

**Rhodes J, Barnardo D E, Phillips S F, Rovelstad R A & Hofmann A F.** Increased reflux of bile into the stomach of patients with gastric ulcer. *Gastroenterology* 57:241-52, 1969. [Gastroenterology Unit and Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, MN]

Bile acid concentrations in the stomach were found to be significantly higher in patients with gastric ulcer compared with matched controls. Since bile acids break the gastric mucosal barrier and damage gastric mucosa, the reflux may play a role in the pathogenesis of gastric ulcer. [The SC1<sup>®</sup> indicates that this paper has been cited in more than 425 publications.]

### Does Bile Cause Gastric Ulcer?

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My intention on going to the Mayo Clinic in September of 1967 was to examine inhibition of gastric acid secretion by duodenal acidification. But, because of difficulties, I turned my attention to duodeno-gastric reflux in patients with gastric ulcer. William Capper, a Bristol surgeon, had encouraged me to explore the area because he had shown reflux in patients with gastric ulcer radiologically, whilst Du Plessis in South Africa had suggested that bile acids played a causative role in gastric ulcer by damaging the mucosa.

By the late 1960s, people were weary of endless studies on gastric secretion that contributed little to our understanding of ulcer disease. A further series of gastric analyses was viewed with scepticism—even disdain—by some of my superiors. One redeeming feature of our simple project was the use of radioactive bile acids to label the bile salt pool and facilitate serial measurements of bile acid concentrations, giving the project a seal of scientific respectability. The results, with free bile reflux after the meal in gastric ulcer patients but not in normals, showed a striking difference between groups and supported previous observations. This compelled those in the field to look at something other than acid secretion.

The work was of contemporary interest because of three parallel developments; Horace Davenport had recently reported on the gastric mucosal barrier to hydrogen ion diffu-

sion with observations on detergents which damaged the barrier. The potential role of bile acids in disease was topical and pursued by Alan F. Hofmann in the department. A third area was recognition that increased acid secretion was unusual in gastric ulcer, and any attempt to implicate Dragstedt's hypothesis for hypersecretion was woefully inadequate and inappropriate to most patients.

If one takes the simple concept that peptic ulcer is a consequence of acid breaking through the gastric mucosa defense, then in the absence of increased acid secretion, some tangible concept to focus on possible mechanisms responsible for maintaining or breaking the mucosal defense was required. Our clinical findings in the late 1960s may have provided this with a further stimulus to explore the mucosal barrier. Major developments since then have included direct measurements of the visible mucous layer on gastric epithelium and the pH gradient across mucus with measurements of bicarbonate secretion by the epithelium to maintain the "mucus-bicarbonate barrier." Additional clinical observations have focused on the role of bile reflux after gastric surgery with the importance of preserving pyloric function, and in esophagitis a recognition that simultaneous incompetence of both pyloric and esophageal sphincters is common. In the therapeutic area, the drive to explore effective measures to strengthen the mucosal barrier has been lessened by the advent of potent agents to reduce acid secretion.

Since research endeavour is directed towards, and not at, the truth, at any one time we can only take pieces of the jigsaw and suggest how they may fit together. Subsequent findings invariably lead to a reappraisal with further investigation. Bile reflux into the stomach is common and associated with pathology. We simply drew attention to the phenomenon at a time when there was current interest in bile acids, the gastric mucosal barrier, and damage to gastric mucosa. Together these combined to substantiate an interesting concept.

1. Rhodes J. Etiology of gastric ulcer. *Gastroenterology* 63:171-82, 1972.
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