Alcohol and acetaldehyde metabolism in Caucasians, Chinese and Amerinds

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Ethanol (0.4 to 0.8 g/kg in 30 minutes) was given by mouth to 102 healthy young volunteers (37 Caucasian men, 21 Caucasian women, 20 Chinese men and 24 Ojibwa men). Venous blood concentrations of ethanol and acetaldehyde 60, 90, 120 and 150 minutes after the end of drinking were measured by gas chromatography. The calculated rates of ethanol metabolism in the Caucasian men and women did not differ, but the overall group means for subgroups of Caucasians (103.6 mg/kg·h), Chinese (136.6 mg/kg·h) and Ojibwa (182.7 mg/kg·h) with decreasing postabsorption values differed significantly from each other. Mean acetaldehyde values paralleled the rates of ethanol metabolism: Ojibwa, 14.6 μg/ml; Chinese, 10.0 μg/ml; and Caucasians, 9.4 μg/ml. The high rate of ethanol metabolism in Amerind subjects differs from previous findings. Habitual level of alcohol consumption, proportion of body fat and genetic factors appear to account for most of the group differences.

De l'éthanol (0.4 à 0.8 g/kg en 30 minutes) a été administré par voie orale à 102 jeunes volontaires sains (37 Caucasiens, 21 Caucasiennes, 20 Chinois et 24 hommes de la tribu Ojibwa). Les concentrations veineuses en éthanol et en acétaldéhyde ont été déterminées par chromatographie en phase gazeuse 60, 90, 120 et 150 minutes après la fin de l'ingestion de l'alcool. Chez les Caucasiens, hommes et femmes, les vitesses calculées du métabolisme de l'éthanol n'étaient pas différentes, mais les moyennes de groupes pour les Caucasiens (103.6 mg/kg·h), les Chinois (136.6 mg/kg·h) et les Ojibwas (182.7 mg/kg·h), avec des valeurs décroissantes après ingestion, étaient significativement différentes. La teneur en acétaldéhyde était proportionnelle à la vitesse du métabolisme de l'éthanol: 14.6 μg/ml chez les Ojibwas, 10.0 μg/ml chez les Chinois et 9.4 μg/ml chez les Caucasiens. Le fort taux de métabolisme de l'éthanol retrouvé chez les Amérindiens se distingue de ce qui a été observé antérieurement. La consommation habituelle d'alcool, le rapport des graisses corporelles et des facteurs génétiques semblent expliquer la plupart des différences entre les groupes.

In the last 5 years there have been several studies[1-3] comparing two or more racial groups with regard to relative rates of metabolism of ethanol and acetaldehyde. Other studies[2,4,5] have compared racial groups with respect to their physiologic responses to ethanol. Significant racial differences have been reported in both types of comparisons.

In 1971 Fenna and colleagues[1] reported a study of Canadian Inuit, Indians and Caucasians to whom ethanol had been given intravenously. They found that the three races were similar in the amount of ethanol required to achieve and maintain a blood concentration of approximately 125 mg/dl but the rate of metabolism, as calculated from the rate of disappearance of ethanol from the blood after the end of infusion, was greater in Caucasians. Lieber[6] has commented that these results seem contradictory. Fenna and colleagues[1] also reported that the average consumption of alcohol correlated significantly with the rate of alcohol metabolism in Indians but not in Caucasians. This lack of correlation in Caucasians is contrary to the observations of numerous other investigators.[6,7] In contrast, Bennion and Li[3] reported recently that American Indians from the area of Phoenix, Arizona metabolized ethanol at the same rate as Caucasian subjects (92 to 93 mg/kg·h). Ewing, Rouse and Pellizzari[2] compared Caucasians and Orientals in the United States for blood ethanol and acetaldehyde concentrations following oral intake. Though no data on ethanol disappearance rates were given, the groups were said not to differ significantly. However, within sexes Orientals tended to exceed (not significantly) Caucasians in mean highest acetaldehyde value, while males exceeded females significantly ($P < 0.02$) when data were pooled for the two races.

