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Ethanol-Induced Change in Cardiac and Endogenous Opiate Function and Risk for Alcoholism

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Susceptibility to alcoholism varies with age, gender, and familial background. Youthful nonalcoholic males with multigenerational family histories of male alcoholism seem at particular risk. Previous investigations suggest that such males are characterized by abnormal psychophysiological response, while sober and alcohol-intoxicated; additional recent studies indicate that the endogenous opiate systems are involved in mediating ethanol reinforcement and modulating intake. We first compared cardiac response to alcohol administration among young (mean = 22.8 years), nonalcoholic men and women with multigenerational, unigenerational, and negative family histories of alcohol dependence and abuse. Then, we compared the ethanol-induced cardiac response of the males in these three groups to that of currently alcohol-dependent older males and age-matched nonalcoholic male controls. Finally, we examined ethanol-induced change in plasma β-endorphin and cortisol levels among a subset of the nonalcoholic males, divided into those with high and low levels of postethanol administration heart-rate increase. Nonalcoholic males with multigenerational family histories of male alcoholism were characterized by significantly higher [$t(301) = 5.70, p < 0.0001$, Cohen's $d = 0.73$] levels of ethanol-induced heart-rate increase than nonalcoholics from all other comparison groups. The magnitude of their increase matched that of current male alcohol-dependents. Nonalcoholic males with high levels of ethanol-induced heart-rate increase also produced significantly more plasma β-endorphin after consuming alcohol. Peak production of β-endorphin was highly correlated ($r = 0.861, p < 0.001$) with magnitude of heart-rate increase. A subset of those at risk for alcoholism may be characterized by sensitivity to ethanol-induced reward, marked by heightened ethanol-induced, heart-rate increase, mediated by ethanol stimulation of endogenous opiate production. This subset might contain those who, once alcoholic, would differentially benefit from treatment with opiate antagonists.

Key Words: Alcoholism, Sons of Alcoholics, Alcohol Intoxication, Heart Rate, β-Endorphin.

ALCOHOLICS AND their nonalcoholic relatives constitute the two populations most frequently studied by those searching for a marker for the alcoholic predisposition. Research conducted on members of the former group targets the appropriate individuals, by definition, but late, and risks confusing cause with consequence. Research conducted on the latter, by contrast, casts an indiscriminate net, because a large proportion of the general population (perhaps 40%[1]) has a close alcoholic relative. Restriction of investigation to relatives of alcoholics characterized by the presence of additional risk factors could conceivably heighten the probability of success. Such restriction might first involve selection by gender and age. Males are diagnosed as alcohol-abusing or dependent two[1] to five[2] times more frequently than females, and seem at particular risk between the ages of 18 and 24.[3,4] Combination of pedigree, gender, and age places youthful nonalcoholic sons of alcoholics at risk approximated conservatively as 4-fold.[5,6] Sons of *male* alcoholics (SOMAs), furthermore, are not characterized by the confounding presence of fetal alcohol syndrome.

More careful specification of family history might further concentrate susceptibility, and improve the quality of the experimental subject pool. Absolute density of alcoholic familial pedigree helps determine risk for (previous-year) alcohol dependence, among current drinkers, independently of age, race, gender, and socioeconomic status.[1] Individuals with second- or third-degree alcoholic relatives are at 1.51 times increased risk, those with first-degree alcoholic relatives at 1.91 times risk, but those with alcoholic first- and second- or third-degree relatives at 2.79 times risk.[1] Risk for SOMAs with extensive, multigenerational familial histories (MFHs) of alcoholism is, therefore, some indeterminate multiple of four times increased risk for males, two to three times further increase for youth, and three times risk for extensive family history.

Preadolescent MFH SOMAs seem more behaviorally disinhibited, less able to abstract and plan, and more autonomically reactive than controls, free from familial alcoholism, matched for age, IQ, and socioeconomic status.[7] As young adults, they display a comparable pattern of cognitive deficit[8] and (sober) cardiovascular hyperreactivity—reactivity that can be dampened by a legally intoxicating dose of alcohol.[9–12] Study of SOMAs with lesser family histories of alcoholism has revealed, similarly, increased susceptibility to childhood conduct and hyperactivity disorders,[13,14] potential[15,16] presence of group performance deficits on tests of cognitive function,[17,18] and abnormalities in neuropsychophysiological response.[18,19] Additional investigations have demonstrated the tendency of such individuals to consume more alcohol and other psychoactive drugs, to begin such use at an earlier age, and to suffer from more related pathology.[20] Any or all of these character-

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istics might mark or underlie their increased tendency to develop alcoholism.

Our earlier reports tentatively suggested (positive,[9,11] negative[10]) that young adult MFH SOMAs may also manifest comparatively heightened resting baseline heart rate, while acutely alcohol-intoxicated. Pihl and Peterson[21] have hypothesized that a psychomotor stimulant-like response to alcohol may underly this heart-rate increase. Theoretically comparable forms of heart-rate increase have been associated with excitation of the dopaminergically mediated behavioral activation[22–24] or psychomotor exploratory system. Such excitation may constitute the biological basis for increased incentive reward, which, properly defined, means affective or motivational response to cues of satisfaction.[25] Many, if not all, drugs with abuse potential share psychomotor stimulant and associated rewarding properties.[26,27] Alcohol is certainly capable of directly stimulating the dopaminergic system,[28,29] but there are indirect methods whereby such activation might take place, as well.

An ever-broadening base of evidence suggests that opiate-mediated reinforcement mechanisms—that frequently, if not inevitably, involve psychomotor system stimulation[27]—play a key role in regulation of alcohol intake among animals and human beings. For example, low doses of morphine seem to "prime" drinking among rats; higher doses suppress consumption.[30] Of more direct relevance to the present investigation are reports suggesting that the C57BL/6 alcohol-preferring mice produce more (hypothalamic) β-endorphin after exposure to alcohol than DBA/2 alcohol-avoidant strains.[31,32] Provisional evidence exists suggesting that a similar pattern of response characterizes human social drinkers with MFHs of alcoholism[33]; recent extension of this study to examination of dose response among a new group of similarly selected subjects provided replication.[34] Current studies indicate, as well, that administration of the opiate antagonist naltrexone to alcoholic human drinkers significantly reduces consumption.[35,36]

The present investigation was therefore designed first to determine whether young nonalcoholic MFH SOMAs are in fact characterized by elevated postethanol administration resting baseline heart rate, in comparison with a variety of control groups (male and female) with and without extensive family histories of alcoholism (nonalcoholic and alcoholic), and second to determine what relationship, if any, exists between ethanol-induced production of β-endorphin/cortisol and exaggerated postethanol administration baseline heart-rate increase.

