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Aversive Reactions and Alcohol Use in Europeans

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Two hundred subjects of European descent completed a questionnaire about alcohol use and reactions to alcohol. Eleven subjects (5.5%) reported that they always experienced unpleasant reactions after small amounts of alcohol, and these subjects reported significantly lower levels for quantity and frequency of habitual alcohol use, and fewer drinks in the preceding 7 days, than the other subjects. Reactions to alcohol, either genetic or acquired, can therefore be significant in determining alcohol use in non-Asian groups.

Key Words: Alcohol Intake, Alcohol Reactions.

THE ALCOHOL FLUSH reaction experienced by many Japanese, Chinese, and other Asian people[1–4] has been shown to be due to a deficiency of the mitochondrial isoenzyme of aldehyde dehydrogenase (ALDH; EC 1.2.1.3),[5–7] which leads to increased levels of circulating acetaldehyde after alcohol is taken.[8,9] The unpleasant nature of the reaction leads many of those affected to abstain from alcohol, and the incidence of alcohol dependence is much lower in ALDH2 deficient subjects than in other Japanese.[10,11]

Similar reactions, due to ALDH deficiency[12] but with a different molecular basis,[13] have been described in American Indians, and a few subjects of European origin have been described who have a deficiency of the cytoplasmic ALDH1.[14]

The prevalence of reactions to alcohol, their effects on alcohol consumption, and their mechanisms, have not been fully explored in Europeans; it has generally been assumed that they are rare and of little importance. However, factors that limit alcohol consumption are important for the individuals affected; and increased knowledge of their prevalence and effects should lead to a greater understanding of population consumption patterns and of variation in alcohol metabolism. Detailed biochemical studies on affected individuals can then investigate mechanisms such as allergies, defects in aldehyde dehydrogenase genes, or other genetic or environmental causes.

We have investigated the frequency of reactions to small amounts of alcohol in a group of European subjects and tested for effects of self-reported reactions on alcohol use.

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SUBJECTS AND METHODS

The subjects were 87 men and 113 women, aged between 28 and 45 years. They were drawn from a group of twin subjects who had taken part, some 10 years previously, in an experimental study of genetic and environmental effects on alcohol metabolism and intoxication.[15] That study had included ingestion of 0.75 g/kg of ethanol and measurement of performance of a number of tasks over the subsequent 4 hr; all the subjects of this current study had then been able to tolerate that dose of alcohol, equivalent to about five standard drinks. The genetic background of the subjects was mainly north European, with a minority descended from migrants from southern Europe; as far as we know, none were of Asian descent. Approval for the current study was given by the Ethics Review Committee of the Central Sydney Area Health Service and subjects gave informed consent.

Subjects answered a questionnaire that included questions about alcohol use and reactions to alcohol; the question about reactions to alcohol was:

> "Do you experience unpleasant reactions, such as flushing of the face or body, itching, drowsiness, or palpitations after drinking a small amount of alcohol (say, one or two drinks)?"
> and the available answers were "Always," "Sometimes," and "Never."

Information about alcohol use was gathered from the subjects' responses to a number of questions; they were asked to place themselves in one of nine categories for the number of drinks in a typical week, and in one of seven categories for frequency of drinking; they were asked for an estimate of the number of drinks they would take in a drinking day during the week and in a drinking day at the week-end; and they filled in a chart showing the number of drinks they had in each of the last 7 days, allowing calculation of the number of drinks in the past week.

Initial analysis showed that the responses "Sometimes" and "Never" were similar in their effects on alcohol use, so the subjects were divided into two categories for further statistical analysis; those who replied "Always" to the alcohol reaction question and those who replied "Sometimes" or "Never." Comparisons between groups were made by the Kruskal-Wallis and Mann-Whitney tests.

RESULTS

Out of 200 subjects, 11 answered that they always experience unpleasant reactions after alcohol and 57 that they sometimes do so. The proportions in these two categories are therefore 5.5 (SE 1.6)% and 28.5 (SE 3.2)%, respectively. A higher proportion of the women than of the men replied that they 'always' reacted to alcohol (7.1% in the women and 3.4% of the men) but this difference was not significant ($p = 0.355$, Fisher's test).