We present additional data on racial differences in ethanol and acetaldehyde metabolism. The findings, obtained in 58 Caucasians, 20 Chinese and 24 Ojibwa in Ontario, differ from those of both Fenna and colleagues[1] and Bennion and Li.[3]

Subjects

All individuals were healthy volunteers aged 18 to 33 years who denied using cannabis, barbiturates or tranquillizers routinely (for all, results of urine tests for these drugs were negative at the time of study). The Caucasians and Chinese were residents of Toronto and were primarily university students. The Indians were Ojibwa from the area of Kenora, Ont. The Caucasians included both men and women; the men were divided into subgroups of Jewish and non-Jewish subjects because of the known relative genetic

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Table I—Description of groups studied

Subject group	No.	Mean age* (yr)	Mean values ± SE			
			Height (cm)	Weight (kg)	Leanness†[8]	Habitual alcohol consumption‡
Caucasian						
Men						
Non-Jewish	29	23.5	177.8 ± 1.3	74.4 ± 1.7	42.43 ± 0.30	29.2 ± 4.4
Jewish	8	23.4	173.6 ± 1.3	68.0 ± 1.5	42.63 ± 0.46	12.0 ± 3.1
Women, non-Jewish	21	21.4	161.8 ± 1.5	59.1 ± 1.7	41.70 ± 0.41	12.4 ± 2.3§
Chinese men						
Dose (g/kg)						
0.4	4	22.8	170.8 ± 3.3	59.0 ± 7.1	44.21 ± 0.98	27.0 ± 13.3
0.6	16	22.6	167.4 ± 1.9	59.3 ± 2.4	43.16 ± 0.35	11.9 ± 3.5
Ojibwa men	24	24.3	176.8 ± 0.9§	76.4 ± 2.4	41.91 ± 0.41§	38 — 76¶

*Range of ages, 18 to 33 yr.
†Height/weight $^{0.333}$.
‡Units per month (1 U = 1 drink of spirits or 1 bottle of beer or 1 glass of wine); maximum within ethnic group: Caucasian, 80; Chinese, 58; Ojibwa, (?) 240.
§One observation missing.
¶Accurate data could not be obtained for all the Ojibwa. The mean is greater than that of the o ther groups but the exact value is uncertain. If only reliable data are included (n = 18) the mean is 38.1 U/mo. If questionable data are included the mean exceeds 76.

isolation of Jews, as demonstrated by the higher frequency of certain genetic diseases such as Tay-Sachs disease, and because of the traditionally low rate of alcoholism among Jews. The Chinese were all male and primarily of Cantonese ancestry. The Ojibwa were all male. Details on numbers, ages, body habitus (height, weight and leanness index) and habitual alcohol consumption are presented in Table I.

Methods

Subjects were tested in pairs beginning at either 8 am or 6 pm. Possible influence of diurnal variation in the rate of ethanol metabolism was offset by the testing of approximately equal proportions of each subject group at the two times. Subjects were asked to refrain from use of alcohol for 24 hours before the test, and from food for at least 4 hours. About 60% of the subjects in each group were fasting when they came for testing and were given a standard light meal (orange juice, toast and milk) at least 60 minutes before the test drink of alcohol. However, it was not possible to control closely the food intake of the subjects. The minimum interval between the last meal and the test drink was 60 minutes; the mean interval ranged from about 100 minutes for the Ojibwa to 224 minutes for the Caucasian Jewish men.

Following a physical examination subjects were asked to fill out a brief questionnaire on personal history, including details of their average use of alcohol. It was later found that the information on alcohol use was not uniformly reliable and a more detailed questionnaire was sent to all subjects after the study. Satisfactory answers were received from almost all subjects except the Ojibwa; repeated attempts to contact this group were unsuccessful.