METHODS

Subjects: Youthful Nonalcoholic Males and Females

Data for nonalcoholic subjects were gathered from 307 nonabstinent males (n = 221) and females (n = 86) between the ages of 18 and 40. One hundred twelve of these subjects (92 males and 20 females) had an extensive multigenerational history of severe male alcoholism: *at minimum*, an alcohol-dependent biological father, alcohol-dependent paternal grandfather, and alcohol-abusing or dependent paternal uncle or brother. Forty-seven additional subjects (30 males and 17 females) had a history of unigenerational [unigenerational family history (UFH)] familial alcohol dependence, limited in the past two generations to the biological father. The remaining 148 subjects (99 males and 49 females) had no familial history (FH−) whatsoever of alcohol abuse or dependence among their siblings or other first- or second-degree relatives in the previous two generations of biological relatives.

Subjects were voluntary participants in a continuous high-risk project sponsored by the Douglas Hospital–McGill University Alcohol Research Project. Various aspects of this project have been described in previous communications, and data included herein were drawn from these studies,[9–12,37] and from unpublished investigations run more recently. The bulk of the data reported herein is new. The most recent previous report,[37] which described the cumulative project, to that date, included 85 (male) subjects: 36 with an extensive MFH of severe male alcoholism; 16 with a history of UFH alcohol dependence, limited in the past two generations to the biological father; and 33 with FH− of alcohol abuse or dependence among their siblings or among relatives in the previous two generations. The present sample contains an additional 136 males [for a total of 221 males (92 MFH, 30 UFH, and 99 FH−)] and 86 females (20 MFH, 30 UFH, and 49 FH−).

Subjects were recruited through newspaper and posted advertisements, screened initially by telephone, and interviewed personally for psychiatric status, by a qualified clinician, in accordance with the *Diagnostics and Statistical Manual of Mental Disorders* (DSM-III[38] or III-R[39]) standards. In the case of the MFH and UFH subjects, available family members were personally interviewed, in accordance with DSM criteria. Unavailable family members were diagnosed in accordance with Family History Research (FHR) Diagnostic Criteria.[40] In the case of FH− subjects, who were comparatively plentiful and easily obtained, family members were diagnosed solely through application of FHR diagnostic criteria.* All subjects scored 5 or less on the Brief Michigan Alcoholism Screening Test[42] and were neither dependent on nor abused alcohol according to DSM criteria. Subjects were excluded from participation if they had mothers who had been or who were presently characterized by one or more symptoms of alcohol abuse or dependence (according to DSM[37,38] or FHR-D[39] criteria), if they were undergoing treatment for any active physical or psychiatric medical condition, and if they were characterized by the presence of a schizophrenic disorder (active or in remission) or schizophrenic first- or second-degree relative.

Subjects: Alcoholic Males and Age-Matched Male Controls

The alcoholic group was composed of 12 (2 FH−, 3 UFH, and 7 MFH) comparatively older alcohol-dependent males (diagnosed by qualified physician, in accordance with DSM-III-R criteria) selected immediately before their participation in medical treatment for their alcohol dependence. These subjects were paired with 10 approximately age-matched male controls (5 FH−, 2 UFH, and 3 MFH). Alcohol-dependent subjects were administered ethanol as a consequence of their participation in a screening procedure designed to establish their suitability for participation in an experimental pharmacological treatment program for alcohol dependence, as part of a multisite research project. Alcohol-dependent potential subjects who, at entry, reported abstinence for >15 days, or who presented intermittent alcoholism, defined as <2 interruptions of alcohol abuse over the previous 3 years—each interruption of more than 2-months duration—were not included in the study. Subjects reporting concurrent drug addition or "secondary" alcoholism [associated with preexisting psychopathology, such as schizophrenia, major affective disorder,

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* *The sole use of FHR diagnostic criteria (and single informations) for selection of the FH− subjects may have heightened the number of "false-positives" (those who were considered FH−, but who actually had undetected alcoholic relatives) in this group, relative to the MFH and UFH groups.[41] We attempted to control for this potential lack of sensitivity by eliminating any FH− subjects who reported even mildly suspicious levels of alcohol use among their relevant relatives.*

antisocial or borderline personality disorder, major organic syndromes (e.g., Korsakoff's syndrome), liver failure, or severe physical consequences of alcohol abuse] were also excluded from participation. DSM-III-R criteria were used during the clinical assessment to rule out additional substance abuse and mental disorders. Use of sedative, anxiolytic, antidepressant, or other prescription drugs had to be discontinued for at least 2 weeks before the beginning of the study. Concomitant use of other medications was checked at every visit.

Procedure: Heart-Rate Analysis

All subjects refrained from alcohol consumption for 24 hr, and from food and beverage consumption for 4 hr before testing. Subjects were not allowed to smoke during the testing period. Because testing required ~6 hr (including recovery time), and because people seldom consume alcohol in the morning, subjects were generally assessed in the afternoon. All subjects were required to read and sign an informed consent form; were weighed; and were asked to complete a self-report questionnaire concerning age, education (years of formal schooling completed), average weekly frequency of alcohol consumption, and average quantity consumed per drinking occasion. All subjects were then seated in a reclining chair, in a quiet, darkened, comfortable room, attached to a polygraph, and asked to relax. Baseline measures of heart rate were taken during the following 6 to 10 min, by experimental personnel blind to group status. After completing 1 of 4 brief moderately stressful experimental tasks,[12,43,44] each subject was administered three beverages consisting of 95% pure USP ethanol mixed 5:1 with orange juice, and asked to consume them within 20 min. Twenty minutes later—to allow time for alcohol absorption—each subject was administered a breathalyzer test, asked once again to relax for 6 to 10 min, assessed for resting baseline heart-rate levels, and administered experimental tasks. Nonalcoholic subjects were tested under the influence of 1 of 3 different alcohol doses; 0.75, 1.00, and 1.32 ml of 95% USP alcohol/kg of body weight. These doses generally produce blood alcohol levels (BALs) between 0.08 and 0.11%,[12] and are large enough to produce substantive pharmacologically mediated cognitive and psychophysiological effects among young social drinking males and females.[12,43,44,45] Alcoholic subjects and age-matched controls were tested at 1.00 ml/kg. Subjects were paid $5.00 an hour for their participation.

