SIR HANS KREBS delivered the Penn Lecture-ship in 1969 on the subject of “Alcohol Dehydrogenase.” He commenced his talk with some observations about the distribution of this enzyme throughout the animal kingdom. He asked the questions: Why is this enzyme so ubiquitous? What function does it serve in animals that have not become expert brewers? Sir Hans pointed out that animals are sometimes accidental ingestors of alcohol; for example, the African elephant that becomes drunk and dangerous after eating the fruit of the marula tree. Moreover, Krebs and Perkins recently demonstrated that ethanol is a “normal” constituent of the portal venous blood of the rat as a consequence of being formed in and absorbed from the GI tract. It appears, therefore, that the livers of many animals other than man are exposed to the hazards of alcohol either by accident or because of production by microorganisms residing in the rumen or gut. Sir Hans answered his posed questions by suggesting that alcohol may have lethal toxicity were it not for alcohol dehydrogenase. The enzyme is in greatest abundance in the liver, and, therefore, may “protect” the animal from poisoning from this route of entry. It is of interest that the heart contains no alcohol dehydrogenase and perhaps this fact tells a story.

How is alcohol metabolized?

Alcohol delivered to the liver is oxidized in the presence of alcohol dehydrogenase, a zinc-containing enzyme. The product is acetaldehyde, which is further oxidized to acetyl CoA in the presence of acetaldehyde dehydrogenase, which is also found in the liver. Both of these oxidations are accomplished by the reduction of NAD⁺ (nicotinamide adenine dinucleotide). The acetyl CoA has a multitude of possible fates, including complete oxidation to CO₂ and H₂O with the consequent production of energy. If the capacity of alcohol dehydrogenase in the liver is overwhelmed by the abundance of substrate, alcohol overflows into the systemic blood and the pharmacologic effects on the central nervous system produce the delightful syndrome which has been both a comfort and a curse to homo sapiens.

Fundamental knowledge concerning the metabolic defects or abnormalities in alcoholic cardiomyopathy is vanishingly small. In a relatively few
reports the effects of alcohol on cardiac metabolism have been studied in experimental animals. Alcohol appears to inhibit fatty acid oxidation and cause an increased incorporation of fatty acids into triglycerides in the isolated perfused heart and in heart homogenates. These effects on lipid metabolism have been demonstrated when alcohol has been added directly to the perfusion fluid or medium or in hearts removed from animals that have ingested alcohol.

Regan et al. observed a negative arteriocoronary sinus difference for SGOT, potassium, and phosphate in dogs and man following the oral administration of alcohol. This “leakage” of intramyocardial constituents lasted for 4–5 hours, and only occurred when the blood alcohol concentration reached 200 mg%. The results were interpreted to mean that alcohol had a transient direct toxic effect on the cardiac cell membranes. Interestingly, the same intracellular materials leak from the myocardium following experimental and clinical myocardial ischemia. Regan’s group and Wendt et al. measured arteriocoronary sinus differences of plasma free fatty acids (FFA) and triglyceride (TG) following alcohol administration and both investigators found decreased extraction of FFA but disagreed on the triglyceride changes. The mixed venous plasma concentrations of major cardiac substrates change considerably after consumption of alcohol; how much these changes in substrate influence uptake of other substrates needs to be clarified. Decreased uptake of FFA by the heart would be consistent with the foregoing observations of the inhibition of fatty acid oxidation by alcohol ingestion.

Wendt et al. also described a negative arteriocoronary sinus difference for zinc following alcohol ingestion. The significance of this finding is unclear because of the absence of alcohol dehydrogenase in heart. Wendt and co-workers also reported the leakage of two intramitochondrial enzymes in a group of alcoholic patients, implying a rather severe degree of cellular damage. However, the importance of this observation was eclipsed by the lack of any relationship between the timing of alcohol ingestion, the presence of cirrhosis, the presence of cardiomyopathy, or the stress of exercise. Much more investigative work has been done on the metabolic and pathogenetic effects of alcohol on the liver, but the precise relationship between alcohol and cirrhosis is still unclear. It is a point of interest in this regard that alcoholic cirrhosis and alcoholic cardiomyopathy seldom coexist in the same patient.

As far back as 1873 Walshe described heart disease in association with alcoholism: “a localized form of cirrhosis occurring in the myocardial wall and trabeculae carneae in the absence of impaired coronary circulation.” In 1884 Bollinger described epidemic cardiomegaly in Munich and related it to the enormous beer consumption of its residents (“Munchen Bierherz”). Nevertheless, serious attention to the role of alcohol in the pathogenesis of cardiomyopathy is comparatively recent. In considering a relationship between alcohol and myocardial disease, a distinction must be made between the effect of alcohol per se, the effect of metabolites of alcohol after it has passed through the liver, the effects of constituents of commercial alcoholic beverages, and the effects of accompanying nutritional deficiencies.

What are possible pathogenetic factors?

1. Alcohol is a cellular toxin. Is it the agent that produces the cardiac damage? Or, is it altered in the liver and are the blood composition changes (e.g. triglyceride) the mediators of damage?

2. Is acetaldehyde the toxic substance? Is it 10 times more toxic than ethanol on a milligram-formilligram basis.

3. Lieber believes that the relative accumulation of reduced nicotinamide adenine dinucleotide (NADH) leads to pathologic changes in the liver. The same explanation is obviously not valid for heart.

4. Is lipid accumulation a problem? Do accumulated triglycerides or other lipids cause membrane functional defects or somehow interfere with myofibrillar work?

5. Many alcoholics have hypomagnesemia. Is this a result of increased lactate excretion? The rise in plasma lactate concentration consequent to alcohol consumption leads to increased lactate excretion and excessive loss of magnesium.

6. Do nonalcoholic constituents of the brew cause the trouble? The Bantu is susceptible to cardiomyopathy which some have attributed to local beer brewed in iron pots. Cardiomyopathy is frequently encountered in France where the wine has been found to contain much larger quantities of iron than American wine. Alcohol is known to enhance iron absorption from the gut. The tragic consequences of additives (cobalt) in beer made by the thoughtless brewers of Omaha and Quebec are familiar to cardiologists. Is it possible that other trace materials which find their way into the final
product could have pathologic effects on the myocardium over a long time span.

(7) There is a higher incidence of cardiomyopathy in certain ethnic groups. Could there be a "constitutional" defect (analogous to the syndromes of glucose-6-phosphate dehydrogenase deficiency) in which no clinical consequences are evident until stressed by exogenous alcohol?

(8) Or is alcoholic cardiomyopathy the product of a combination of factors? Given a constitutional predisposition (such as has been postulated in patients who develop alcoholic cirrhosis) do poor nutrition, viral infection, and nonalcoholic constituents play a role by aggravating the toxic effects of alcohol or its metabolites?14

ARTHUR F. WHEREAT
JOSEPH K. PERLOFF

References
Ethyl Alcohol and Myocardial Metabolism
ARTHUR F. WHEREAT and JOSEPH K. PERLOFF

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