Back-Diffusion of CO₂ and Its Influence on the Intramural pH in Gastric Mucosa

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We have examined the back-diffusion of CO₂ generated by buffering HCl with NaHCO₃ in the stomach, observed its influence on the pH in the wall of the gastric mucosa, and compared its effects with those of HCl. Isolated stomachs of 17 anesthetized dogs were exposed to either (1) 250 ml NaCl at pH 7, or (2) 125 ml HCl (12.5 meq) + 125 ml NaHCO₃ (12.5 meq) to generate 12.5 meq CO₂ in the stomach, or (3) 250 ml HCl alone to give either 12.5 or 35 meq HCl in the stomach. Samples of gastric fluid and arterial blood were collected every 20 min for 6 hr and analyzed for pH and pCO₂. The intramural pH of the gastric wall was measured by hollow viscus tonometry. The pCO₂ in gastric juice rose to 1184 ± 139 mm Hg upon the generation of CO₂ in the stomach. The half-time of the CO₂ generated by the buffering of acid was 32 ± 4 min and of the pCO₂ was 18.7 ± 0.7 min. The half-time of an equimolar amount of HCl was 2 hr 42 min ± 40 min. The disappearance of the CO₂ was accompanied by a rise in intragastric pH from 6.0 ± 0.01 to 6.8 ± 0.09 (P < 0.05), and by a fall in intramural pH in the gastric wall from control values of 7.31 ± 0.05 to 6.3 ± 0.8 (P < 0.001). In contrast the pH in gastric fluid did not change and the pH in the intramural fluid did not fall below control values following the administration of 12.5 or 35 meq HCl alone.

INTRODUCTION

Upon contact with bicarbonate secretions in the duodenum, gastric acid is buffered by being transformed from a strong acid (HCl) into a weaker acid (H₂CO₃) with a pKₐ of 6.1. The dissociation of this weak acid yields CO₂ and induces a rise in pCO₂ in the luminal fluid that has been observed to be as high as 800 mm Hg [24, 29]. Neutralization of the acid is achieved by the disposal of the CO₂. Isotopic studies using ¹⁴C-labeled bicarbonate have shown that 95% of the CO₂ formed by the buffering of gastric acid is disposed of by the lungs [27]. Thus the disposal of gastric acid in the duodenum is, in effect, achieved by the conversion of acid present in one form (H⁺) to acid present in another form (CO₂) that can be exhaled from the lungs.

Although in healthy subjects buffering of gastric acid by bicarbonate occurs in the duodenum, in some patients, such as those with gastric ulcers, buffering of acid by bicarbonate secretions may occur in the stomach [2, 8, 21]. In this study we have examined the possibility that the buffering of acid by bicarbonate in the stomach might increase the gastric mucosal permeability to acid by transforming acid present in a relatively impermeable form (H⁺) to acid present in a more permeable form (CO₂).

METHODS

Experimental Model

After an 18-hr fast 22 adult mongrel dogs weighing between 12 and 20 kg were anesthetized with pentobarbital. Their stomachs were isolated by ligatures placed around the pylorus and esophagus. A polyethylene catheter for the intermittent sampling of luminal fluid was placed into the stomach and se-
cured with two purse string sutures. The stomach was irrigated clear with saline and emptied. A second catheter, with heparin lock, was placed into the femoral artery for the intermittent sampling of blood. The stomach was filled with 250 ml of normal saline and the abdomen closed with towel clips allowing only the polyethylene tube to transverse the abdominal wound. Samples of luminal fluid and arterial blood were collected anaerobically at 20-min intervals thereafter and placed onto ice. Care was taken to discard any fluid contained in the dead space. After 1 hr the gastric contents were aspirated completely and replaced with 250 ml of test fluid (see below). Further samples were collected at 20-min intervals thereafter for another 4 hr. After the last sample had been collected the volume of fluid remaining in the stomach was aspirated completely and measured. Previous studies have shown that the fractional loss of fluid collected by aspiration alone with an open pylorus decreases linearly as the volume of fluid aspirated increased, and to be negligible when the volume of fluid aspirated exceeded 100 ml [10]. The fractional loss has also been shown to be negligible when fluid was prevented from leaving the stomach [19]. No inert marker was, therefore, used to aid in the measurement of the large volume (±200 ml) of fluid remaining in the stomach at the end of these experiments in which gastric emptying was prevented by pyloric ligature.

