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INVITED REVIEW

Acute reactions to alcohol

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Abstract

Where the experience of alcohol is unpleasant because of adverse reactions to small amounts, alcohol consumption is likely to be low and alcohol dependence rare. This is shown by many studies of Asian subjects who experience the alcohol flush reaction (AFR) due to inherited aldehyde dehydrogenase (ALDH) deficiency. Alcohol reactions are less common and on average less severe in non-Asian subjects, but they do occur and can affect alcohol consumption. Information about alcohol reactions and their consequences in Europeans is reviewed, and such reactions are compared with those caused by mitochondrial ALDH deficiency in Asians.

Introduction

The biological factors which influence alcohol use or addiction may relate to the individual's personality and ability to control their behaviour, or to their subjective experience of alcohol and its rewards and disadvantages. The consequences of variation in this 'alcohol experience' in a general sense have been highlighted by the studies of Schuckit[1] and others (see[2]) on susceptibility to intoxication, and in a more specific way by the work of many groups on the Asian alcohol flush reaction.

In northern Asian populations (principally in China, Japan and Korea), the alcohol flush reaction has been characterized in its symptoms, enzymology, molecular biology and clinical consequences; but the occurrence and effects of reactions to alcohol in other ethnic groups have attracted less attention. Although less common and usually less severe in non-Asian populations, reactions to alcohol can still affect use and dependence but are less well understood. This review will summarize our knowledge of acute reactions to alcohol, and contrast the alcohol flush reaction due to mitochondrial aldehyde dehydrogenase deficiency in Asians with the probably heterogeneous group of reactions to alcohol in other populations.

In this review, the term 'Asian' refers mainly to the countries of north-east Asia, including China, Japan and Korea, or to their inhabitants and their descendants. The term 'European' refers to inhabitants of all European countries and their descendants. In both cases, migration has led to individuals and their genes moving far beyond these original geographical areas. The abbreviation ALDH2 is used for the predominantly mitochondrial, low-K_m form of aldehyde dehydrogenase while ALDH1 refers to the predominantly cytoplasmic, higher-K_m form.

The Alcohol Flush Reaction (AFR) In Asians

Scientific examination of the AFR is comparatively recent, but recognition of its existence can

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be found in Chinese literature dating back many centuries.[3] Wolff[4,5] established that reactions to alcohol (and specifically facial and body flushing) were much more common among Chinese than among Europeans (although he did find that a small proportion of Europeans had similar reactions). He also established that the AFR was congenital, and presumably inherited rather than acquired. Over the subsequent two decades, information has been gathered about the prevalence, cause and consequences of the AFR.

Signs and symptoms

The signs or symptoms of the AFR are variable, but the most common feature is flushing of the face and neck after a small amount of ethanol. One drink (10 g alcohol) is usually sufficient. Some people also have flushing of the body, palpitations, headache, nausea and dizziness. Objective measurements show a rise in skin temperature, tachycardia, hypotension and increased respiration rate.[6–8] Flushing subjects report higher levels of subjective intoxication than controls,[6,9] and body sway[10] and possibly other psychomotor changes are greater. Plasma or blood acetaldehyde concentrations rise to measurable levels (reported to be in the range 5–50 μM[11–13]) but blood ethanol concentrations are similar to those in non-flushers after similar amounts of alcohol.

Biochemical basis of the AFR

Observation of its similarity to the alcohol reactions caused by disulphuram (Antabuse) led to the suggestion that AFR was mediated by high acetaldehyde concentrations,[6] and subsequently it was confirmed that post-alcohol acetaldehyde concentrations in blood were elevated in affected subjects. This could have two explanations: either such subjects had a decreased ability to convert acetaldehyde to acetate because of low ALDH activity or they had an increased rate of conversion of ethanol to acetaldehyde because of high ADH activity.[14]

The ALDH hypothesis was confirmed by the association between AFR and low ALDH activity, specifically an absence of the predominantly mitochondrial, low K_m, ALDH2. This was first shown by enzyme activity measurements and isoenzyme electrophoresis[15,16] and subsequently by characterization of the molecular defect[17] and demonstration that both homozygotes and heterozygotes with ALDH2*2 have the enzyme deficiency.[18] The amino acid change in the ALDH2 protein is from glutamate at position 487 to lysine, and this is due to a change in the corresponding gene sequence from GAA to AAA.[19] The molecular interactions which bring about low ALDH2 activity in heterozygotes are now partly understood[20] and it is believed that although the AFR is inherited as a dominant condition, heterozygotes have some residual ALDH2 activity and therefore experience less intense reactions than ALDH2*2 homozygotes.