Procedure: β-Endorphin and Cortisol Analysis

All subjects arrived at the research unit at 8:00 AM on the testing day, after abstaining from breakfast that morning and from ethanol for the previous 48 hr. A venous catheter was placed in each subject's nondominant arm; he was then allowed to rest. At 8:30, subjects were provided with a light breakfast, consisting of two slices of unbuttered toast. Fluid intake was limited to water. Smoking was forbidden for the duration of the experimental procedure. At 9:00 AM, a blood sample was drawn, and each subject was given either 0.75 or 1.00 ml 95% USP ethanol/kg body weight mixed with two parts of unsweetened orange juice. Beverages were consumed within 5 min. Additional blood samples were drawn at 15, 45, and 120 min.

Measurement of the plasma content of IR-β-endorphin was performed by radioimmunoassay using antiserum specific to the C-terminus of β-endorphin 1-31, at a final dilution of 1:30,000. The antiserum cross reacts at ~100% with bovine β-lipotropin and α-*N*-acetylated β-endorphin 1-31, and ~70% with bovine β-endorphin 1-27. This antiserum shows no cross-reactivity with ACTH, α-melanocyte-stimulating hormone, β-melanocyte-stimulating hormone, α-endorphin, or γ-endorphin.[46] Before the radioimmunoassay, the β-endorphin-like peptides were extracted from the plasma using C_{18} SepPak cartridges from Waters Scientific.[47] The intra- and interassay coefficients of variation were 3.5 and 12.4%, respectively. For estimation of plasma cortisol levels, plasma was extracted in absolute ethanol, and cortisol was determined by radioimmunoassay in accordance with the previously published procedure[48] using a cortisol antiserum (F3-314; Endocrine Sciences, Tarzan, CA) at a final dilution of 1:1,000. The intra- and interassay coefficients of variation were 9 and 11%, respectively. Contribution of these cross-reactions in normal human plasma determinations is small due to the ordinarily low concentrations of desoxycortisol and cortione relative to cortisol. Total cortisol (bound plus free) was determined by this method.

For characterization of the molecular weight forms of the plasma β-endorphin-like peptides, 10 ml of pooled plasma—collected at time 0 (before ethanol ingestion) and at time 45 (postethanol consumption) (interval characterized by maximum increase in plasma β-endorphin)—were extracted using C_{18} SepPak cartridges.[47] The extract was evaporated in a speed vacuum-concentrating centrifuge (Savant) connected to a freeze dryer (Labconco), redissolved in 50% acetic acid, and fractionated by gel filtration on a Sephadex G-75 column (50 × 0.5 cm). Successive 0.5-ml fractions were collected. Content of IR-β-endorphin in each fraction was determined after evaporation, using radioimmunoassay specific for β-endorphin.[48]

Ethics

Procedures for evaluation of cardiac response among youthful nonalcoholic subjects were reviewed and approved by the McGill University Department of Psychology Human Subjects Committee. Procedures for evaluation of cardiac response among alcohol-dependent males and age-matched controls, and for determination of plasma β-endorphin and cortisol levels, were approved by the Douglas Hospital Human Subjects Committee.

RESULTS

Comparison of Male and Female Nonalcoholics: Ethanol-Induced Heart-Rate Change

The analyses in this section included data drawn from all six groups of nonalcoholics: FH− (male, $n = 99$; female, $n = 49$), UFH (male, $n = 30$; female, $n = 17$), and MFH (male, $n = 92$; female, $n = 20$).

Demographic and Other Descriptive Variables. Five separate 3 (risk group) × 2 (sex groups) ANOVAs were conducted for age, education, ethanol dose received, BAL, and mean number of self-report alcohol drinks/week. Analysis of age revealed significant main effects for risk [$F(2,301) = 5.31, p < 0.0054$] and for sex [$F(1,301) = 6.68, p < 0.0097$], with male subjects older than their female counterparts. Post-hoc Fisher's least-squares difference test revealed that MFH subjects were significantly older ($p < 0.0002$) than FH− subjects. Analysis of education revealed significant main effects for sex [$F(1,301) = 10.39$, $p < 0.0013$], with female subjects more well-schooled than their male counterparts. Analysis of dose revealed main effects of sex [$F(1,301) = 11.86, p < 0.0006$], with male subjects receiving significantly more ethanol than females. Blood alcohol level was first corrected for dose differences, before analysis. This correction was completed by covarying ethanol dose received from BAL (independently for each group), and then by adding the individual group means to the resultant residuals. BAL and dose were correlated at 0.556 ($p < 0.330$). Corrected and raw BALs were correlated at 0.980 ($p < 0.0001$). Analysis of BAL (corrected for dose) revealed no significant main or interaction effects. Mean number of self-report alcohol drinks/week was positively skewed in its original form, and was therefore subjected to square root transformation before analysis, as recommended by Tabachnick and Fiddell.[49] Analysis of drinks/week (square root) revealed significant main effects of sex [$F(1,301) = 18.31$, $p < 0.00001$], with male subjects—

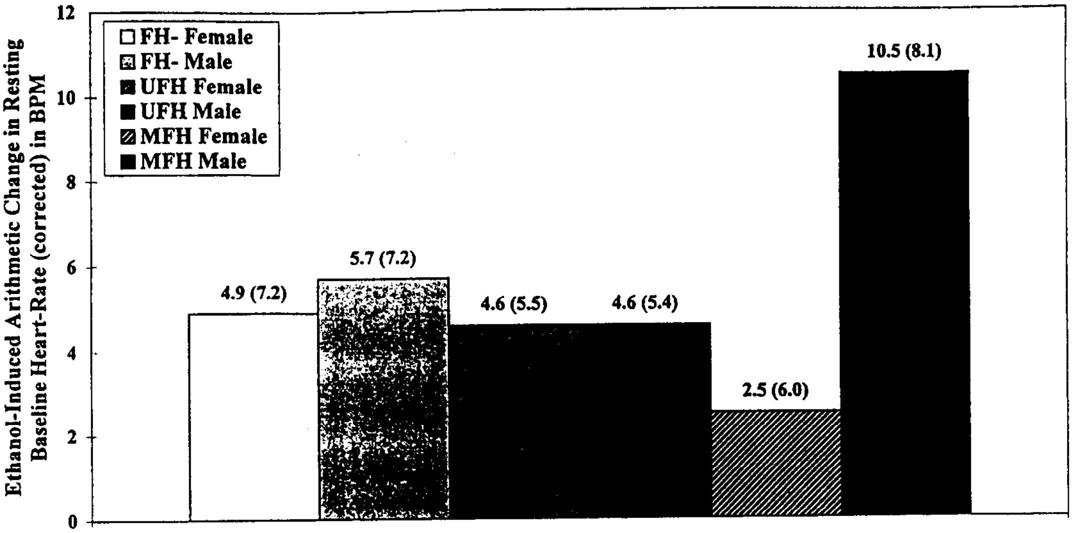

Fig. 1. Ethanol-induced arithmetic heart-rate change (corrected for demographic and alcohol administration variance) in BPM, among youthful nonalcoholics: FH−, UFH, and MFH males and females. Means and (SDs) are indicated.

unsurprisingly—consuming more alcohol than their female counterparts.

