect approaches must therefore be taken. Hence, the importance of measuring catalase activity in human blood as a valid marker of the propensity to consume alcohol. Thus, through simple blood sampling, the propensity for future consumption of alcohol might be predicted by catalase activity. The validity of this approach is further increased by the fact that catalase in blood and in brain were found to be highly correlated in rats (Amit & Aragon, 1988). The possible ramifications of this approach, naturally, sparked an investigation of the role of catalase in the regulation of alcohol intake in humans (Koechling & Amit, 1992). Specifically, the purpose of this study was to examine the possibility that catalase in human erythrocytes may represent a correlate of alcohol intake. Findings from a study using volunteers, showed a significant positive relationship between catalase activity and typical amount of alcohol consumed over a 30 day time period. Results from a multiple regression analysis showed that, even after accounting for the contribution of six other variables to the variance, catalase

activity made the highest single contribution to the overall variance in alcohol intake.

These results (Koechling & Amit, 1992), together with the existing body of evidence from animal research (Aragon & Amit, 1992a, 1992b; Aragon et al., 1985c, 1987, 1989, 1991; Koechling & Amit, in press; Rotzinger et al., 1993; Tampier & Mardones, 1983), support the notion that catalase activity could also act as a biological marker for alcohol consumption among individuals who have a family history of alcoholism. This possibility opens up a way for examining the role biological markers, such as catalase activity, may play in the identification of individuals who may be at risk for the development of alcohol dependence. The literature pertaining to this issue will be reviewed in subsequent sections.

II. Family History and the Risk of Alcoholism

It has been well established that alcoholism often 'runs in families' (Cotton, 1979; Schuckit, Goodwin & Winokur, 1972; Winokur, Reich, Rimmer, & Pitts, 1970). This truism had always suggested that there is a genetic contribution for the vulnerability towards the development of alcoholism. More specifically, in a review of the literature Cotton (1979) found that the incidence of alcoholism is higher in relatives of alcoholics, as compared to that found in relatives of controls. Winokur et al. (1970), found that this relationship was higher in first-degree relatives of male alcoholics but not of females. Adoption (Bohman, Sigvardsson & Cloninger,

1981; Cadoret; 1990; Goodwin, Schlusinger, Hermansen, Guze, & Winokur, 1973) and twin studies (for a review, see Searles, 1990; Cadoret 1990) have also demonstrated a genetic contribution of the vulnerability towards alcoholism.

The search for risk factors, or those factors which contribute to the increased likelihood of developing alcoholism, has recently received considerable interest (Searles, 1990). This search for risk factors often begins with the identification of individuals who have a family history of alcohol abuse or of dependence (FH+), but who themselves may not necessarily be alcoholic. Such individuals are typically compared with individuals who have no family history of alcohol abuse or of dependence (FH-). In general, FH+ individuals and FH- individuals have been compared in terms of their performance on a variety of behavioral, physiological, and psychological tests, in order to identify markers which may predispose individuals to alcohol use and abuse. These studies are not technically considered to be behavior-genetic in nature since they do not allow the delineation of genetic and of environmental effects. Nevertheless, these markers are of considerable value inasmuch as they point to a possible predisposition towards alcohol use and abuse (Searles, 1990); and, because it has been established that alcoholism runs in families (Cotton, 1979; Winokur et al., 1970). Therefore, these studies are generally classified as being part of the body of research on the genetics of alcoholism (Searles, 1990). This area of research has generally been divided into four major areas, concerning four different types of markers, namely:

neuropsychological, or cognitive; electrophysiological; trait; and, biological. Before reviewing the respective areas of the literature concerning the markers for a predisposition towards alcohol use and abuse, a summary of the general nature of markers follows in the next section.

A. What is a Marker?

The term 'marker' can denote either genetic or non-genetic bases for an active state or predisposition towards a particular disease (Rowe, 1990). The presence of a marker does not necessarily imply a causal relationship with alcoholism since environmental and other factors, including social and psychological ones, may modulate the expression of a particular marker (Rauduco-Thomas, Garcia, Faure, & Lemay, 1984; Rowe, 1990; Tarter, Moss, & Laird, 1990).

Sub-classification of markers has yielded a variety of different types of markers (Rauduco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990). The most general term, a 'biological marker' refers to a characteristic concomitant to a particular condition or disease (Rauduco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990). Biological markers can be sub-divided into 'state markers' or 'trait markers'. A state marker refers to a feature associated with the active expression of a particular disease. State markers are often used for diagnostic assessments and denote the presence of a disease state (ie. low serum albumin levels in liver disease). Trait markers, on the other hand, may occur

independently of the active expression of any particular disease state, and can be characteristic of the individual throughout their life-span. Trait makers often act as indicators for the predisposition for a disease. For instance, the trait of 'obesity' may predispose an individual to heart disease.

Trait markers are usually further classified into 'genetic' and 'other' markers (Rauduco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990). Genetic markers, by definition, must be present in persons affected by the disease itself. Conversely, trait markers that do not fit the profile of genetic markers are simply termed 'other' markers (Rowe, 1990).

Genetic markers are also sub-divided into 'phenotypic', or 'DNA' markers (Rauduco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990). Phenotypic markers include all markers which indirectly reflect gene expression in the domains of morphology, biochemistry, physiology, or behavior. DNA markers, based on the analysis of DNA sequences, allow for the detection and the identification of specific gene activity. Phenotypic markers, in turn, are divided into 'linkage', and 'association' markers (Rauduco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990). A linkage marker consists of a phenotype where the gene is known to be physically proximal to the gene underlying any particular condition in question, and known to be correlated with such genes. An association marker, on the other hand, is functionally and causally related to a particular disease itself. Thus, while association markers are considered to be an integral part of the disorder, or assumed to reflect a biological

process which may culminate in the disorder, this is not necessarily the case for linkage markers. Association markers tend to be more often identified with biochemical, neurophysiological, and enzymatic characteristics associated with alcoholism (Tarter et al., 1990).

Finally, association markers are further classified into 'observable', and 'evokable' markers (Rauduco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990). Observable markers are described as being always present; whereas the evokable markers are solely revealed following a 'biological challenge', for instance 'alcohol challenge paradigms' (Schuckit, 1987, 1991), wherein subjects are challenged to consume a given dose of alcohol within a specific time period and then evaluated.

The following sections will more specifically focus on aspects of four different research areas pertaining to markers: neuropsychological, or cognitive; electrophysiological; trait; and, biological.

1. Neuropsychological and Cognitive Trait Markers

Neuropsychological deficits, which include decreased verbal IQ scores and increased errors on various neuropsychological batteries, have been reported in offspring of alcoholics when compared to controls (Alterman, Bridges, & Tarter, 1985; Drejer, Thielgaard, Teasdale, Schlusinger, & Goodwin, 1985; Gabrielle & Mednick, 1983). However, it is interesting to note that neuropsychological and cognitive differences between FH+ and FH- individuals disappeared following alcohol challenge tests (Nagoshi & Wilson, 1987), and

when effects due to prior alcohol consumption history were controlled for (Hesselbrock, Stabenau, & Hesselbrock, 1985b). Although static ataxia (measured by the body sway test) has been identified as a potential evoked neuropsychological trait marker for the development of alcoholism (Schuckit, 1991), the literature to date has yielded equivocal results that are difficult to reconcile. Varying test conditions such as the extent of body sway; the extent to which eyes were closed or open during the test itself; and, the question as to whether testing sessions were run before or after alcohol challenge tests; have all produced conflicting results (Hegedus, Tarter, Hill, Jacob, & Winston, 1984; Lipscomb, Carpenter, & Nathan, 1979; Schuckit, 1987). Accordingly, to date, neuropsychological trait markers have not demonstrated good predictive validity with regards to a differentiation between FH+ and FH- with regard to their respective in predispositions towards alcoholism (Tarter et al., 1990; Searles, 1990).

2. Electrophysiological Markers

Over the past few decades, electrophysiological aberrations in alcoholics have been extensively investigated with the use of electroencephalographic (EEG) and event-related potentials (ERP) (for review, see Begleiter & Platz, 1972; Porjesz & Begleiter, 1983). For many years, differences between alcoholics and controls on EEG alpha production, auditory brain stem potential, and P3 components of the ERP to target stimuli; were considered to be the consequences

of the neurotoxic effects of chronic alcohol exposure on the brain (Porjesz & Begleiter, 1991). Recently, however, evidence has emerged to suggest that these electrophysiological aberrations antecede the development of alcoholism, and may represent phenotypic markers for the predisposition towards alcoholism (Porjesz & Begleiter, 1991). For instance, it was reported (Begleiter, Porjesz, Bihari, & Kissin, 1984; Begleiter & Porjesz, 1990) that pre-adolescent sons of alcoholics exhibit a decrease of the P300 wave following presentation of a visual signal. Others (Gabrielli, Mednick, Volavka, Pollock, Schlusinger & Stil, 1982) reported increased beta waves in FH+ compared to FH- individuals, although this finding was not replicated as yet (Pollock, Volavka, Goodwin, Mednick, Gabrielli, Knoop, & Schlusinger, 1983). Furthermore, it was also found that FH+ subjects showed decreased P300 wave and slow alpha wave activity subsequent to an alcohol challenge test (Polich, Burns, & Bloom, 1988).

Several competing hypotheses have been suggested to explain these differences in electrophysiological aberrations between FH+ and FH- individuals with regards to the etiology of alcoholism. Begleiter et al. (1984; Begleiter & Porjesz, 1990) have suggested that the reduced P300 amplitude could constitute a phenotypic marker for visual short term memory impairment which would consequently interact with an individual's current monitoring of his or her own behavior. Volavka, Pollock, Gabrielli and Mednick (1985) hypothesized that the EEG data support the tension

reduction hypothesis of alcoholism, while Schuckit (1987) suggested that in high risk individuals there may be an association between decreased ethanol reaction and electrophysiological activity. Taken together, it seems that at this point there is no agreement concerning the theoretical explanations and implications of the reported electrophysiological differences between FH+ and FH- groups.

3. Psychological Trait Markers

In general, the search for an 'alcoholic personality' has borne little fruit, and has produced largely equivocal results (Barnes, 1979). More recently, several traits have been found to differentiate children of FH+ and of FH- individuals, including high novelty-seeking and low harm avoidance (Cloninger, 1987a, 1987b); impulsivity and under-control in boys (Jones, 1981); traits related to antisocial-personality disorder (Vaillant, 1983; Zucker & Lisansky-Gomberg, 1986); arousability (temperament) and higher levels of activity in infancy, two traits known to have a large heritability component (Tarter et al., 1990). To date, however, no studies have followed-up FH+ individuals with a particular trait marker in order to determine whether or not these individuals actually developed a dependence on alcohol at a later age (Tarter et al., 1990). Thus, the predictive validity of these trait markers has not yet been ascertained.

4. Biological Markers

In a series of studies, Schuckit and colleagues (1984, 1987; Schuckit & Rayes, 1979; Schuckit, 1991) have compared the effects of alcohol and of placebo challenges in sons of alcoholics and of controls on multiple variables. Evidence from these types of studies have suggested that FH+ individuals, as opposed to FH- subjects, showed (Schuckit, 1991) a decreased responsivity to alcohol in terms of body sway (static ataxia); and, of decreased self-reported subjective feelings of intensity of intoxication compared to the FH- group (Schuckit, 1991). These differences were specific to alcohol, in that cocaine and amphetamine did not produce any differences between those groups (Schuckit, 1991). No differences between FH+ and FH- individuals were found with regards to alcohol metabolism measured in terms of absorption or clearance rates of ethanol, time to peak blood alcohol concentrations (BAC), or maximum BAC (Nagoshi & Wilson, 1987; Schuckit, 1991).

In addition, differences in biochemical sensitivity and reactivity to alcohol have been well established for individuals who lack an isozyme for ALDH (Harada, Agarwal, Goedde, & Ishikawa, 1983; Teng, 1981; Wolff, 1972). More specifically, it has been shown that these types of individuals exhibit an increased sensitivity to the euphoric and to the depressant properties of alcohol (for review see Teng, 1981). FH+ and FH- groups, however, could not be differentiated on the basis of this biochemical marker (Teng, 1981).

Furthermore, several in vitro studies have been carried out in an attempt to reliably identify biochemical markers that differentiate between FH+ and FH- individuals. The search for these biochemical markers included an examination of low monoamine oxidase (MAO), an enzyme that catalyzes the oxidative deamination of neurotransmitter catecholamines, indoleamines and various trace amines (Alexopoulos, Lieberman, & Frances, 1983; Tabokoff, Lee, De-Leon-Jones, & Hoffman, 1985; Von Knorring & Oreland, 1985); low brain serotonin, measured by peripheral metabolites (Boismare, Lhuintre, Daoust, Moore, Saligaut, & Hillemand, 1987) and, low plasma gamma-aminobutyric acid levels (Moss, Yao, Burns, Maddlock & Tarter, 1992). In addition, numerous pituitary and brain opioid peptides and other pituitary hormones (ie. thyrotropin-releasing hormone, prolactin, vasopressin, and melanphore-stimulating hormones) has also been examined as potential biochemical markers (Esaky & Linnoila, 1991; Tarter et al., 1990). Overall, these neurochemical studies, which focused largely on monoaminergic and peptidergic systems, have not succeeded in elucidating a brain substrate underlying alcoholism (Moss et al., 1992; Ryback, Rawlings, Negron, Correa-Corans, Cirelli, & Chobanian, 1986; Tarter et al., 1991).

As previously stated, to date no studies have followed-up FH+ individuals along a particular biological marker in order to determine whether or not these individuals actually developed a dependence on alcohol (Tarter et al., 1990). In order to address this

issue, a longitudinal study has been recently launched by Schuckit et al. (Schuckit, 1991). Since the results of this longitudinal study will not become available for some time, at the present time the predictive validity of these biological markers has not yet been ascertained.

5. Concluding Remarks on Markers

During the past three decades, a vast body of evidence has emerged in support of the notion that 'alcoholism runs in families' (Cadoret, 1990; Heath, 1990-91; Rowe, 1990; Searles, 1988, 1990; Tarter et al., 1990). Thus, a wide consensus has evolved in support of the concept that the risk of 'becoming an alcoholic' is, at least in part, genetically transmitted. Following this adage, more recently, researchers focused their attention on the identification of a genetic marker for alcoholism and more specifically, for the biological mechanisms and other concomitant factors which may mediate the expression of this genetic transmission (Heath 1990-91; Porjesz & Begleiter, 1991; Schuckit, 1991; Searles, 1990; Tarter at al., 1990). To date, researchers have taken a non-theoretical approach, and have relied largely on post-hoc explanations of findings concerning the determination of potential markers that may differentiate between FH+ and FH- individuals.

A cohesive theoretical framework which would allow for the testing of a priori assumptions would help explain findings regarding the determination of potential biological markers, and furthermore,

would provide a much needed bridge between animal and human research in this area.

III. The Present Investigation

In recent years considerable evidence has emerged suggesting that acetaldehyde, the primary metabolite of alcohol, may be mediating many of the reinforcing properties of alcohol (Amit and Smith, 1989; Brown et al., 1980; Myers et al., 1984; Smith et al., 1990; Takayama & Uyeno, 1985). Given the control exerted by the central nervous system on motivated behavior in general, and on consummatory behavior including ethanol intake in particular, it would follow that the identification of the mechanism controlling the formation of acetaldehyde in the central nervous system may help elucidate factors controlling the propensity of an organism to ingest alcohol. Furthermore, it may also help clarify the propensity to develop a dependence on alcohol. Recently, evidence began to emerge (Aragon et al., 1992; Cohen et al., 1980; Gill et al., 1992; DeMaster et al.,1986; Sinet et al., 1980) that the enzyme catalase may be a viable metabolic pathway for the oxidation of alcohol to acetaldehyde in the brain. In addition, recent reports support the notion that the activity of catalase may be mediating many of the behavioral effects of ethanol (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989, 1991; Koechling & Amit, in press; Tampier & Mardones, 1983). More specifically, individual differences in catalase activity have been shown to predict levels of alcohol consumption in rats (Amit &

Aragon, 1988). Based on this evidence, Amit and Aragon (1988) suggested that catalase may, through the production of acetaldehyde in brain, be a biological marker determining the propensity of an organism to ingest alcohol.

This latter claim provided the impetus and rationale for the investigation of the role of catalase in the regulation of alcohol intake in a human population. Recent results (Koechling & Amit, 1992) of studies examining the nature of this relationship, suggested that the activity of catalase in human erythrocytes was a significant positive predictor of human alcohol consumption.

These results (Koechling & Amit, 1992) together with the existing evidence from animal research (Amit & Aragon, 1988; Aragon & Amit, 1987, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989, 1991, 1992; Koechling & Amit, in press; Tampier & Mardones, 1983) added support for the contention that inherent catalase activity in specific target tissues could function as a biological marker for the affinity to drink alcohol. The activity of catalase could be used to identify those individuals who may be prone to high alcohol consumption and thus, who may be at risk for the development of alcohol dependence. The most efficient way of testing this hypothesis would be through an examination of the patterns of relation between catalase activity and alcohol consumption in FH+ and in FH- individuals.

However, before it would be possible to proceed with testing the hypothesis concerning the nature of catalase as a biological marker for the propensity to consume alcohol, the question as to

whether or not catalase was an evokable marker or an observable marker associated with the consumption of alcohol had to be addressed. The first experiment of the present dissertation was designed to examine the possibility, by using an alcohol challenge paradigm, that differences in catalase activity reflect their induction by alcohol intake rather then their activity as predictors.

Thus, the present series of studies was designed to first test this initial hypothesis by:

(1) ruling out the possibility that the acute administration of alcohol produced a short-term induction of catalase measured over a 24 hour period;

(2) ruling out the contribution of prior alcohol consumption history to the possible induction of catalase;

(3) examining the effect of acute administration of alcohol on breath alcohol content (BAC) over a 24 hour period in order to ensure that subjects consumed the alcohol.

The present series of studies were then designed to examine the central question underlying the bulk of the research of the present dissertation, namely, whether or not there are any significant differences in the pattern of relation between catalase activity and alcohol consumption in FH+ and in FH- individuals.

The central focus of the present dissertation is therefore to investigate the role of catalase, in human erythrocytes, and by implication, the role of centrally-acting acetaldehyde in the mediation of alcohol consumption. The specific aim of this dissertation was to examine this broader question in a more specific

framework: **The differential contribution of catalase to its relationship with alcohol consumption in FH+ and FH- individuals.**

EXPERIMENT 1

Several reports in the literature (Fazekas, 1965; Gambassi & Maggi, 1952) suggested that acute doses of alcohol produced transient increases in catalase activity in human blood over a 7-hour post-ingestion period. More specifically, Fazekas (1965) found that, in male volunteers, following the intake of alcohol (0.5 and 1.5 g/kg), catalase activity increased substantially at 1.0 to 3.0 hours post-ingestion. Similar results were also reported by Gambassi and Maggi (1952). However, the earlier research (Fazekas, 1965; Gambassi & Maggi, 1952) relied exclusively on male volunteers, used small sample sizes (n = 5), restricted sampling to a 7 hour time period post alcohol ingestion, and did not include control groups ingesting non-alcoholic fluids.

