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This Week's Citation Classic®

Lieber C S & DeCarli L M. Hepatic microsomal ethanol-oxidizing system: *in vitro* characteristics and adaptive properties *in vivo*. *J. Biol. Chem.* **245**:2505-12, 1970.
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A hepatic microsomal ethanol-oxidizing system (MEOS) was described in men and rats and shown to be distinct from alcohol dehydrogenase and catalase but cytochrome P-450-dependent. After chronic ethanol feeding, MEOS activity increased significantly *in vitro*, associated with an accelerated blood ethanol clearance *in vivo*. [The *SCI*® indicates that this paper has been cited in over 440 publications since 1970.]

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Until the 1970s, it was generally believed that the main pathway for ethanol metabolism involved hepatic cytosolic alcohol dehydrogenase (ADH), with a minor contribution from the peroxisomal catalase. Non-ADH ethanol oxidizing activity found in other subcellular fractions was usually attributed to a H_2O_2-dependent reaction mediated by contaminating catalase, especially since this oxidative activity showed preference for methanol rather than ethanol, did not oxidize higher alcohols (such as butanol), and was exquisitely sensitive to catalase inhibitors.[1] In the 1960s, it had become known, however, that liver microsomes metabolize various xenobiotic agents and are capable of an adaptive enzymic response to drug administration with, as a morphological counterpart, proliferation of the membranes of the endoplasmic reticulum. The observation in rats as well as in man[2] that chronic ethanol consumption was associated with such proliferation suggested to me that microsomes might also be the site of ethanol metabolism, as subsequently documented in our *Citation Classic* article. Because of the properties of the microsomal ethanol-oxidizing system (MEOS), including cofactor requirements and response to inhibitors, we concluded that a cytochrome P-450-dependent mono-oxygenase system was involved. This thesis stirred up a decade of extensive experimentation with lively and, at times, acrimonious debate.[1] The issue was finally settled after (a) separation from the microsomes of a fraction devoid of ADH and catalase that contained the bulk of MEOS activity and oxidized higher alcohols (which are not substrates for catalase)[3] and (b) reconstitution of the MEOS using purified NADPH cytochrome P-450 reductase, phospholipids, and semipurified cytochrome P-450, including the demonstration of an ethanol-specific form of cytochrome P-450 with high activity toward ethanol as a substrate.[4] The latter was confirmed more recently with purified proteins in the rabbit.[5]

The paper has been highly cited not only because it highlighted a new pathway for the metabolism of ethanol, but also because it improved our understanding of the metabolic adaptation to ethanol after chronic ethanol consumption. Furthermore, it opened up a novel approach to the interactions of ethanol with a variety of xenobiotic agents.[6] Indeed, cross induction with other microsomal drug-metabolizing systems may explain, in part, the tolerance of alcoholics to many other drugs. Contrasting with ethanol pretreatment (which activates the system), the presence of ethanol was found to decrease drug detoxification, in part through competition for this common microsomal pathway, explaining the exacerbation of drug effects when ethanol is present. Induction of the microsomes was also discovered to be associated with enhanced activation of a variety of solvents used in industry and common medications such as analgesics, thereby explaining the enhanced susceptibility of the alcoholic to the potential hepatotoxicity of these agents. We also found that the ethanol-induced specific form of cytochrome P-450 has an exceptionally high affinity for some carcinogens such as dimethylnitrosamine. Some endocrine (including steroid) abnormalities of the alcoholic and nutritional disorders (involving vitamin D and particularly vitamin A) can also now be understood on the basis of ethanol-microsomal interactions. Finally, through the induction of the microsomal system, excessive ethanol consumption results in enhanced production of the toxic metabolite acetaldehyde that has been incriminated in a number of adverse effects, including dependence to ethanol and various manifestations of alcohol-induced liver injury.[6]

1. **Ziegler D M, Thurman R, Tephly T S & Lieber C S.** Discussion. (Estabrook R W, Gillette J R & Leibman K C, eds.) *The Second International Symposium on microsomes and drug oxidations*. Baltimore: Williams & Wilkins, 1972. p. 458-60.
2. **Lane B P & Lieber C S.** Ultrastructural alterations in human hepatocytes following ingestion of ethanol with adequate diets. *Amer. J. Pathol.* **49**:593-603, 1966. (Cited 130 times.)
3. **Teschke R, Hasumura Y & Lieber C S.** Hepatic microsomal alcohol-oxidizing system: affinity for methanol, ethanol, propanol, and butanol. *J. Biol. Chem.* **250**:7397-404, 1975. (Cited 75 times.)
4. **Ohnishi K & Lieber C S.** Reconstitution of the microsomal ethanol-oxidizing system: qualitative and quantitative changes of cytochrome P-450 after chronic ethanol consumption. *J. Biol. Chem.* **252**:7124-31, 1977. (Cited 115 times.)
5. **Koop D R, Morgan E T, Tarr G E & Coon M J.** Purification and characterization of a unique isozyme of cytochrome P-450 from liver microsomes of ethanol-treated rabbits. *J. Biol. Chem.* **257**:8472-80, 1982.
6. **Lieber C S.** *Medical disorders of alcoholism: pathogenesis and treatment*. Philadelphia: Saunders, 1982. 589 p.