Ethanol-Induced Heart-Rate Change. Ethanol-induced baseline heart-rate change scores were derived from measures of sober and alcohol-intoxicated resting baseline heart rate. Sober resting baseline heart rate was defined as mean beats per minute (BPM), sampled once per second for the last 90 sec of the 6- to 10-min (sober) relaxation period. Alcohol-intoxicated resting baseline was defined as mean BPM, sampled once per second for the last 90 sec of the second 6- to 10-min (postethanol) relaxation period. Simple arithmetic change (raw) was calculated by subtracting sober from alcohol-intoxicated mean baseline heart-rate measures.*

Three (risk group) × 2 (sex group) analysis of covariance (ANCOVA) on arithmetic heart-rate change, corrected for between-subject variation in age [$F(1,296) = 0.64$, $p < 0.4250$], education [$F(1,296) = 1.41$, $p < 0.2351$], ethanol dose received [$F(1,296) = 1.44$, $p < 0.2295$]; BAL (corrected) [$F(1,296) = 12.66$, $p < 0.0004$] and mean number of self-report alcoholic drinks/week (square root) [$F(1,296) = 4.85$, $p < 0.0276$] revealed nonsignificant main effect of risk [$F(2,296) = 0.83$, $p < 0.4366$]; significant main effects for sex [$F(1,296) = 5.57$, $p < 0.0182$]; and a significant interaction between risk and sex [$F(2,296) = 5.13$, $p < 0.0065$]. Planned comparison testing (contrasts) revealed (1) significant differences between the MFH male group mean and that of the combined means of the other groups [two-tailed $t(301) = 5.70$, $p < 0.0000001$, effect size (Cohen's[50] d, expressed in standard deviation units = [(10.55 BPM − 5.00 BPM)/7.63] = 0.73 (0.2 is considered a "small" effect, 0.5 a "moderate" effect, and 0.8 a "large" effect)] and (2) no significant differences between the other means, considered singly (MFH women versus combined mean for FH− and UFH men and women) or in combination (FH− and UFH men, combined vs. FH− and UFH women, combined). It should also be noted that Cohen's[50] d = [(10.55 BPM − 5.71 BPM)/8.04] = 0.60 (larger than moderate size) for the more stringent comparison of MFH versus FH− men only. Statistics reported for arithmetic change (corrected) were also completed for raw and corrected percentage and residual change scores, with essentially identical results. All raw and corrected change scores, regardless of derivation technique, correlated at $r > 0.85$ ($p < 0.00001$). Figure 1 provides graphic representation of the corrected results; Table 1 presents relevant raw data (unweighted means and standard deviations).

It is possible, alternatively, that the MFH group obtained a significantly higher mean because *a greater proportion of individuals truly at risk* fell into that category, rather than *because all MFH individuals are at increased risk.* In light of this possibility, and after Tukey's[51] observation that "a body of data can—and usually should—be analyzed in more than one way" (p. 83), we reclassified the nonalcoholics into those above and below 11.48 BPM ethanol-induced arithmetic heart-rate change (corrected), which was the mean for the entire sample (7.58 BPM) plus one-half the standard deviation (SD = 8.82), and conducted a χ^2 analysis of this group category by risk [χ^2 ($df5$) = 39.4, $p < 0.00001$]. More than twice as many MFH males (2.11 times) as expected by chance alone were in the high mean arithmetic heart-rate change group. This was 43.5% of the total

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* *Note: Arithmetic change is a valid indice only in those cases where initial baseline measurements are equivalent. In the present case, three (risk group) × 2 (sex group) ANOVA for sober resting baseline heart rate revealed no significant main effect [risk* $F(2,301) = 0.13$, $p < 0.88$, *sex* $F(1,301) = 0.03$, $p < 0.85$*] or interaction effect [risk × sex* $F(2,301) = 1.15$, $p < 0.32$*]. Three × 2 ANCOVA (including age, education, and square root of drinks/week as covariates) revealed similar equivalence: no significant covariate effects (all F's < 1.9, all p's < 0.17), and no significant main or interaction effects (all F's < 1.5, all p's < 0.23).*

Table 1. Demographic and Other Relevant Descriptive Variables, Pre- and Postethanol Resting Baseline Heart Rates, and Raw Ethanol-Induced Arithmetic Heart-Rate Change for FH−, UFH, and MFH Male and Female Youthful Nonalcoholics: Unweighted Means and SDs

	Age		Education		Ethanol Dose/ kg body weight		BAL (corrected)		Alcoholic drinks/week (SqR)		Heart rate baseline pre-ethanol		Heart rate baseline postethanol		Arithmetic change raw	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
FH−																
Female	21.4	2.2	14.8	1.1	1.00	0.00	0.107	0.033	1.6	0.9	66.9	9.5	71.6	11.1	4.8	7.6
Male	22.3	3.1	14.7	1.9	1.04	0.16	0.109	0.026	2.2	1.0	69.1	10.5	75.1	11.5	6.0	7.9
Total	21.5	2.9	14.8	1.7	1.03	0.13	0.108	0.028	2.0	1.0	68.3	10.2	74.0	11.5	5.6	7.8
UFH																
Female	21.5	2.7	15.1	1.1	1.00	0.00	0.096	0.021	2.0	1.1	68.2	7.4	72.5	8.7	4.3	5.9
Male	24.0	4.3	13.6	2.2	1.13	0.16	0.105	0.026	2.4	1.1	69.3	10.6	73.3	9.1	4.0	7.6
Total	23.1	4.0	14.2	2.0	1.08	0.14	0.101	0.024	2.2	1.1	68.9	9.5	73.0	8.9	4.1	7.0
MFH																
Female	23.3	3.1	14.7	0.7	1.00	0.00	0.098	0.028	1.6	0.7	69.0	12.6	70.7	9.1	1.7	8.0
Male	23.6	3.9	13.6	2.4	1.02	0.14	0.109	0.029	2.5	1.3	66.6	10.1	77.3	13.0	10.7	9.2
Total	23.6	3.8	13.8	2.2	1.02	0.13	0.107	0.029	2.4	1.2	67.0	10.5	76.1	12.6	9.1	9.7
Female																
Total	21.9	2.6	14.8	1.0	1.00	0.00	0.103	0.030	1.7	0.9	67.6	9.9	71.6	10.1	4.0	7.4
Male																
Total	23.1	3.7	14.1	2.2	1.04	0.15	0.108	0.027	2.4	1.1	68.0	10.4	75.8	11.9	7.7	8.8
All	22.8	3.5	14.3	2.0	1.03	0.13	0.107	0.029	2.2	1.1	67.9	10.2	74.6	11.6	6.7	8.6

