

DeCarli L M & Lieber C S. Fatty liver in the rat after prolonged intake of ethanol with a nutritionally adequate new liquid diet. *J. Nutrition* 91:331-6, 1967.

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The technique of feeding of alcohol as part of totally liquid diets produced an animal model with much greater ethanol intake than had heretofore been possible, while maintaining dietary control. It provided a new tool for the study of many pathologic disorders associated with alcoholism. [The *SCJ*® indicates that this paper has been cited in over 410 publications.]

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In response to the need to develop an animal model with an alcohol consumption of clinical relevance, a totally liquid diet incorporating ethanol was devised. Two key features made this approach successful: by receiving nothing else but this liquid diet, the animals, in order to eat or to drink, were forced to take the alcohol and, with it, whatever nutritional formula was experimentally required. Providing the diet in a liquid form also allowed for stricter pair-feeding of controls than had been possible previously.

The formula described in this paper is a modification of an earlier formulation made with amino acids and published in 1963.<sup>1</sup> To minimize costs, the very expensive amino acid mixtures were replaced by casein, and at the same time, sucrose was replaced by a dextrin maltose mixture that more closely resembled carbohydrates commonly found in foods. The fat content, selected to mimic the average American diet at the time the original formula was devised (43 percent of total calories), was reduced to 35 percent, in keeping with the trend to consume less dietary fat. Vitamins, minerals, and lipotropes were incorporated in the diet to meet or exceed the nutritional requirements as published at that time.

One challenging problem was to obtain a stable suspension of all required nutrients with the alcohol. It was the friendship gained through a decade of close, daily collaboration that allowed us to over-

come the frustration involved. After many unsuccessful trials, adequate stabilization of the diet was finally achieved through painstaking formulation of optimal proportions, mixing procedures, and some days spent at a local dairy firm to acquire the tricks of the trade, such as the use of nutritionally acceptable suspending agents.

Prior to the development of this model, alcohol had been commonly administered to animals in their drinking water. With the latter system, however, ethanol intake is insufficient to cause any liver damage when the diet is adequate because animals have a natural aversion for alcohol. By contrast, with the liquid diet technique, intake is sufficient to sustain appreciable levels of ethanol in the blood. Under these conditions, ethanol is capable of producing a fatty liver in the absence of dietary deficiency, refuting the long-held view that alcohol was not more toxic to the liver than isocaloric carbohydrates.<sup>2</sup> Over the last two decades, improvements and variations of the formula have been made reflecting new dietary information and specific experimental needs.<sup>3</sup>

We believe this paper is frequently cited because it presented the first satisfactory experimental model for the study of the pathogenesis and treatment of alcohol-related pathology. This model provides normal liver morphology in control animals, whereas in those animals given alcohol, it results not only in a fatty liver but also in striking ultrastructural changes. In addition, it produces a score of lesions in other tissues, as well as diverse metabolic, endocrine, and nervous system abnormalities that mimic disorders seen in the alcoholic, such as hyperlipemia, physical dependence, and the fetal alcohol syndrome.

Hundreds of studies carried out worldwide and aimed at elucidating these conditions were made possible by our liquid diet approach. When adapted to the baboon, this technique also allowed, for the first time, the experimental production of alcoholic cirrhosis,<sup>4</sup> thereby settling the controversy concerning the direct etiologic role of ethanol. The strict pair-feeding also facilitated the assessment of alcohol-nutrition interactions.<sup>5</sup>

Finally, application of this procedure led to the discovery of a new pathway of ethanol metabolism, the cytochrome P-450-dependent microsomal ethanol oxidizing system.<sup>6</sup> The unusual affinity of the ethanol-inducible cytochrome P-450 for a score of xenobiotics allowed for a better understanding of the tolerance of alcoholics to other drugs as well as to alcohol and of their enhanced susceptibility to the toxicity of commonplace analgesics, industrial solvents, and carcinogens.

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