Experimental Protocols

1. Controls. Five dogs were used as controls. In these dogs the test fluid placed into the stomach consisted of 250 ml normal saline.

2. Back-diffusion of H⁺. Seven dogs were used to determine the rate at which H⁺ diffused from the stomach. In the first four dogs the test fluid consisted of 12.5 meq HCl diluted in normal saline to a final volume of 250 ml to give an in vitro concentration of 140 meq/liter.

3. Back-diffusion of CO₂. Five other dogs were used to determine the rate at which CO₂ diffused from the stomach. In each of these dogs 12.5 meq HCl and 12.5 meq NaHCO₃ were introduced simultaneously into the stomach to give a final volume of 250 ml and to generate 12.5 meq CO₂ in the stomach and a maximum in vitro CO₂ concentration of 50 meq/liter in an acidic environment.

4. Diffusion of CO₂ in stomach vs duodenum. The permeability of gastric mucosa to CO₂ was compared with permeability of duodenal mucosa in another five dogs. In these dogs the stomach and duodenum were separately isolated by ligatures placed around the esophagus, pylorus, and distal duodenum. Pancreatic and biliary secretion was not interrupted. Both gastric and duodenal pouches were cannulated. The gastric pouch was filled with 200 ml normal saline and the duodenal pouch with 50 ml normal saline. Samples of fluid were collected at 20-min intervals for 1 hr and more frequently for the next 90 min. The volume of fluid aspirated was replaced with an equal volume of saline. After the first hour the dogs were made to rebreathe into a bag containing 100% O₂ for 30 min to raise the pCO₂ in the arterial blood. The dogs were allowed to breathe spontaneously again for the last hour.

Measurement of pH and pCO₂

The pH and pCO₂ in samples of arterial blood and the pCO₂ in samples of luminal fluid were measured with a pH/blood-gas analyzer (IL Micro 13 Instrumentation Laboratory, Lexington, Mass.). The pH in luminal fluid was measured with a separate pH electrode (Radiometer, Copenhagen). The calibration of the instruments was checked at the beginning and end of each experiment. The acidity [H⁺] in samples of luminal fluid was determined from the measurements of pH in the manner described by
Moore and Scarlata [19]. The correction factor applicable to our experiments for conversion of hydrogen ion activity \([H^+]\) to hydrogen ion concentration \([H^+]\) was derived by adding known amounts of HCl to normal saline that had been incubated in a volume of 250 ml in the stomach (Fig. 1).

**Measurement of Intramural pH**

The pH in the wall of the stomach was measured by hollow viscus tonometry [1]. The intramural pH was calculated from the \(pCO_2\) in luminal fluid and the bicarbonate concentration in arterial blood with the Henderson-Hasselbach equation. This method of measuring intramural pH \((pHi)\) depends upon the assumption that \(CO_2\) is freely diffusible in the cell membrane, and that the \(pCO_2\) in the luminal fluid equilibrates with that in the wall of the gut. It depends also upon the knowledge that the \(pCO_2\) within cells is linearly related to the \(pCO_2\), in their extracellular environment [23]. It is also dependent upon the assumption that the bicarbonate concentration in the wall of the gut is the same as that being delivered to the gut in arterial blood. Using this method the \(pH_i\) in the wall of the stomach was found to be \(7.47 \pm 0.03\) in 16 dogs and in the duodenum to be \(7.33 \pm 0.03\) in 10 dogs when measured 1 hr after allowing the \(pCO_2\) in luminal fluid to equilibrate with that in the wall of the gut. The validity of calculating the intramural pH in this manner was established by direct measurement with a micro-glass pH probe (Microelectrodes Ind., Londonderry, N. H.) placed in a submucosal tunnel in preliminary studies incorporating 114 paired readings in the stomach, small bowel, and colon of 16 dogs. The validity of calculating the intramural pH in this manner was determined in a variety of conditions, including intestinal ischemia and the presence of exogenous acid in the stomach. No attempt was made to maintain the pH in the lumen at any fixed level during these validation experiments (Fig. 2).

**Statistics**

The data were expressed as a mean ± standard error of the mean and statistical significance assessed by \(t\) tests.