SqR, square root.

Table 2. χ^2 Results: Risk Groups (All Nonalcoholics) by Corrected Arithmetic Heart-Rate Change Groups

	FH− F (n = 49)	FH− M (n = 99)	UFH F (n = 17)	UFH M (n = 30)	MFH F (n = 20)	MFH M (n = 92)	All (n = 307)
Below mean							
Actual	44	86	15	27	18	52	242
Expected	39	78	13	24	16	73	242
χ^2	0.7	0.8	0.2	0.5	0.3	5.8	8.3
Above mean							
Actual	5	13	2	3	2	40	65
Expected	10	21	4	6	4	19	65
χ^2	2.8	3.0	0.7	1.8	1.2	21.6	31.1
All							
χ^2	3.5	3.8	0.9	2.2	1.5	27.4	39.4

F, females; M, males.

sample of MFH men (compared with 10.2% of FH− females, 13.1% of FH− males, 11.8% of UFH females, 10.0% of UFH males, and 10% of MFH females). Table 2 portrays the results: actual and expected distributions by group with χ^2.

Comparison of Male Nonalcoholics with Male Alcoholics and Male Age-Matched Controls: Ethanol-Induced Heart-Rate Change

The analyses in this section included data drawn from all five groups of males: 99 FH−, 30 UFH, and 92 MFH nonalcoholics, 12 alcohol-dependents, and 10 controls approximately age-matched with the alcohol-dependents.

Demographic and Other Descriptive Variables. ANOVA revealed that risk groups differed significantly in age [$F(4,238) = 58.94$, $p < 0.00001$], education [$F(4,238) = 6.75$, $p < 0.00001$], ethanol dose received [$F(4,238) = 3.29$, $p < 0.0121$], and square root of drinks/week [$F(4,238) = 82.43$, $p < 0.00001$]. ANCOVA revealed that risk groups differed significantly in BAL (corrected for dose) {dose covariate effect [$F(1,237) = 1.31$, $p < 0.2524$]; risk effect [$F(4,237) = 2.81$, $p < 0.0261$]}. Post-hoc Fisher's least-squares difference test revealed (1) that FH− subjects were significantly younger than all others, that UFH and MFH subjects were significantly younger than Alcohol-dependents and Older FH− Controls, and that Alcohol-dependents were significantly younger than Older FH− Controls ($p < 0.05$ for all comparisons); (2) that FH− subjects were more educated than all others, and that MFH subjects were more educated than Older FH− Controls ($p < 0.05$ for all comparisons); (3) that UFH subjects received more ethanol than all others ($p < 0.05$); (4) that FH− and MFH subjects had higher BALs (corrected for dose) than Alcohol-dependents and Older FH− Controls ($p < 0.05$); and (5) that FH−, UFH, and MFH subjects consumed more drinks/week (square root) than Older FH− Controls. All groups consumed fewer drinks/week (square root) than Alcohol-dependents (all comparisons, $p < 0.05$).

Ethanol-Induced Heart-Rate Change. Ethanol-induced baseline heart-rate arithmetic change scores were derived as described previously. There were no significant differences in initial baseline measurements [$F(4,238) = 1.11$,

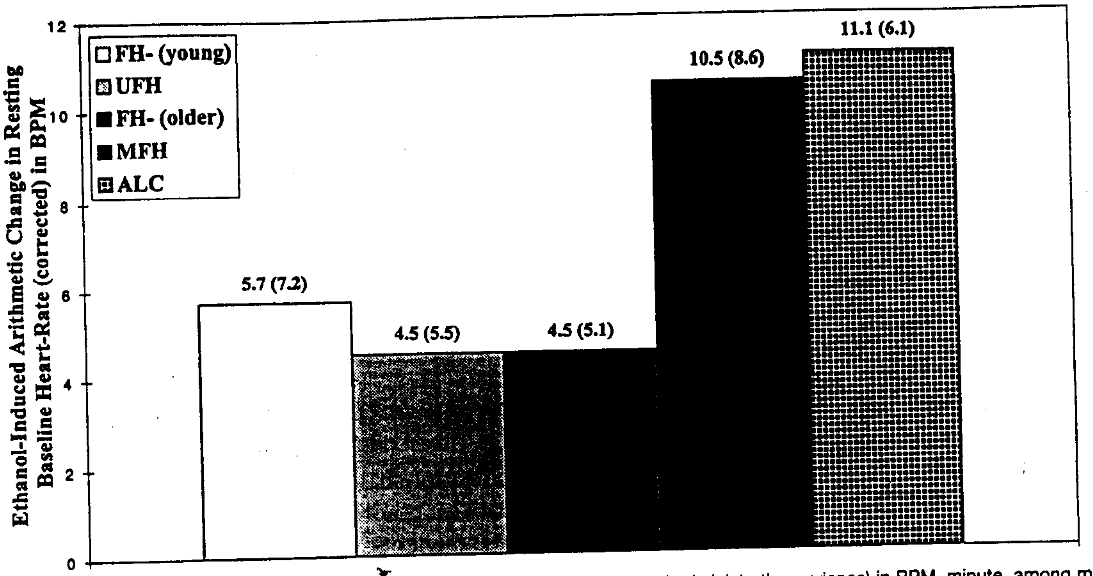

Fig. 2. Ethanol-induced arithmetic heart-rate change (corrected for demographic and alcohol administration variance) in BPM, minute, among males: FH−, UFH, and MFH youthful nonalcoholics, older alcohol-dependents, and controls approximately age-matched for the alcohol-dependents. Means and (SDs) are indicated.