Although the idea that ADH type was the main determinant of the AFR could not be sustained, a recent report[21] suggests that ADH2 type may modify the intensity of the AFR. These authors found that, among ALDH2 heterozygotes, facial flushing after alcohol was more common in ADH2*12 or 22 subjects than in ADH2*1 homozygotes. Possible differences in the conversion of ethanol to acetaldehyde in the skin were cited as the most probable explanation of this ADH effect.

The AFR can be blocked by histamine[22] and prostaglandin[23] antagonists, suggesting that acetaldehyde causes flushing through release of vasoactive compounds, which in turn produces the symptoms. Inhibition of alcohol dehydrogenase by 4-methylpyrazole also greatly reduces acetaldehyde levels and the flushing and cardiovascular symptoms, even in a comparatively low dose which only reduces the rate of alcohol metabolism by about 20%.[12] There is also evidence (discussed below) that opiate antagonists can block a number of types of alcohol-induced flushing.

Prevalence

The prevalence of aldehyde dehydrogenase deficiency, and of the ALDH2*2 allele, varies between populations.[24] The highest gene frequencies, of around 0.25, are in Japan, with significant numbers in Korea and in China as a whole (but not in ethnic minorities within China[25]) and some in countries of south-eastern Asia which have significant numbers of people of Chinese ancestry. People in India, Russia and other parts of Asia, Australia and the Pacific islands, Europe, Africa and America do not have the ALDH2*2 allele. The ALDH2 deficiency reported in some native American groups[26] does not seem to be due to ALDH2*2,[27] with one possible exception. A group of Native Americans from Brazil was

reported to show an ALDH2*2 gene frequency of 0.17[24] but no further information about this group or its ancestry was given.

Consequences of the AFR

As might be anticipated, people with the AFR drink less[28] and are less likely to be alcohol dependent[25,29] than non-flushing subjects recruited from the same ethnic group. However, there is evidence that social pressures to drink can overcome the deterrent effects of the AFR, at least in ALDH2 heterozygotes, and the prevalence of ALDH2*12 genotype in alcoholics in Japan has been increasing over recent years.[30]

It has been suggested that where a person with ALDH2 deficiency does become alcohol-dependent they will progress to alcoholic liver disease more rapidly.[31] This is difficult to assess without prospective studies, and at present the evidence is weak. A positive result would support suggestions that acetaldehyde is harmful and plays a role in the development of alcoholic liver disease, by reacting with hepatic proteins and provoking an immune response.[32,33]

Outstanding issues

A number of discrepancies in the generally accepted view, outlined above, were discussed by Chao.[34] These relate to whether the AFR in ALDH2 heterozygotes is necessarily dysphoric and aversive, or whether some of its aspects might be reinforcing for alcohol use. For example, although flushing subjects rated themselves higher for 'clumsy' and 'confused' 30 or 60 minutes after taking alcohol, they also rated themselves significantly higher on 'high' and 'great overall' than non-flushers.[9]

There is variation in the degree of flushing and other symptoms, and distinctions have been made between moderate and severe, or slow and fast, reactions.[35] 'Atypical' or 'slow' flushing was reported by Higuchi *et al.*[36] to increase significantly the risk of alcohol dependence in Japanese men and women, compared to the risk in non-flushers. A similar increase in alcohol abuse or dependence in slow flushers was reported among aboriginal people in Taiwan.[25]

The variation in presence or severity of the reactions shows a strong and highly significant association, but not a one-to-one correspondence, with ALDH2 genotype. For example, Higuchi *et al.*[28] found that 47% of Japanese with enzymatically active ALDH2 said that they always (14%) or sometimes (33%) flushed after alcohol. It is possible that ADH2 type plays a role in such alcohol reactions; two groups have reported that ADH2*2 increases flushing or skin blood flow changes[21,37] but the details of the ADH–ALDH interaction differ.