All subjects were given a standard dose of ethanol in orange juice, to be consumed in 30 minutes. For all subjects except the Chinese the dose was 0.8 g of ethanol per kilogram of body weight. Because of the greater sensitivity of the Chinese (three subjects, whose data are not included in this report, vomited after a dose of 0.8 g/kg) the dose for them was reduced, 4 subjects receiving 0.4 g/kg and 16 receiving 0.6 g/kg.

Blood samples were taken from the antecubital vein 60, 90, 120 and 150 minutes after the end of drinking. These times were chosen because it was expected that the peak blood ethanol concentrations would be reached at or before 60 minutes, so that the four values would decrease on a curve.[9,10] The samples were deproteinized immediately for determination of ethanol and acetaldehyde concentrations on a gas chromatograph by the head-space technique of Duritz and Truitt.[11]

Significance of differences between group means for computed values of ethanol and acetaldehyde metabolism was determined by two-tailed *t*-tests and F-tests.

Results

The descriptive data in Table I indicate two important differences among the subject groups. First, the proportion of body fat, as reflected by the body-build index,[8] or leanness, varied significantly among the three major groups of men ($F = 4.19$; $df = 2.77$; $P < 0.05$). The Chinese were the leanest, their mean index being significantly different from those of the pooled Caucasian men and the Ojibwa ($P < 0.05$ and $P < 0.01$, respectively). Second, the two Caucasian male subgroups differed significantly ($P < 0.05$) in habitual alcohol consumption but the

Table II—Blood ethanol concentrations at various times after consumption of standard dose of ethanol*

Subject group	No.	Mean concentration (mg/dl) ± SE			
		60 min	90 min	120 min	150 min
Caucasian					
Men					
Non-Jewish	29	73.7 ± 3.5	71.9 ± 2.7	67.3 ± 2.7	62.3 ± 2.3
Jewish	8	60.1 ± 5.6	56.6 ± 4.2	56.2 ± 3.3	49.6 ± 2.5
Women, non-Jewish	21	69.3 ± 3.4	68.6 ± 3.2	66.4 ± 4.0	61.2 ± 3.6
Chinese men					
Dose (g/kg)					
0.4	4	16.5 ± 2.3	10.0 ± 1.7	5.5 ± 1.7	2.7 ± 0.9
0.6	16	37.0 ± 3.0	33.6 ± 3.7	27.2 ± 2.3	21.9 ± 2.5
Ojibwa men	24†	74.6 ± 5.0	62.0 ± 3.3	55.9 ± 2.7	50.9 ± 4.4

*The dose was 0.8 g/kg except for the Chinese subjects.
†Except for 90 min, where no. = 23.

Table III—Blood acetaldehyde concentrations at various times after consumption of standard dose of ethanol

Subject group	No.	Mean concentration (μg/ml) ± SE				
		60 min	90 min	120 min	150 min	Total period*
Caucasian						
Men						
Non-Jewish	29	9.77 ± 0.80	9.06 ± 0.65	9.35 ± 0.96	8.91 ± 0.80	9.27 ± 0.71
Jewish	8	10.43 ± 1.20	10.48 ± 1.45	8.95 ± 1.30	10.51 ± 1.40	10.09 ± 1.15
Women, non-Jewish	21	8.31 ± 0.64	8.16 ± 0.73	8.16 ± 0.59	8.43 ± 0.69	8.26 ± 0.58
Total group	58	9.33 ± 0.49	8.93 ± 0.47	8.86 ± 0.55	8.96 ± 0.51	9.02 ± 0.44
Chinese men						
Dose (g/kg)						
0.4	4	5.90 ± 0.53	6.25 ± 0.88	6.18 ± 1.50	4.50 ± 1.23	5.71 ± 0.89
0.6	16	10.49 ± 1.07	11.24 ± 1.12	9.83 ± 1.12	8.80 ± 0.86	10.09 ± 0.71
Ojibwa men	24	14.22 ± 0.67	14.45 ± 0.82	13.69 ± 0.57	13.43 ± 0.64	13.95 ± 0.47

*Mean values over the four times.

two Chinese subgroups did not. The Caucasian men drank significantly more (pooled data; $P < 0.05$) than both the Chinese men receiving the higher test dose of ethanol and the Caucasian women. The Ojibwa men drank more than all the other groups, but statistical comparisons were not carried out because of unreliability of some of the data.