Generally, the early data obtained from humans (Fazekas, 1965; Gambassi & Maggi, 1952) are inconsistent with results from animal data, which suggested that catalase activity did not change as a function of acute or chronic exposure to ethanol (Amit & Aragon, 1988; Aragon et al., 1985c). Aragon et al. (1985c), for example, showed that catalase activity remained unchanged when rats were given ethanol as their exclusive source of fluid over a 25 day period.

Given this inconsistency between data obtained from humans and from animals, the first study was designed to assess whether or not the acute ingestion of alcohol would alter the activity of catalase in human blood over a 24 hour time period. The study was also intended to incorporate more recently developed methodology

using an oxygen electrode. It was expected that results from this study would yield evidence which might help to determine the directionality of the relation between catalase activity and alcohol consumption under a regimen of acute ingestion of alcohol. Furthermore, it would also be of interest to determine, whether or not individuals' prior alcohol consumption history contributed to a potential induction of catalase.

As mentioned before, earlier research (Fazekas, 1965; Gambassi & Maggi, 1952) in this area did not include non-alcohol control groups, and relied exclusively on data from a small group of male volunteers without regard to their alcohol consumption history. It was therefore also of interest to ascertain whether or not the potential induction of catalase varied as a function of gender and of prior alcohol consumption history. This part of experiment 1 is presented in phase 1.

In phase 2, the effects of acute administration of alcohol on blood alcohol content (BAC) were determined. The rationale for the inclusion of BAC measurement in experiment 1, was to obtain a non-verbal verification of alcohol consumption by subjects. In addition, it was of interest to determine whether or not potential group differences in BAC might be consistent with those found in the literature (Allen, Eckhardt, & Wallen, 1988; Frezza, DiPadova, Pozzato, Terpin, Baraona, & Lieber, 1990; Julkunen, Tannnbaum, Baraona, & Lieber, 1985; Reich, 1988; Salaspuro, 1986) suggesting that females have higher mean BAC than did males. Thus, results from phase 2 would yield evidence concerning the conformity of the

present sample with other reports in the literature, as it related to BAC.

Method

Subjects

A total of 80 Caucasian, english-speaking subjects--40 men and 40 women--took part in the experiment. Volunteers were recruited from the student population of Concordia and McGill universities. Subjects suffering from diabetes, hypertension, or hyperthyroidism were not included (2.5%, [n = 2]) in this study because of earlier reports suggesting that the activity of catalase might be altered in these individuals (Csontos & Jaklosky, 1966; Kursaki, Saito, Kaji, Kojima, & Saito, 1986; Watala, Bryszewska, Stefaniak, & Nowak, 1986; Wei, Heghinian, Bell, & Jakschik, 1986). The initial sample size was reduced to 78 individuals (Mean age: 24.77, sd = 6.19, range: 19-51), 38 females (Mean age: 24.82, sd: 6.98, range:19-51) and 40 males (Mean age: 24.72, sd: 5.42, range: 19-45), since 2 females were found to be suffering from diabetes and/or hypertension.

Materials

Vodka (40% EtOH) and orange juice were used. The Vodka was mixed in orange juice at a ratio of 1:3. A breath alcohol screening device (Alco-Sensor III) designed to measure blood alcohol concentrations (mg of alcohol per 100 ml of blood); a digital

manual stop-watch (Tag Heuer) to record the time period to consume alcohol; and, a scale (Detector Scale Inc., Model: 3PY 1002) to measure subjects' body weight; were all used for the purpose of this experiment.

Alcohol swabs were used to clean the fingertip of each subject before blood collection. An autolet machine (Ulster Scientific) was used to prick the finger with a sterile stainless steel needle. Blood was collected in ammonium heparin coated tubes to which 5 µl of 1% heparin solution had been added prior to the blood collection. Band-aids were used to cover the pin-prick. All needles and platforms were used only once, and discarded after individual usage.

Questionnaires. The Concordia Alcohol Screening Questionnaire (CASQ)--developed in our laboratory--provided demographic information, medical history, prescription and non-prescription drug usage, and alcohol drinking history (see Appendix A). This information was used to assess quantity and frequency of alcohol (beer, wine and spirits) consumed in a 30-day period. Q-Value, an index of daily alcohol intake based on a method developed by NIAAA (Armor & Polich, 1982; Polich, Armor, & Braiker, 1981) which has received ratings of good reliability, and has been widely used (Armor & Polich, 1982; Hesselbrock, Babor, Hesselbrock, Meyer, & Workman, 1983; Koechling & Amit, 1992; Polich et al., 1981) was used in the present study. A Q-Value of 3.54, for example, would describe an individual who had consumed 3.5 ounces of 40% alcohol on a typical day, and this over any given

typical 30-day period. Q-Value has been operationally defined (also see Appendix B) as being the total daily alcohol consumed in any type of alcoholic beverage--adjusted by alcohol content to ounces (oz) of 40% alcohol equivalence--over a typical period of 30 days (Armor & Polich, 1982; Hesselbrock et al., 1983; Koechling & Amit, 1992; Polich et al., 1981). A yearly calendar was provided to help "jog" the memory of informants with respect to their alcohol consumption frequency.

Procedure

Subjects were asked to abstain from alcohol or any other drug use (with the exception of nicotine, caffeine or prescribed drugs) for a 24-hour period prior to the experimental sessions. Subjects were also asked to have a light breakfast before attending the experimental sessions, which took place between 8 a.m. and 1 p.m. All subjects were given a food voucher to be used after attending the first of the two sessions. Subjects were requested to abstain from alcohol or any other drug use (with the exception of nicotine, caffeine or prescribed drugs) until attendance at the second session on the following day. Following the completion of the experimental sessions, subjects were also eligible for a lottery ticket, the prize valued at $500.

All subjects were briefed on the experimental protocol, and were required to sign an informed consent form (see Appendix C). Their body weight was then measured and they were informed that smoking, and food and beverage consumption (other than beverages

presented during the testing session), were not permitted during the sessions. During the first session, prior to consumption of fluids, subjects were also asked to complete the CASQ.

Subjects were randomly assigned to one of two experimental groups (for a detailed description of the group distribution see Table 1), and presented with either orange juice (control), or vodka (40% EtOH) and orange juice (0.5 g of ethanol/kg body weight; 1:3 ratio alcohol - orange juice). The time period allotted for the beverage consumption was three minutes. Subjects were also asked to provide four 100 µl blood samples which were collected from each subject at 0.0, 0.5, 2.0, and 24.0 hours after beverage consumption. All blood samples were kept on ice until reaching the laboratory, and every effort was made to transport these samples to the laboratory as promptly as possible. The time of blood collection, and the drawn blood volume, were recorded. In addition to blood sampling, a breath alcohol screening device was used to determine blood alcohol content (BAC) in each subject at 0.0, 0.5, 2.0, and 24.0 hours after beverage consumption. A sterile mouth-piece adaptor was used for each subject. The time of BAC sampling and percentage of blood alcohol readings were recorded.

Biochemical Analysis: Upon reaching the laboratory, the blood samples were prepared by diluting 5 µl aliquots of whole blood with 2995 and 2495 µl of 10 millimolar potassium phosphate buffer (Ph = 7). From each of the diluted samples, two 850 µl sub-samples were taken to yield a total of four samples; and, 20 µl of whole blood were kept for later hemoglobin analysis. All

Table 1

Group Distribution for Experiment 1.

Drug	Gender	n
Control	--	36
Alcohol	--	42
Control	Female	18
Control	Male	18
Alcohol	Female	20
Alcohol	Male	22

samples were subsequently frozen at -70º C. until biochemical analysis could be carried out. Catalase activity was measured using a Clark oxygen electrode (Del Rio, Ortega, Lopez & Gorge, 1977), using the method described by Aragon et al. (1985c) and by DeMaster et al. (1986). This assay is based on the measurement of the initial rate of oxygen released by catalase in an oxygen-free buffer. Hemoglobin analysis was carried out using a spectrophotometer with absorption at 540 nm (Sigma Diagnostics, Procedure No. 525, 1984). Assay results were expressed in terms of the reaction rate of catalase in nmoles of oxygen per minute per μg of hemoglobin (nmoles O2/min/μg Hb).

Results

Results of Phase 1

In order to determine potential group differences in catalase activity a 2 (drug group) x 2 (gender) x 3 (time-of-sampling) analysis of variance (ANOVA) with the last factor as repeated measure, was computed. Significant main effects for drug ($F(1, 66) = 21.42$, $p<.001$) and a significant main effect for time-of-sampling ($F(3, 198) = 6.58$, $p<.001$) were obtained as well as a significant gender x time-of-sampling ($F(3, 198) = 2.80$, $p<0.04$). Post-hoc comparisons were carried out using Fisher's Protected t-tests (Cohen & Cohen, 1989).

Post-hoc tests for the main effect of drug (alcohol/control) showed that, overall, the alcohol group was significantly higher in mean catalase activity ($t(69) = 4.78$, $p<.001$) compared to the

control. Furthermore, significant baseline differences in mean catalase activity, prior to the ingestion of fluids, (see Figure 1) between subjects in the alcohol group and controls ($t(69) = 3.72$, $p<.001$) were obtained.

Given the baseline differences between the alcohol group and the control group, the data were converted to percent-change from baseline scores, and an additional 2 (drug group) x 2 (gender) x 4 (time-of-sampling) analysis of variance (ANOVA) with the last factor as repeated measure, was computed. A significant main effect for time-of-sampling ($F(3, 198) = 3.68$, $p<.01$) was obtained.

Post-hoc tests for the main effect of time-of sampling showed that mean catalase at time 4 [24-hours] was significantly lower (see Figure 2) compared to time 1 [0-hours] ($t(69) = 2.56$, $p<.01$).

In order to assess whether prior alcohol consumption history contributed to the variance in catalase activity, this same analysis was repeated using prior alcohol consumption history (Q-Value) as a covariate. Results (ANCOVA) remained the same (see Appendix D). In other words, the effects attributable to individuals' prior alcohol consumption history did not alter the previous results which had shown no main effect for drug on mean catalase activity.

In summary, the results from the ANOVA (when, in order to correct for baseline differences in catalase activity, percentage of change from baseline scores were used) revealed no main effect for drug on mean catalase activity. The results, however, showed that mean catalase activity at 24-hours post-fluid-ingestion, was significantly lower than mean catalase activity prior to any fluid

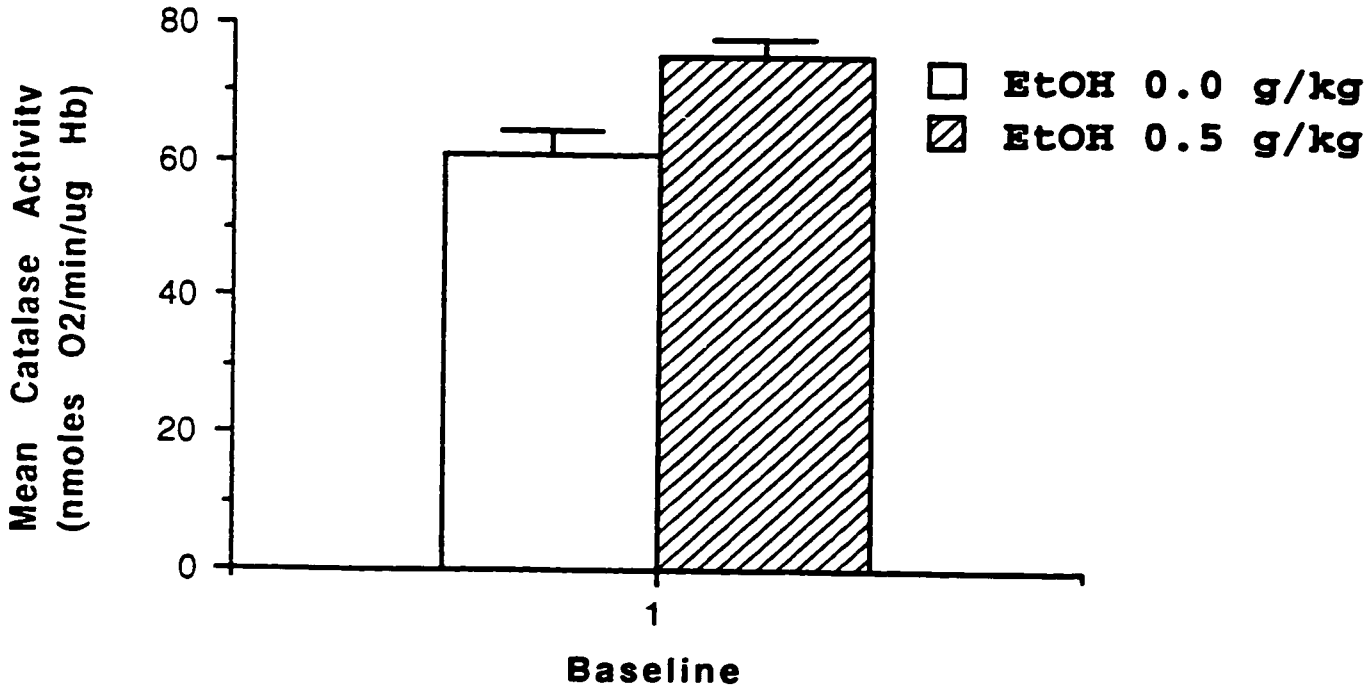

Figure 1. Mean catalase activity at baseline of individuals assigned to the alcohol (n = 42) or control (n = 36) condition ($p < .001$).

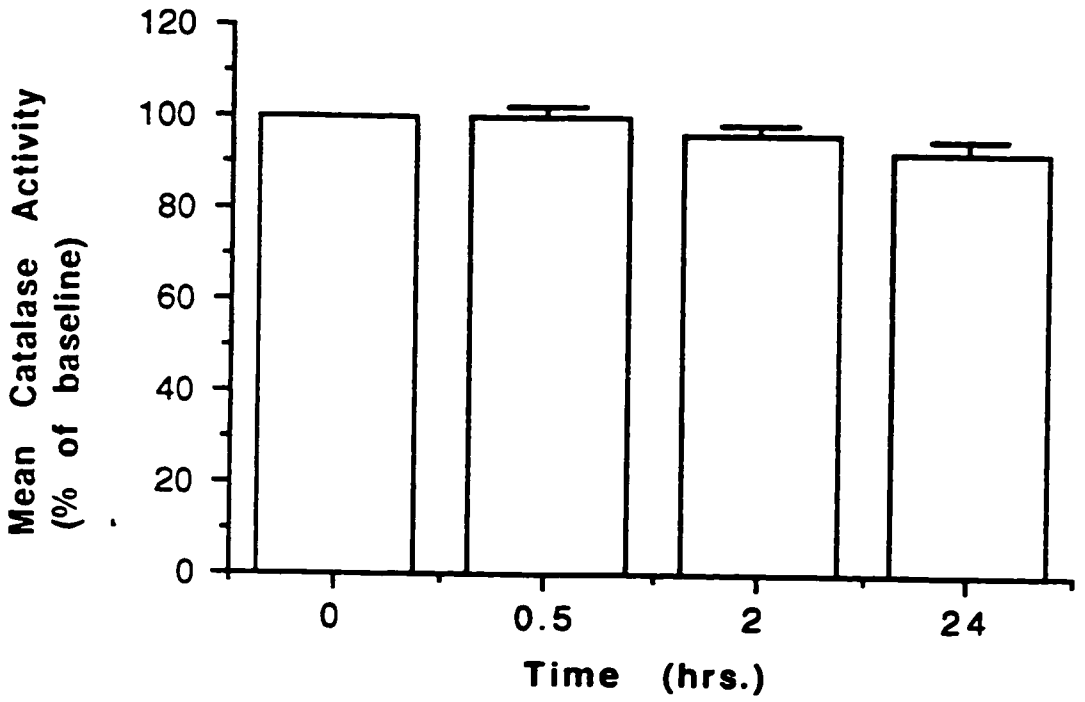

Figure 2. Mean catalase activity (% change of baseline, N = 78) as a function of time of sampling (hrs.).

ingestion (at 0.0 hours). In addition, the results remained the same when the effects of individuals' prior alcohol consumption history on catalase activity were covaried out of the analysis. Thus, the lack of an alcohol effect on catalase could not be attributed to individuals' prior alcohol consumption history.

Results for Phase 2

In order to determine potential group differences in BAC, a 2 (drug group) x 2 (gender) x 4 (time-of-sampling) analysis of variance (ANOVA) with the last factor as repeated measure, was computed. Significant main effects for drug ($F(1, 66) = 115.83$, $p<.001$); for gender ($F(1, 66) = 4.40$; $p<.04$); and a significant main effect for time-of-sampling ($F(3, 198) = 38.12$, $p<.001$); were obtained. Furthermore, results from the ANOVA revealed significant interactions for drug x gender ($F(1, 66) = 4.43$, $p<.04$); time-of-sampling x drug ($F(3, 198) = 38.18$, $p<.001$); time-of-sampling x gender ($F(3, 198) = 3.68$, $p<.01$); and time-of-sampling x drug x gender ($F(3, 198) = 3.67$, $p<.01$). Post-hoc comparisons were carried out using Fisher's Protected t-tests (Cohen & Cohen, 1989).

Post-hoc tests for the main effect of drug showed that, overall, the alcohol group was significantly higher in mean BAC ($t(69) = 10.32$, $p<.001$) compared to the control group (see Figure 3). Post-hocs for the main effect of gender showed that, overall and collapsed across all time periods, there were no significant differences in mean BAC between males and females ($t(69) = 1.28$, $p<.2$). Post-hocs for the drug x gender interaction, however, showed

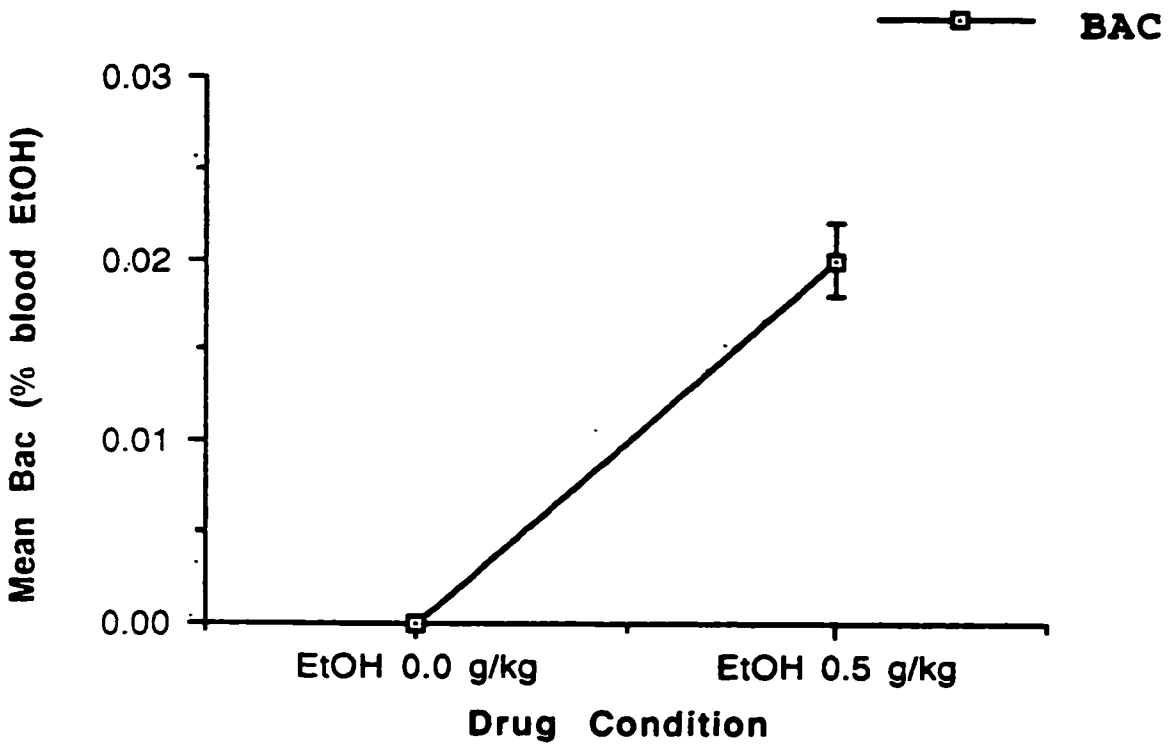

Figure 3. Mean BAC of individuals who had received either alcohol (n = 42) or control (n = 36) solutions ($p < .001$).