Table 3. Demographic and Other Relevant Descriptive Variables, Pre- and Postethanol Resting Baseline Heart Rates, and Raw Ethanol-Induced Arithmetic Heart-Rate Change for Males Only: FH−, UFH, and MFH Youthful Nonalcoholics, Older Alcohol-Dependents, and Controls Approximately Age-Matched for the Alcohol-Dependents: Unweighted Means and SDs

	Age		Education		Ethanol dose/ kg body weight		BAL (corrected)		Alcoholic drinks/week (SqR)		Heart rate baseline Pre-ethanol		Heart rate baseline Postethanol		Arithmetic change raw	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
FH− (young)	22.3	3.1	14.7	1.9	1.04	0.16	0.109	0.026	2.2	1.0	69.1	10.5	75.1	11.5	6.0	7.9
UFH	24.0	4.3	13.6	2.2	1.13	0.16	0.105	0.026	2.4	1.1	69.3	10.6	73.3	9.1	4.0	7.6
FH− (older)	39.3	6.3	12.1	4.9	1.00	0.00	0.089	0.033	1.3	0.8	70.0	8.2	72.9	8.3	2.9	5.5
MFH	23.6	3.9	13.6	2.4	1.02	0.14	0.109	0.029	2.5	1.3	66.6	10.1	77.3	13.0	10.7	9.2
ALC	34.2	7.6	12.3	2.7	1.00	0.00	0.087	0.020	8.3	1.6	70.5	7.0	79.7	8.9	9.2	7.3
All	24.3	5.7	13.9	2.5	1.04	0.15	0.106	0.028	2.6	1.7	68.2	10.1	75.8	11.7	7.6	8.7

SqR, square root.

$p < 0.3516$]. ANCOVA with education, BAL, and ethanol dose received included as covariates revealed significant effects of the risk group [$F(4,235) = 6.18$, $p < 0.0001$], nonsignificant covariate effects of education [$F(1,235) = 0.23$, $p < 0.6345$], and dose [$F(1,235) = 2.45$, $p < 0.1175$] and significant covariate effects of BALs [$F(1,235) = 25.89$, $p < 0.00001$]. Age was not included as a covariate, because the analysis specifically contained a control group approximately age-matched with the Alcohol-dependents (in fact, significantly older). Drinks/week was not included because differences in drinking are inevitably associated with alcoholism and constitute a central feature of the criteria (alcoholism) of interest. Planned comparison testing revealed (1) that the MFH and Alcohol-dependent groups did not differ significantly in heart-rate response to alcohol [two-tailed $t(235) = 0.260$, $p < 0.7951$]; (2) that the mean heart-rate response of these two groups combined differed significantly from the mean of the FH−, UFH, and Older Control groups (combined) [two-tailed $t(235) = 3.734, p < 0.0002$]; (3) that the means of the FH−, UFH, and Older Control groups did not differ {first comparison, mean of FH− and UFH combined versus mean of older control [two-tailed $t(235) = 1.366, p < 0.7953$]; second comparison, means of FH− versus UFH [two-tailed $t(235) = 1.1974$, $p < 0.4675$]; and (4) finally, that the mean of the Alcohol-dependent group differed significantly from the mean of the FH−, UFH, and Older Control groups (combined) [two-tailed $t(235) = 2.4815, p < 0.0131$]. Statistics were also completed for raw and corrected percentage and residual change scores, with essentially identical results. Figure 2 provides graphic representation of the corrected results; Table 3 presents relevant raw data (unweighted means and standard deviations).

We also completed a χ^2 analysis of this dataset, on the presumption, as described previously, that heightened risk is characteristic of individuals, rather than groups. We reclassified the males into those above and below 11.524 BPM ethanol-induced arithmetic heart-rate change (corrected for education, BAL, and ethanol dose received), which was the mean for the entire male sample (7.59 BPM) plus one-half the standard deviation (SE = 7.88), and conducted a χ^2 analysis of this group category by risk [χ^2 (df 4) = 33.12, $p < 0.00001$]. Approximately twice as many MFH males (1.70 times) and alcohol-dependents (2.0

Table 4. χ^2 Results: Risk Groups (Male Only) by Corrected Arithmetic Heart-Rate Change Groups

	FH− (young) (n = 99)	UFH (n = 30)	FH− (older) (n = 10)	MFH (n = 92)	Alcoholics (n = 12)	All (n = 243)
Below mean						
Actual	83	27	10	53	6	182
Expected	74	22	7	69	9	182
χ^2	1.9	0.9	0.8	3.7	1.0	8.3
Above mean						
Actual	13	3	0	39	6	61
Expected	25	8	3	23	3	61
χ^2	5.7	2.7	2.5	11.0	3.0	24.8
All						
χ^2	7.5	3.6	3.4	14.6	4.0	33.1

times) were in the high mean arithmetic heart-rate change group. This was 42.4% of the total sample of MFH men and 50% of the alcohol-dependents (compared with 13.1% of young FH− males, 10.0% of UFH males, and 0.0% of the older FH− males). Table 4 portrays the results: actual and expected distributions by the group with χ^2.

Comparison of Male Nonalcoholics Categorized by Magnitude of Ethanol-Induced Heart-Rate Change: Ethanol-Induced β-Endorphin and Cortisol Production

Analyses in this section included data drawn from a subsample of 13 (3 FH− and 10 MFH) of the nonalcoholic young males described previously. These 13 subjects were divided into two groups, in accordance with the magnitude of their ethanol-induced arithmetic heart-rate change during the heart-rate assessment procedure (corrected as detailed for the entire nonalcoholic sample). The High Heart-Rate Change (n = 5) group contained those whose heart rate increased more than the subsample mean (10.83 BPM); the Low Heart-Rate Change (n = 8) group contained those whose heart rate increased less and, interestingly, included all three FH− subjects. Biochemical data were drawn from investigations and previously reported by Gianoulakis et al.[33,34]

Demographic and Other Descriptive Variables. The Heart-Rate Change groups did not differ significantly in age (mean = 22.7, SD = 3.2), education (mean = 14.5, SD = 1.71), ethanol dose received [during the heart rate (mean = 1.05, SD = 0.12) or β-endorphin/cortisol (mean = 0.87, SD = 0.13) procedures], blood alcohol level (corrected for dose) during the heart-rate assessment procedure (mean = 0.108, SD = 0.003) (BALs were unavailable for the β-endorphin/cortisol procedure), or mean number of self-report alcoholic drinks/week (square root) (mean = 2.4, SD = 0.13).