A problem arose in interpreting the mean blood ethanol values after consumption of the test dose (Table II) because an appreciable proportion of each group, except for the four Chinese men receiving the lower dose of ethanol, showed an increase in concentration between 60 and 90 minutes instead of the expected decrease. Each group mean showed the expected decrease with time but this was distorted by the values in individuals who were still absorbing ethanol from the digestive tract. The two Chinese groups differed in mean values, as expected from their different doses.

The mean blood acetaldehyde values (Table III), in contrast, should be reliable since the acetaldehyde concentration is independent of the ethanol concentration when the latter is above approximately 25 mg/dl. Since there was no consistent trend with time, the mean value for the total period was useful in comparing the groups. The three Caucasian groups did not differ significantly among themselves, so data for the total Caucasian group were used for group comparisons. The Ojibwa mean value for the total period was higher than that of any other group, the difference from the means of the total Caucasian group ($P < 0.001$) and the Chinese men who received the higher dose ($P < 0.001$) being highly significant. The means for the total Caucasian group and the Chinese men who received the higher dose did not differ significantly.

To obtain a better basis for comparing rates of metabolism, we made further tabulations on data from selected subgroups of the individuals in Tables I, II and III using the following criterion for selection: the ethanol value at 150 minutes was equal to or less than that at 120 minutes, which in turn was equal to or less than that at 90 minutes, and these three values were not equal. Data for the three Caucasian subgroups did not differ significantly among themselves and were pooled. The mean ethanol and acetaldehyde values for the four groups are presented in Figs. 1 and 2, respectively.

In these selected subgroups the rate of decrease of the ethanol concentration was calculated for each individual as the slope of the concentration curve between 90 and 150 minutes after consumption of the test dose. The individual values were also converted to estimates of rate of ethanol metabolism (mg/kg·h) over the same period by calculation of the product β x r in the conventional Widmark equation.[9,10] Acetaldehyde values again showed no significant trend over time, so that the mean acetaldehyde value over the four times was calculated for each individual. The group means for rate of decrease of blood ethanol concentration, rate of ethanol metabolism and acetaldehyde concentration are shown in Table IV.

The mean slope of the blood ethanol

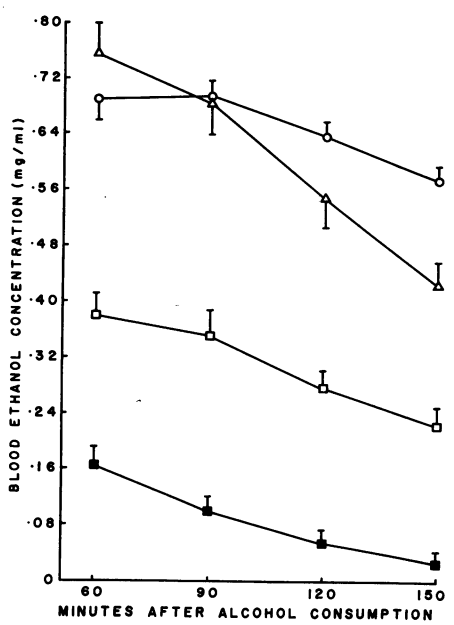

FIG. 1—Blood ethanol concentrations in four subgroups of subjects at four times after oral administration of a standard dose of ethanol. Subjects, all with decreasing blood ethanol values over the last three times, are represented by symbols as follows: triangles, Ojibwa (n = 12); circles, Caucasians (n = 37); white squares, Chinese receiving higher dose (n = 15); black squares, Chinese receiving lower dose (n = 4). Each symbol indicates group mean; vertical bar represents positive or negative half of standard error.