In view of these questions, studies which integrate genotypes, biochemical and physiological changes after alcohol and self-report data on intoxication, with data on alcohol use and abuse in Asian subjects, are still needed to confirm whether the causative chain between ALDH2 type and the prevalence of alcohol dependence is correctly understood.

Alcohol reactions in European populations

There is no doubt that alcohol reactions do occur in European, and presumably all other non-Asian, populations. Their intensity seems to vary, but for the most part they are not as obvious as the AFR. In a few cases a cause or mechanism is reasonably clear but in most there is no known cause; acetaldehyde is central to the Asian AFR but its significance for alcohol reactions in Europeans is still uncertain.

Much of the available information has been gathered by asking the subjects whether they get unpleasant reactions after small amounts of alcohol, rather than by observations and measurements. In one way, this is appropriate: it is probable that the subjects' perceptions are at least as important in affecting their drinking behaviour as the reactions' cause or objective intensity.

Because the reactions to alcohol which occur in non-Asian subjects are poorly characterized and probably heterogeneous, the term 'alcohol flush reaction' (AFR) which has been used for the Asian form caused by ALDH2 deficiency will be avoided. Instead, it seems best to refer to 'alcohol reactions' at least until the classification and causes of non-Asian reactions are clearer. As a tentative classification four main groups may be identified, due to drug interactions, genetic ALDH deficiency, immune reactions and idiopathic.

Reactions due to drug/alcohol interactions

A number of drugs have been found to cause acute reactions to small amounts of ethanol.

These reactions are similar to the Asian AFR, although they can be either less or more intense, and facial flushing is a prominent feature. The drugs include disulphuram,[38] calcium carbimide,[39] chlorpropamide and other oral hypoglycaemic agents,[40,41] metronidazole[42] and cephalosporins.[43] Variations in the effects of chlorpropamide is now thought to be dose- or concentration-related rather than depending on the type of diabetes present.[41] Most of these drugs act by inhibiting ALDHs. In some cases this has been shown *in vitro* while in others high post-alcohol acetaldehyde concentrations have been shown *in vivo*.[38–40,44,45]

At least some aspects of the chlorpropamide alcohol flush (CPAF) can be reversed by naloxone;[46] alcohol-induced performance impairment was dramatically reduced by naloxone in CPAF, but not control, subjects. Other forms of alcohol-induced flushing, including that occurring in patients with rosacea[47] and the Asian AFR[48] may also be prevented by pre-treatment with parenteral opiate antagonists, although this was not the case with oral naltrexone.[49] These experiments suggest that the flush may be mediated by endorphin release, which may lead to some rewarding as well as aversive aspects of the flushing.

Genetic deficiency of ALDH

The prevalence of ALDH deficiencies in European and other non-Asian groups has not been defined but it appears to be much lower than the prevalence of self-reported reactions. Although exhaustive screening for ALDH mutations in alcohol-reacting subjects has not been carried out, the twin study referred to below shows that European alcohol reactions have, taken as a whole, low heritability and the majority cannot be due to a single genetic defect. ALDH2 deficiency, whether due to the ALDH2*2 mutation or others, appears to be uncommon outside Asia but uncharacterized ALDH2 deficiencies have been found in Chile and Equador.[26,50,51] A silent ALDH2 mutation (not causing an amino acid change or loss of activity) has been described recently in a Native American group.[52] A variant form of cytosolic ALDH1, with less intense staining for ALDH enzyme activity than normal, was obtained from two subjects from China and Thailand.[53]

A small number of European subjects have been reported in whom acute reactions to alcohol are associated with deficiency of the mainly cytoplasmic ALDH1.[54] Two of nine European flushers showed low erythrocyte ALDH activity; in one there was around half the mean control activity and in the other activity was less than 20%. Variation in electrophoretic mobility of the ALDH1, and quantitation of ALDH1 protein by immunohybridization, strongly suggested mutations affecting enzyme activity and/or protein stability.

Further investigation[55,56] of the family of the subject with the lowest erythrocyte ALDH activity showed multiple relatives with below-normal ALDH, in a pattern consistent with autosomal dominant inheritance, and an associated restriction fragment length polymorphism in the ALDH1 gene. It was also noted that both grandfathers of the initial subject had been alcoholics, but no enzyme or RFLP investigations could be done on them. Testing of the initial subject with alcohol showed no difference in plasma acetaldehyde concentrations from control subjects.