β-Endorphin Levels. β-Endorphin levels (millimoles per liter) were first corrected for variance in ethanol dose received during the β-cortisol assessment procedure. Corrected and raw β-endorphin levels correlated at between 0.82 and 0.99 at all time/ethanol periods (all p's < 0.0006). Two (group) × 4 (time/ethanol) repeated-measures ANOVA, with corrected β-endorphin levels as the dependent measure, revealed significant main effects of group [$F(1,51) = 38.51, p < 0.0001$] and time/ethanol [$F(3,51) = 8.21, p < 0.0003$] and significant interaction between group and time/ethanol [$F(3,51) = 6.91$, $p < 0.0010$]. Figure 3 provides graphic representations of the results and means/SDs. Cohen's[50] effect size d for change in β-endorphin at T15 = [(7.72 mmol − 3.47 mmol)/7.89] = 0.54; at T45 = [(40.6 − 5.8)/24.4] = 1.43; and at T120 = [(18.28 − 6.51)/16.53] = 0.71.

Three separate ANCOVAS, conducted upon corrected β-endorphin levels, with level at time 0 (pre-ethanol administration) included as a covariate, revealed significant effects of covariate [$F(1,10) = 10.64, p < 0.0085$] but not level [$F(1,10) = 0.63, p < 0.4471$] at time 15 (mean low group = 15.26, SD = 7.86; mean high group = 20.03, SD = 7.70), insignificant covariate [$F(1,10) = 1.37, p < 0.2694$] but significant level [$F(1,10) = 35.52, p < 0.0001$] effects at time 45 (mean low group = 10.34, SD = 7.78; mean high group = 64.43, SD = 12.15), and insignificant covariate [$F(1,10) = 0.10, p < 0.7531$] but significant level [$F(1,10) = 7.40$, $p < 0.0216$] effects at time 120 (mean low group = 12.86, SD = 8.82; mean high group = 39.28, SD = 15.0). Peak level (time = 45) of residual corrected ethanol-induced β-endorphin change correlated significantly with magnitude of corrected ethanol-induced arithmetic change in heart rate ($r = 0.861$, $p < 0.0002$). Data points were evenly spread along the regression line.

Reliability of these results was checked by recategorizing subjects by magnitude of β-endorphin change (instead of heart-rate change). Means were calculated by dividing the sum of residual-corrected change at time 15, 45, and 120 by three. The High β-endorphin Change group (n = 5) contained those subjects who fell above the subsample mean; the Low β-endorphin Change group (n = 8) contained those who fell below, including, as in the case of the previous categorization, all three FH− subjects. Group members did not differ in age, education, and ethanol dose received (heart-rate or β-endorphin assessment procedure). However, differences emerged for mean number of raw [$F(1,12) = 6.07, p < 0.0314$] and square-root [$F(1,12) = 6.20$, $p < 0.0300$] self-report alcoholic beverages per week: the High β-Change group consumed an average of 9.0, SD = 0.7; the Low β-Change group 4.4, SD = 2.6; and Cohen's effect size d = [(9 − 4.4)/3.9] = 1.18. Two (group)

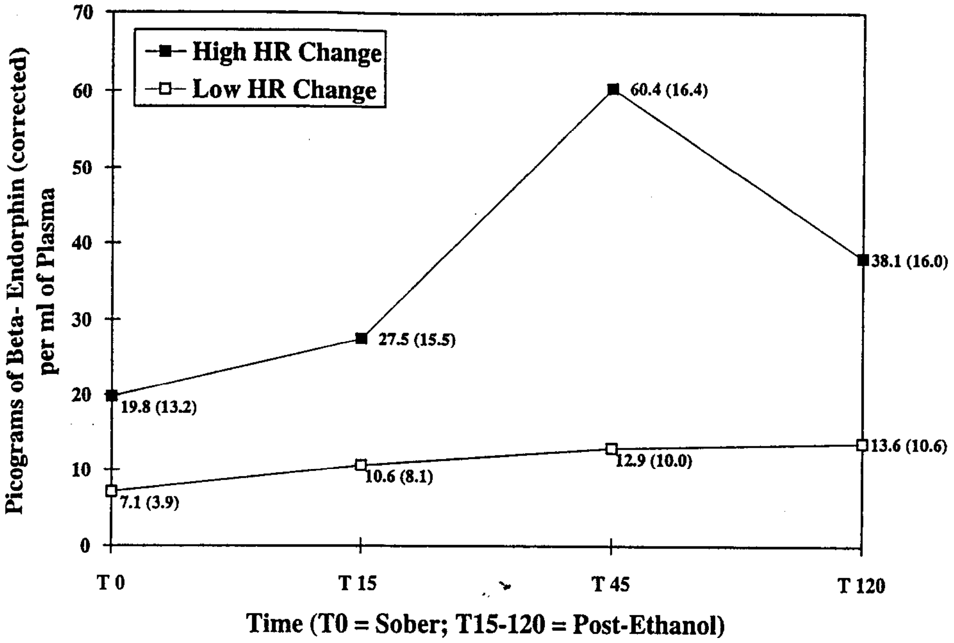

Fig. 3. Pre- and postethanol administration plasma β-endorphin levels (corrected), by ethanol-induced heart rate (HR) change group (high and low). Means and (SDs) are indicated.

$\times$ 2 (sober/intoxicated) repeated-measures ANOVA, with heart-rate (corrected after ethanol, as described previously as the dependent measure, revealed no significant main effect of group, significant main effect of ethanol [$F(1,25) = 48.43, p < 0.00001$], and significant interaction between group and ethanol [$F(1,25) = 6.95, p < 0.0231$]. The High β-Change group mean heart rate increased 16.44 BPM, from 61.56 (SD = 9.4) to 78.00 (SD = 13.5); the Low β-Change group increased 7.77 BPM, from 62.16 (SD = 9.1) to 69.93 (SD = 12.1). Cohen's[50] effect size d for average-corrected heart-rate change = [(6.58 BPM − 5.8 BPM)/24.4] = 1.43.