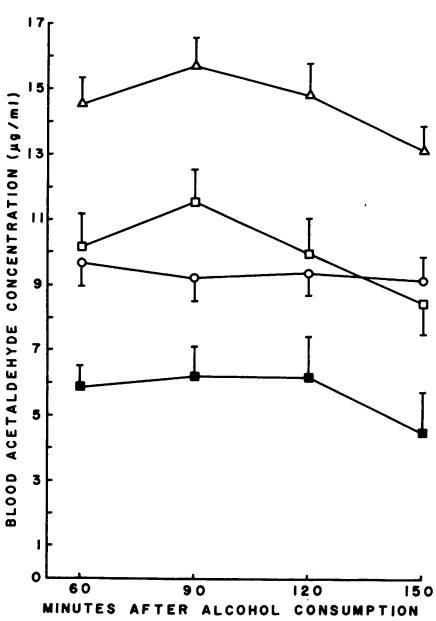

FIG. 2—Blood acetaldehyde concentrations in same four subject subgroups as in Fig. 1.

Table IV—Measures of ethanol and acetaldehyde metabolism in subgroups of subjects with descending postabsorptive blood ethanol curves

Subject group*	Mean values ± SE		
	Ethanol disappearance rate (mg/dl·h)	Ethanol metabolism rate (mg/kg·h)†	Mean acetaldehyde concentration (μg/ml)
Caucasians (pooled)	12.1 ± 1.0	103.6 ± 6.4 (9.8‡ — 172.1)	9.38 ± 0.63
Chinese			
Dose (g/kg)			
0.4	7.2 ± 0.9	—	5.71 ± 0.89
0.6	12.7 ± 1.8	136.6 ± 8.1 (77.6 — 175.9)	10.02 ± 0.75
Ojibwa	25.9 ± 3.6	182.7 ± 12.8 (114.9 — 250.5)	14.57 ± 0.58

*Numbers of subjects included, as fractions of totals in each original group, were 37/58, 4/4, 15/16 and 12/24, respectively.
†Extremes of range are in parenthesis below each group mean. Each of the three distributions is normal, as judged by tests of skewness and kurtosis.
‡Next lowest value in this group was 40.4.

curve was significantly greater ($P < 0.001$) for the Ojibwa group than for the Caucasians or for the Chinese subjects receiving the higher dose, but the slopes for the last two groups did not differ. Detailed comparison with the slopes for the Chinese subjects receiving the lower dose was not warranted because their curves were obviously nonlinear.

The computed rates of ethanol metabolism similarly indicated significantly higher values ($P < 0.001$ and < 0.005, respectively) for the Ojibwa than for the Caucasians and the Chinese group receiving the higher dose; the values for the last two also differed significantly from each other ($P < 0.01$). The mean acetaldehyde values again corresponded in order to the slopes of the ethanol disappearance curves, the Ojibwa value being significantly higher ($P < 0.001$) than those for the Caucasians and the Chinese receiving the higher dose; the slopes of the last two did not differ significantly. The Chinese group receiving the lower dose of ethanol had acetaldehyde values much below those of the other groups, as would be expected from the fact that their ethanol values were below that required for saturation of the alcohol dehydrogenase system. An incidental and as yet unexplained finding is that one subject, excluded because of vomiting, showed remarkably high acetaldehyde values, including a value of 72.1 μg/ml at 120 minutes.

Some distribution parameters of the ethanol metabolism rates within the three racial groups are given in Table IV. Each group showed considerable variation about its mean rate, but the amount of variation, as measured by standard deviations, was similar in the three groups. The range of rates within a group varied from twofold to fourfold (ignoring the one very low Caucasian rate).