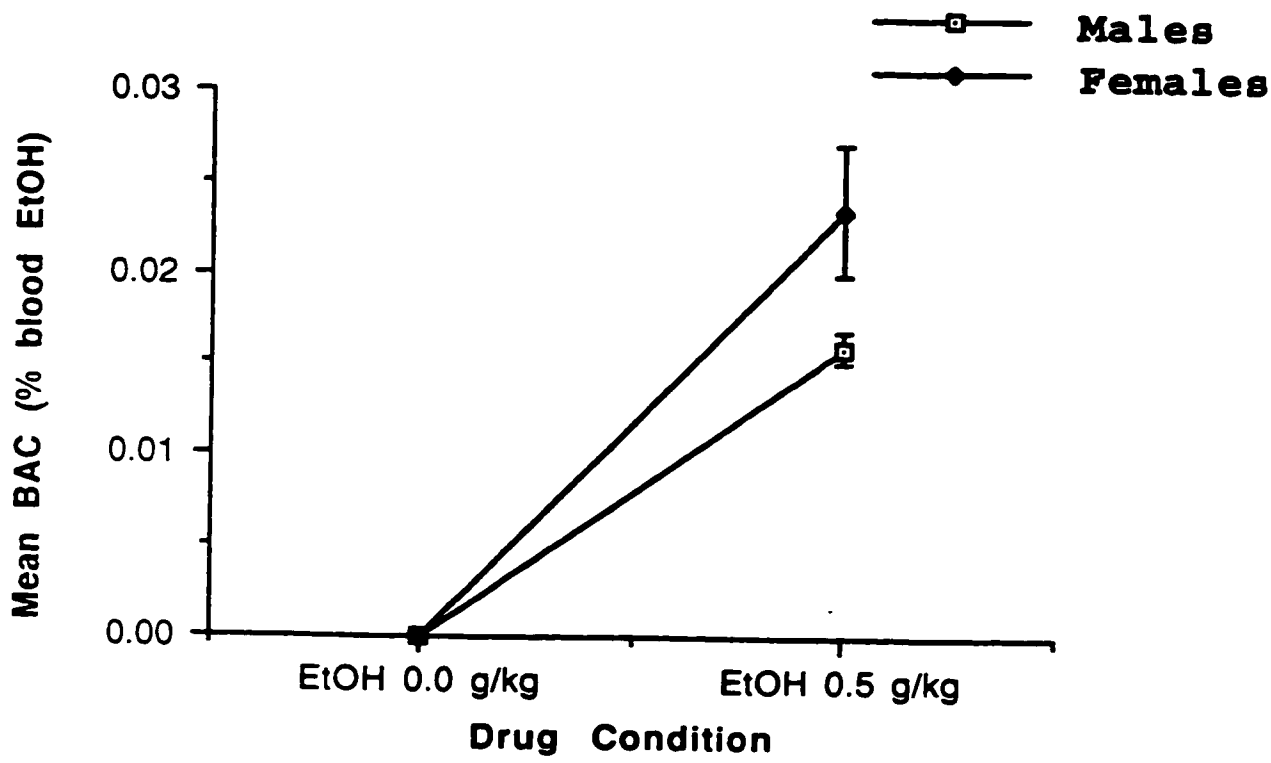

Figure 4. Mean BAC of males (n = 40) and of females (n = 38) who had received either alcohol (n = 42; n = 20 females; n = 22 males) or control (control n = 36; n = 18 females; n = 18 males) solutions ($p < .001$).

(see Figure 4) that mean BAC was significantly higher for the alcohol condition compared to the control condition for males ($t(32) = 18.15$, $p<.001$) and for females ($t(34) = 6.81$, $p<.001$) collapsed across all time-periods. For the alcohol condition, females had significantly higher mean BAC ($t(34) = 2.131$, $p<.04$) compared to males.

In order to assess whether prior alcohol consumption history contributed to the variance, this same analysis was repeated using prior alcohol consumption history (Q-Value) as a covariate. Results (ANCOVA) remained the same (see Appendix E). To elaborate, the effects attributable to individuals' prior alcohol consumption history did not alter the previous results, showing that mean BAC was higher for the alcohol condition compared to the control condition, and that females had higher mean BAC than males in the alcohol condition.

In summary, results from the ANOVA revealed that for individuals in the alcohol group, mean BAC was significantly higher than that of the control group. For the alcohol condition, females had significantly higher mean BAC compared to males. The results remained the same when the effects of individuals' prior alcohol consumption history on BAC were covaried out of the analysis. Thus, the present results showing higher mean BAC for the alcohol condition compared to the control condition, and, for the alcohol condition, higher mean BAC for females compared to males, could not be attributed to individuals' prior alcohol consumption history.

Discussion

The results of phase 1 showed that the activity of catalase in blood did not vary as a function of acute administration of alcohol. Results of the analysis also showed that regardless of drug condition, catalase activity was lower at 24-hours post-fluid-ingestion compared to baseline. However, it is noteworthy that at 24-hours post-fluid ingestion the number of samples was reduced due to subject attrition (n = 8 subjects dropped out). This decrease in the number of subjects may have contributed to the decrease in catalase activity at this point in time for both the alcohol and the control group.

In addition, these results did not change when the effects due to prior alcohol consumption history were covaried out of the analysis, suggesting that catalase activity is also not induced by alcohol consumption history.

The lack of effect of the acute ingestion of alcohol on catalase activity was not consistent with earlier reports (Fazekas, 1965; Gambassi & Maggi, 1952) which had suggested that acute doses of alcohol produced short-term increases in catalase activity in humans. This inconsistency in findings may be partly attributable to the fact that none of these earlier studies had incorporated control groups receiving non-alcoholic beverages into their design. Furthermore, comparison between studies is precluded due to differences in methodology, inasmuch as earlier studies (Fazekas, 1965; Gambassi & Maggi, 1952) had small sample sizes (n = 5), restricted their samples to males, and had relied

on older methods of biochemical analysis for catalase. These possible differences in methodology may also have contributed to inconsistencies in findings between the present and earlier studies.

Results from the present study, while showing a lack of overall effect of alcohol ingestion on catalase activity, are consistent with those obtained from animal studies (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989, 1992). The results from the animal research suggested that prior acute alcohol intake did not alter catalase activity.

In addition, the present finding showing the failure of acute alcohol ingestion to induce catalase is consistent also with previous human research (Koechling & Amit, 1992), showing that alcohol intake by subjects during their most recent 30-day period was not related to their catalase activity. Moreover, it was recently reported (Koechling & Amit, 1992) that alcohol intake over a typical, but not the most recent, 30 day period was significantly correlated with catalase activity. This finding, together with the previously mentioned observation that recent drinking was not related to catalase activity, further supports the notion that catalase activity may not be induced by prolonged drinking prior to catalase measurement. It follows that if catalase was indeed induced by prolonged periods of drinking, indices of both recent and typical drinking would have to have been related to catalase activity. In this respect, the current findings showing that the

results of the analysis did not change when effects due to prior alcohol consumption were covaried out of the analysis, further supports the earlier findings in humans in terms of the above mentioned comment regarding the relation between catalase activity and typical drinking (Koechling & Amit, 1992).

Thus, at this point, the evidence from animal (Amit and Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989, 1992) and human studies (Fazekas, 1965; Gambassi & Maggi, 1952; Koechling & Amit, 1992) would tend to argue against acute induction of catalase activity following alcohol intake.

In order to ensure that subjects actually consumed the alcohol, the effects of acute administration of alcohol on BAC were examined in phase 2. The results showed that mean BAC was higher for the alcohol condition compared to the control condition. Furthermore, in the alcohol condition, females had a higher mean BAC compared to males. In addition, the results pertaining to the gender differences in BAC for the alcohol condition, as well as the finding that BAC was higher for the alcohol condition, remained unchanged when the effects attributable to individuals' prior alcohol consumption history were statistically controlled for.

The present findings showing higher BAC for the alcohol condition compared to the control condition were verified via breathalizer tests (Allen et al., 1988; Reich, 1988; Salaspuro, 1986). It has been found that, using a breathalizer instrument to measure the increase of BAC, it is possible to reliably measure

blood alcohol content following alcohol ingestion for a minimum of six hours post-alcohol-ingestion (Allen et al., 1988; Reich, 1988; Salaspuro, 1986). Thus, the present results of phase 2 suggested that none of the subjects consumed alcohol 6 hours prior to the experimental session and that they did not consume alcohol 24-hours post-fluid ingestion. Furthermore, the results showing that mean BAC was only elevated for individuals who had received the alcoholic beverage, suggested that only these individuals actually consumed the alcoholic beverage received during the testing session. Thus, via the measurement of BAC it was possible to ensure that subjects actually consumed the alcoholic beverage presented during the experimental session, and that subjects in the control group had not consumed any alcohol at all during the experimental session.

The current finding that females have higher BAC than males is also congruent with previous research findings (Frezza et al., 1990; Julkunen et al., 1985). It has been found (Jones & Jones, 1976) that females become intoxicated after drinking smaller quantities of alcohol than those needed to produce intoxication in males. Two possible hypotheses have been proposed to explain this gender-difference in response to alcohol.

First, females have lower total body water content than do males of comparable size (Frezza et al., 1990; Jones & Jones, 1976; Julkunen et al., 1985). After alcohol is consumed, it diffuses uniformly into all body fluids, both intra- and extra-cellularly (Frezza et al., 1990; Jones & Jones, 1976; Julkunen et al., 1985).

Thus, because of their lower quantity of body fluids, females may achieve higher concentrations of blood alcohol than males after drinking equivalent amounts of alcohol (Frezza et al., 1990; Jones & Jones, 1976; Julkunen et al., 1985).

The second hypothesis proposed that diminished activity of alcohol dehydrogenase in the stomach may also contribute to the gender-related differences in blood alcohol concentrations. Julkunen and colleagues (1985) demonstrated in rats, that a substantial amount of alcohol is metabolized by gastric alcohol dehydrogenase before it enters systemic circulation. This 'first-pass metabolism' of alcohol in the stomach decreases the overall availability of alcohol to the system. Frezza et al. (1990) reported that in females, because of the gender-specific diminished activity of gastric alcohol dehydrogenase, first-pass metabolism was lower than that found in males, and that first-pass metabolism was virtually non-existent in alcoholic females.

In addition, phase 2 results suggested that the effects due to individuals' prior alcohol consumption history did not contribute to the overall variance in BAC, since results remained the same when these effects were covaried out of the analysis. This finding is consistent with those of others (Allen et al., 1988; Reich, 1988; Salaspuro, 1986) who developed norms for the general population using a breathalizer apparatus to measure BAC, and who showed that individuals' BAC was not affected by prior alcohol consumption history.

Thus, the results obtained in phase 1 of the present study established that catalase activity is not evoked by the acute administration of alcohol, and that catalase activity is probably also not induced by individuals' drinking history. The results obtained in phase 2 established that the acute administration of alcohol, increased BAC to a greater degree in females than it did in males, suggesting that BAC is higher for females than it is in males.

Given that the acute administration of alcohol failed to induce the activity of catalase, the following series of experiments examined, using a much larger sample, whether or not the activity of catalase is a potential biological marker for alcohol intake. More specifically, it was of interest to examine whether the activity of catalase differentially predicts alcohol consumption in FH+ and FH- individuals.

EXPERIMENT 2

Results from experiment 1 established that catalase activity was not induced by acute administration of alcohol. In addition to the above, these findings led to the conclusion that the relation between catalase activity and alcohol intake must be uni-directional. The data showed that the consumption of alcohol did not affect the activity of catalase, at least over a 24-hour period. It followed, logically, that it was catalase activity that exerted control over voluntary ethanol intake, and not the converse. These results justified a further investigation of the role of catalase as a potential biological marker which may be controlling, at least in part, the propensity to consume alcohol.

This contention of catalase as a biological marker was also based on previous data from human studies (Koechling & Amit, 1992) and on an existing body of evidence from animal research (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b; 1985c; 1992; Gill et al., 1992; Tampier & Mardones, 1983). As a whole, these data suggested that the activity of catalase in blood may be a predictor of alcohol consumption. In other words, the data supported the contention that the activity of catalase in blood could act as a biological marker for the affinity of organisms to voluntarily ingest alcohol. If the assumptions outlined above were valid, it would then logically follow that there should be differences in the patterns of catalase activity and of alcohol intake between persons with or without family history of alcoholism. It would further follow that the pattern of relation between catalase

activity and alcohol intake would differ in these two sub-populations. This, in fact, was the working hypothesis underlying Experiment 2. Experiment 2 was therefore designed to investigate the possibility that the pattern of relation between catalase activity and alcohol consumption would differ in individuals with a FH+ as opposed to FH-. This hypothesis was examined in phase 1. Phase 2 of experiment 2 was designed primarily to investigate two additional questions. Does catalase activity explain a significant portion of the variance in alcohol intake in the presumably genetically predisposed FH+ individuals? Also, given that catalase activity may in fact represent a covariate of variables which had previously been found (Koechling & Amit,1992) to predict alcohol intake, it was of interest to determine whether or not and to what extent other variables may contribute to the relation between Q-Value and catalase activity in the predisposed FH+ individuals.

Method

Subjects

Volunteers were recruited from a university population or via newspaper advertisement (53% of the sample), and from drug rehabilitation centers (Addiction Unit, Montreal General Hospital: 16%; Maison Jean La Pointe: 15%; Phoenix Foundation: 16% of the sample). A total of 607 subjects--353 males and 254 females--took part in the experiment. Mean age was 34.32 years (sd = 11.57).

To ensure a relatively homogeneous sample in which the relation between catalase and Q-Value could be examined without the influence of confounding factors, the following exclusion criteria were applied:

1. subjects (n = 56) suffering from either diabetes (4.1% [n = 25]), hypertension (2.8% [n = 17]), or hyperthyroidism (2.3% [n = 14]), were eliminated because of reports that catalase activity may be altered in these individuals (Csontos & Jaklosky, 1966; Kursaki et al., 1986; Watala et al., 1986; Wei et al., 1986).
2. individuals (16% [n = 97]) who reported chronic usage of drugs other than alcohol--including cocaine/crack, heroine, marijuana, or prescription drugs--were eliminated from the sample in order to reduce the presence of possible confounding variables (Gold, 1986; Koechling & Amit, 1992; Miller, Gold, Belkin, & Klahr, 1989).
3. individuals who had been either adopted and/or for whom family history was not provided (2% [n=15]), were excluded.
4. individuals who were above 70 years of age (1% [n = 6]) were excluded because they were under-represented in the sample, and thus, results would not be generalizable to these individuals.
5. individuals who had catalase activities above 160 (1% [n = 4]) were excluded, again, because they were under-represented in the sample, and thus, results would not be generalizable to these individuals.
6. individuals, who scored '0' on the MAC scale (0.5% [n = 3]) were excluded, again, because they were underrepresented in the sample, and thus, results would not be generalizable to these individuals.

7. individuals who scored above 44 oz/day on Q-Value (1% [n = 5]) were excluded, again, because they were under-represented in the sample, and thus, results would not be generalizable to these individuals.

The final sample size consisted of 421 individuals, 237 males with a mean age of 34.71 (sd = 10.91), and 184 females with a mean age of 34.32 (sd = 12.32). The range of age was 18 to 68 years for females and 18 to 70 for males. Demographic information is presented in Tables 2, 3, and 4. Subjects were drawn primarily from an english speaking population in Montreal (english = 73% [n = 307]; french = 27% [n = 114]). Typically, subjects were married; had completed some community college or university education; and, if they were employed, were employed as were their fathers, in semi-skilled occupations.

Materials

Questionnaires: A total of three paper-and-pencil questionnaires were used. These were, the CASQ (see: Experiment 1); the Michigan Alcoholism Screening Test (MAST); and, the MacAndrew Scale (MAC), a sub-scale of the Minnesota Multiphasic Personality Inventory (MMPI). All three instruments were translated into French. English and French versions were used as appropriate.

The MAST, originally developed by Selzer (1971), was used as a measure of alcohol-related problems. The MAST consists of a checklist of 25 questions requiring "yes" or "no" answers (see Appendix F). The MAST is presently considered to be one of the

Table 2

Descriptive Statistics For Selected Variables Of The Total Sample (N = 421).

Variable	% of Sample	Mean (SD)	Range
Age (Total Sample N = 421)		34.54 (11.54)	18 - 70
Time of Blood Collection (hrs.)		12.94 (3.19)	07 - 20
Q-Value (% EtOH/oz/day)		05.29 (1.05)	00 - 34
Years Smoked (years)		10.79 (10.85)	00 - 45
Current Smoking	71%		
Cannabis Use	26%		
Cocaine/Crack Use	16%		
Prescription Drug Use	38%		
Allergies	31%		

Table 3

Descriptive Statistics For Selected Variables For Males Of The Total Sample (N = 237).

Variable	% of Sample	Mean (SD)	Range
Age (Males N = 237)		34.71 (10.91)	18 - 70
Time of Blood Collection (hrs.)		12.50 (2.81)	08 - 20
Q-Value (% EtOH/oz/day)		06.25 (6.07)	00 - 34
Years Smoked (years)		11.56 (10.66)	00 - 39
Current Smoking	76%		
Cannabis Use	32%		
Cocaine/Crack Use	23%		
Prescription Drug Use	34%		
Allergies	27%		

Table 4

Descriptive Statistics For Selected Variables For Females Of The Total Sample (N = 184).

Variable	% of Sample	Mean (SD)	Range
Age (Females N = 184)		34.32 (12.32)	18 - 68
Time of Blood Collection (hrs.)		13.50 (3.54)	07 - 20
Q-Value (% EtOH/oz/day)		04.08 (4.63)	00 - 32
Years Smoked (years)		09.82 (11.04)	00 - 45
Current Smoking	64%		
Cannabis Use	18%		
Cocaine/Crack Use	08%		
Prescription Drug Use	41%		
Allergies	36%		

most sensitive instruments for the detection of alcohol abuse (Gibbs, 1983; Hedlund & Vieweg, 1984; Magruber-Habib, Fraker, & Peterson, 1983; Mischke & Venneri, 1987; Skinner & Sheu, 1982; Willenbring, Christensen, Spring, & Rasmussen, 1987); and, has recently received cross-cultural validation among in- and out-patients residing in Switzerland and Italy (Garzotto, Bratta, Pistoso, & Faccincani, 1988; Yersin, Trisoni, Paccaud, Gutzwiller, & Magenat, 1989). The classic cut-off value of 'more than' or 'equal to 5' was used to identify and to classify individuals considered to be suffering from alcohol-related problems (Selzer, 1971).

