CC/NUMBER 20
MAY 14, 1984

This Week's Citation Classic™

Skillman J J, Gould S A, Chung R S K & Silen W. The gastric mucosal barrier: clinical and experimental studies in critically ill and normal man, and in the rabbit. *Ann. Surg.* 172:564-84, 1970.

[Department of Surgery, Harvard Medical School and Beth Israel Hospital, Boston, MA]

Permeability of the gastric mucosa to instilled hydrochloric acid and acid secretion was studied in 26 seriously ill patients, in normal human subjects, and in rabbits. Half of the seriously ill patients (in whom use of steroids, hypotension, renal failure, jaundice, and a lethal outcome was more common) had strikingly increased back-diffusion of H^+ ions in comparison to the less seriously ill patients and to normal subjects. The rabbit experiments showed that a short period of hemorrhagic shock also had a disruptive effect on the gastric mucosal barrier to H^+. The data suggested that disruption of the stomach's normal functional barrier to secreted acid might be a clue to the pathogenesis of acute stress ulceration. [The SCI® indicates that this paper has been cited in over 155 publications since 1970.]

John J. Skillman
Department of Surgery
Beth Israel Hospital
Harvard Medical School
Boston, MA 02215

February 10, 1984

"Our work on the gastric mucosal barrier was stimulated by the experiments of the eminent physiologist from Michigan, Horace Davenport, whose work on this subject, which was started in 1962 at the Mayo Clinic during a sabbatical year with Charles Code,[1] revived an even older concept of the regulation of the acidity in the stomach proposed by the Swedish medical chemist Torsten Teorell. Teorell proposed, in 1939, that there was a continuous diffusion of hydrochloric acid from the gastric lumen into mucosa, which he called 'back-diffusion,' and a simultaneous diffusion of sodium chloride from mucosa to lumen that accounted for the reduction in acidity in the stomach.[2] Based on his experiments with agents which produced damage to the gastric mucosa,[3,4] Davenport suggested the possibility in 1965 that the apparent low rates of acid secretion in patients with chronic gastric ulcer disease might be caused by increased back-diffusion of acid across a damaged mucosa.[5]

"In 1969, we found that eight of the first 150 patients admitted to our newly opened respiratory-surgical intensive care unit had massive hemorrhage from acute, multiple, gastric ulcers, almost all of which were located in the fundus of the stomach.[6] Seven of these eight patients died. The presence of respiratory failure, hypotension, sepsis, jaundice, and renal failure suggested a clinical syndrome which set the stage for the development of acute stress ulceration.

"Investigations in our seriously ill patients were stimulated by the unsolved clinical problem (stress ulceration) and the concepts on the damage to the gastric mucosa suggested by Davenport's timely work. Our own study showed that the gastric mucosa of seriously ill patients (especially those with multiple complications) had strikingly abnormal permeability to instilled acid. The status of the gastric mucosal integrity could not be predicted from standard tests of gastric secretion (basal acid output and augmented histamine tests). We suggested that abnormal permeability of the stomach to acid in the presence of poor mucosal perfusion might be related to the subsequent development of acute gastric ulceration and hemorrhage. Subsequent experiments in animals by Kivilaakso, working in William Silen's laboratory, showed that impairment of buffering capacity in the gastric mucosa, rather than tissue anoxia, is the key factor leading to ulceration during hemorrhagic shock.[7]

"There may be two reasons why this paper has been cited frequently. First, it was one of the first human studies of the barrier function of the stomach in critically ill patients. The work attempted to dissect a clinical problem in intensive care units which was often fatal and which was occurring with an alarming frequency. Second, the paper provided a rational basis for a regimen of prevention of stress ulceration with antacid based on the experiments of hemorrhagic hypotension in rabbits. The experiments in rabbits, which were conducted by Raphael Chung in Silen's laboratory, showed that buffering of gastric acid with sodium lactate significantly reduced the amount of back-diffusion of acid and prevented gastric ulceration.

"Titration of gastric juice to a pH > 3.5 by the hourly instillation of antacid in seriously ill patients has become the mainstay of stress ulceration prophylaxis in most intensive care units.[8] This regimen has eliminated almost completely the clinical problem of acute stress ulceration of the stomach. A recent review of stress ulceration can be found in an entire issue of the *World Journal of Surgery*."[9]

1. **Davenport H W, Warner H A & Code C F.** Functional significance of gastric mucosal barrier to sodium. *Gastroenterology* 47:142-52, 1964. (Cited 220 times.)
2. **Teorell T.** On the permeability of the stomach mucosa for acids and some other substances. *J. Gen. Physiol.* 23:263-74, 1939. (Cited 90 times since 1955.)
3. **Davenport H W.** Gastric mucosal injury by fatty and acetylsalicylic acids. *Gastroenterology* 46:245-53, 1964.
4. ----------. Citation Classic. Commentary on *Gastroenterology* 46:245-53, 1964. *Current Contents/Clinical Practice* 9(7):16, 16 February 1981.
5. ----------. Is the apparent hyposecretion of acid by patients with gastric ulcer a consequence of a broken barrier to diffusion of hydrogen ions into the gastric mucosa. *Gut* 6:513, 1965. (Cited 90 times.)
6. **Skillman J J, Bushnell L S, Goldman H & Silen W.** Respiratory failure, hypotension, sepsis and jaundice—a clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. *Amer. J. Surg.* 117:523-30, 1969. (Cited 95 times.)
7. **Kivilaakso E & Silen W.** Pathogenesis of experimental gastric-mucosal injury. *N. Engl. J. Med.* 30:364-9, 1979.
8. **Priebe H J & Skillman J J.** Methods of prophylaxis in stress ulcer disease. *World J. Surgery* 5:223-33, 1981.
9. **Ritchie W P, Jr.,** ed. Stress ulcer and erosive gastritis. (Whole issue.) *World J. Surgery* 5(2), 1981. 162 p.

