

# This Week's Citation Classic

**Lieber C S & Schmid R.** The effect of ethanol on fatty acid metabolism; stimulation of hepatic fatty acid synthesis *in vitro*. *J. Clin. Invest.* **40**:394-9, 1961. [Thorndike Mem. Lab. and Second and Fourth (Harvard) Med. Services, Boston City Hosp., and Dept. Med., Harvard Med. Sch., Boston, MA]

**Liver slices incubated with ethanol had a significant increase in total fatty acids. The incorporation of acetate-C<sup>14</sup> into fatty acids was stimulated and C<sup>14</sup>O<sub>2</sub> production from palmitate-1-C<sup>14</sup> depressed. Another NADH generating system reproduced this effect, while a hydrogen receptor reversed it. [The SC® indicates that this paper has been cited over 210 times since 1961.]**

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"This investigation was carried out at the Thorndike Memorial Laboratory of the Harvard Medical School, where I had joined Charlie Davidson in 1958 to study alcoholic liver disease. The accepted dogma at the time was that liver disease of the alcoholic was not due to alcohol itself, but merely to the malnutrition commonly associated with alcoholism, a view most clearly enunciated by the Nobel laureate Charles Best, who wrote in 1949 that 'there is no more evidence of a specific toxic effect of pure ethyl alcohol upon liver cells than there is for one due to sugar.'<sup>1</sup> However, since it was known that alcohol is oxidized almost exclusively in the liver, I was fascinated by the possibility that it might cause disease through some interference with liver metabolism. A direct way to test this hypothesis was to add alcohol to liver tissue *in vitro* to ascertain whether any change could be observed. Liver slices were therefore incubated in the presence of labeled substrates with or without ethanol. Rudi Schmid, who had joined the unit a year before, taught me the *in vitro* techniques. For

tracing of the labels, a liquid scintillation counter was needed. The only instrument then available in Boston was located in the New England Nuclear plant. We rented it on a 'minute' basis; I regularly rushed through the snowy streets to count a few vials. The results were worth the effort: alcohol was found to exert striking effects on the metabolism of the liver, including promotion of lipogenesis and inhibition of lipid oxidation. Since oxidation of ethanol is associated with reduction of NAD to NADH, I hypothesized that the redox shift may be responsible. Indeed, effects of ethanol were mimicked by another NADH generating system (sorbitol) and prevented by a hydrogen acceptor (methylene blue).

"This paper is often quoted because it documented two new fundamental concepts: (1) Ethanol exerts direct effects on the liver which might play a role in the development of liver disease. (2) Some of these effects on the liver could be traced to the metabolism of ethanol. The hepatotoxicity was subsequently established *in vivo*: with the development of a new alcohol feeding technique as part of a nutritionally adequate, totally liquid diet, rats were shown to develop a fatty liver, the first stage of alcoholic liver disease, in the absence of dietary deficiencies. This was later confirmed in man.<sup>2</sup> Eventually, the final and irreversible stage of liver disease, namely cirrhosis, was produced in the baboon despite adequate diets.<sup>1</sup> The second key idea, namely the link between ethanol effects and its metabolism, led to the demonstration by us and others that alcoholic hyperuricemia, ketosis, hypoglycemia, and various other metabolic complications can be ultimately attributed to such a mechanism. Extension of this concept prompted studies concerning the hepatotoxicity of acetaldehyde. Further investigation of the metabolism of ethanol resulted in the discovery of an alternate pathway in the microsomes associated with activation and inactivation of drugs, hepatotoxic agents, carcinogens, and endogenous steroids"<sup>4</sup>

1. Best C H, Hartroft W S, Lucas C C & Ridout J H. Liver damage produced by feeding alcohol or sugar and its prevention by choline. *Brit. Med. J.* **2**:1001-6, 1949.
2. Lieber C S, Jones D P & DeCarli L M. Effect of prolonged ethanol intake: production of fatty liver despite adequate diets. *J. Clin. Invest.* **44**:1009-21, 1965.
3. Lieber C S, DeCarli L M & Rubin E. Sequential production of fatty liver, hepatitis and cirrhosis in subhuman primates fed ethanol with adequate diets. *Proc. Nat. Acad. Sci. US* **72**:437-41, 1975.
4. Lieber C S. Liver adaptation and injury in alcoholism. *N. Eng. J. Med.* **288**:356-62, 1973.