Alcohol-induced flushing in subjects with ALDH1 deficiency suggests that this cytoplasmic, higher-K_m enzyme may have a role in aldehyde metabolism *in vivo*. However, the small number of ALDH1-deficient subjects so far studied, and the failure to find high post-alcohol acetaldehyde concentrations, make it hard to establish that the low ALDH activity truly causes the flushing.

Immunological factors

A number of case reports have described subjects with apparent anaphylactic reactions to alcohol (see[57]). Such reactions can be life-threatening but this appears to be rare. It is not clear from these case reports whether the reaction is induced by ethanol itself, or a metabolite; nor is it known whether these reactions represent an extreme form of the reactions to alcohol reported by many people, or a distinct and unrelated phenomenon.

Less severe reactions which were ascribed to immune mechanisms were reported by Israel *et al.*[58] in approximately 0.5% of a randomly contacted non-Asian population in Toronto; a number of these subjects also reported allergies to other materials including pollens and drugs. Recruitment of further subjects, by advertisement, yielded 12 who met criteria for hypersensitivity to alcohol and they showed an increase in serum IgE anti-(acetaldehyde protein adduct)

Table 1. *Estimates of prevalence of self-reported alcohol reactions in subjects of European descent*

Source	Type	Number of subjects	Proportion reacting (%)	
			Men	Women
Edfors-Lubs[59]	'Alcohol allergy'	14000	6	3
Schwitters *et al.*[64]	Flushing	626	29*	29*
Israel *et al.*[58]	Hypersensitivity	1000	0.1	0.5
Ward *et al.*[56]	Flushing	192	9	48
Whitfield & Martin[60]	Any unpleasant reaction	334		
	Always		4	7
	Sometimes		19	38
Slutske *et al.*[61]	Any adverse reaction	5831		
	Always		6	14
	Sometimes		33	38
	Flushing			
	Always		2	8
	Sometimes		13	24
	Sleepiness			
	Always		3	7
	Sometimes		24	24

*The prevalence figures given by Schwitters *et al.* did not distinguish between male and female subjects.

reactivity compared with controls. A questionnaire-based study by Edfors-Lubs[59] showed that around 5% of subjects reported an 'allergy to alcohol' and that people who did so were more likely to report asthma or eczema. This also supports the concept of an allergic basis for at least some of the alcohol reactions which occur in Europeans.

These reports suggest that some people develop an allergy to acetaldehyde-modified proteins which produces symptoms after consumption of a small amount of alcohol. Presumably, acetaldehyde produced from ethanol after drinking reacts with proteins to form adducts which provoke the reaction; but the reasons why this occurs in some people but not others are unknown.

Idiopathic alcohol reactions

The majority of alcohol reactions in Europeans have no known cause. We can, however, determine their prevalence and consequences. This has generally been done by questionnaires, and it is worth considering the wording of the questions used. The characteristics of the reactions of interest include an unpleasant component, and one brought on by a small amount of alcohol. Some of the surveys have asked whether such reactions occur on every occasion of alcohol consumption or only sometimes, and others have asked about individual symptoms such as flushing, palpitations or nausea. Ideally, the questions should cover the frequency (always or sometimes) of each of the individual symptoms.

Early studies were concerned mainly with differences between Asians and Europeans in the prevalence of flushing after alcohol, and produced estimates for Europeans of between 5% and 10%. More detailed surveys have appeared with the past 3 years, with larger numbers of subjects and more information gathered from them.

Table 1 shows that some reactions to alcohol (not necessarily flushing) occur in around 5–10% of subjects every time they drink. Substantially more people say that this sometimes happens, and in either case it is more common (or at least reported more often) in women.

In a survey of medical students of European descent in London, Ward *et al.*[56] found that 9% of men and 48% of women gave positive replies to the question 'Do you flush after consuming alcoholic beverages?' Among 334 subjects of European descent in Australia, Whitfield & Martin[60] found that 4% of men and 7% of women reported unpleasant reactions which occurred every time they consumed alcohol, while an additional 19% of men and 38% of women sometimes reacted. In a larger study reported by Slutske *et al.*,[61] 5831 subjects of mainly European descent in Australia yielded a similar prevalence.