The MAC was originally designed to identify individuals for potential alcohol abuse. It was developed using a normative group of male psychiatric out-patients (MacAndrew, 1965). This questionnaire requires true or false responses to 49 items (see Appendix G). Subjects' total raw scores were converted to t-scores, and only t-scores were used for statistical analyses in accordance with procedures for standard validity for the MMPI (Hathaway & McKinley, 1983).

There has been some controversy concerning the validity and reliability of the MAC. Some investigators (Babor, Kranzler, & Lauerman, 1989; Jacobson, 1983) have claimed that the MAC is a valid test for the detection of alcoholism. Others (Andrucci, Archer, & Pancoast, 1989; Burke & Markus, 1977; Craig, 1984; Clopton, 1978; Davis, Colligan, Morse, & Offord, 1987; Gottesman & Prescott, 1988; Moore, 1985; Burke, 1983; Otto, Lang, Megargee, & Rosenblatt, 1988) have concluded that although this instrument

was not specifically designed to identify alcohol abuse, it could be used for the detection of substance abuse in general. Given these questions concerning the validity and reliability of the MAC, it was of interest to determine whether the MAC, in the present subject population, would contribute to the overall variance in Q-Value in individuals with a FH+.

Family history of alcoholism was assessed in all subjects via a family tree tracing over two generations. It was operationally defined as the existence of any biological relative in those generations who had suffered from, or was currently suffering from alcohol-related problems such as loss of employment, marital problems and/or loss of driver's license (e.g. Dawson, Harford, & Grant, 1992; Hesselbrock, Hesselbrock, & Stabeau, 1985a; Schuckit, 1991). The biological relatives assessed included siblings; parents; maternal and paternal aunts and uncles; as well as maternal and paternal grandparents.

Procedure

Subjects were asked to abstain from alcohol or any other drug (with the exception of nicotine, caffeine or prescribed drugs) for a 24-hour period prior to the testing session. Among subjects from the treatment centers, drug abstinence was verified via urine analysis.

Following the completion of the informed consent form (see Appendix H) and the three questionnaires (CASQ, MAST, and MAC), a blood sample (~100 µl) was collected from the middle finger of

each subject. This sample was kept on ice until reaching the laboratory. Every effort was made to transport these samples to the laboratory as promptly as possible. The time of blood collection, and blood volume, were recorded. All other procedures were the same as those described in experiment 1.

Results

Phase 1

This study was designed primarily to investigate two questions. First, are there differences in mean catalase activity and in mean Q-Value between FH+ and FH- individuals? Second, given the relation between alcohol intake (Q-Value) and catalase activity (Koechling & Amit, 1992), does the degree of relationship between catalase activity and alcohol intake differ for FH+ compared to FH- individuals?

Of the total sample (N = 421), 229 individuals satisfied the criteria for FH-, and 192 individuals satisfied the criteria for FH+. Results from an independent t-test for catalase activity showed (see Figure 5) that FH+ individuals had higher mean catalase activity when compared to FH- individuals ($t(419) = 3.59$, $p<0.001$). Similarly, results from an additional t-test for Q-Value showed (see Figure 6) that FH+ individuals also had higher mean Q-Value compared to FH- individuals ($t(419) = 5.38$, $p<0.001$).

When the relation between catalase activity and Q-Value were examined separately for potential differences between FH+ and FH- individuals, statistical analysis revealed the following:

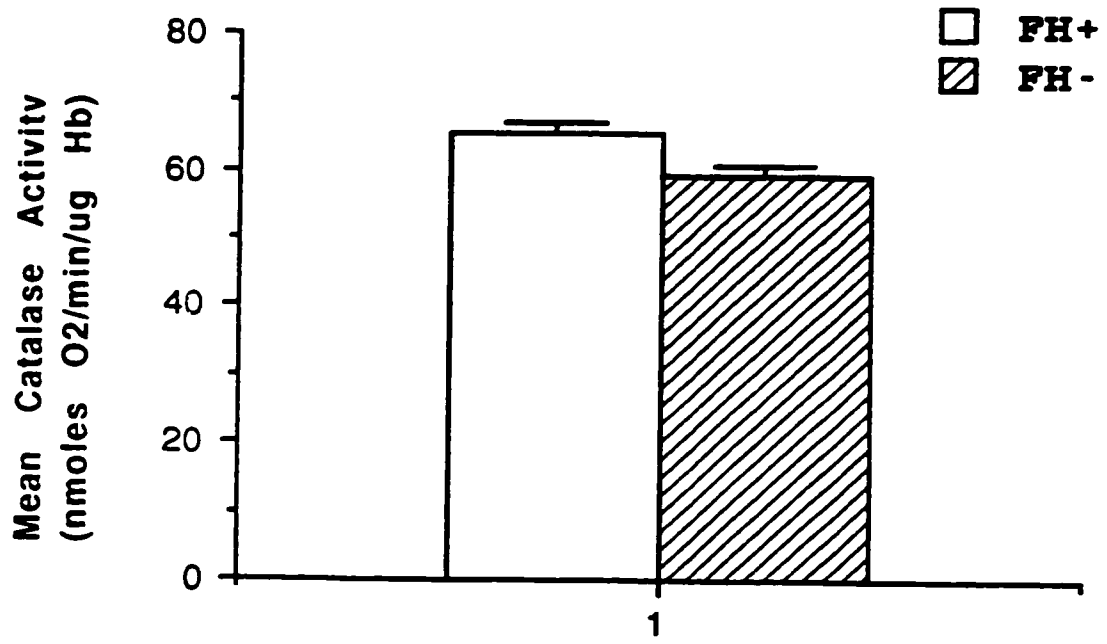

Figure 5. Mean catalase activity of FH+ (n = 192) and of FH- (n = 229) individuals (p <.001).

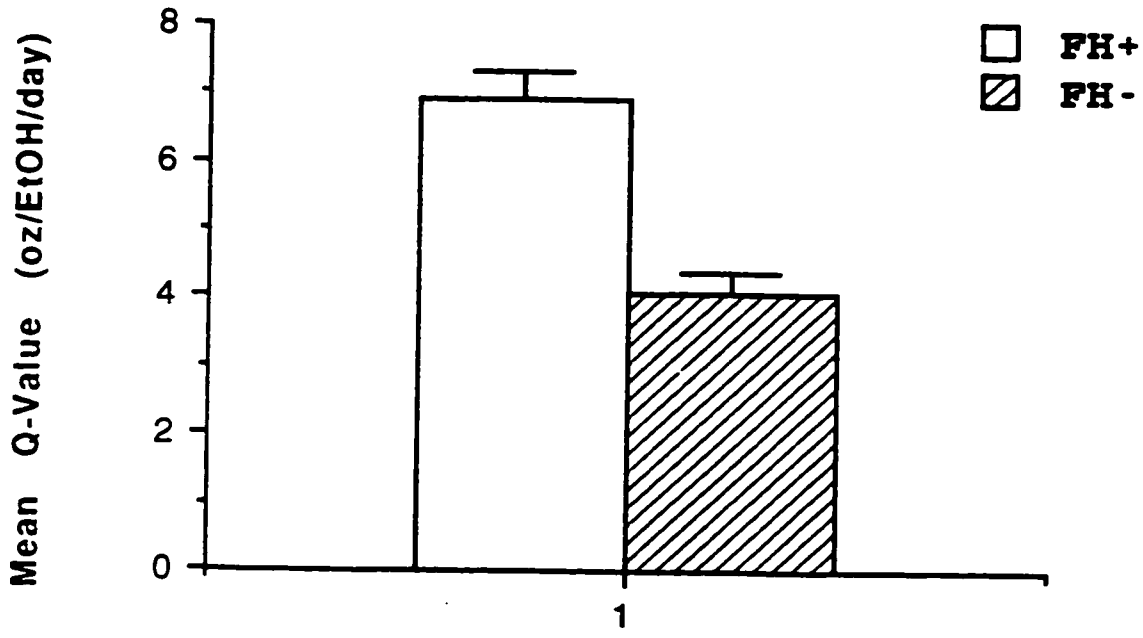

Figure 6. Mean Q-Value of FH+ (n = 192) and of FH- (n = 229) individuals ($p < .001$).

For FH- individuals, a significant correlation ($r(227) = .26$, $p<.001$, $n = 229$) was obtained between catalase activity and Q-Value (see Figure 7) accounting for 7% of the variance. For FH+ individuals, a significant correlation ($r(190) = .47$, $p<.001$, $n = 192$) emerged between catalase activity and Q-Value (see Figure 8) accounting for 22% of the variance. In order to statistically compare the size of correlations for FH+ and FH- individuals, Fisher's r to z transformations for comparisons between independent samples were computed (Cohen & Cohen, 1989). Results showed that the size of the correlation between catalase activity and Q-Value was significantly larger for FH+ individuals when compared to FH- individuals ($z = 2.35$, $p<.01$).

Thus, overall, these results showed that FH+ individuals had significantly higher mean catalase activity compared to FH- individuals. The results also showed that FH+ individuals had significantly higher mean alcohol intake compared to FH- individuals. Differences in the pattern and size of correlation between catalase activity and Q-Value were also obtained for FH+ and FH- individuals. It was found that the size of the correlation between catalase activity and Q-Value was significantly higher for FH+ than for FH- individuals.

Phase 2

Given that the results of phase 1 showed that the size

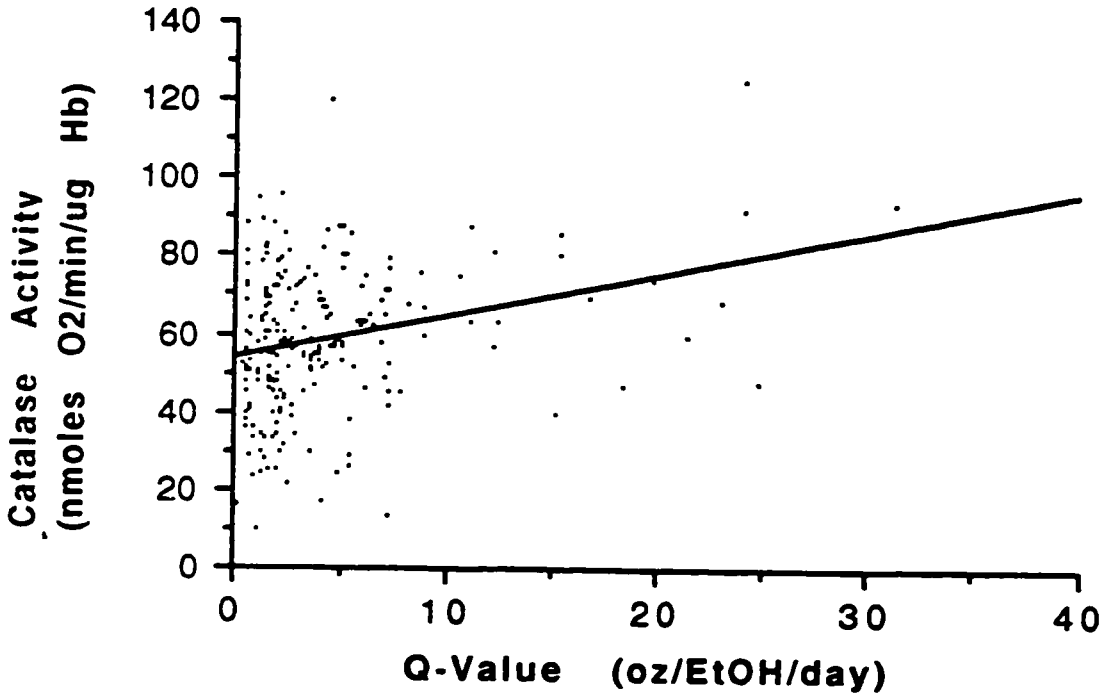

Figure 7. Catalase activity in relation to Q-Value in FH- individuals (r = .26, p <.001, n = 229).

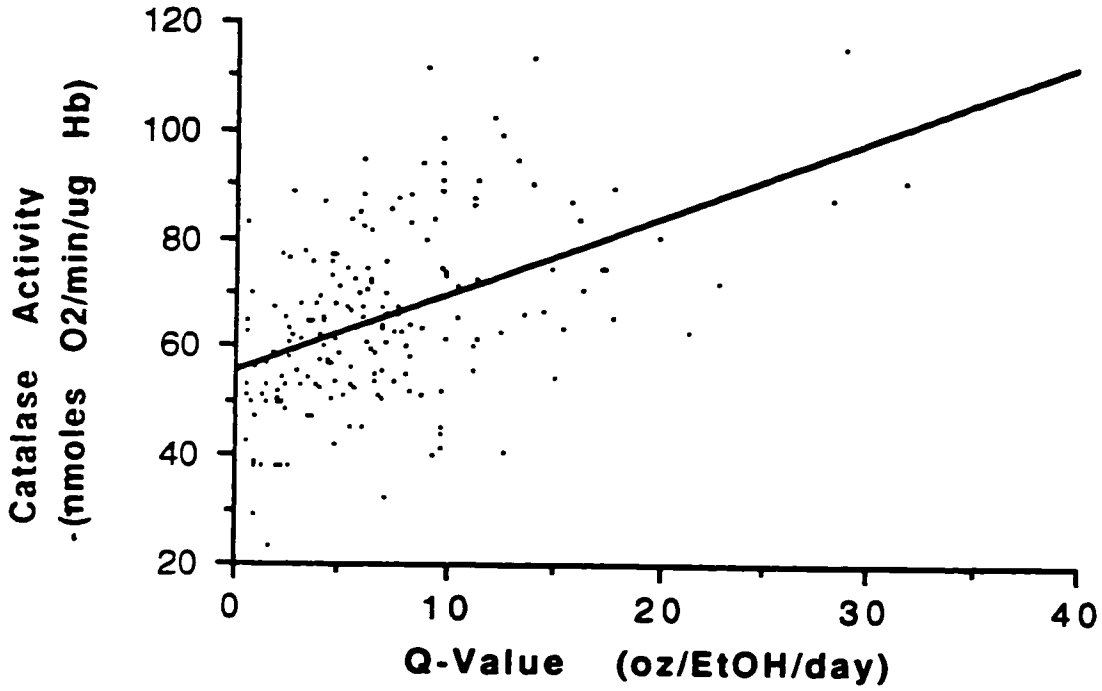

Figure 8. Catalase activity in relation to Q-Value in FH+ individuals (r = .47, p <.001, n = 192).

of the correlation between catalase activity and Q-Value was significantly larger for FH+ as compared to FH- individuals, it was of interest to further examine, in FH+ individuals, the relation between catalase activity and Q-Value. Phase 2 of experiment 2 was designed to further investigate two basic questions. First, does catalase activity explain a significant portion of the variance in Q-Value for FH+ individuals? Second, what other variables may contribute to the relation between Q-Value and catalase activity in FH+ individuals? In an attempt to answer these questions, a hierarchical regression analysis with Q-Value as the dependent measure was performed. Prior to this hierarchical regression, a preliminary regression was carried out. The latter were employed to identify those variables which accounted for a significant portion of the overall variance, and to control for the influence of 'nuisance' variables (Tabachnick & Fidell, 1989). The predictor variables were divided into six sets (see Table 5) and selected based on previous research reports (Koechling & Amit, 1992). Once the pertinent variables had been determined, the final hierarchical regression was computed to further assess the influence of selected predictor variables on Q-Value.

Tests of Assumptions

The data used in the subsequent analyses were tested to ensure that all assumptions regarding multiple regression analyses were met. The data were examined for normality; univariate and

Table 5

Order Of Entry Of Independent Variables

Set 1. Demographic and Experimental Variables

Gender (male/female)

Age (years)

Education (years)

Time of Blood Collection (hours)

Set 2. Medical Variable

Allergies (yes/no)

Set 3. Smoking Variables

Current Smoking (yes/no)

Years Smoked (years)

Set 4. Illegal & Prescription Drug Variables

Cannabis Use (yes/no)

Cocaine/Crack Use (yes/no)

Prescription Drug Use (yes/no)

Set 5. Questionnaire Variables

MAC (t-scores)

MAST (< 5 or > 5)

Set 6. Biochemical Variable

Catalase (nmoles O^2/min/μg Hb)

multivariate outliers; multicollinearity and singularity; linear relations among all independent variables; dependent variable; and, for ratio of cases to independent variables to ensure that assumptions for multiple regression analyses were met.

Tests of skewness revealed that some of the variables were not normally distributed. In order to improve normality, logarithmic transformations were performed on alcohol intake (Q-Value) and square root transformations were carried out on the number of years an individual reported having smoked (Years-Smoked). Z-score transformations and examination of the Mahalanobis distance measure ($p<.0001$) failed to reveal any univariate or multivariate outliers. Inspection of the residual plots for the dependent measure using all predictors indicated that the assumptions for normality, linearity and homoscedasticity of residuals were met. Pair-wise correlations between the dependent and independent variables and tolerance values, determined that no problems of multicollinearity/singularity existed.

All variables showed bivariate correlations that were moderate in size (see Table 6); however, none of the variables demonstrated correlations that were high enough to indicate variable redundancy (Cohen & Cohen, 1983; Tabachnick & Fidell, 1989). Of the total sample ($N = 192$) missing cases ($n = 3$) were eliminated for the purpose of the present analysis, reducing the sample to 189 subjects. The cases to independent variables ratio was 15:1, which was adequate for hierarchical regression analyses (Tabachnick & Fidell, 1989).

Table 6

Bivariate Correlations Between All Independent Variables for FH+ Individuals (N = 189)

	Gender	Age	Education	Allergies	C-Smoking	Y-Smoked	Cannabis Use	Cocaine /Crack	P-Drugs Use	MAC	MAST	Catalase
Age	.05											
Education	-.04	-.08										
Allergies	-.14	-.17	.06									
Current-Smoking	.17	.01	-.10	.01								
Years-Smoked	.11	.46	-.21	-.11	.56							
Cannabis Use	.16	-.32	.02	.06	.19	-.14						
Cocaine/Crack Use	.16	-.22	-.09	.03	.21	-.02	.47					
Prescription D. Use	-.09	.12	.03	.12	.02	.12	-.03	-.05				
MAC	.12	.19	-.46	-.16	.39	.40	-.02	.29	.01			
MAST	.16	.28	-.18	-.16	.36	.40	.07	.14	.10	.50		
Catalase	.00	.07	-.08	-.10	.10	.01	.01	-.01	-.05	.12	.13	
Q-Value	.17	.29	-.25	-.19	.30	.35	.05	.18	-.05	.48	.57	.47

Dichotomous variables were dummy-coded for entry into the analyses. Gender was coded as: "1"= male, "0"= female, while the MAST scores were coded as: "1"= alcohol-related problems, "0"= no alcohol-related problems. Allergies, Current-Smoking, Cannabis Use, Cocaine/Crack Use, and Prescription Drug Use were coded as: "1"= yes, "2"= no. The variable Education was measured in years and coded in levels as: "1"= some public school, "2"= completed public school, "3"= some high school, "4"= completed high school, "5"= some community college or university, "6"= completed community college or university, "7"= completed post-graduate or professional degree.

