CC/NUMBER 23
JUNE 9, 1980

This Week's Citation Classic

Isselbacher K J & Greenberger N J. Metabolic effects of alcohol on the liver.
N. Engl. J. Med. **270:**351-6, 402-10, 1964.
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Alcohol has many effects on hepatic, carbohydrate, protein, and lipid metabolism. Many of the actions of alcohol on the liver cell are of a direct or toxic nature. Other effects are indirect and the result of changes in the redox state of the hepatocyte secondary to ethanol oxidation. Our knowledge of the metabolic actions of alcohol has provided insight into the mechanism of alcohol-induced hyperlipidemia, hyperuricemia, and hypoglycemia. [The *SCI*® indicates that these papers have been cited over 350 times since 1964.]

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November 1, 1979

"My interest in alcohol and alcohol metabolism, which served as a basis of this article, had a somewhat unique origin. In 1955-56, while an investigator at the NIH and working in association with Herman Kalckar, we were fortunate to discover the mechanism of the genetic defect causing the hereditary disorder galactosemia.[1] The fundamental defect in galactosemia was shown to involve a deficiency in the enzyme, galactose-1-P0$_4$ uridyl transferase. In the course of studying the reactions involved in the normal interconversion of galactose to glucose, it became evident to us that in addition to uridyl transferase, there was also the step involving the isomerase reaction whereby UDP-galactose is converted to UDP-glucose. This isomerization is catalyzed enzymatically by UDP-galactose-4-epimerase, which requires and is stimulated by NAD but is inhibited by NADH.

"I was aware of numerous older clinical studies showing that alcohol ingestion results in impairment of galactose metabolism by the liver, an observation which in fact had served as the basis of the (now abandoned) galactose tolerance test to assess liver disease and alcohol-induced liver injury. Combining this observation with the then recently described reactions involving the uridine nucleotides in the metabolism *of* galactose and glucose, it seemed reasonable to postulate that alcohol might be interfering with hepatic galactose metabolism at one of these enzymatic steps. From my studies with Kalckar, I knew that the UDP-galactose-4-epimerase enzyme was extremely sensitive to inhibition by NADH. Since the oxidation of alcohol by the liver involved the reduction of NAD to NADH, it appeared to me therefore the most likely step to be inhibited by alcohol was the one involving the interconversion of UDP-galactose and UDP-glucose. I then was able to confirm this postulate[2] with my colleague, Stephen M. Krane (now well recognized for his work in collagen metabolism in rheumatoid arthritis) who at the time was measuring changes in NAD/NADH levels under various experimental conditions. It was thus shown by us, and amply confirmed later by others, that alcohol metabolism by the liver affects the redox level in the liver cell, and that the resultant increased NADH concentration inhibits the hepatic oxidation of alcohol at the epimerase step.

"Numerous alcohol-related studies followed. I temporarily abandoned further studies on galactosemia and examined the effects of alcohol on hepatic metabolism. These metabolic effects proved to be legion—the major ones involving interference in carbohydrate, protein (including lipoprotein), and lipid metabolism. It was our research in this area that led the then editor of the *New England journal of Medicine* (Joseph Garland) to invite me to review this area for a broad medical audience. This resulted in this highly cited article which I prepared with one of my most able research fellows, Norton J. Greenberger, now chairman and professor of medicine at the University of Kansas Medical Center.

"Although from 1964 to the present my research has taken me to other areas (esp. studies of intestinal and malignant cell surface structure and function), I have attempted to continue my studies of alcohol metabolism Our studies have resulted in further observations on the role and possible mechanism of alcohol in the inhibition of intestinal nutrient transport, interference with liver cell regeneration, and potentiation of hepatic viral injury. An update of our many investigations in this area led to the publication of a more recent review dealing with alcohol and its metabolic effects."[3]

1. Isselbacher K J, Anderson E P. Kurshashi K & Kalckar H M. *Science* **123:**635-6. 1957
2. **Isselbacher K J & Krane S M.** *J. Biol. Chem.* **236:**2394-8. 1962.
3. Isselbacher *K J. N* *Engl. J. Med.* **296:**612-6, 1977.