Discussion

Fenna and colleagues[1] claimed that Canadian Indians metabolize ethanol more slowly than Caucasians, while Bennion and Li[3] reported no difference. Ewing and associates[2] found no significant differences between Chinese and Caucasians in metabolic rate for ethanol or in mean highest blood acetaldehyde value. The studies by Ewing and associates and by Bennion and Li are more comparable to ours since the ethanol was given orally, while Fenna and colleagues administered it intravenously. The doses used in the various studies differed considerably, ranging from 0.3 or 0.4 ml/kg[2] to about 1.5 ml/kg (1.2 g/kg).[3] The use of a very low dose by Ewing and associates probably resulted in submaximal rates of ethanol metabolism, so that interpretation of their acetaldehyde values is difficult.

Because of the delayed absorption of ethanol from the digestive tract in some of our subjects it was necessary to restrict critical analysis to the data of those with a declining (postabsorptive) ethanol curve. Some caution is required in drawing inferences from our data but the comparisons among these subgroups suggest some differences with respect to the rate of ethanol metabolism. The value of 103.6 ± 6.4 mg/kg·h for the Caucasians is in excellent agreement with values in the literature.[9,10] The apparently higher value for the main Chinese group (136.6 ± 8.1 mg/kg·h) is a new finding, so that no comparison with previously published figures is possible.

Part of the difference betwen Caucasian and Chinese subjects is probably attributable to the relative leanness of the latter. Ethanol distribution is confined essentially to body water; additional fat increases the total body weight and decreases the fraction of it that is relevant to ethanol metabolism. The Widmark calculation does not correct for this. Of two individuals with identical lean body mass and identical absolute rates of ethanol metabolism, the one with less fat will have a higher calculated rate in mg/kg·h. However, this factor seems unlikely to account for the whole difference. Separate calculations for the Caucasian non-Jewish men and women indicated ethanol metabolism rates of 110.2 ± 9.4 and 98.2 ± 11.0 mg/kg·h, respectively — a difference of about 10% This is in good agreement with an 11% difference in percent body water measured in comparable male and female subjects.[12] On this basis the Caucasian men in our study would have had to be about 30% more obese than the Chinese to account for the difference in ethanol metabolism — and they were not.

It is not obvious why our results for Indians differ from those of Fenna and colleagues.[1] The mean ethanol metabolism rate for their Caucasian subjects (144.9 mg/kg·h) was unusually high. Possible reasons for the different results are differences in usual consumption of ethanol, route of administration of ethanol, mean age (39 and 35 years for their Indian and Caucasian subjects, respectively), type of Indian population, initial blood value of ethanol (about 125 mg/dl in their study; 70 to 74 mg/dl in ours) and duration of peak value (maintained for 60 minutes in their study; not maintained in ours). It is not obvious that the usual consumption of ethanol differed greatly between the two Indian groups but it is probable that they were of different ethnic and linguistic stocks. In addition, their subjects were mainly hospital inpatients, while ours were in good health. The other differences do not seem likely to have had major effects.

The study by Bennion and Li[3] is more comparable to ours since all subjects were healthy young volunteers, the ethanol was given by mouth and blood ethanol values were measured by gas chromatography. Neither the tribal affiliation nor the linguistic group of their Indian subjects was mentioned and data on body habitus were not provided. However, their Indian subjects were appreciably heavier than their Caucasian subjects (82.2 ± 4.9 v. 70.0 ± 2.2 kg, respectively). The Pima Indians in Arizona are among the most obese of all populations studied.[13] If Bennion and Li's subjects were drawn from this or a similar population, a rate of ethanol metabolism (in mg/kg·h) apparently equal to that of the Cauca-

sian subjects would actually correspond to a higher rate per kilogram of lean body mass. The Widmark calculation, contrary to the statement by Bennion and Li, does not correct for difference in body habitus.