Variables were grouped into six sets (demographic and experimental variables, subjects' medical variable, smoking variables, illegal and prescription drug use, questionnaire variables, and biochemical variable) and these sets were entered into the regression in a hierarchical manner (see Table 5). The order of entry of the sets of variables was based on findings obtained in a previous study (Koechling & Amit, 1992), with variables of greatest interest entered on the last step in order to determine the successive influence of each predictor set on alcohol intake (Q-Value).

Preliminary Regression Analysis

A preliminary hierarchical regression was computed using all sets of independent variables (see Table 5). The purpose of this

preliminary regression was to determine the significant predictors for the dependent measure, Q-Value. The results of this analysis (see Appendix I) were as follows: The significant predictor variables of Gender, Age, and Education from the first set; Current-Smoking from third set; Cocaine-Crack Use from the fourth set; the MAC and MAST questionnaires from the fifth set; and, Catalase from the final set; met the criterion ($p<.10$) for inclusion in further analysis. Only these variables were used in the final regression analysis.

Hierarchical Multiple Regression

Following the preliminary analyses, a hierarchical regression was carried out using only the significant predictor variables, and entered in the previously described order. Although only Gender, Age, Education, Current-Smoking, Cocaine/Crack Use, MAC, MAST, and Catalase were significant, there was a possibility that other non-significant predictor variables may have contributed to the significance of the above mentioned six variables. Hence, an additional hierarchical regression was computed using only those variables that were found to be significant at the same points during the preliminary analysis.

A five-step hierarchical regression analysis was conducted with Q-Value as the dependent variables (see Table 7). The standardized regression coefficient (Beta), semi-partial correlation squared (sr^2), R^2, adjusted R^2, and change in R^2 (R^2 change) for each step of the regression are shown in Table 7. Of the

Table 7

Summary of Hierarchical Regression predicting Alcohol Consumption (Q-Value) (N=189)

Variable	r	Beta	sr^2	F
Step 1				
Gender	.17	.148	.02	4.75**
Age	.29	.261	.07	14.81***
Education	-.25	-.224	.05	10.91***
R^2 = .16 ***				
Adjusted R^2 = .14				
Step 2				
Current-Smoking	.30	.263	.07	15.70***
R^2 = .22 ***				
Adjusted R^2 = .21				
R^2 Change = .07 ***				

*** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$

Variable	r	Beta	sr^2	F
Step 3				
Cocaine/Crack Use	.18	.171	.03	6.28**
R^2 = .25 ***				
Adjusted R^2 = .23				
R^2 Change = .03 *				
Step 4				
MAC	.48	.171	.02	4.72**
MAST	.57	.387	.10	30.76***
R^2 = .41 ***				
Adjusted R^2 = .39				
R^2 Change = .16 ***				
Step 5				
Catalase	.47	.383	.14	57.25***
R2 = .55***				
Adjusted R^2 = .53				
R^2 Change = .14 ***				

*** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$

demographic variables entered on the first step, Gender, Age, and Education accounted for a significant portion of the variance ($F(3, 185) = 13.13$, $p<.01$). All the variables entered on step 1 accounted for a significant proportion of unique variance (see Table 7), with Age accounting for 7% ($F(1, 180) = 14.81$, $p<.01$). In the second step Current-Smoking was added to the equation. This variable increased the amount of shared variance by 6% (Finc. (1, 184) = 15.73, $p<.01$). In the third step the addition of Cocaine/Crack Use to the equation, resulted in a significant increase (3%) in the proportion of shared variance (Finc. (1, 183) = 6.27, $p<.05$). In the fourth step the questionnaire variables MAC and MAST were added to the other variables in the equation. The addition of these variables increased the amount of shared variance by 16% (Finc. (2, 181) = 24.77, $p<.01$), with the MAST contributing 10% ($F(1, 180) = 30.76$, $p<.001$) in unique variance. In the final step, the addition of catalase to the other variables in the equation resulted in a significant increase (14%) in the shared variance (Finc. (1, 180) = 57.22, $p<.01$) with catalase accounting for 14% in unique variance ($F(1, 180) = 57.25$, $p<.001$).

When comparing the standardized regression coefficients as shown in Table 7, it becomes evident that Education has a negative Beta weight and that Catalase and MAST are weighed more heavily than all other variables. Catalase activity made the highest single contribution to the overall variance, although, being male,

increasing in age, having lower education, currently smoking, using cocaine/crack, increasing scores on the MAC, and having alcohol-related problems (MAST) also explained a significant portion of the variance in alcohol intake (Q-Value).

In conclusion, even after accounting for the variance of 12 other predictor variables, catalase activity still contributed the highest amount in unique variance (14%) in the overall variance in alcohol intake.

Discussion

Results of Experiment 2 established that individuals with a FH+ had significantly higher mean catalase activity than those with a FH-. Similarly, it was found that FH+ individuals had higher mean alcohol intake than those with a FH-. Most importantly, however, differences in the pattern and size of correlation were obtained when FH+ and FH- individuals were compared. It was found that the size of the correlation between catalase activity and alcohol intake was significantly higher for FH+ compared to FH- individuals. In order to rule out the possibility that catalase may represent a covariate of one or more variables, the data for FH+ individuals were subjected to hierarchical regression analysis. Results from the hierarchical regression analyses showed that, even after accounting for the influence of twelve other variables, catalase activity in FH+ individuals still contributed the highest amount in unique variance (14%) in the overall variance in alcohol intake. Furthermore, it was found that being male, increasing in age, having lower education,

currently smoking, using cocaine/crack, increasing scores on the MAC, having alcohol related problems (MAST), and increasing catalase activity, explained a significant portion of the variance in alcohol intake. These results showing that catalase activity was the strongest single predictor of alcohol intake in FH+ individuals, suggested that catalase activity may, in fact be a biological marker for the propensity to consume alcohol in FH+ individuals, and this increased propensity may contribute to the development of alcoholism.

In general, the present results are consistent with previous evidence (Cadoret, 1990; Heath, Meyer, Eaves, & Martin, 1991a; Heath, Meyer, Jardine, & Martin, 1991b; Schuckit, 1990; Searles, 1988, 1990) suggesting a role for a genetic predisposition in the development of alcohol abuse. The present results are also consistent with evidence (Begleiter et al., 1984; Hesselbrock et al., 1985b; Schuckit, 1984, 1987) implicating biological markers as key factors in the identification of mechanisms related to the potential development of alcohol abuse. The question of which factors may be inherited and implicated in the possible development of alcohol abuse has been in dispute in the literature (Searles, 1990). Given that operational definitions of alcoholism differed between studies and that these definitions were vague at best (Searles, 1990; Pollock & Earleywine, 1992), it was not surprising that there was a large discrepancy in findings regarding the possible genetic mechanisms underlying the dependence on alcohol (Pollock & Earleywine, 1992). The present results suggested that what may be inherited by

persons at high risk for the development of alcoholism, is the predisposition to consume large amounts of alcohol, rather than the inheritance of the 'disease' of alcoholism per se. This was further substantiated by the finding that the MAST, a widely used diagnostic instrument for alcoholism (Gibbs, 1983; Hedlund & Vieweg, 1984; Magruber-Habib et al., 1983; Mischke & Venneri, 1987; Skinner & Sheu, 1982; Willenbring et al., 1987) was not as strong a predictor as was catalase which, in turn, accounted for the highest proportion of the overall variance in alcohol intake. Again, for this reason, the findings of the present study suggested that what may be genetically transmitted is the propensity to consume large quantities of alcohol, and not the transmission of the 'disease' of alcoholism per se. These findings are also consistent with recent findings (Heath et al., 1991a, 1992b) suggesting that, when comparing MZ and DZ twins-pairs, significantly higher heritability rates were found for the quantity of alcohol consumption, rather than for alcoholism itself. Since previous research has concentrated largely on identifying mechanisms for the genetic transmission of alcoholism, rather than focusing on the quantity of alcohol consumed, this may help to explain the large discrepancies found in the literature (Searles, 1988, 1990; Pollock & Earleywine, 1992) regarding genetic markers for alcoholism. If we assume that the process which leads to the dependence on alcohol involves the consumption of large quantities of alcohol, a behavior that is governed by principles of learning and motivation (Smith & Amit, 1990), it

seemed logical to rely on measures of alcohol consumption for the present study.

The current results also support data reported earlier by Koechling and Amit (1992), and further substantiate the conclusion that catalase activity in erythrocytes is a significant predictor of voluntary alcohol intake. Furthermore, the present results are consistent with data obtained from animal studies (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989; 1992; Koechling & Amit, in press; Rotzinger et al., 1993; Tampier & Mardones, 1983) which suggest that catalase activity may play a role in the mediation of a variety of ethanol's behavioral effects (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985c, 1989, 1991; Tampier & Mardones, 1983) and, more importantly, that catalase activity may play a role in the regulation of ethanol intake in animals (Amit & Aragon, 1988; Aragon et al., 1985c).

The previously cited evidence also provided further support for research (Cohen et al., 1980; DeMaster et al., 1986; Sinet et al., 1980) which has suggested that catalase may be a viable metabolic pathway for the oxidation of alcohol to acetaldehyde in the brain. In this respect, the current results showing that mean catalase activity was significantly higher in FH+ individuals, compared to FH- individuals, as well as the finding that catalase activity while correlated with alcohol intake in FH- individuals, this correlation was significantly higher in FH+ individuals, suggested that these differences in catalase activity may be related to differences in the

production of acetaldehyde by catalase in the brain. These findings may also lend support to the contention that acetaldehyde may be mediating the reinforcing properties of alcohol (Amit and Smith, 1989; Smith et al., 1990; Von Wartburg, 1980).

In conclusion, the present investigation represents the first step towards the identification of a mechanism underlying the genetic predisposition towards high alcohol consumption and, consequently, towards the subsequent development of alcoholism. More specifically, the present findings suggested that the mechanisms underlying this susceptibility may be mediated by the production of acetaldehyde in the brain via the metabolic activity of catalase, and further, that catalase activity may therefore serve as a marker for the identification of individuals who, due to their affinity to consume large amounts of alcohol, may be at risk for the development of alcoholism.

GENERAL DISCUSSION

The present series of experiments examined the relation of catalase and Q-Value in terms of its differential contribution to alcohol consumption in FH+ and FH- individuals. Before, however it would be possible to proceed with testing the hypothesis concerning the nature of catalase as a biological marker for the propensity to consume alcohol, the issue as to whether catalase was an observable rather than an evocable marker had to be addressed (Radouco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990). The main reason for addressing this issue was to determine whether catalase activity, as a potential biological marker for the propensity to consume alcohol, had predictive validity for future alcohol intake. Accordingly, the question as to whether catalase was a predictor of future alcohol intake, or whether catalase activity was a marker for past or recent alcohol intake needed to be addressed. Thus, the first experiment was designed to examine the possibility, by using an alcohol challenge paradigm, that differences in catalase activity reflect their induction by recent alcohol intake rather than their activity as predictors of future alcohol intake.

Phase 1 of experiment 1 demonstrated that catalase activity in males and females was not induced by the acute administration of alcohol, and that catalase activity probably also was not induced by individuals' prior alcohol consumption history. This lack of effect of alcohol on catalase activity observed in the present study was inconsistent with earlier reports (Fazekas, 1965; Gambassi &

Maggi, 1952), which had suggested that acute doses of alcohol produced short-term increases in catalase activity in humans measured over a 7-hour time period. This inconsistency in findings may be partially due to the fact that none of these earlier studies (Fazekas, 1965; Gambassi & Maggi, 1952) incorporated into their designs control groups receiving non-alcoholic beverages, and that these earlier studies were based on older, less reliable methods of biochemical analysis for catalase. More specifically, in these early studies catalase activity was measured exclusively in a small group of male volunteers (n = 5 per group) before and after alcohol ingestion sampled over a 7-hour time period. Given the design, used in these early studies (Fazekas, 1965; Gambassi & Maggi, 1952), effects due to potential fluctuations in baseline catalase activity, post-fluid-ingestion, effects due to the small sample sizes, and effects due to individuals' prior alcohol consumption history, were not controlled for. In addition, the designs of these early studies excluded females, and relied exclusively on male volunteers. Considering the methodological short-comings of these early studies (Fazekas, 1965; Gambassi & Maggi, 1952), the findings of these studies may have been too confounded to allow for a reliable and valid interpretation of the data. Further, they may have also been too confounded to allow for meaningful comparisons between the present and early findings.

Results from the present study showing a lack of effect of alcohol on catalase activity are congruent with those obtained from animal studies (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989, 1991; Koechling & Amit, in press; Rotzinger et al., 1993; Tampier & Mardones, 1983). In general, the results of these animal studies suggested that prior ethanol intake would not alter catalase activity. More specifically, Aragon et al. (1985c) showed that brain catalase activity did not differ between groups of animals exposed to ethanol and those exposed to water only. Furthermore, findings from a second study (Aragon et al., 1985c) showed that brain catalase activity in groups of rats forced to drink ethanol presented as their exclusive source of fluid over a 25 day period, did not differ from groups of rats exposed to water. Further support for lack of induction of catalase by ethanol intake in rats was provided by Amit and Aragon (1988) in a second study. They (Amit & Aragon, 1988) showed that blood catalase activity in young (approximately 60 days of age), ethanol naive rats, was positively correlated with later ethanol consumption at around 100 days of age.

In addition, this lack of effect of alcohol intake on catalase activity was also congruent with findings of previous human studies (Koechling & Amit, 1992), showing that alcohol intake by subjects over their most recent 30-day period was not related to their catalase activity. More specifically, Koechling and Amit (1992) found that catalase activity was positively correlated

with alcohol intake consumed over a typical, but not the most recent, 30-day period. This finding, together with the previously mentioned observation that recent drinking was not related to catalase activity, further supported the lack of effect of alcohol intake on catalase activity. It follows that if catalase was indeed induced by prolonged periods of of drinking (ie. at least over the most recent 30 days), indices of both recent and typical drinking would have been related to catalase activity. Furthermore, the contention regarding the lack of effect of alcohol intake on catalase activity was further substantiated by findings obtained in experiment 1 showing that the results of the analysis of variance examining the potential effects of alcohol intake on catalase activity did not change when effects due to prior alcohol consumption history were covaried out of this analysis. Taken together, these results suggested that catalase activity may neither be induced by the acute, nor by the long-term ingestion of alcohol.

The purpose of phase 2 of experiment 2 was to examine the effect of acute administration of alcohol on BAC over a 24-hour period in order to ensure that subjects consumed the alcohol presented to them during the experimental session. The results obtained in phase 2 of experiment 2 demonstrated that none of the subjects consumed alcohol prior to the experimental session and further, that they did not consume alcohol 24-hours post-fluid ingestion. Furthermore, the results showed that mean BAC readings were only elevated for individuals who had received the alcoholic beverage as opposed to those who had consumed the non-alcoholic

beverage. Lastly, the present findings established that the acute administration of alcohol increased BAC to a greater degree in females than it did in males, suggesting that blood alcohol levels is higher for females compared to males.

These findings are congruent with previous research findings (Allen et al., 1988; Frezza et al., 1990; Julkunen et al., 1985; Reich, 1988; Salaspuro, 1986). Results from these studies (Allen et al., 1988; Reich, 1988; Salaspuro, 1986) suggested that it is possible, to reliably monitor, using a breathalizer apparatus to measure BAC, an individual's prior, for a minimum of six hours, alcohol consumption level. Furthermore, the current results showing that BAC, in the alcohol condition, was higher for females as compared to males, is consistent with findings of studies (Frezza et al., 1990; Julkunen et al., 1985) suggesting that females become intoxicated after drinking smaller quantities of alcohol than those needed to produce intoxication in males. Taken together, the present findings of phase 2 of experiment 2 demonstrated that individuals who were assigned to the alcohol condition actually consumed the alcoholic beverage.

Since catalase activity was not induced by acute administration of alcohol, and thus, was not an evocable marker (Radouco-Thomas et al., 1984; Rowe, 1990; Tarter et al., 1990) associated with alcohol intake, experiment 2 addressed the following question regarding the potential predictive validity of

catalase, namely: whether or not catalase may be a biological marker for the propensity to consume alcohol. More specifically, it was of importance to examine whether the activity of catalase differentially predicted alcohol consumption in FH+ and in FH- individuals. In phase 1 of experiment 2 it was found that FH+ individuals had higher mean catalase activity than those observed in FH- individuals. When the relation between catalase and alcohol intake was examined, differences in the size of the correlations between catalase activity and Q-Value were obtained for FH+ compared to FH- individuals. It was found that the size of the correlation between catalase activity and alcohol intake was significantly higher for FH+ than it was for FH- individuals. The fact that the correlation between catalase activity and alcohol intake was significantly higher in FH+ individuals, and that catalase activity in FH+ individuals accounted for a significantly higher proportion (22%) of the variance in alcohol intake, provided the impetus to examine in greater detail the relation between catalase activity and alcohol intake in FH+ individuals. It was of importance to rule out the possibility that catalase activity may represent a covariate of one or more variables, since it may have been possible that other predictors of alcohol intake may have contributed to the shared variance between catalase activity and alcohol intake in FH+ individuals. Thus, to rule out potential rival hypotheses suggesting that the shared variance between other predictor variables and catalase may potentially account for the obtained correlation between catalase and alcohol intake in FH+ individuals, in phase 2 of

experiment 2, data for FH+ individuals were subjected to a hierarchical regression analyses. The selection and order of entry of predictor variables of alcohol intake were based on previous studies (see Koechling & Amit, 1992). Data obtained through the preliminary hierarchical regression analyses showed that, even after accounting for the influence of twelve other variables, catalase activity in FH+ individuals still made the highest single contribution (14%) to the overall variance in alcohol intake. Data obtained from the final hierarchical regression analysis showed that although being male, increasing in age, having lower education, currently smoking, using cocaine/crack, higher scores on the MAC, and having alcohol-related problems (MAST) were all predictors of alcohol intake, catalase activity was the strongest single predictor of alcohol intake. After accounting for the variance of all of the other predictor variables, catalase activity in FH+ individuals still contributed 14% to the overall variance in alcohol intake.

The present finding, showing that FH+ individuals had higher catalase activity and alcohol consumption rates compared to FH- individuals, gave rise to the possibility that previous long-term alcohol consumption may have altered catalase activity. This issue needed to be addressed in order to further assess the predictive validity of catalase as a marker for future alcohol intake. Although the present finding showing that FH+ individuals had higher catalase activity as well as higher alcohol consumption rates compared to FH- individuals might support such a contention, several lines of investigation would argue strongly against the

possibility of an induction of catalase by previous long-term alcohol intake. First, if one accepts the notion that catalase may be induced by prolonged drinking in FH+ individuals, then this notion must also hold true for FH- individuals for the following reasons: The correlation between alcohol intake and catalase activity, although significantly smaller in magnitude, was also significant for FH- individuals. Furthermore, the range of values obtained in catalase activity for non-drinkers was similar in both FH+ and FH- individuals, a finding which also argued against the possible induction of catalase. Second, the finding of an earlier study (Bjorneboe, Johnson, Bjorneboe, Marklund, Skylv, Hoiseth, Backe-Wiig, Morland & Drevon, 1988) suggested that both alcoholics and non-alcoholics had similar levels of catalase activity. This finding would argue strongly against the conclusion that chronic alcohol consumption altered catalase activity. Moreover, alcoholics included in the Bjorneboe et al. study (1988) consumed ten times the amount of alcohol consumed by non-alcoholics over a time span that ranged from 2 years up to 30 years, were physically dependent on alcohol, suffered from pathology of the liver, and showed cerebellar atrophy. Third, the previously mentioned finding, that alcohol intake over the most recent, but not typical 30-day period was not correlated with catalase activity (Koechling & Amit, 1992), further argues against the possibility that prolonged drinking produced an induction of catalase. If this had been the case, indices of both

recent and of typical drinking would have to have been correlated with catalase activity. Moreover, the present findings obtained in experiment 1 showing no change in results when the effects of prior alcohol consumption were statistically controlled, further supported the contention that prolonged drinking did not alter catalase activity. Fourth, results from animal studies wherein ethanol was the sole fluid consumed over a 25 day period, suggested that catalase activity did not change as a function of chronic exposure to ethanol (Aragon et al., 1985c). Further, Amit and Aragon (1988) also showed that catalase activity measured in young, ethanol naive rats, correlated positively with later ethanol consumption. Thus, the findings from the animal studies (Amit & Aragon, 1988; Aragon et al., 1985c) further support the contention that previous long-term exposure to ethanol does not alter catalase activity. Taken together, findings from human studies (Bjorneboe et al. 1988; Koechling & Amit, 1992), animal studies (Amit & Aragon, 1988; Aragon et al., 1985c), and the present findings showing a lack of effect for the induction of catalase, suggest that a study of the chronic effects of alcohol ingestion on catalase activity in humans would likely confirm the present contention.