Slutske *et al.* were able to compare the preva-

lence of individual symptoms, and the degree to which alcohol-reacting subjects experienced multiple symptoms. The intercorrelations among the reaction checklist items were in the range 0.2–0.6, suggesting that at least some subjects either experience only one or two symptoms or that some symptoms were more vividly recalled than others. The strongest correlations were between nausea, headache and palpitations, which were less common symptoms than flushing.

It is not clear whether the gender difference is due to a difference in the physiological response to alcohol or to gender differences in perceptions and willingness to acknowledge the effects of alcohol. It has recently been reported[62] that women have higher post-alcohol acetaldehyde concentrations than men, and that blood acetaldehyde and plasma oestradiol are significantly and positively correlated. This study did not test whether ALDH activity was decreased by oestrogens, but this is one possibility.

Observed effects of alcohol

Studies in which flushing was observed or measured after a test dose of alcohol have shown conflicting results. Whitfield & Martin[60] reported no agreement between self-report of alcohol reactions and skin temperature changes measured by a temperature probe taped to the cheek, but the self-report was obtained some years after the alcohol challenge test. Ward *et al.*,[56] using a more sensitive technique which measured skin blood flow, found that Caucasian flushers had greater blood flow changes than non-flushers but substantially less than an Asian flushing subject.

A substantial degree of flushing after a test dose of alcohol was observed in 13% of male and 40% of female Hungarian subjects from Budapest, and 19% of males and 33% of females from an ethnic minority group of Moldavian Hungarians.[63] However, the observed degree of flushing after alcohol was not compared with the subjects' self-reports of their usual reactions to alcohol. The gender difference in observed flushing suggests a true physiological difference in the response to alcohol.

The effect of alcohol reactions on phsiological, psychomotor and subjective responses to alcohol was reported by Whitfield & Martin.[60] Heart rate and blood pressure changes after alcohol were no greater in the reacting subjects, but body sway increased more in the subjects who reported always reacting than in those who sometimes or never did so. Similarly, those who always reacted assessed themselves as being more intoxicated, and as less confident of being able to drive, despite similar blood alcohol concentrations.

Alcohol reactions, use and dependence

Several studies failed to find associations between flushing or other reactions to alcohol, and drinking behaviour in European-descent subjects.[64–66] However, Whitfield & Martin[67,60] found that subjects who reported unpleasant alcohol reactions did report drinking less, by a number of measures and at two different times. Slutske *et al.*[61] also found that subjects who always experienced alcohol reactions drank less frequently, and slightly less per occasion, than the other subjects. On the other hand, Ward *et al.*[56] found that flushing did not decrease reported alcohol intake; indeed it was associated with (non-significantly) higher consumption among the men. All these studies were on predominantly Anglo-Celtic subjects, in the United Kingdom, Australia, Canada or the United States.

A study of an ethnic minority group in Hungary[68] found that around 45% of subjects reported facial flushing after alcohol, with little difference between men and women. Despite this high prevalence of flushing, alcohol consumption in this group was high and indeed the flushing was stated to be more likely to occur in those who consumed more than 30 ml (about 25 g) of ethanol per day. This illustrates the confusing relationship between reactions to alcohol and alcohol consumption, and the variation which may occur between groups with different traditions.

The relationship between alcohol reactions and alcohol dependence has been approached in two ways. In the first, subjects who are at high genetic risk of alcohol dependence are identified and the prevalence of reactions is determined by self-report or observation and compared with a low-risk group. The second approach is retrospective, and subjects who are old enough to have substantial drinking experience are asked about alcohol reactions and also about their personal history of various indicators of alcohol dependence.

Schuckit & Duby[69] reported that young family-history-positive men had significantly more facial flushing after 0.75 ml/kg (0.6 g/kg) of ethanol than family-history-negative controls matched for

their own alcohol consumption. Similarly, Slutske *et al.*[61] found some evidence that flushing in men (but not women) was associated with higher reported rates of alcohol problems in their parents.

Turning to retrospective studies, Whitfield & Martin[60] found no difference in the number of positive responses to questions on dependence symptoms but there were few dependent subjects (particularly among the women) and few men who reported reactions. Slutske *et al.*, on the other hand, found strong indications that alcohol reactions (occurring always or sometimes) were associated with increases in dependence symptoms in both men and women. The temporal and causative relationships between alcohol reactions and dependence are uncertain. It would be useful to know that the occurrence of alcohol reactions preceded dependence, but this would require a prospective study.

