mucus is approximately 25% of $\mathbf{D}_{H^+}$ in free solution.[1,6–8] This modest decrease in permeability can not, of itself, add much to the overall barrier function of the gastric mucosa. $\mathbf{D}_{H^+}$ in free solution at 37 °C is 6.6×10^{-5} cm^2/sec. A typical $\mathbf{D}_{H^+}$ through native (unprocessed) gastric mucus[8] is $1.75 \cdot 10^{-5}$ cm^2/sec. This latter figure translates into a flux through a 100 µm thick mucus gel of ~8 µmol/cm^2/sec. Transmucosal proton flux can be roughly estimated by measuring the decrease in proton concentration in a pylorus-ligated stomach in which acid secretion has been maximally inhibited. Assuming a surface area of 10 cm^2 for a rat stomach, transmucosal proton flux, calculated in this fashion is only 0.008 µmol/cm^2/sec, only 0.1% of the proton flux per area that is crossing the mucus.[9] Thus, the modest permeability barrier presented by gastric mucus in and of itself probably plays little if any role in protecting the underlying epithelium from luminal acid.

Possible protective function of mucus

Since mucus is likely to play only a small role in terms of its overall permeability to proton diffusion, what other functions might it have? One of the most logical functions of mucus is to stabilize a transgel pH gradient. Numerous studies have documented, with the use of microelectrodes slowly advanced through the gel, that the pH within the mucus gel gradually increases as the electrode is advanced towards the mucosa. With luminal pH above 2, pH values as high as 7 have been measured juxtamucosally (just above the luminal membranes of the surface epithelial cells). The genesis of this pH gradient is believed to be due to the neutralization of inwardly permeating protons by secreted bicarbonate ions. In order to achieve a stable pH gradient, it is thought that a modest permeability barrier, as provided by the mucus gel, is sufficient to stabilize an unstirred layer, enabling the perpetuation of a pH gradient. An example of a gel-stabilized gradient would be the concentration gradient surrounding the well of an Ouchterlony agar plate. This hypothesis, though logical and appealing, has been questioned, since microelectrode measurements indicate that the pH gradient can extend beyond the surface of visible adherent mucus.[10] Recent observations of gel pH have also provided data inconsistent with this hypothesis (see below).

Another possibility is that the mucus, even with its modest permeability barrier, plays an important role in damping the rapid shifts of proton concentration that occur in the stomach after meals. In humans, 24 hour pHmetry indicates that proton concentrations in the bulk luminal fluid can change 3 log orders in 10 minutes.[11] Such rapid changes in luminal pH would stress the epithelial cells, which have homeostatic mechanisms, such as sodium-proton exchange, that actively remove influxing protons from the intracellular milieu, preserving cell viability.[1] Since some of these mechanisms take several minutes to be maximally activated, the modest permeability barrier presented by gastric mucus could effectively damp the large fluctuations of luminal pH, providing a more gradually changing environment for the epithelial cells. The importance of the mucus gel in preserving intracellular pH (pH_i) during luminal acidification has been shown repeatedly in rat gastric mucosa, where perturbations that decrease transgel proton permeability also preserve pH_i during acid challenge (for a review, see[12]). For example, treatments such as bismuth salts and human spasmolytic peptide both help preserve pH_i during acid superfusion in an *in vivo* preparation of gastric mucosa during acid challenge by increasing the barrier function of mucus, without altering other known defensive mechanisms such as mucosal blood flow.[13–15] Both treatments decreased the $\mathbf{D}_{H^+}$ of mucus without affecting its thickness, thereby enhancing its barrier function.

The Hydrophobic Layer

Several groups have documented the existence of a hydrophobic layer at the luminal surface of gastric mucus,[4,16–18] although an earlier paradigm suggested that the apical membrane of the epithelial cells itself was hydrophobic.[19] The layer is thought to impede inward proton flux by virtue of its hydrophobic nature. Indeed, correlative studies of mucus hydrophobicity, as measured by contact angle goniometry, and gastric mucosal injury, have demonstrated clear associations between this measure and gastroprotection. For example, prostaglandins, which are known gastroprotective compounds, increase the contact angle (hydrophobicity) of the mucus gel, whereas damaging compounds, such as NSAIDs, decrease the contact angle.[17] Hydrophobicity has also been measured in clinical circumstances, such as *Helicobacter pylori* infections, which decrease the contact angle. Criticisms of this theory, however, have been directed at the technique, which involved drying the mucosa prior to contact angle measurement, and the lack of supportive evidence obtained *in vivo* that the hydrophobic layer actually impedes proton permeation. The thermodynamic stability of a lipid monolayer, as envisioned by some investigators, has also been questioned. Nevertheless, the concept of a hydrophobic layer is attractive inasmuch as it might decrease $\mathbf{D}_{H^+}$ much more than would be measured in Ussing chambers. Furthermore, we have observed that carbon particles, which are hydrophobic, adhere readily to the surface of gastric mucus *in vivo*, but not to duodenal mucus, suggesting differing surface characteristics of the mucus secreted by either organ.