Catalase as a Marker for the Propensity to Consume Alcohol

The present findings showed that catalase activity in FH+ individuals was significantly higher compared to FH- individuals. This finding suggested that catalase activity may be inherently

higher in FH+ compared to FH- individuals. Furthermore, current findings also demonstrated that alcohol intake was significantly higher in FH+ compared to FH- individuals. Taken together, these findings supported the contention that the inherent activity of catalase in FH+ individuals may predispose them towards a higher propensity to consume alcohol. These findings are consistent with previous reports suggesting that genetic markers associated with a predisposition towards alcoholism may be related to individual differences in the metabolism of alcohol (Amit et al., 1986; Bosron & Li, 1986; Tarter et al., 1990).

Current findings showed that catalase activity was correlated with alcohol intake in both FH+ and in FH- individuals, although accounting for a much smaller amount of variance in the FH- group. These results also supported data reported earlier by Koechling and Amit (1992) showing a positive relation between alcohol intake and catalase activity in a group of volunteers. Taken together, these findings further substantiated the conclusion that catalase activity in erythrocytes may be a significant predictor of alcohol intake. Furthermore, the present results showing a relation between catalase activity and alcohol intake, are also consistent with data obtained from animal studies (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989; 1991; Tampier & Mardones, 1983). Findings obtained in these animal studies suggested that catalase activity may play a role in the mediation of a variety of ethanol's behavioral effects, including ethanol consumption (Amit & Aragon, 1988; Aragon & Amit, 1992a,

1992b; Aragon et al., 1985c; Koechling & Amit, in press; Rotzinger et al., 1993); ethanol-induced locomotor depression (Aragon et al., 1989); narcosis and lethality (Aragon et al., 1991; Tampier & Mardones, 1983); and, ethanol-induced CTA (Aragon et al., 1985b). Most importantly, the findings (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985c; Koechling & Amit, in press; Rotzinger et al., 1993) suggesting that catalase activity may play a role in the regulation of ethanol intake in animals, is consistent with the present results suggesting that catalase activity in erythrocytes may be a predictor of alcohol intake in humans.

The present results showed that the relation between catalase activity and alcohol intake in FH+ was significantly greater than that of FH- individuals, and accounted for a higher proportion of the variance. This provided the rationale for a more detailed examination of this relation in FH+ individuals. In this respect, it was of importance to rule out the possibility that other predictors of alcohol intake may have contributed to the shared variance between catalase activity and alcohol intake in FH+ individuals. Data obtained from the final hierarchical regression analysis showed that, although being male, increasing in age, having lower education, currently smoking, using cocaine/crack, increasing scores on the MAC, and having alcohol-related problems (MAST) were all significant predictors, catalase activity was the strongest single predictor of alcohol intake. Even after all other predictor variables had entered the regression equation, catalase activity in FH+ individuals still contributed 14% to the overall variance in alcohol

intake. These results showing that catalase in FH+ individuals was the strongest predictor of alcohol intake, suggested that catalase activity may be a biological marker for the propensity to consume alcohol in FH+ individuals; and, that this propensity may contribute to an increased risk for the development of alcoholism. These results demonstrating that the inherent activity of catalase was significantly higher in FH+ individuals, together with the finding that catalase was the strongest predictor of alcohol intake in FH+ individuals, are consistent with reports in the literature suggesting that predispositional factors participate in the development of alcoholism. Family history studies (Cotton, 1979; Schuckit et al., 1972; Winokur et al., 1970), as well as investigations of twins (Cadoret, 1990; Searles, 1990), and of adoptees (Bohman et al., 1981; Cadoret, 1990; Goodwin et al., 1973) have established that alcoholism is a familial disorder that may be inherited by the offspring. Further, the present results are also consistent with evidence (Porjesz & Begleiter, 1991; Schuckit, 1991; Tarter et al., 1990) implicating biological markers as key factors in the identification of mechanisms related to the potential development of alcoholism. Findings obtained from these at-risk studies (Porjesz & Begleiter, 1991; Schuckit, 1991; Tarter et al., 1990) suggested that neuropsychological (Alterman et al., 1985; Tarter et al., 1990), electrophysiological (Porjesz & Begleiter, 1991; Volavka et al. 1985), psychological (Cloninger, 1987a, 1987b; Tarter et al., 1990), and biological markers (Esaky & Linnoila, 1991; Schuckit, 1991), which have been found to differentiate FH+ and FH- individuals, may

mediate the genetic expression of alcohol abuse. Further, findings from these at-risk studies (Porjesz & Begleiter, 1991; Schuckit, 1991; Tarter, 1991) suggested that markers identifying differential physiological and psychological responses to alcohol may be implicated in the potential development of alcohol abuse. Taken together, the present findings, showing that FH+ and FH- individuals can be differentiated on the basis of catalase activity and in terms of the relation between catalase activity and alcohol intake, are consistent with the above mentioned studies (Porjesz & Begleiter, 1991; Schuckit, 1991; Tarter, 1991) suggesting that the identification of biological markers may help elucidate the possible genetic determinants for alcohol intake and the subsequent development of alcohol abuse. Furthermore, the current finding showing that catalase activity predicted alcohol intake, rather than predicting alcoholism, as measured by the MAST, was also congruent with recent findings (Heath et al., 1991a, 1992b) suggesting that, when comparing MZ and DZ twin-pairs, higher heritability rates were observed for the quantity of alcohol consumed, rather than for 'alcoholism' per se. Results from the above-mentioned twin studies (Heath et al., 1991a, 1991b) are also consistent with findings from at-risk studies (Porjesz & Begleiter, 1991; Schuckit, 1991; Tarter, 1991) suggesting that what markers may identify, is a differential responding between FH+ and FH- individuals to alcohol, rather than to alcohol abuse itself. Moreover, the present findings together with findings, from twin studies (Heath et al., 1991a, 1991b) and at-risk studies (Porjesz & Begleiter,

1991; Schuckit, 1991; Tarter, 1991) suggested that what may be inherited by FH+ individuals, is the predisposition to consume large amounts of alcohol, rather than the inheritance of the 'disorder' of alcoholism per se.

The present findings demonstrating that catalase activity was a strong predictor of alcohol intake in FH+ individuals and thus, the suggestion that catalase activity may be a biological marker for propensity of organisms to consume alcohol, is also consistent with the previous reports (Amit et al., 1986; Amit & Aragon, 1988; Smith et al., 1990) suggesting a role for catalase and, by implication, a role for centrally-acting acetaldehyde in the mediation of alcohol consumption. More specifically, the present findings supported the contention that central ethanol metabolizing enzymes may play a role in alcohol consumption behavior by regulating the rate of formation and degradation of acetaldehyde in brain (Amit et al., 1986; Amit & Aragon, 1988; Smith et al., 1990). The source of centrally-acting acetaldehyde, which has been implicated in the mediation of several of the reinforcing properties of ethanol in animals (Brown et al., 1980; Myers et al., 1984; Takayama & Uyeno, 1985) and humans (Behar et al., 1983; Brown et al., 1983; Peachey, 1989), may be formed directly in brain by catalase. It has been demonstrated that catalase has the capacity to metabolize ethanol to acetaldehyde in brain homogenates (Aragon et al., 1992; Cohen et al., 1980; Gill et al., 1992), which suggested that catalase is also involved in the formation of acetaldehyde. The putative ability to synthesize acetaldehyde, via catalase, in the mediation of a variety

of ethanol-mediated behaviors has also been demonstrated (Amit & Aragon, 1988; Aragon & Amit, 1992a, 1992b; Aragon et al., 1985a, 1985b, 1985c, 1989; Koechling & Amit, in press; Rotzinger et al., 1993; Tampier & Mardones, 1983). As previously stated, particularly, the findings (Amit & Aragon, 1988; Aragon et al., 1985c; Koechling & Amit, in press; Rotzinger et al., 1993) suggesting that catalase activity, through its control of the formation of acetaldehyde, may play a role in the regulation of ethanol intake in animals, are consistent with the present results suggesting that catalase activity may be a predictor of the propensity to consume alcohol in individuals a risk for the development of alcohol abuse.

Conclusion

The present results obtained in experiment 1 showed that catalase activity was not induced by the acute consumption of alcohol, and probably neither by the chronic prior consumption of alcohol. This suggested that catalase may be a predictor of future alcohol intake. Support for the contention that catalase may be a predictor of future alcohol intake was obtained by the results of experiment 2. These results, showing that catalase activity was significantly higher in FH+ than in FH- individuals, suggested that FH+ individuals may inherently have higher catalase activity. Further results of experiment 2 showed that catalase activity in FH+ individuals was the strongest single predictor of alcohol intake, even after accounting for the influence of several other

variables. Taken together, these results supported the contention that catalase activity may be a predictor of the propensity to consume alcohol in FH+ individuals, and thus, that catalase activity may contribute to the identification of individuals at risk for the subsequent development of alcoholism.

A logical extension of the present line of research would be to focus on further elucidating the predictive validity of catalase as a potential biological marker of alcohol intake in individuals at risk for the development of alcohol abuse. A marker with predictive validity and reliability must identify individuals at risk; it must be present before the onset of drinking, as well as before any other comorbid psychopathology; and, it must be specific to alcoholism (Tarter et al., 1990). To date, no marker has been identified that meets these criteria (Searles, 1990; Tarter et al., 1990). It is our contention that the present results seem to have satisfied the above-mentioned definition of a marker to a greater degree than have most previous reports in the literature, in that previous researchers relied on non-theoretical, post-hoc explanations of findings (Searles, 1990; Tarter et al., 1990), and were largely unable to rule out potential effects attributable to prior alcohol consumption (Esaky & Linnoila, 1991; Rowe, 1990; Tarter et al., 1990). However, based on the present results and other collaborative evidence (Amit & Aragon, 1988; Aragon et al., 1985c; Bjorneboe et al., 1988; Koechling & Amit, 1992), the possible

induction of catalase produced by acute and chronic prior consumption of alcohol were ruled out, thus suggesting that the activity of catalase may be present before the onset of drinking. Hence, based on the present results, a large-scale longitudinal-prospective study may be justified in order to further investigate the predictive validity and reliability of catalase as a biological marker for future alcohol consumption. The sample for this project would consist of three different age cohorts, to reflect the influence of social/environmental factors:

1. Pre-adolescents age 8 to 12 who are likely to have consumed little or no alcohol; 2. Adolescents age 13 to 18 who are likely to have consumed some alcohol, and; 3. Young adults age 18 to 25 who are likely to have established more stable patterns of alcohol consumption. These three age-cohorts would be followed-up for a period of 2 years in order to investigate whether or not the activity of catalase would identify individuals at risk. In addition, it would help to determine whether the activity of catalase is marker that is specific to alcoholism, as opposed to other drugs of abuse. This type of study would allow for multiple sampling of catalase activity and alcohol intake, and hence, would yield evidence as to the reliability and validity of both measures. Lastly, results from this study would also yield evidence as to the criteria for the predictive validity and reliability of catalase as a marker for the propensity to consume alcohol in FH+ individuals in particular, but also for the general population, thus identifying individuals who might be at risk for the development of alcoholism.

In summary, the key findings in the present dissertation were as follows. Differences in catalase activity among individuals did not reflect a possible induction by prior alcohol intake but, rather, these differences in catalase activity may be predictors of future alcohol intake. Not surprisingly, it was found that mean catalase activity was higher in FH+ individuals compared to FH- individuals. as was their alcohol intake. A central finding of this dissertation was that catalase activity made a significantly higher contribution to the variance of alcohol intake in FH+ individuals compared to FH- individuals. Further results from hierarchical regression analyses showed that, even after accounting for the influence of several other variables, catalase activity in FH+ individuals made the highest single contribution to the overall variance in alcohol intake. These results suggested that catalase activity may in fact be a biological marker for the propensity to consume alcohol, and that this increased propensity may contribute to the development of alcoholism.

The present evidence provided further support for research (Aragon et al., 1992; Cohen et al., 1980; DeMaster et al., 1986; Sinet et al., 1980) which has suggested that catalase may be a viable metabolic pathway for the oxidation of alcohol to acetaldehyde in the brain. In this respect, the current results showing that mean catalase activity was significantly higher in FH+ individuals, compared to FH- individuals; as well as the finding that catalase activity in FH+ individuals less so in FH- individuals, was a significant predictor of alcohol intake; suggest that these differences

in catalase activity may be related to differences in the production of acetaldehyde by catalase in the brain. These findings also lend support to the contention
that acetaldehyde may be mediating the reinforcing properties of alcohol (Amit and Smith, 1989; Smith et al., 1990; Von Wartburg, 1980).

In conclusion, the present investigation represents the first step towards the identification of a mechanism underlying the genetic predisposition towards high alcohol consumption and, consequently, towards the development of alcoholism. More specifically, the present findings suggested that the mechanisms underlying this susceptibility, may be mediated by the production of acetaldehyde in the brain via the metabolic activity of catalase. Catalase activity may therefore serve as a marker for the identification of individuals who, due to their affinity to consume large amounts of alcohol, may be at risk for the development of alcoholism.

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Appendix A

The Concordia Alcohol Screening Questionnaire (CASQ)

(Questionnaire de Concordia pour mesurer la consommation d'alcool)

Date:____/____/____
day year month

Subject no. ____ ___

SEX: Male___ Female___

DATE OF BIRTH: _____/_____/_____
day month year

MARITAL STATUS

___ single
___ married/common law
___ separated/divorced
___ widowed

HIGHEST LEVEL OF EDUCATION

___ some public school
___ completed public school
___ some high school
___ completed high school
___ some community college or university
___ completed community college or university
___ post graduate or professional degree

USUAL OCCUPATION

___ unemployed
___ professional specify:_____
___ self-employed
___ semi-skilled labourer
___ business, managerial
___ student
___ homemaker
___ retired
___ other specify:_____

FATHER'S OCCUPATION

___ unemployed
___ professional specify:_____
___ self-employed
___ semi-skilled labourer
___ business, managerial
___ retired
___ other specify:_____

Subject no. ___

MEDICAL HISTORY (CONTINUED)

PLEASE INDICATE IF YOU HAVE TAKEN ANY OF THE FOLLOWING NONPRESCRIPTION DRUGS. IF YES, PLEASE ESTIMATE HOW MANY DAYS YOU HAVE TAKEN THESE DRUGS DURING THE LAST 30 DAYS.

	HOW MANY DAYS DURING THE LAST 30 DAYS
1. narcotic analgesics (i.e. heroin, opium)	___
2. sedative hypnotics (i.e. quaaludes)	___
3. cannabis (i.e. marijuana, hashish)	___
4. cocaine/crack	___
5. hallucinogens (i.e. LSD, mescaline)	___
6. inhalants	___

Subject no.___

RECENT DRINKING HISTORY

PLEASE THINK BACK CAREFULLY AND TRY TO REMEMBER THE APPROXIMATE DATE OF YOUR LAST DRINK OF BEER, WINE OR LIQUOR? (if you do not remember the exact date, record the month and year.)

DATE OF YOUR **LAST DRINK OF ALCOHOL**: _____/_____/_____
(Please use calendar provided.) day month year

THE REMAINING QUESTIONS ARE ABOUT THE 30 DAY PERIOD **BEFORE** YOUR LAST DRINK.

THIS 30 DAY PERIOD BEGINS ON: ____/_____/____
day month year

DURING THE 30 DAY PERIOD ON HOW MANY DAYS DID YOU DRINK BEER, WINE OR LIQUOR? number of days ____

DURING THIS 30 DAY PERIOD, ON HOW MANY DAYS DID YOU DRINK BEER? ____ number of days

ON A TYPICAL DAY WHEN YOU DRANK BEER, HOW MUCH BEER DID YOU DRINK? (Please check off as many as applicable.)

12oz (cans or bottles) ___ 16oz ___ king cans ___ quarts___

12oz light beer ___ draft glass ___ draft stein___

DURING THAT 30 DAY PERIOD, ON HOW MANY DAYS DID YOU DRINK WINE? ____ number of days

ON A TYPICAL DAY WHEN YOU DRANK WINE, HOW MUCH WINE DID YOU DRINK?

4oz glass ___ half litre ___ litre ___ cooler ___ other ___

Subject no. ___

RECENT DRINKING HISTORY (CONTINUED)

DURING THAT 30 DAY PERIOD, ON HOW MANY DAYS DID YOU DRINK HARD LIQUOR, SUCH AS WHISKEY, VODKA OR GIN? ___ number of days

ON A TYPICAL DAY WHEN YOU DRANK HARD LIQUOR, HOW MUCH DID YOU DRINK?

mixed drinks ___ shots ___ pints (16oz) ___ fifths (26oz) ___

quarts (32oz) ___ other (specify: ____oz)

If you indicated mixed drinks above, how many ounces of liquor are in your typical drink? ____oz (1 shot = 1oz; jigger/finger = 1.5oz).

THESE PREVIOUS QUESTIONS HAVE BEEN ABOUT THE 30 DAYS LEADING UP TO YOUR LAST DRINK. WAS THIS 30 DAY PERIOD TYPICAL OF THE YEAR LEADING UP TO YOUR LAST DRINK. (If so, please specify whether you drank more or less than usual.)

Subject no. ___

FAMILY HISTORY

THE FOLLOWING QUESTIONS REFER TO THE ALCOHOL USE BY MEMBERS OF YOUR FAMILY. TO THE BEST OF YOUR RECOLLECTION, ESTIMATE THE AMOUNT AND TYPE OF ALCOHOL TAKEN BY VARIOUS MEMBERS OF YOUR FAMILY (use scale below to rate the amount of alcohol consumed).