The acetaldehyde results of the present study can be compared only with those of Ewing and associates[2] for Chinese and Caucasians. Our mean acetaldehyde values are comparable to the maximum values reported by Ewing and associates but considerably higher than those reported by a number of other investigators.[14-16] No explanation is readily available. Under certain conditions acetaldehyde can be released in vitro from human blood containing ethanol.[17] We did not use thiourea as an inhibitor of nonenzymatic oxidation,[15,18] but such oxidation would have been insignificant since the samples were deproteinized promptly. Moreover, group comparisons in our study seem valid because the same technique was used throughout. As indicated above, critical comparison of our results with those of Ewing and associates is not possible because of differing ethanol doses. The fact that the only persons who vomited during the present study were Chinese (one of whom had an extremely high acetaldehyde value), even though more Caucasians were tested (58 v. 23), could be consistent with either higher acetaldehyde values or greater sensitivity to acetaldehyde in some Chinese subjects.

The most striking finding in the acetaldehyde data was the approximately 50% higher mean value in Ojibwa compared with Caucasian and Chinese subjects. The Ojibwa had a higher reported regular consumption of alcohol than the other subjects and this is consistent with the steeper slope of ethanol disappearance from the blood.[6] A higher rate of ethanol metabolism would be expected to yield a higher steady-state concentration of acetaldehyde since acetaldehyde oxidation follows first-order kinetics. This combination of faster ethanol disappearance and elevated acetaldehyde plateau differs from the findings of Korsten and colleagues[15] in alcoholic patients, in whom acetaldehyde oxidation may have been impaired presumably because of a biochemical lesion of liver mitochondria.[15,19]

It seems unlikely that a difference in habitual consumption of alcohol can account for all of the difference in rate of ethanol metabolism in our Ojibwa and Caucasian subjects. Bennion and Li[3] also observed a positive correlation between alcohol intake and rate of metabolism. Among their Indian subjects, heavy drinkers (of over 360 ml of alcohol per week, corresponding to over 80 U/mo in our scale) metabolized ethanol 19 ± 7% more rapidly than light drinkers (of less than 180 ml/wk). In our study the Ojibwa subjects metabolized ethanol 76 ± 16% more rapidly than the Caucasians. If we assume that about 20% is accounted for by greater alcohol intake, and that any correction for difference in leanness would tend to increase the disparity in rate of metabolism, there remains a substantial difference in rate to be accounted for by other factors. We suggest that genetic differences between Caucasians and both Chinese and Indian subjects may be among these factors.

There are both theoretical grounds and empirical evidence for genetic diversity among widely separated groups of North American Indians. Population genetics theory predicts random genetic drift (change in gene frequency) in small isolated populations. Several striking examples of probable genetic drift have been found in an Ojibwa population living about 240 km north of the region from which our Ojibwa subjects were drawn.[20] Linguistic evidence suggests that the Indian subjects in the studies by Fenna and colleagues,[1] Bennion and Li[3] and ourselves represent three long-separated populations. The Ojibwa language is a class of the Macro-Algonquian ("Algonkin-Wakashan") language phylum.[21] The Arizona Indians' linguistic phyla are Na-Dene, Aztec-Tanoan and Hokan-Siouan;[21] the complete absence of language overlap with the Ojibwa implies a separation of 1000 to 10 000 years' duration between the two groups. The Albertan Indian language phyla are Na-Dene, Macro-Algonquian and Hokan-Siouan,[21] so that there is some overlap with both other groups, implying more recent contact. Nevertheless, the major linguistic differences among the three groups imply the potential for considerable genetic diversity. Therefore one should not expect identity for any specific metabolic process among different Amerind groups. It would be helpful if future studies of native peoples included tribal or linguistic details.

Despite the problems discussed above, the major findings of the present study indicate (a) that Chinese subjects metabolize ethanol more rapidly than Caucasians, (b) that our Ojibwa subjects metabolize ethanol more rapidly than both other groups but the interpretation may be complicated by their greater habitual consumption of alcohol, and (c) that, because of the considerable range of rates within each group and the overlap between groups, the mean rate for any group does not accurately predict the rate for any given individual within it.

The reportedly greater sensitivity to ethanol in Oriental and Amerind subjects[2,4,5] is not explainable on the basis of slower ethanol metabolism than in Caucasians and is therefore presumably related to inherent differences in sensitivity. The relevance of these factors to alcoholism remains to be established.

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