

This Week's Citation Classic™

CC/NUMBER 50
DECEMBER 10, 1984

Rubin E & Lieber C S. Hepatic microsomal enzymes in man and rat: induction and inhibition by ethanol. *Science* 162:690-1, 1968.

[Dept. Pathology, Mt. Sinai Sch. Medicine, City Univ. New York, and Sect. Liver Disease and Nutrition, Bronx Veterans Administration Hosp., NY]

In rat and in man, chronic alcohol feeding increased the activity of hepatic drug-metabolizing enzymes. *In vitro*, alcohol also inhibited the activities of these detoxifying systems. These observations provided evidence that, in addition to changes in the central nervous system, the resistance of chronic alcoholics to the action of many drugs is, in part, caused by metabolic adaptation in the liver, and that inhibition of drug-metabolizing enzymes in the liver contributes to the increased sensitivity of inebriated persons to sedatives. [The *SCJ*® indicates that this paper has been cited in over 265 publications since 1968.]

Emanuel Rubin
Department of Pathology and
Laboratory Medicine
Hahnemann University School of Medicine
Philadelphia, PA 19102

November 13, 1984

"My interest in alcoholism and drug metabolism was first aroused some 14 years before this project was undertaken. When I was an intern at the Boston City Hospital, the indigenous population enjoyed the consumption of spirits to such an extent that we considered almost any patient an alcoholic until proved otherwise. When 'drying out,' these patients required remarkably large doses of sedatives, while during periods of inebriation they were unusually sensitive to such drugs. Some years later, the association between the induction of microsomal drug-metabolizing enzymes in the liver and hypertrophy of the smooth endoplasmic reticulum (SER) was demonstrated, as was the role of cytochrome P450.¹

"I later reported that in rats and volunteers chronically given alcohol, hypertrophy of the SER occurred.^{2,3} It seemed that alcohol might act as an inducer of the mixed-function oxidase system, thus leading to metabolic tolerance of drugs in the clinical situation to which I alluded. Accordingly, we fed rats alcohol for a few weeks and demonstrated in hepatic microsomes that a variety of drug-metabolizing enzymes were increased.

"Since the history of research in alcoholism was encumbered by numerous studies in the rat that

had no relevance to man, I felt that these findings would be accepted as conclusive only if the induction of drug-metabolizing enzymes were demonstrated in man. I recruited three nonalcoholic volunteers and fed them alcohol for about two weeks. Homogenates of liver biopsy tissue displayed a two- to threefold increase in the capacity to metabolize pentobarbital *in vitro*, compared with specimens taken before the experiment.

"Since drugs oxidized by the hepatic mixed-function oxidase system, when administered simultaneously, were known to inhibit each other's metabolism, it seemed reasonable that if alcohol acted as a drug, its presence might inhibit the metabolism of other drugs. *In vitro*, alcohol indeed inhibited the microsomal metabolism of the same compounds whose oxidation had been induced in rat microsomes by chronic alcohol ingestion. These studies provided evidence that cross-tolerance to drugs in chronic alcoholics involved not only changes in the central nervous system, but metabolic adaptation in the liver as well. Moreover, apart from the additive depressant effects of alcohol and sedatives on the central nervous system, the inhibition of drug-metabolizing enzymes during acute alcohol consumption contributes to the dangers associated with the combined intake of sedatives and alcohol.

"I surmise that this paper is a *Citation Classic* because it explained well-known clinical phenomena on a molecular basis. The inhibition of drug-metabolizing enzymes was also one of the earliest observations of an effect of alcohol on the liver that is clearly not related to the effects of its metabolism—a concept that has received increased attention in recent years. It also provided strong evidence for the concept that chronic alcohol consumption leads both to injury and to adaptation, and that in some instances, these are closely related. I followed these observations with studies in man and rats showing that alcohol not only affects the activities of drug-metabolizing enzymes but, as predicted, that chronic alcohol ingestion accelerates the disappearance of drugs from the blood and that acute alcohol ingestion inhibits this clearance. These studies were confirmed by others in a variety of clinical and experimental situations,⁴ and served as a basis for close attention to regulating the dosage of many types of drugs in alcoholics."

1. Conney A H. Pharmacological implications of microsomal enzyme induction. *Pharmacol. Rev.* 19:317-53, 1967.

[See also: Conney A H. Citation Classic. *Current Contents/Life Sciences* 22(3):14, 15 January 1979.]

2. Rubin E & Lieber C S. Early fine structural changes in the human liver induced by alcohol.

Gastroenterology 52:1-13, 1967. (Cited 140 times.)

3. Rubin E, Hutterer F & Lieber C S. Ethanol increases hepatic smooth endoplasmic reticulum and drug-metabolizing enzymes. *Science* 159:1469-70, 1968. (Cited 245 times.)

4. Detrich R A & Petersen D R. Interaction of ethanol with other drugs. (Majchrowicz E & Noble E P, eds.)

Biochemistry and pharmacology of ethanol. New York: Plenum Press, 1979. Vol. II, p. 283-302.