SCALE	DRINKING LEVEL
0	no drinks at all
1	1 drink or less/week
2	2-7 drinks/week
3	8-14 drinks/week
4	15-21 drinks/week
5	22-28 drinks/week
6	29-35 drinks/week
7	more than 35 drinks/week

	SEX	AMOUNT (use rating scale)	TYPE OF ALCOHOL
BIOLOGICAL FATHER		---	----------
BIOLOGICAL MOTHER		---	----------
BIOLOGICAL BROTHERS/SISTERS	---	---	----------
	---	---	----------
(specify sex)	---	---	----------
	---	---	----------
	---	---	----------
WIFE/HUSBAND		---	----------
CHILDREN			
(specify sex)	---	---	----------
	---	---	----------
	---	---	----------
	---	---	----------

Subject no. ___

FAMILY HISTORY (CONTINUED)

HAS ANY MEMBER OF YOUR FAMILY HAD ANY PROBLEMS ASSOCIATED WITH ALCOHOL USE (i.e. traffic violation or accident, medical problems such as liver disease, loss of employment, family difficulty, psychological counselling ...etc). PLEASE SPECIFY FAMILY MEMBER (i.e. maternal grandmother, uncle on father's side) AND PROBLEM.

HAVE ANY MEMBERS OF YOUR FAMILY EVER RECEIVED TREATMENT FOR ALCOHOLISM? IF SO, PLEASE SPECIFY (i.e. paternal grandmother).

Date ____/____/_____
jour mois année

Sujet no. ____ ___

SEXE: Male___ Femelle___

DATE DE NAISSANCE: _____/_____/_____
jour mois année

STATUT MARITAL

___ célibataire
___ marié/conjoint de fait
___ séparé/divorcé
___ veuf

NIVEAU D'EDUCATION

___ quelques années d'école primaire
___ a complété l'école primaire
___ quelques années d'école secondaire
___ a complété l'école secondaire
___ quelques années de collège ou d'université
___ a complété le collège ou l'université
___ études supérieures ou grade professionnel

EMPLOI HABITUEL

___ sans travail
___ professionnel spécifiez:_____
___ travailleur indépendant
___ travailleur manuel
___ commerçant, gérant
___ étudiant
___ femme au foyer
___ à la retraite
___ autre spécifiez:_____

EMPLOI DU PERE

___ sans travail
___ professionnel spécifiez:_____
___ travailleur indépendant
___ travailleur manuel
___ commerçant, gérant
___ à la retraite
___ autre spécifiez:_____

Sujet no.___

DOSSIER MEDICAL

FUMEZ- VOUS? NON___ OUI___

Si oui, précisez le NOMBRE de cigarettes que vous fumez par jour et le nombre d'ANNEES durant lequel vous avez fumé?

___ cigarettes/jour ___ années

Si non, avez vous déjà fumé? NON___ OUI___ Si oui, durant combien d'années avez vous fumé? ___années

AVEZ VOUS DEJA EU:

1. Diabète ___
2. Hypertension ___
3. Retinitis pigmentosa ___
4. Hyperthyroidisme ___
5. Allergies ___ specifiez: _____

POURRIEZ-VOUS INDIQUER SI VOUS AVEZ PRIS LES MEDICAMENTS SUIVANTS. SI OUI, PRECISEZ LE NOMBRE DE JOURS OU VOUS LES AVEZ PRIS AU COURS DES 30 DERNIERS JOURS.

	NOMBRE DE JOURS AU COURS DES 30 DERNIERS JOURS
1. analgésiques narcotiques (i.e. morphine, codeine)	___
2. hypnotiques sédatifs (i.e. seconal, nembutal)	___
3. stimulants (i.e. benzedrine, dexedrine)	___
4. tranquillisants (i.e. valium, librium)	___
5. anti-convulsifs	___
6. antibuse/temposil	___
7. antibiotiques (i.e. penicillin)	___
8. anti-histaminiques	___
9. autre specifiez:_____	___

Sujet no. ___

DOSSIER MEDICAL (SUITE)

POURRIEZ-VOUS INDIQUER SI AVEZ PRIS LES DROGUES SUIVANTES. SI OUI, SPECIFIEZ LE NOMBRE DE JOUR OU VOUS LES AVEZ PRISE AU COURS DES 30 DERNIERS JOURS.

	NOMBRE DE JOURS AU COURS DES 30 DERNIERS JOURS
1. analgésiques narcotiques (i.e. héroine,opium)	___
2. hypnotiques sédatifs (i.e. quaaludes)	___
3. canhabis (i.e. marihuana, hachisch)	___
4. cocaine/crack	___
5. hallucinogènes (i.e. LSD, mescaline)	___
6. inhalations	___

Sujet no.___

CONSOMMATION D'ALCOOL

APRES REFLEXION ATTENTIVE, POURRIEZ VOUS INDIQUER LA DATE APPROXIMATIVE OU VOUS AVEZ PRISE VOTRE DERNIER VERRE DE BIERE, DE VIN OU DE SPIRITUEUX. (Si vous ne vous souvenez pas du jour exact specifiez le mois et l'année)

DATE DE LA DERNIERE PRISE D'ALCOOL: _____/_____/_____
(S.V.P. utilisez le calendrier) jour mois annee

LES QUESTIONS SUIVANTES PORTENT SUR LES 30 JOURS QUI PRECEDENT VOTRE DERNIERE PRISE D'ALCOOL.

DATE QUI DEBUTE CETTE PERIODE DE 30 JOURS: ____/____/_____
jour mois annee

DURANT CES 30 JOURS, PENDANT COMBIEN DE JOURS AVEZ VOUS CONSOMME DE LA BIERE, DU VIN OU DES SPIRITUEUX? nombre de jours ____

DURANT CES 30 JOURS PENDANT COMBIEN DE JOURS AVEZ VOUS CONSOMME DE LA BIERE? ____ nombre de jours

LORS D'UNE DE CES JOURNEES HABITUELLES, LORSQUE VOUS AVEZ CONSOMME DE LA BIERE, COMBIEN EN AVEZ VOUS PRIS? (Cochez un plusieurs ou réponse si nécessaire)

12oz (bouteille ou canette) ___ 16oz ___ king cans ___

quarts___ 12oz bière légère ___ bock ___

Sujet no. ___

CONSOMMATION D'ALCOOL (SUITE)

DURANT CES 30 JOURS PENDANT COMBIEN DE JOUR AVEZ VOUS CONSOMME DU VIN? ____ nombre de jours

LORS D'UNE JOURNEE HABITUELLE, LORSQUE VOUS AVEZ CONSOMME DU VIN, COMBIEN EN AVEZ VOUS PRIS?

verre de 4oz: ___ demi litre ___ litre ___ cooler ___

autre ___

DURANT CES 30 JOURS PENDANT COMBIEN DE JOUR AVEZ VOUS CONSOMME DES SPIRITUEUX? ____ nombre de jours

LORS D'UNE JOURNEE HABITUELLE, LORSQUE VOUS AVEZ CONSOMME DES SPIRITUEUX COMME LE GIN, WHISKY, VODKA, COMBIEN EN AVEZ VOUS PRIS?

boissons melangees ___ dose___ demi litre (16oz) ___

25oz___ quarts (32oz) ___ autre (specifiez: ____oz)

Si vous avez cochez la reponse boissons melangées, quelle quantite de spiritueux etait presente dans votre boisson habituelle? ____oz

LES QUESTIONS AUXQUELLES VOUS VENEZ DE REPONDRE PORTAIENT SUR VOTRE CONSOMMATION D'ALCOOL AU COURS DES 30 JOURS QUI PRECEDAIENT VOTRE DERNIERE CONSOMMATION. POURRIEZ VOUS INDIQUER SI CETTE PERIODE DE 30 JOURS EST REPRESENTATIVE DE VOTRE CONSOMMATION ANNUELLE D'ALCOOL. (Si non, indiquez alors si votre consommation au cours des 30 jours etait plus ou moins grande.)

Sujet no. ___

RENSEIGNEMENTS FAMILIAUX

LES QUESTIONS SUIVANTES PORTENT SUR LA CONSOMMATION D'ALCOOL DANS VOTRE FAMILLE. S'IL VOUS PLAIT, ESTIMEZ LA QUANTITE ET LE TYPE D'ALCOOL CONSOMME PAR LES MEMBRES DE VOTRE FAMILLE. (Utilisez l'échelle si dessous.)

ECHELLE	QUANTITE
0	0 verre/semaine
1	1 ou moins/semaine
2	2-7 verres/semaine
3	8-14 verres/semaine
4	15-21 verres/semaine
5	22-28 verres/semaine
6	29-35 verres/semaine
7	plus que 35 verres/semaine

	SEXE	QUANTITE (utilisez l'echelle)	TYPE D'ALCOOL
PERE BIOLOGIQUE		---	----------
MERE BIOLOGIQUE		---	----------
BIOLOGIQUES FRERES/SOEURS	---	---	----------
	---	---	----------
(specifiez sexe)	---	---	----------
	---	---	----------
	---	---	----------
EPOUX (SE)		---	----------
ENFANTS			
(specifiez sexe)	---	---	----------
	---	---	----------
	---	---	----------
	---	---	----------

Sujet no. ___

RENSEIGNEMENTS FAMILIAUX (SUITE)

AVEZ VOUS DES MEMBRES DE VOTRE FAMIILE QUI ONT EU DES PROBLEMES LIEZ A L'ALCOOL (accident d'automobile,infraction de la route, problemes tels que des maladies hépathiques, perte d'emploi, problemes familiaux, conseiller psychologique ...etc). SPECIFIEZ LE MEMBRE DE VOTRE FAMILLE(i.e. grandmère maternelle, oncle du coté du père) ET LE PROBLEME.

AVEZ VOUS DES MEMBRES DE VOTRE FAMILLE QUI ONT RECU DES TRAITMENTS POUR L'ALCOOLISME? SI OUI, PRECISEZ (i.e. grandpère paternel).

Appendix B
Example of Calculation for Q-Value

Calculation of Q-Value

Q-Values were calculated from data obtained via the CASQ. Examples of the CASQ, relevant to Q-Value calculations are shown on pages 40 to 41. The example (pp. 40-41) shows the questions and responses given by a subject concerning alcohol consumption over a 30-day period. The responses to these questions were used to calculate Q-Value as follows:

$$\underline{\text{Q-Value}} = (\underline{\text{FB}} \times \underline{\text{QB}}) + (\underline{\text{FW}} \times \underline{\text{QW}}) + (\underline{\text{FL}} \times \underline{\text{QL}}) / \underline{\text{F}}.$$

$\underline{\text{FB}}$, $\underline{\text{FW}}$, & $\underline{\text{FL}}$ = Frequencies (days) of beer, wine and spirits consumption respectively.

$\underline{\text{QB}}$, $\underline{\text{QW}}$ & $\underline{\text{QL}}$ = Quantities (ounces) x % alcohol content of beer, wine and spirits respectively.

Thus from the example given:

$$\underline{\text{Q-Value}} = [15 \times 48\ (0.05)] + [6 \times 16.7\ (0.12)] + [4 \times 3\ (0.43)] / 15 = \underline{3.54}.$$

Subject no. SAMPLE

RECENT DRINKING HISTORY

PLEASE THINK BACK CAREFULLY AND TRY TO REMEMBER THE APPROXIMATE DATE OF YOUR LAST DRINK OF BEER, WINE OR LIQUOR? (if you do not remember the exact date, record the month and year.)

DATE OF YOUR LAST DRINK OF ALCOHOL: (Please use calendar provided.) 04 / 08 / 90
day month year

THE REMAINING QUESTIONS ARE ABOUT THE 30 DAY PERIOD BEFORE YOUR LAST DRINK.

THIS 30 DAY PERIOD BEGINS ON: 04 / 07 / 90
day month year

DURING THE 30 DAY PERIOD ON HOW MANY DAYS DID YOU DRINK BEER, WINE OR LIQUOR? number of days 15

DURING THIS 30 DAY PERIOD, ON HOW MANY DAYS DID YOU DRINK BEER? 15 number of days

ON A TYPICAL DAY WHEN YOU DRANK BEER, HOW MUCH BEER DID YOU DRINK? (Please check off as many as applicable.)

12oz (cans or bottles) 4 16oz ___ king cans ___ quarts___

12oz light beer ___ draft glass ___ draft stein___

DURING THAT 30 DAY PERIOD, ON HOW MANY DAYS DID YOU DRINK WINE? 6 number of days

ON A TYPICAL DAY WHEN YOU DRANK WINE, HOW MUCH WINE DID YOU DRINK?

4oz glass ___ half litre 1 litre ___ cooler ___ other ___

Subject no. ~~SAMPLE~~

RECENT DRINKING HISTORY (CONTINUED)

DURING THAT 30 DAY PERIOD, ON HOW MANY DAYS DID YOU DRINK HARD LIQUOR, SUCH AS WHISKEY, VODKA OR GIN? _4_ number of days

ON A TYPICAL DAY WHEN YOU DRANK HARD LIQUOR, HOW MUCH DID YOU DRINK?

mixed drinks ___ shots 3 pints (16oz) ___ fifths (26oz) ___

quarts (32oz) ___ other (specify: ____oz)

If you indicated mixed drinks above, how many ounces of liquor are in your typical drink? ____oz (1 shot = 1oz; jigger/finger = 1.5oz).

THESE PREVIOUS QUESTIONS HAVE BEEN ABOUT THE 30 DAYS LEADING UP TO YOUR LAST DRINK. WAS THIS 30 DAY PERIOD TYPICAL OF THE YEAR LEADING UP TO YOUR LAST DRINK. (If so, please specify whether you drank more or less than usual.)

Yes, it was typical

Appendix C
Consent Forms for Subjects in Experiment 1

Consent Form

I, _____, age_____, consent to take part in a research project entitled "Alcohol metabolizing enzymes and alcohol consumption" to be conducted at the Center for Studies in Behavioral Neurobiology, Concordia University. The risks, purposes and procedures have been explained to me and I understand that my participation will involve the following:

1. The purpose of this study is to determine the role of alcohol metabolizing enzymes in the regulation of alcohol consumption.

2. I will be required to participate in a testing session lasting no longer than three hours in duration. The time of testing will be made at a time convenient to both myself and the investigators. For a period of twenty-four hours prior and also subsequent to this testing session I will be required not to consume any alcoholic beverage. In addition, I will be required to return to attend an additional testing session, which will take place exactly twenty-four hours after the first testing session. This second testing session will last no longer than 30 minutes.

3. During this session, I will complete a paper and pencil test and be interviewed. In addition, three blood samples (2-3 drops) and three breath samples will be taken. The first blood sample and the first breath sample will be taken at the beginning of the session, while the second set of samples will be collected 30 minutes later and the third set of samples will be taken one hour and thirty minutes after the collection of the second sample. The procedure for the breath sample involves blowing expelled air into an alcohol breathelizer instrument. The procedure for the blood sample will involve a small pin prick made to the tip of the finger. Little risk is associated with this method, although, I may experience some slight bruising and inflammation. After the collection of the first blood and breath sample I will be given either a single sweetened alcoholic beverage or a sweetened beverage to drink.

4. Twenty-four hours following the first session, I will partake in a second session, during which I will provide a fourth blood and breath sample and will be interviewed.

5. I will refrain from taking any drug or alcohol (with the exception of nicotine, caffeine or prescribed medication) for 24 hours prior and subsequent to the first testing session.

6. I may expect no therapeutic benefit from my participation in this study.

7. Participation is completely voluntary and as such I may withdraw from the study at any time. Such withdrawal will not adversely influence my future participation in experiments conducted at the Center for Studies in Behavioral Neurobiology.

8. Any information learned about me in the course of the study or prior to it will be confidential and will be protected in the same way as hospital records. The results of the study will be available only to the investigators, who may use the results for scientific purposes, such as publication in a scientific journal or presentation at a scientific meeting as long as my child is not identified as a participant in the study.

9. I understand that, upon request, any data collected about myself will be made available to me and I will receive a full explanation of the findings of the study when they become available.

_____
Date

_____ _____
Subject's Signature Witness

Appendix D

Experiment 1

Source Table for ANCOVA with Catalase Activity as the Dependent Variable using Q-Value as the Covariate

Source	Sum of Squares	D.F.	Mean Square	F	Tail Prob.
Drug (D)	2.18	1	2.18	0.00	.9568
Gender (G)	342.15	1	342.15	0.46	.4985
D x G	1028.17	1	1028.17	1.39	.2423
Q-Value (covariate)	121.46	1	121.46	0.13	.8245
1 Error	48749.23	66	738.62		
Time-of-Sampling (T)	2591.63	3	863.88	3.68	.0130
T x D	525.54	3	175.18	0.75	.5253
T x G	1067.31	3	355.77	1.52	.211
T x D x G	503.47	3	167.82	0.72	.543
2 Error	46440.63	198	234.54		

Appendix E

Experiment 1

Source Table for ANCOVA with BAC as the Dependent Variable using Q-Value as the Covariate

Source	Sum of Squares	DF.	Mean Square	F	Tail Prob.
Drug (D)	.02693	1	.02693	113.46	.0001
Gender (G)	.00097	1	.00097	4.09	.0473
D x G	.00106	1	.00106	4.45	.0387
Q-Value (covariate)	.00002	1	.00002	.10	.7504
1 Error	.01543	66	.00024		
Time-of-Sampling (T)	.02712	3	.00904	38.12	.0001
T x D	.02716	3	.00905	38.18	.0001
T x G	.00262	3	.00087	3.68	.013
T x D x G	.00261	3	.00087	3.67	.0132
2 Error	.04695	198	.00024		

Appendix F

The Michigan Alcoholism Screening Test (MAST)
(Questionnaire de Michigan pour diagnostiquer l'alcoholisme)

MAST THIS QUESTIONNAIRE RELATES TO DRINKING BEHAVIOUR. PLEASE READ EACH STATEMENT CAREFULLY AND INDICATE YOUR RESPONSE BY CHECKING THE BOX BESIDE THE YES OR THE NO. MAKE SURE YOU ANSWER ALL THE QUESTIONS.

