Leading article

Mucus-bicarbonate barrier — shield or sieve

It is now almost 30 years since Heatley\(^1\) first published his mathematical model of the mucus barrier to acid-pepsin attack. At that time, techniques were not available to evaluate the components of his model and the existence of a pH gradient across mucus gel, sustaining the cell surface at near neutral pH despite luminal acid, could not be confirmed. During the last decade advances in technology, coupled with the development of potent inhibitors of gastric acid secretion have allowed definition of the components of the mucus-bicarbonate barrier together with confirmation of the existence of a pH gradient from lumen to epithelial cell surface.\(^2\) The molecular structure of mucus gel glycoprotein has been identified and methods developed for measuring gel thickness in unfixed mucosal samples.\(^3-5\) The existence of alkali secretion by gastric and proximal duodenal mucosa has been shown in a number of species, including man, and the mechanisms of bicarbonate transport explored.\(^6\) Finally, using pH sensitive microelectrodes the existence of a pH gradient, remarkably similar to that proposed by Heatley, has been shown across gastric and duodenal mucus gel in animals and man.\(^7-8\)

Experiments have also been conducted to evaluate the functional significance of this mucus-bicarbonate barrier. Damaging agents, such as bile salts and non-steroidal anti-inflammatory drugs, inhibit gastric alkali secretion and reduce the magnitude of the mucus pH gradient.\(^7-10\) In contrast, protective prostaglandins either increase alkali secretion and the magnitude of the pH gradient or prevent the detrimental effects of bile salts and non-steroidal anti-inflammatory drugs.\(^9-10\) There is also evidence that the magnitude of gastric and duodenal alkali secretion may be influenced by the luminal environment. Animal and human studies have shown that increasing luminal acidity results in increased alkali secretion, suggesting the existence of an autoregulatory mechanism that adjusts the mucus-bicarbonate barrier to prevailing luminal acidity.\(^11-12\) More recently investigators have explored the possibility that ulcer healing drugs may act by enhancing the mucus-bicarbonate barrier. In this issue of Gut, Professor Konturek and coworkers present evidence that the healing action of colloidal bismuth (De-Nol) may be partly mediated by its stimulatory effects on gastroduodenal alkali secretion and local prostaglandin metabolism.\(^13\) There is also evidence that sucralfate (Antepsin) and the aluminium component of certain antacids have similar actions on alkali secretion and mucosal prostaglandin synthesis.\(^14\) The inference from such observations is that there is a relationship between the ulcer healing actions of these drugs and their effects on the mucus-bicarbonate barrier and local prostaglandin metabolism.
At first glance, the reader could now conclude that the perplexing problem of mucosal defence against acid and pepsin attack has at last been resolved and that the mucus-bicarbonate barrier provides the shield that protects the epithelium from its noxious luminal environment. Unfortunately the story does not have a happy ending. There are a number of flaws in the hypothesis that the mucus-bicarbonate barrier provides the major component of mucosal defence. It has been reported that the gastric mucus pH gradient may be overwhelmed by luminal pH of less than 1.5; and this occurs daily in the healthy stomach. Although protective prostaglandins have been shown to increase mucus gel thickness and alkali secretion by gastroduodenal mucosa, histological studies of mucosae 'protected' by prostaglandins have shown substantial damage to the surface epithelium with preservation of the deeper mucosal structures and gastric glands. Such observations suggest that the site of prostaglandin mediated protection may be below the epithelial layer and therefore independent of the mucus-bicarbonate barrier that covers the normal mucosa. These studies have also shown the existence of another type of mucus-bicarbonate barrier, termed the mucus cap, which may be of greater importance than the normal mucus layer for epithelial repair. The mucus cap consists of a thick layer of sloughed superficial epithelial cells, fibrin and mucus covering the damaged mucosa, into which diffuses alkali from interstitial tissue. It has been suggested that after damage to the superficial epithelium, this barrier prevents exposure of cell nests in the gastric pit to luminal acid and pepsin, allowing the cells to migrate over denuded lamina propria and cover epithelial defects (restitution). Removal of the mucus cap appears to delay functional recovery of the mucosa and it is possible that prostaglandins help maintain the barrier function of the cap by maintaining mucosal blood flow and thus delivery of alkali, oxygen and nutrients to the interstitial space and removal of any hydrogen ions into the venous circulation.

What then is the functional role of the mucus-bicarbonate barrier overlying normal epithelium? This layer undoubtedly does prevent exposure of the epithelium to an acidic environment at luminal pH over 1.5. At lower pHs it is possible that other defence mechanisms would be recruited, such as the surface active phospholipid layer, cell membrane impermeability to hydrogen ions or the process of restitution. The normal mucus-bicarbonate barrier provides little defence against ethanol damage and, from experimental observations, probably does little to prevent mucosal damage by bile salts and non-steroidal anti-inflammatory drugs. The role played by the mucus-bicarbonate barrier in peptic ulcer pathogenesis is equally contentious. Defects in mucus gel structure and the alkali response to luminal acidification have been shown in peptic ulcer disease, but how these contribute to ulcer formation remains speculative. A generalised defect in the mucus-bicarbonate barrier cannot explain the focal nature of chronic peptic ulcer and its predisposition for certain anatomical sites. This argument would also apply to the other protective zones such as surface active phospholipids (gastric only), impermeability of the apical cell membrane/intercellular junctions and restitution. However, coupled with focal defects in blood flow, such generalised abnormalities could result in localised ulcers. Once such an ulcer has formed, clearly the epithelial mucus bicarbonate barrier disappears from the ulcerated tissue and is unlikely to contribute further to the ulcering process. The healing of such ulcers
would also involve a complex process with the re-establishment of a connective tissue matrix and vascular network, as well as re-epithelialisation. The inflammatory response present in chronic ulcers may well play an important role in the healing process. Although prostaglandins and other ulcer healing agents enhance the mucus-bicarbonate barrier that overlies healthy epithelium, it is difficult to envisage what importance this would have in accelerating chronic ulcer healing. It would appear more realistic to propose that enhancement of the mucus-bicarbonate barrier would be of greater value in ulcer prophylaxis. A strengthened barrier would perhaps prevent recurrence of peptic ulcer after initial healing, or may be important in preventing widespread erosive gastritis or stress ulceration in severely ill patients. The observations of Professor Konturek and others, on the effect of ulcer healing agents on alkali secretion by gastroduodenal mucosal are therefore of great interest, although I suspect of little relevance to chronic ulcer healing.

W D W REES

University of Manchester School of Medicine,
Hope Hospital,
Salford M6 8HD

References


The Editor and Technical Editor wish all readers of *Gut* a Happy Christmas and Prosperous New Year.

---

**Forthcoming Scientific Meetings of the British Society of Gastroenterology**

**SPRING 1988** — 23–25 March
University of Leicester

**AUTUMN 1988** — 13–16 September
University of Sheffield

*For details of registration please contact:*

The Administrative Secretary,
BSG, 3 St Andrew’s Place,
Regent’s Park,
London NW1 4LB.

*Tel: 01–387 3534 (International 44–1–387 3534)*