Mechanisms of idiopathic alcohol reactions

The Australian studies of alcohol reactions[67,61] were conducted on twin subjects so inferences about heritability can be drawn from the monozygotic and dizygotic pair concordances. The existence of monozygotic pairs discordant for alcohol reactions rules out an enzyme deficiency of the classical type as the sole cause of the reactions. However, there was evidence in the larger of these studies for a greater concordance in monozygotic than dizygotic pairs, with a heritability estimate of around 0.3. This could be due either to a minority of the reactions being strongly heritable, or to all subjects having some individual level of genetic predisposition modified by environmental influences.

The relationship to allergy and acetaldehyde–protein adducts is shown by two reports[58,59] but again it is hard to determine from the published data whether this is the main cause in only a minority of subjects, or a contributing factor in many, or both.

Possible mechanisms relating to dependence are speculative; there may be errors due to retrospective recall or poor design of questions, or there may be a true causal relationship between some types of alcohol reaction and the development of dependence. If something which causes flushing or other reactions also predisposes to dependence, then we have to assume that aspects of the alcohol reactions are pleasurable or reinforcing for some people. This would be consistent with the data on self-reports of mood after alcohol in Asian flushing subjects, and with the effects of opiate antagonists on flushing mentioned above. This association of alcohol reactions and dependence requires further study but the prospective design which is desirable is likely to be difficult in practice.

The Asian AFR and other alcohol reactions: points of similarity and difference

Clearly, the Asian alcohol flush reaction and the reactions which occur in other ethnic groups have different mechanisms and modes of inheritance. There is a different gender ratio, with women outnumbering men by 2 : 1 or more (depending on how reactions are measured) among Europeans. Physiological changes such as skin temperature or blood flow, and heart rate, are greater in Asians and acetaldehyde concentrations rise to detectable levels. However, when comparing reactions to alcohol in Asians and non-Asians one should remember that the milder reactions of unknown cause may occur in a proportion of ALDH2*1 homozygous Asian subjects as well as in non-Asians.

It seems likely that many of the reactions reported by Europeans represent extremes of the normal range of susceptibility to intoxication or to vasodilation from alcohol; but this would not invalidate their effects on drinking. The acute response to alcohol, whether or not it produces noticeable physiological changes such as flushing, is probably a determinant of alcohol use in a more general sense and there may be seemingly paradoxical aspects to it. In differing ways, both those with a substantial response to alcohol and those with no response at all might find alcohol use unrewarding.

Finally, acetaldehyde is clearly central to the Asian AFR, but is it important in the European reactions? And is it involved in the proposed increased risk of alcohol dependence? The association between deficiency of an enzyme capable of metabolizing acetaldehyde, ALDH1, and flushing after alcohol in some subjects certainly suggests that acetaldehyde has a role in these subjects' reactions. However, no increase in plasma acetaldehyde after alcohol could be found.[56] Similarly, the demonstration of IgE antibodies to acetaldehyde–protein adducts by Israel *et al.*[58] places acetaldehyde in the chain of events leading to alcohol

hypersensitivity reactions but these seem to be comparatively uncommon and account for less than 10% of European alcohol reactions. If we accept the theory that acetaldehyde is involved in the development of alcohol dependence, then the association between alcohol reactions and dependence might be explained; but although such theories are extremely durable (see[70]) they have proved almost impossible to test experimentally.

Conclusions

Case reports and observation in social situations leave no doubt that there are some European people who experience unpleasant or even dangerous reactions to small amounts of alcohol, and who avoid it for that reason. Surveys have shown that there are substantial numbers of people, particularly women, who report some unpleasant symptoms after drinking, but many of these symptoms only occur sometimes.

The effect on alcohol use in these subjects is variable and appears to be modified by social factors, so its importance in public health terms is undefined. Definition of more homogeneous subgroups of reactions, based on symptoms and/or mechanisms, should produce a better estimate of their effects on alcohol use.

Paradoxically, there is evidence that people who experience and report alcohol reactions may be at increased genetic risk of alcohol dependence. One of the challenges facing researchers is to define a subgroup of such people and to determine the mechanisms. In the long term, this will probably be the most important result of research in this area.

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