

Danzinger R G, Hofmann A F, Schoenfield L J & Thistle J L. Dissolution of cholesterol gallstones by chenodeoxycholic acid. *N. Engl. J. Med.* 286:1-8, 1972. [Gastroenterology Unit, Mayo Clinic and Mayo Foundation, Rochester, MN]

This paper demonstrated that the ingestion of a pure, naturally occurring human bile acid, chenodeoxycholic acid (CDC), produced gradual dissolution of radiolucent (cholesterol) gallstones in four of seven women. Dissolution took from six to 22 months with the only notable side effect of dose-related diarrhea. This work, therefore, opened a whole new vista for the management of a common human disease. [The SCJ[®] indicates that this paper has been cited in over 355 publications since 1972. It more than fulfilled Ingelfinger's expectations.]

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"In 1969, as the only Canadian and surgeon among a group of internationally recognized gastroenterologists, I learned that Les Schoenfield and John Thistle had demonstrated that the ingestion of pure chenodeoxycholic acid (CDC) (which Alan Hofmann had obtained in small quantity from Weddel Pharmaceuticals in England) by patients with gallstones greatly improved the solvent capacity of their bile for cholesterol. A fellow was required to see if such altered bile would induce dissolution of cholesterol gallstones. I leaped at the opportunity!

"Our initial problem was to obtain an adequate supply of encapsulated pure CDC. Then we proceeded to convince physicians in the Mayo Clinic to allow us to 'shanghai' patients who had come for surgical treatment of their gallstones. Simultaneously, we faced the problem of obtaining precise radiographs for accurate follow-up measurements of stone size, i.e., the gallbladder is mobile and its contained movable stones are seldom spheres. Complete dissolution

presented a lesser problem, but that, too, had hazards since tiny stones could easily hide in the contrast material. Definitions were made and limitations for accepting change in size were reluctantly accepted.

"Nothing is ever new! Rewbridge had reported the disappearance of gallstones after the ingestion of bile salts in 1937,¹ but was unable to repeat his initial results with subsequent supplies. Although he had not analyzed his original batch of bile salts, we guessed that his initial supply must have been extremely rich in CDC.

"We presented our initial results to an NIH-sponsored symposium in Phoenix in October 1971, where Franz Ingelfinger, then editor of the *New England Journal of Medicine*, was present. Intrigued by our presentation, he proposed, over cocktails, that if he had the manuscript when he left in 48 hours, it might be the lead article for 1972. You can imagine our enthusiasm and resolve. We rented a typewriter, each of us took a segment, and we began to write furiously. Without figures and photographs (which we promised would follow within ten days), the manuscript was completed at 6:00 a.m., whereupon I hailed a taxi to the Phoenix airport where I placed it in Ingelfinger's hand just before his flight left for Boston. We made it!

"The best recent review is that of the NIH-supported National Cooperative Gallstone Study.² Perhaps 20 percent of all patients with gallstones could benefit from this form of therapy. Recurrence rate after dissolution has not been resolved. Stone recurrence could necessitate several episodes of therapy during a patient's life or continued small daily doses after dissolution. CDC and its 7-beta, hydroxy epimer—ursodeoxycholic acid—are available for routine therapy in Japan and many European countries. We are presently attempting to supply knowledge gained from these compounds to manipulate bile composition more efficiently and to prepare more potent pharmaceutical agents."

1. Rewbridge A G. The disappearance of gallstone shadows following the prolonged administration of bile salts. *Surgery* 1:395-400, 1937.

2. Schoenfield L J, Lachin J M, the Steering Committee (Baum R A, Habig R L, Hanson R F, Hersh T, Hightower N C, Jr., Hofmann A F, Lasser E C, Marks J W, Mekhjian H, Okun R, Schaefer R A, Shaw L, Soloway R D, Thistle J L, Thomas F B, Tyor M P) & the National Cooperative Gallstone Study Group. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone Study. *Ann. Intern. Med.* 95:257-82, 1981.