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Invited Editorial: Genetic Investigations of Alcohol Metabolism and of Alcoholism

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Alcoholism, the most common serious human behavioral disorder in the United States and many other countries, is a worthy challenge for elucidating and modeling genetic and environmental interactions. Interviews of 20,000 individuals at five U.S. sites in the Epidemiological Catchment Area project indicate that, on the basis of widely accepted diagnostic criteria, 19% of men and 4% of women have manifested alcohol abuse or alcohol dependence (Cloninger 1987). For millennia, excessive drinking and its social and medical consequences have been noted to "run in families"; most adoption, twin, and half-sibling studies have now demonstrated significant hereditary contributions (see Seixas et al. 1972; Goedde and Agarwal 1987). Alcoholism cannot be diagnosed in persons unexposed to the triggering environmental agent, namely, ethanol. Predisposing hereditary traits must interact with this exogenous chemical, as well as with cultural and interpersonal forces. Thus, alcoholism can be considered an "ecogenetic disorder."

The assignment of this phenotype in genetic or epidemiological studies is complicated. The status of children is usually unascertainable. Exposure histories in adults are poorly characterized. The official definition is complex (APA 1987, pp. 167–169, 173–179). In fact, the phenotype "alcoholism" is a poor starting point. There is probably extensive heterogeneity of predispositions both for drinking behavior and for organ damage. Thus, I believe investigators should target specific phenomena in the development of alcoholism and organ-specific effects of alcoholism in a reductionist approach that later can be integrated. Analogous reductionist approaches to anemias and to coronary heart disease have been highly productive.

Five levels of investigation can be suggested as a framework for such studies: (1) predisposing personality, cognitive, neurophysiological, and cultural factors in drinking behaviors; (2) susceptibility to acute effects; (3) metabolism of ethanol; (4) central nervous system phenomena; e.g., tolerance, dependence, and addictability; and (5) susceptibility to specific medical and behavioral complications.

From analyses of hundreds of pedigrees after detailed interviews and biochemical assays, Cloninger (1987) proposed that alcohol-seeking behavior is influenced by three heritable dimensions of personality: "novelty-seeking," "harm avoidance," and "reward dependence." These characterizations—also described as "impulsivity," "cautiousness," and "difficulty stopping use of alcohol," respectively—may reflect underlying differences in monoaminergic pathways and in EEG patterns (Propping et al. 1981). Schuckit (1987) investigated subjective, cognitive, psychomotor, and hormonal responses to alcohol ingestion in young men (matched for frequency and duration of drinking) with and without alcoholic fathers; observed differences suggest decreased reaction to low doses of ethanol in sons of alcoholics.

Differences in drinking behavior due to uncomfortable or embarrassing acute flushing reactions to ethanol have been attributed to inherited polymorphic differences in metabolism of ethanol and acetaldehyde, with high concentrations of acetaldehyde thought to trigger the flushing (see below). The active agent may be histamine or another vasoactive mediator, or it may be a condensation product or protein adduct of acetaldehyde. There also may be inherited variation in the formation of diols or in the hepatic P450 microsomal oxidizing system, which is induced by such diverse

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chemicals as acetone, trichloroethylene, pyrazole, imidazole, isoniazid, and ethanol.

There are dissociations between tolerance and dependence (withdrawal seizures) and differences among inbred and selected mouse strains, suggesting genetic influences on neurotransmitter and peptidergic pathways (Tabakoff and Hoffman 1987). We do not know whether there is cross-addictability for ethanol with addictability to opiates or other agents. However, acetaldehyde and biogenic amines can form condensation products that have opiate-like structures (Myers 1980) or that may act on benzodiazepine receptors (Kuriyama et al. 1987).