DATE: YR MO DA

1. DO YOU FEEL YOU ARE A NORMAL DRINKER?
   ☐1 YES ☐2 NO
2. HAVE YOU EVER AWAKENED THE MORNING AFTER SOME DRINKING THE NIGHT BEFORE AND FOUND THAT YOU COULD NOT REMEMBER A PART OF THE EVENING BEFORE?
   ☐1 YES ☐2 NO
3. DOES YOUR SPOUSE (OR PARENTS) EVER WORRY OR COMPLAIN ABOUT YOUR DRINKING?
   ☐1 YES ☐2 NO
4. CAN YOU STOP DRINKING WITHOUT A STRUGGLE AFTER ONE OR TWO DRINKS?
   ☐1 YES ☐2 NO
5. DO YOU EVER FEEL BAD ABOUT YOUR DRINKING?
   ☐1 YES ☐2 NO
6. DO FRIENDS OR RELATIVES THINK YOU ARE A NORMAL DRINKER?
   ☐1 YES ☐2 NO
7. ARE YOU ALWAYS ABLE TO STOP DRINKING WHEN YOU WANT TO?
   ☐1 YES ☐2 NO
8. HAVE YOU EVER ATTENDED A MEETING OF ALCOHOLICS ANONYMOUS (AA) BECAUSE OF YOUR DRINKING?
   ☐1 YES ☐2 NO
9. HAVE YOU GOTTEN INTO FIGHTS WHEN DRINKING?
   ☐1 YES ☐2 NO
10. HAS DRINKING EVER CREATED PROBLEMS WITH YOU AND YOUR SPOUSE?
    ☐1 YES ☐2 NO
11. HAS YOUR SPOUSE (OR OTHER FAMILY MEMBER) EVER GONE TO ANYONE FOR HELP ABOUT YOUR DRINKING?
    ☐1 YES ☐2 NO
12. HAVE YOU EVER LOST FRIENDS OR GIRLFRIENDS/BOYFRIENDS BECAUSE OF DRINKING?
    ☐1 YES ☐2 NO
13. HAVE YOU EVER GOTTEN INTO TROUBLE AT WORK BECAUSE OF DRINKING?
    ☐1 YES ☐2 NO
14. HAVE YOU EVER LOST A JOB BECAUSE OF DRINKING?
    ☐1 YES ☐2 NO
15. HAVE YOU EVER NEGLECTED YOUR OBLIGATIONS, YOUR FAMILY, OR YOUR WORK FOR TWO OR MORE DAYS IN A ROW BECAUSE OF DRINKING?
    ☐1 YES ☐2 NO
16. DO YOU EVER DRINK BEFORE NOON?
    ☐1 YES ☐2 NO
17. HAVE YOU EVER BEEN TOLD YOU HAVE LIVER TROUBLE? CIRRHOSIS?
    ☐1 YES ☐2 NO
18. HAVE YOU EVER HAD DELIRIUM TREMENS (DTS), SEVERE SHAKING, HEARD VOICES OR SEEN THINGS THAT WEREN'T THERE AFTER HEAVY DRINKING?
    ☐1 YES ☐2 NO
19. HAVE YOU EVER GONE TO ANYONE FOR HELP ABOUT YOUR DRINKING? (DO NOT INCLUDE THIS CONTACT WITH THE FOUNDATION.)
    ☐1 YES ☐2 NO
20. HAVE YOU EVER BEEN IN A HOSPITAL BECAUSE OF DRINKING? (DO NOT INCLUDE THIS CONTACT WITH THE FOUNDATION.)
    ☐1 YES ☐2 NO
21. HAVE YOU EVER BEEN A PATIENT IN A PSYCHIATRIC HOSPITAL OR ON A PSYCHIATRIC WARD OF A GENERAL HOSPITAL WHERE DRINKING WAS PART OF THE PROBLEM? (DO NOT INCLUDE THIS CONTACT WITH THE FOUNDATION
    ☐1 YES ☐2 NO
22. HAVE YOU EVER BEEN SEEN AT A PSYCHIATRIC OR MENTAL HEALTH CLINIC, OR GONE TO A DOCTOR, SOCIAL WORKER OR CLERGYMAN FOR HELP WITH AN EMOTIONAL PROBLEM IN WHICH DRINKING HAD PLAYED A PART? (DO NOT INCLUDE THIS CONTACT WITH THE FOUNDATION.)
    ☐1 YES ☐2 NO
23. HAVE YOU EVER BEEN ARRESTED, EVEN FOR A FEW HOURS, BECAUSE OF DRUNK BEHAVIOUR?
    ☐1 YES ☐2 NO
24. HAVE YOU EVER BEEN ARRESTED FOR DRUNK DRIVING OR DRIVING AFTER DRINKING?
    ☐1 YES ☐2 NO
25. CODER

QUESTIONNAIRE DE MICHIGAN

(MAST)

Ce questionnaire porte sur votre comportement face à l'alcool. Veuillez, s'il vous plaît, lire attentivement les questions et répondre par un vrai (V) ou un faux (F) à toutes les questions.

1. Est ce que vous vous considerez comme un buveur typique?_____
2. Est ce que vous vous êtes déjà reveillé le matin avec des pertes de mémoire apres avoir bu la veille?_____
3. Est ce que votre époux(se) (ou vos parents) s'inquiètent ou se plaignent de votre consommation d'alcool?_____
4. Est ce que vous pouvez toujours arrêter de boire après un ou deux verres si vous le desirez?_____
5. Etes-vous parfois inquiet au sujet de votre consommation d'alcool?_____
6. Est que vos amis et votre famille vous considèrent comme un consommateur d'alcool normal?_____
7. Etes-vous toujours capable d'arrêter de boire quand vous voulez?_____
8. Est ce que vous avez déjà assisté à une réunion des "Alcooliques Anonymes" à cause de votre consommation?_____
9. Vous êtes-vous déjà battu lorsque vous avez bu?_____
10. L'alcool a-t-il déjà créer des problèmes entre vous et votre époux(se)?_____
11. Est ce que votre époux(se) (ou un membre de votre famille) ont déjà cherche le secours d'une tierce personne à cause de votre consommation?_____
12. Avez vous déjà perdu des amis ou petit(e) ami(e) à cause de l'alcool?_____
13. Avez vous déjà eu des problèmes au travail à cause de l'alcool?_____
14. Avez vous déjà perdu un emploi à cause de la boisson?_____
15. Avez vous déjà negligé vos résponsabilités, votre famille ou votre travail pour plus de deux jours consécutifs à cause de l'alcool?_____

16. Est ce que vous buvez parfois avant midi?_____

17. Est ce que vous avez déjà eu des problèmes de foie?_____

18. Après avoir bu, avez vous déjà eu du delirium tremens ou de violents tremblements, entendu des voix imaginaires ou vu des objets qui n'étaient pas là?_____

19. Avez vous déjà cherché de l'aide de quelqu'un à cause de votre consommation d'alcool?_____

20. Avez vous déjà été dans un hôpital à cause de la boisson?_____

21. Votre consommation d'alcool a telle contribué à un problème qui vous a conduit à être patient dans un hôpital psychiatrique ou dans un département de psychiatrie dans un hôpital générale?_____

22. Avez vous déjà consulté un psychiatre, un psychologue, un assistant social, un medecin ou un prêtre pour des problèmes psychologiques dans lesquels la boisson jouait un rôle?_____

23. Avez vous déjà été arrêté par la police, même pour quelques heures, dans un état d'ivresse?_____

24. Avez vous déjà été arrête par la police pour conduite d'une auto en état d'ériété?_____

Appendix G

The MacAndrew Scale (MAC)

(Questionnaire de MacAndrew)

THE MacANDREW SCALE

This inventory consists of numbered statements. Read each statement and decide whether it is true as applied to you or false as applied to you.

You are to mark your answers on the answer sheet you have. If a statement is TRUE or MOSTLY TRUE as applied to you, blacken between the lines in the column headed T. If a statement is False or NOT USUALLY TRUE, as applied to you, blacken between the line in the column headed F. If a statement does not apply to you or it is something that you don't know about, make no mark on the answer sheet.

Remember to give your OWN OPINION of yourself. Do not leave any blank spaces if you can avoid it.

In marking your answers on the number sheet, be sure that the number of the statement agrees with the number on the answer sheet. Make your marks heavy and black. Erase completely any answer you wish to change. Remember, try to make some answer to every statement.

---

1. I like to read newspaper articles on crime.
2. Evil spirits possess me at times.
3. I have a cough most of the time.
4. My soul sometimes leaves my body.
5. As a youngster I was suspended from school one or more times for cutting up.
6. I am a good mixer.
7. Everything is turning out just like the prophets of the Bible said it would.
8. I have not lived the right kind of life.
9. I think I would like the kind of work a forest ranger does.
10. I am certainly lacking in self-confidence.
11. I do many things which I regret afterwards (I regret things more or more often than others seem to).
12. I enjoy a race or a game better when I bet on it.
13. In school I was sometimes sent to the principal for cutting up.
14. My table manners are not quite as good at home as when I am out in company.

15. I know who is responsible for most of my troubles.

16. The sight of blood neither frightens me nor makes me sick.

17. I have never vomited blood or coughed up blood.

18. I like to cook.

19. I used to keep a diary.

20. I have had periods in which I carried on activities without knowing later what I had been doing.

21. I liked school.

22. I am worried about sex matters.

23. I frequently notice my hand shakes when I try to do something.

24. My parents have often objected to the kind of people I went around with.

25. I have been quite independent and free from family rule.

26. I have few or no pains.

27. I have had blank spells in which my activities were interrupted and I did not know what was going on around me.

28. I sweat very easily even on cool days.

29. I have often felt strangers were looking at me critically.

30. If I were a reporter I would very much like to report sporting news.

31. I have never been in trouble with the law.

32. I seem to make friends about as quickly as others do.

33. Many of my dreams are about sex matters.

34. I cannot keep my mind on one thing.

35. I have more trouble concentrating than others seem to have.

36. I do not like to see women smoke.

37. I deserve severe punishment for my sins.

38. I played hooky from school quite often as a youngster.

39. I have at times had to be rough with people who were rude or annoying.

40. I was fond of excitement when I was young (or in childhood).

41. I enjoy gambling for small stakes.

42. If I were in trouble with several friends who were equally to blame, I would rather take the whole blame than to give them away.

43. While in trains, buses, etc., I often talk to strangers.

44. Christ performed miracles such as changing water into wine.

45. I pray several times every week.

46. I readily become one hundred per cent sold on a good idea.

47. I have frequently worked under people who seem to have things arranged so that they get credit for good work but are able to pass off mistakes onto those under them.

48. I would like to wear expensive clothes.

49. The one to whom I was most attached and whom I most admired as a child was a woman (mother, sister, aunt, or other woman).

ANSWER SHEET

1	T	F	16	T	F	31	T	F	46	T	F
2	T	F	17	T	F	32	T	F	47	T	F
3	T	F	18	T	F	33	T	F	48	T	F
4	T	F	19	T	F	34	T	F	49	T	F
5	T	F	20	T	F	35	T	F			
6	T	F	21	T	F	36	T	F			
7	T	F	22	T	F	37	T	F			
8	T	F	23	T	F	38	T	F			
9	T	F	24	T	F	39	T	F			
10	T	F	25	T	F	40	T	F			
11	T	F	26	T	F	41	T	F			
12	T	F	27	T	F	42	T	F			
13	T	F	28	T	F	43	T	F			
14	T	F	29	T	F	44	T	F			
15	T	F	30	T	F	45	T	F			

QUESTIONNAIRE DE MacANDREW

Le présent inventaire est constitué d'une suite d'énoncés. Il s'agit de lire chacun de ces énoncées et d'indiquer s'il vous convient ou s'il ne vous convient pas.

Répondez aux questions suivantes par vrai (V) ou faux (F).

Rappelez-vous qu'il s'agit d'indiquer l'opinion que vous avez de vous-même. Dans toute la mesure du possible, repondez à chacun des articles.

---

1. J'aime lire la rubrique des crimes dans les journaux._____
2. Je suis parfois possédé par de mauvais esorits._____
3. Je tousse la plupart du temps._____
4. Il arrive parfois à mon esprit de quitter mon corps._____
5. Quand j'étais jeune, je fus renvoyé une fois ou plus pour indiscipline._____
6. Je suis tout à fait sociable._____
7. Tout arrive exactement comme les prochètes de la bible l'avaient predit._____
8. Je n'ai pas mené le genre de vie que j'aurais dû._____
9. Je crois que j'aimerais bien le travail de garde-forestier._____
10. Je manque certainement de confiance en moi-même._____
11. Je commets beaucoup d'actions que je regrette ensuite (Je regrette des choses d'avantage, ou plus souvent, que semblent les autres)._____
12. Je prends davantage plaisir à une course ou à un jeu lorsque je peux parier._____
13. A l'école, il m'est arrivé parfois d'être envoye chez le principal pour un indiscipline._____
14. Mes manières à table ne sont pas aussi bonnes à la maison que lorsque je mange en dehors avec quelqu'un._____
15. Je sais qui est résponsable de la plupart de mes ennuis._____
16. La vue de sang ne m'effraie ni ne me rend malade._____

17. Je n'ai jamais vomi ni craché de sang._____

18. J'aime faire la cuisine._____

19. J'avais l'habitude de rédiger un journal personnel._____

20. A certains moments, j'ai faits des choses que, par la suite, je n'ai pas eu souvenance d'avoir faites._____

21. J'aimais bien l'école._____

22. Les quetions sexuelles me causent de l'inquietude._____

23. Je remarque souvent que ma main tremble lorsque j'essaie de faire quelque chose._____

24. Mes parents ont souvent désapprouvé la sorte de personne avec qui j'étais ami._____

25. Parfois, je fais un peu de commérage._____

26. J'éprouve peu ou pas de douleurs._____

27. J'ai éprouve des blancs de mémoire au cours desquels mon activité s'arrêtait et je n'avais pas conscience de ce qui se passait autour de moi._____

28. Je transpire facilement même quand le temps est frais._____

29. J'ai souvent senti que des étrangers me regardaient d'un oeil récrobateur._____

30. Si j'etais journaliste, j'aimerais beaucoup rédiger les nouvelles du sport._____

31. Je n'ai jamais eu de démêlés avec la justice._____

32. J'ai l'impression de me faire des amis aussi vite que les autres._____

33. Bon nombre de mes rêves sont à contenu sexuel._____

34. Je suis incapable de me concentrer sur un objet._____

35. J'éprouve plus de difficulte à me concentrer que semblent en éprouver les autres._____

36. Je n'aime pas voir les femmes fumer._____

37. Je mérite un châtiment sévère pour mes péchés._____

38. Quand j'étais enfant, il m'est arrivé très souvent de faire l'école buissonière._____

39. J'ai dû parfois être brutal avec des gens grossiers ou importuns._____

40. Quand j'étais jeune (ou dans mon enfance) je raffolais des plaisirs excitants._____

41. Au jeu, j'aime parier de petites sommes._____

42. Si mes amis et moi avions des ennuis dont nous serions également responsables, je préférais assumer tout le blâme plutôt que de trahir mes amis._____

43. Je parle souvent à des étrangers quand je voyage en train, en autobus, etc._____

44. Le Christ a accompli des miracles, par exemple, celui de changer l'eau en vin._____

45. Je prie plusieurs fois par semaine._____

46. Je m'emballe facilement et complètement pour une bonne idée._____

47. J'ai souvent travaille pour des gens qui, semble-t-il, arrangent les choses de façon à accraparer tout le credit pour un bon travail mais qui sont capables d'imputer leurs erreurs à leurs subalternes._____

48. J'aimerais porter les vêtements dispendieux._____

49. La personne à qui j'étais le plus attaché, et qui j'admirais le plus, dans mon enfance, fut une femme. (Mère, soeur, tante ou autre femme.)_____

Appendix H
Consent Form for Subjects in Experiment 2
(Formule de Consentment pour les volontaires)

CONSENT FORM

I, _____, age _____, consent to take part in a research project entitled "Alcohol metabolizing enzymes and alcohol consumption" to be conducted at the Centre for Studies in Behavioral Neurobiology, Concordia University. The risks, purposes and procedures have been explained to me and I understand that my participation will involve the following:

1. The purpose of the study is to determine the role of alcohol metabolizing enzymes in the regulation of alcohol consumption.

2. I will be required to participate in a single testing session lasting no longer than one hour in duration. The time of testing will be made at a time convenient to both myself and the investigators.

3. During this session, I will complete various pencil and paper tests and be interviewed. In addition, a blood sample (2-3 drops) will be taken. The procedure for the blood sample will involve a small pin prick made to the tip of the finger. Little risk is associated with this method, although, I may experience some slight bruising and inflammation.

4. I will refrain from taking any drug or alcohol (with the exception of nicotine, caffeine or prescribed medication) for 24 hours prior to the testing.

5. I may expect no therapeutic benefit from my participation in this study.

6. Participation is completely voluntary and as such I may withdraw from the study at any time. Such withdrawal will not adversely influence my future participation in any experiments conducted at the Centre for Studies in Behavioral Neurobiology.

7. Any information learned about me in the course of the study or prior to it will be confidential and will be protected in the same way as hospital records. The results of the study will be available only to the investigators, who may use the results for scientific purposes, such as publication in a scientific journal or presentation at a scientific meeting as long as I am not identified as a participant in the study.

8. I understand that, upon request, any data collected about me will be made available to me and I will receive a full explanation of the findings of the study when they become available.

_____
Date

_____ _____
Subject's Signature Witness

FORMULE DE CONSENTMENT

Je, _____, agé de _____ ans, consens à participer à ce projet de recherche qui sera effectué au Centre d'Etudes en Biologie Comportementale à l'université Concordia. Les dangers, les buts et la procedure m'ont été expliqués clairement et j'admet que ma participation inclus les points suivants:

1. Le but de cette experience est de determiner la relation entre les enzymes qui métabolisent l'alcool et la consommation de boissons alcooliques.

2. Je vais participer à une séance expérimentale qui ne durera pas plus d'une heure.

3. Pendant la séance, je vais remplir quelques questionnaires. De plus, un échantillion de sang (2 à 3 gouttes) sera relevé en piquant le bout de mon doigt avec une écingle. Peu de risques sont associés à cette procedure mais il est possible que je ressente une légere contusion ou inflammation.

4. Je vais m'abstenir de prendre des drogues ou de l'alcool (à l'exeption de la nicotine, la caféine ou des medicaments) pendant les 24 heures qui precedent la séance experimentale.

5. Je n'attends à aucun avantage thérapeutique.

6. Ma participation est volontaire et je peux me désister de l'expérience en tout temps. Un tel desistement n'aura aucun effet sur ma participation à d'autres experiences qui auront lieu dans l'avenir au Centre d'Etudes en Biologie Comportmentale.

7. Tous les renseignements me concernant recueillis au cours de l'expérience resteront confidentiels. De plus, les résultats de cette etude ne seront disponsibles qu'aux chercheurs qui pourront les utiliser à des fins scientifiques, telles que la publication d'un article ou une presentation orale, à condition que je ne sois pa identifie comme un participant de cette étude.

8. Je considère que toutes les données recueillis qui me concerne me seront disponsible sur demande et je pourrai avoir une explication complete des resultats de l'etude lorsque le projet sera terminé.

_____
Date

_____ _____
Signature du sujet Témoin

Appendix I
Summary of Preliminary Analyses
Predicting Q-Value

Summary of Preliminary Hierarchical Regression predicting Alcohol Consumption (Q-Value) (N=189)

Variable	r	Beta	sr^2	F
Step 1				
Gender	.17	.150	.02	4.89**
Age	.29	.254	.06	13.88***
Education	-.25	-.222	.05	10.74***
Time of Blood Collection	.11	.081	.00	1.44
R^2 = .16 ***				
Adjusted R^2 = .14				
Step 2				
Allergies	-.19	-.121	.01	3.07
R^2 = .17 ***				
Adjusted R^2 = .15				
R^2 Change = .01				

*** p< 0.001 ** p< 0.01 * p< 0.05

Variable	r	Beta	sr^2	F
Step 3				
Current-Smoking	.30	.233	.03	7.62**
Years-Smoked	.35	.058	.00	0.37
R^2 = .24 ***				
Adjusted R^2 = .21				
R^2 Change = .07 ***				
Step 4				
Cannabis Use	.05	.036	.00	.22
Cocaine/Crack Use	.18	.159	.02	4.58**
Prescription Drug Use	-.05	-.070	.00	1.14
R^2 = .28 ***				
Adjusted R^2 = .23				
R^2 Change = .03				

*** p< 0.001 ** p< 0.01 * p< 0.05

Variable	r	Beta	sr^2	F
Step 5				
MAC	.48	.165	.01	4.10*
MAST	.57	.383	.09	28.95***
R^2 = .43 ***				
Adjusted R^2 = .39				
R^2 Change = .15 ***				
Step 6				
Catalase	.47	.383	.14	54.82***
R^2 = .56***				
Adjusted R^2 = .53				
R^2 Change = .14 ***				

*** p< 0.001 ** p< 0.01 * p< 0.05