The effects of unpleasant reactions to small amounts of alcohol on alcohol use as estimated in various ways by the subjects are shown in Table 1. When the responses to the question about reactions to alcohol are used to divide the subjects into three groups (those who 'always,' 'sometimes,' and 'never' have such reactions) there was a significant ($p < 0.05$) difference among the three groups for

Table 1. Effect of Unpleasant Reactions to Alcohol on the Frequency and Quantity of Alcohol Consumption, Estimated from Questionnaire Responses

	Alcohol reaction mean rank				
	Always	Sometimes	Never	p (3-way)	p (2-way)
Estimated number of drinks in a typical week	58.4	95.5	106.2	0.018	0.010
Estimated frequency of drinking	54.0	94.2	106.4	0.007	0.005
Estimated number of drinks on a drinking weekday	48.9	88.2	105.8	0.001	0.002
Estimated number of drinks on a drinking weekend day	44.7	89.2	103.3	0.002	0.001
Number of drinks in the previous 7 days	51.1	92.1	106.8	0.004	0.004

The mean rank allows comparison between subjects with all three possible responses to the alcohol reaction question (lowest rank = smallest amount of alcohol used). The p values are given first for a comparison between all groups (Always/Sometimes/Never) and second for a comparison between subjects who 'Always' react and the other two groups combined.

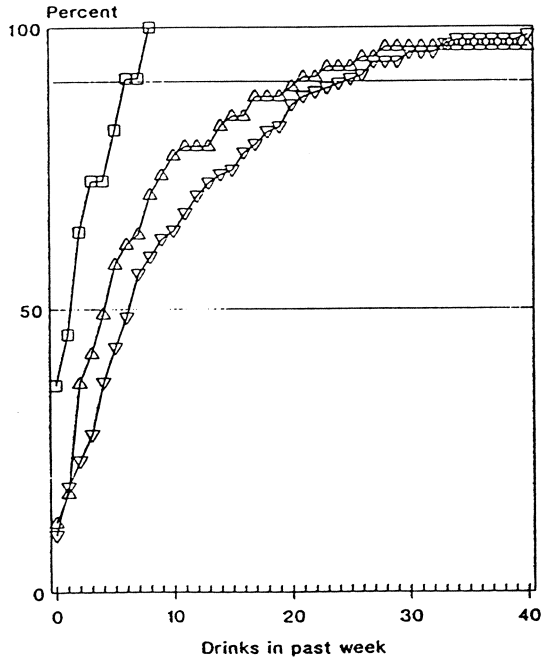

Fig. 1. Comparison of cumulative frequency distributions for number of drinks taken in the past 7 days, by category of response to the question about reactions to alcohol (see text). x-axis: number of drinks in past week, as reported by the subjects; y-axis: cumulative frequency (percentage of subjects in each group reporting this number of drinks or fewer). □——□, subjects replying 'Always'; Δ——Δ, subjects replying 'Sometimes'; ▽——▽, subjects replying 'Never.'

each of the five measures of alcohol consumption. The results for the 'sometimes' and 'never' groups were very similar, as can be seen from the mean ranks in Table 1 and the cumulative frequencies for number of drinks in the previous week shown in Fig. 1. If the subjects are divided into only two groups, those who 'always' react in one and those who 'sometimes' or 'never' react in the other, then these two categories also differ significantly ($p < 0.05$) for all five measures of alcohol intake (Table 1, final column). There were no significant differences for any of the alcohol intake variables between the 'sometimes' and 'never' reacting groups.

Although all the subjects were twins we have not been able to follow up both members of a pair in every case, and there are not enough subjects reporting reactions to formally analyze the results by zygosity. However, it is of interest to note that two of the 11 subjects who 'always' have unpleasant reactions to alcohol were members of monozygotic twin pairs where the co-twin had also participated but had not reported unpleasant reactions.

Seven of the 11 reacting subjects indicated in response to the question "Was there ever a time when you drank too much?" that they had in the past used amounts of alcohol that they now regarded as excessive. Five of these seven also gave positive replies to other questions about alcohol problems, including feeling guilty about their drinking (four subjects), someone else objecting to their drinking (two subjects), and neglecting their usual responsibilities because of drinking (two subjects).

DISCUSSION

Reactions to alcohol which those experiencing them regard as unpleasant are believed to be a significant factor in determining drinking behavior in a number of Asian countries. A number of papers have recorded the prevalence of flushing after consumption of alcohol in Europeans, usually in order to contrast it with the higher prevalence in Asian groups.[1–4] Figures quoted range from 3% to 29% (reviewed in 6). Although the existence of adverse reactions to alcohol in Europeans has been documented, their effects on alcohol use appear not to have been sufficiently studied.