Finally, genetically determined variation in susceptibility to toxic actions in the target organs may influence risks of developing hepatic cirrhosis, recurrent acute pancreatitis, cardiomyopathy, Wernicke-Korsakoff syndrome, or fetal alcohol syndrome. Analysis of twin pairs in the Veterans Administration registry indicated genetic predispositions to cirrhosis and alcoholic psychoses (Hrubec and Omenn 1986). Alcohol can trigger attacks in persons with the hereditary form of pancreatitis (Sibert 1978). Perhaps primary hemochromatosis predisposes to cirrhosis. Consistent abnormalities of thiamine metabolism may yet be found in Wernicke-Korsakoff psychosis. If acetaldehyde toxicity leads to the fetal alcohol syndrome, perhaps the combination of atypical alcohol dehydrogenase (ADH) and deficient mitochondrial aldehyde dehydrogenase (ALDH) in both mother and fetus predisposes. Thus far, susceptibility to organ-specific damage in alcoholic patients is nearly unexplored territory for clinical investigations.

Two papers in this issue of the *Journal* demonstrate progress with the reductionist approach recommended here. Shibuya and Yoshida (1988*a*, 1988*b*) have asked cogent questions about variation in the metabolism of ethanol, susceptibility to acute effects, and susceptibility to alcoholic liver disease in the Japanese population. Their cDNA probes for polymorphic ADH and ALDH sequences permit studies with human white blood cells, rather than depending on autopsy or surgical liver specimens for difficult enzyme assays.

Genotyping of 49 unrelated Japanese revealed a surprising result for ALDH. Many studies have found that about 50% of Orientals are deficient in activity of the low-K_m isozyme of ALDH (Goedde et al. 1979). This mitochondrial isozyme is the first line of defense in metabolizing acetaldehyde. A standard 0.5 g/kg ethanol dose produces acute flushing symptoms and higher peak blood acetaldehyde concentrations in deficient individuals (Harada et al. 1985). Hardy-Weinberg calculations from a presumed homozygous recessive phenotype frequency of 50% have indicated a gene frequency of .7. Instead, Shibuya and Yoshida find .35. They conclude that all of the heterotetramers of $ALDH_2$—not just the atypical homotetramer—must be unstable and/or inactive and that electrophoresis and isoelectric focusing results have been misclassified. I am unaware of other examples of inactive heterotetrameric enzymes, but inactive or unstable heteropolypeptide proteins may underlie certain collagen disorders and other autosomal dominantly inherited conditions.

A direct test of Shibuya and Yoshida's conclusion would be a mixing experiment in vitro. Apparently such an experiment is infeasible, however, because of the very low amounts of atypical homotetramer that can be isolated and because the electrophoretic mobilities are rather close. Their alternative interpretation, the three-allele model, has no supporting evidence and could be eliminated by finding nonflushing offspring of a mating of two persons who have the flushing response.

Shibuya and Yoshida studied both alcohol and ALDH polymorphisms in 23 Japanese patients with alcoholic liver disease. All ALDH genotypes associated with deficient ALDH isozymes were notably infrequent, confirming the results of Yoshihara et al. (1983). The atypical ADH genotype was not associated with higher risk of liver disease. To clinch the argument that acute flushing reactions lead affected individuals to avoid ingesting alcohol and *thereby* avoid the development and complications of alcoholism, it would be helpful to know the drinking histories of Japanese of different genotypes and phenotypes. The molecular probes make feasible such studies, as well as combined hair root phenotyping and cDNA genotyping to try to clarify the unexplained combination of high prevalences of both acute flushing and alcoholism in Eskimos and Native Americans.

Since the $ALDH_2$ polymorphism does not occur in Caucasians, it cannot explain variation in alcoholism-related risks, including 5%–10% prevalence of acute sensitivity, in non-Oriental populations. Atypical ADH may account for some of these flushers and may also contribute among Orientals (Stamatoyannopoulos et al. 1975; Goedde and Agarwal 1987). A. Yoshida, V. Davé, R. J. Ward, and T. J. Peters (personal communication) have recently found deficient and kinetically altered forms of cytosolic $ALDH_1$ in erythrocytes from Caucasian flushers. Like $ALDH_2$, these $ALDH_1$ variants may be fully active only in the normal homotetramer. Since this isozyme is inhibited by chlorpropamide, individuals susceptible to chlorpropamide-induced alcohol

flushing (and to disulfiram-like aversive reaction) should be investigated for additional variants of $ALDH_1$.

With discoveries of predisposing features of alcohol abuse and alcohol dependence, we may be able to mount much more effective genetic counseling and alcoholism prevention programs.

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