Cortisol Levels. Cortisol levels were first corrected for variance in ethanol dose received during the β-cortisol assessment procedure. Corrected and raw cortisol levels correlated at between 0.74 and 0.86 at all time/ethanol periods (all p's < 0.005). Two (High and Low Heart-Rate Change) $\times$ 4 (time/ethanol) repeated-measures analysis, with corrected cortisol level as the dependent measure, revealed no significant main effects of group [$F(1,51) = 0.22, p < 0.6501$], significant main effects of time/ethanol [$F(3,51) = 86.14, p < 0.00001$], and no significant interaction between group and time/ethanol [$F(3,51) = 0.33, p < 0.8006$]. Means for the High Heart-Rate group at time 0, 15, 45, and 120 min were 12.71 (SD = 5.86), 30.60 (SD = 5.84), 21.83 (SD = 3.93), and 7.52 (SD = 2.81), respectively; for the Low Heart-Rate group, 12.67 (SD = 6.53), 28.20 (SD = 5.51), 20.21 (SD = 3.72), and 7.59 (SD = 3.55). Levels of residual corrected ethanol-induced β-endorphin and cortisol change were uncorrelated at time 15, 45, and 120 min (all r's < 0.02855, all p's < 0.9262). No significant correlations emerged between ethanol-induced corrected arithmetic heart-rate change and corrected residual cortisol change at peak (time = 15), 45, or 120 min (all r's < 0.1690, all p's < 0.5796). Finally, no significant differences in heart-rate change whatsoever could be detected by comparing those above the group mean in postethanol cortisol production with those below.

DISCUSSION

The first set of analyses presented herein suggests that MFH SOMAs are in fact differentially susceptible to alcohol-induced resting baseline heart-rate increase—at least in comparison to MFH daughters, UFH sons and daughters, and FH− sons and daughters, selected to provide control for gender and familial environmental effects—and that the difference is moderate to large. Ethanol administration consistently[52] and reliably[53] produces resting heart-rate increase, among members of the general population, but the heart-rate response of MFH SOMAs seems exaggerated. Peterson et al.[37] demonstrated that the magnitude of this response, in combination with other indices of cardiovascular response to ethanol, accounts for a significant proportion of the variance in self-report ethanol consumption, among MFH, UFH, and FH− males. Conrod et al.[43] replicated this finding, using self-report and laboratory measures of ethanol consumption. This relationship is precisely what might be expected, if abnormally heightened postethanol consumption baseline heart-rate marks increased sensitivity to the incentive reward properties of alcohol. The possibility for individual differences in such sensitivity has been well-documented in the animal literature. Various rat strains bred for differential response to alcohol (including preference) are characterized by distinctive patterns of sober and alcohol-intoxicated dopaminergic function[28,29] and vary greatly in sensitivity to alcohol's psychomotor stimulant properties.[54] Furthermore, such sensitivity seems strongly influenced by genetic factors.[55]

The second set of analyses suggest that MFH SOMAs are characterized by heart-rate increase to ethanol of the same magnitude as long term alcohol-dependents (although this conclusion has to be tempered by the fact that many long-term alcohol-dependents, including those in the present sample, are MFH individuals) and that both groups differ from various controls. Other researchers have suggested that alcoholics are, in fact, characterized by comparatively heightened baseline heart-rate increase while acutely intoxicated,[56,57] and that such increases may be predictive of craving for alcohol[56,58] and preference for alcohol reward.[59] It seems possible, as Newlin and Thomson[53] proposed, that MFH SOMAs are typified by comparatively rapid *sensitization* to the putatively psychomotor stimulant or incentive reward effects of ethanol, during the ascending limb of the BAL curve. Some precedent for such a presupposition exists. Sensitivity to the psychomotor stimulant properties of ethanol seems heritable, at least among laboratory animals (at relatively low doses, during the ascending limb of the BAL curve).[60] Sensitization or development of reverse-tolerance to stimulants in general (and cross-sensitization between stimulants) is a common phenomena, particularly during the initial stages of use.[27] The MFH SOMA seems to need less practice than the alcoholic to reap the same benefit from alcohol, assuming that his enhanced heart-rate response is actually indicative of heightened sensitivity to incentive reward.

The third set of analyses are perhaps the most interesting, although they are derived from a small sample, and are therefore sensitive to error. Men who manifest high levels of heart-rate increase to ethanol also manifest high levels of plasma β-endorphin, while intoxicated, and those who have the highest levels of β-endorphin seem to drink more, by their own self-report. β-Endorphin is a very potent endogeneous opiate,[61] and the MFH SOMAs, characterized by accelerated ethanol-induced baseline heart-rate, are producing a large quantity of it in a brief period of time. Is it possible that such individuals are receiving a potent opiate-induced high from socially acceptable doses of ethanol? Plasma β-endorphin can cross the blood–brain barrier[62,63] in sufficient amounts to produce measurable analgesia, alteration in EEG activity, and change in learning.[63,64] Furthermore, ethanol itself alters permeability of that barrier.[65] Alternatively, central levels of β-endorphin—that might more directly affect central brain reward areas—may be as strongly affected by ethanol as the peripheral levels described in this report.

This study suggests, in toto, that MFH males are characterized by an easily assessable and idiosyncratic cardiac response to relatively high doses of ethanol, during the ascending limb of the BAL curve (at least after various stressful experimental challenges), and that a similar response characterizes severe alcoholics. Furthermore, it seems that this cardiac response has a (tentative) biochemical basis, plausibly linked to incentive reward and potentially linked to actual levels of ethanol consumption. The general findings described herein have immediate potential application to treatment design: perhaps prescreening of alcoholics, and analysis of their response to ethanol, might prove significant in the administration of treatment procedure (such as those using naltrexone, or other opiate antagonists). It is of interest to note in this regard, that 5 of 12 of the alcoholics in our group were characterized by essentially average or lesser magnitude of heart-rate increase postethanol consumption, whereas seven were clearly in the heightened range. Did the former five differ from the latter seven in their reasons for drinking? Our sample was not large enough to tell. The findings also have significance for development of prevention programs. Would it be possible, and reasonable, to screen those at familial risk for alcoholism for enhanced response to ethanol (or other rewarding substances) at an early age? Harden and Pihl[7] have recently demonstrated that abnormalities in cardiovascular response to motivationally relevant stimuli characterize nondrinking MFH SOMAs as early as 12 years of age. These subjects, of course, were not administered ethanol. Nonetheless, the general issue of early screening remains of substantial interest and relevance.

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