

# This Week's Citation Classic

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Vlahcevic Z R, Bell C C, Jr., Buhac I, Farrar J T & Swell L. Diminished bile acid pool size in patients with gallstones. *Gastroenterology* 59:165-73, 1970. [Veterans Admin. Hosp., and Depts. Medicine, Surgery, and Biochemistry, Medical College of Virginia, Richmond, VA]

Patients with gallstones were found to have a significantly smaller total bile acid pool than subjects without evidence of gallstones. The findings suggested that a diminished bile acid pool could be an important factor responsible for the production of the abnormal (lithogenic) bile found in patients with gallstones. [The SCI<sup>®</sup> indicates that this paper has been cited in over 305 publications since 1970.]

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"Cholesterol has been recognized as the major constituent of human gallstones since it was first isolated from that source by Poulletier de la Salle in 1763.<sup>1,2</sup> However, it is only within recent years that we have developed an understanding as to how cholesterol is solubilized in bile as a mixed micelle. Adequate proportions of bile acids and lecithin in bile have been found to be essential for the proper solubilization of biliary cholesterol.

"In 1967, Leon Swell had worked with Cecil Enterman at Berkeley and had made the interesting observation that biliary lecithin secretion by the perfused rat liver is directly linked to the availability of bile acids in the system.<sup>3</sup> This was an exciting finding since it suggested that circulating bile acids might play an important role in regulating biliary lecithin secretion *in vivo*, which could have important implications for the proper solubilization of biliary cholesterol.

"It seemed to us that a logical next step to test this hypothesis would be to ascertain if

there was any alteration in the amount of bile acids circulating in the enterohepatic circuit in human subjects with gallstones. Accordingly, we measured the bile acid pool by isotope dilution in subjects with and without gallstones. The data indicated that patients with gallstones had a greatly diminished bile acid pool which was approximately one half that of the subjects without gallstones. Later studies in female and male Caucasians and American Indians confirmed these findings and also showed that the fractional turnover rate of the bile acids was significantly increased.<sup>4,5</sup> The mechanism responsible for the reduction in bile acid pool size was therefore attributed to an increased loss of bile acids coupled with a failure of the liver to synthesize adequate amounts of bile acids to maintain the pool size. We then postulated that gallstone formation in man may be initiated by a decrease in bile acid pool size, which would lead to an inordinate decrease in the secretion of biliary bile acids and lecithin, resulting in bile containing cholesterol microcrystals. More up-to-date information on the present concepts of pathogenesis of cholesterol gallstones has recently been published.<sup>6</sup>

"This paper has been highly cited because it provided a new perspective on the gallstone pathogenesis and served as an impetus for a number of investigations by other workers related to the factors regulating the solubilization of biliary cholesterol. Also, this work formed a basis (at least initially) for the rationale of gallstone dissolution by oral administration of bile salts to expand the bile acid pool. The initial 1970 study was the beginning of a very active scientific collaboration and friendship between myself and Swell, which has continued uninterrupted until the present time."

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2. Ellis C E. Physiology of the sterols, including vitamin D. *Physiol. Rev.* 15:1-97, 1935.
3. Swell L, Enterman C, Leong G F & Holloway R J. Bile acids and lipid metabolism. IV. Influence of bile acids on biliary and liver organelle phospholipids and cholesterol. *Amer. J. Physiol.* 215:1390-6, 1968.
4. Vlahcevic Z R, Bell C C, Jr., Gregory D H, Bulker G, Anttila J P & Swell L. Relationship of bile acid pool size to the formation of lithogenic bile in female Indians of the Southwest. *Gastroenterology* 62:73-83, 1972.
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6. Shaffer S A. Gallstones: current concepts of pathogenesis and medical dissolution. *Can. J. Surg.* 23:517-29, 1980.