We have now found that such aversive reactions affect alcohol use in a significant number of Europeans. About 6% of subjects reported that they always had such reactions, and a further 30% said they sometimes did. The subjects who always suffered such reactions reported low alcohol consumption; this is the outcome which would logically be expected.

However, the one previous report which did examine the relationship between reactions to alcohol and drinking behavior in Europeans (16) came to the paradoxical conclusion that the flushing response was associated with fewer alcohol problems in Asians, but more problems in Europeans. This effect was most apparent in the subjects' accounts of their parents' flushing and alcohol-related problems, but there were also indications that respondents who flushed became intoxicated more frequently than those who did not.

The reported prevalence of reactions to alcohol will depend on the method employed (alcohol challenge with objective measurement of signs, or self-report based on a questionnaire) and on the wording of questions about reactions. Although the difficulties of relying on self-report of alcohol consumption are well-known, inaccurate information will generally lead to the conclusion that no significant association between consumption and a marker or a cause of variation exists rather than generating a spurious association. When dealing with reactions to al-

cohol, there is a strong case for using self-report data because it is the perceptions of the individual that will determine whether behavior is modified by the reactions.

Our question about reactions to alcohol was designed to be general, so as to assess all possible forms of aversive reaction, but reactions perceived as unpleasant, and to a small amount of alcohol (one or two drinks), were specified. The response rate to the option 'sometimes' was unexpectedly high at almost 30%, but it appears that such occasional reactions have little effect on consumption. The group who always have unpleasant reactions, although smaller (6%), are sufficiently affected to use lower amounts of alcohol than is usual. With the number of subjects studied so far, the main division seems to be between the group who always react badly to alcohol and the rest; but further study might show an effect of even occasional reactions on some aspects of drinking behavior.

The alcohol flush reaction in Asians has been shown to be due to ALDH deficiency, inherited as a dominant characteristic.[17] We cannot assume that flushing or other unpleasant reactions in Europeans are due to the same cause, although some subjects with abnormal ALDHs have been described.[14] In fact, some of our subjects' reactions must be nongenetic in origin because we observed two pairs of monozygotic twins discordant for reactions to alcohol. In addition, each of the subjects who reported unpleasant reactions occurred whenever they drank had previously been willing and able to complete an experimental protocol[15] that involved drinking 0.75 g/kg of ethanol; and seven out of 11 reported that they had at some time drunk too much. Although some may have interpreted this question as referring to even a single episode of acute intoxication, they had all been willing to drink in the past. In addition, five of the 11 replied positively to other questions about (relatively minor) alcohol problems.

Because some alcohol reactions must be acquired rather than congenital, mechanisms other than ALDH deficiencies should be considered. In this connection, the report of Edfors-Lubs[18] is particularly interesting. She surveyed a large number of Swedish subjects, asking mainly about allergic conditions such as asthma, hay fever, and dermatitis but also enquiring about 'alcohol allergy.' An alcohol allergy was considered to be present if the subject reported 'reaction such as swelling or itching in the throat or eyes, severe headache, urticaria, nausea with vomiting or unconsciousness,' and was reported by 4.5% of all subjects, 6.1% of men and 3.4% of women. Reactions to alcohol were significantly more common in people who reported asthma, hay fever, eczema, or contact dermatitis. The prevalence of alcohol allergy also decreased significantly with either increasing age or earlier date of birth; the study was conducted at a single time and so it could not distinguish between an effect of age and a secular trend.

Since we did not test the subjects with alcohol on this occasion, we have not been able to observe the nature of the reported reactions, nor did we ask for a detailed description of the symptoms, but it is likely that there are a number of different forms. It has recently been suggested that even the Asian alcohol flush reaction shows heterogeneity.[19] Non-ALDH-related reasons for differences in alcohol reactivity have been suggested by a number of previous authors, including variation in alcohol dehydrogenase,[6,20] and differences in mechanisms mediating the symptoms such as prostaglandins[21] or histamine.[22]

Alternatively, the association of alcohol reactions with other forms of allergy[18] suggests a mechanism not involving ALDH deficiency but rather the generation of modified proteins through reaction with acetaldehyde. Such proteins have been shown to be capable of producing allergic reactions in mice.[23] In people who are at high risk of developing allergic reactions, acetaldehyde-modified proteins might lead to an "alcohol allergy" after some period of normal alcohol use.

We conclude that individual reactions to alcohol, of unknown cause, play a role in determining drinking behavior in subjects of European descent. The nature and mechanism of these reactions require further study with genetic, molecular biological, or immunological methods.

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