**RESULTS**

1. **Controls**

The pH in the lumen of the stomach remained constant for the duration of each control experiment (Fig. 3), as did the \(pCO_2\) (Fig. 4). The \(pCO_2\) in luminal fluid equilibrated over a period of 1 hr with that in
arterial blood (Fig. 5). The volume of fluid added to the stomach at the beginning of each experiment (250 ml) fell by 60 ± 2 ml due to the intermittent sampling of fluid and to the diffusion of fluid from the stomach. The volume of fluid present in the stomach when each sample was collected was calculated in the knowledge that the volume of fluid removed with each sample and the volume of fluid lost by diffusion [3] was the same in each 20-min test period. The rate of acid secretion within each 20-min period, calculated on the basis of these volumes and [H+] gradients, remained very low for the duration of each of these control experiments. The pH in the wall of the stomach, measured by hollow viscus tonometry, fell slightly during the course of the control experiments (Fig. 6).

2. Back-Diffusion of H⁺

The pH in the stomach fell following the addition of HCl and remained fairly constant thereafter (Fig. 3). The pCO₂ did not change from control values (Fig. 4). The volume of fluid (250 ml) added to the stomach at the beginning of each experiment fell by 62 ± 2.4 ml during the 4 hr experiments due to the intermittent sampling of fluid and also to the diffusion of acid from the stomach. The amount of acid present in the stomach at the beginning of each experiment (12.87 ± 1.0 meq) decreased with the passage of time. The $t_{1/2}$ of this H⁺ was 2 hr and 42 ± 40 min (Table 1). The rate at which H⁺ left the stomach during each 20-min test period was linearly related to the average of the [H⁺] gradients present at the beginning and end of each test period (Fig. 7). The positive intercept of this regression equation (0.18 meq/hr) was a reflection of the basal rate of acid secretion, and was of the same order as the basal rate of acid secretion observed in the same dogs during the first hour of each experiment (0.01 ± 0.08 meq/hr). The slope of this regression equation (0.048) provided a measure of the gastric mucosal permeability to H⁺ in the seven dogs studied.

3. Back-Diffusion of CO₂

The pH in the lumen of the stomach rose rapidly toward neutrality following the introduction of HCl and NaHCO₃ into the stomach (Fig. 3). At the same time the pCO₂ in the lumen of the stomach rose to unre-
Fig. 5. Influence of rebreathing into a bag containing 100% O₂ on pCO₂ in arterial blood, duodenal fluid, and gastric fluid in five anesthetized dogs.

Fig. 6. Intramural pH, calculated from pCO₂ in gastric fluid and [HCO₃⁻] in arterial blood, during luminal exposure to 250 ml saline (n = 5), and to either 12.5 meq or 35 meq HCl (n = 7) and 12.5 meq HCl plus 12.5 meq NaHCO₃ (n = 5) each diluted in 250 ml of normal saline. Values obtained during exposure to HCl and NaHCO₃ were significantly lower than those obtained during exposure to either saline or HCl (P < 0.001).
TABLE 1

H⁺ LOG REGRESSION EQUATIONSa

<table>
<thead>
<tr>
<th>r</th>
<th>a</th>
<th>b</th>
<th>t1/2</th>
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<tbody>
<tr>
<td>0.71</td>
<td>15.83</td>
<td>-1.53</td>
<td>2 hr 56 min</td>
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<tr>
<td>0.95</td>
<td>11.56</td>
<td>-1.31</td>
<td>1 hr 23 min</td>
</tr>
<tr>
<td>0.73</td>
<td>11.99</td>
<td>-1.07</td>
<td>4 hr 27 min</td>
</tr>
<tr>
<td>0.87</td>
<td>17.08</td>
<td>-1.26</td>
<td>2 hr 2 min</td>
</tr>
<tr>
<td>x ± SEM</td>
<td>12.87 ± 1.0</td>
<td></td>
<td>2 hr 42 min ± 40 min</td>
</tr>
</tbody>
</table>

a The H⁺ log regression equations observed during exposure to 12.5 meq H⁺ diluted in 250 ml saline and the calculated t₁/₂ of H⁺ in the stomach.

The volume of fluid introduced into the stomach at the beginning of each test period (250 ml) fell by 70 ± 10 ml during the 4-hr experiments. The total amount of CO₂ (TCO₂) calculated from the pH and pCO₂ and from the calculated volume present in the stomach when each sample was taken, fell with the passage of time. The t₁/₂ of the TCO₂ was 32 ± 4 min (Table 3). This t₁/₂ was 5.1 times shorter than the t₁/₂ of an equimolar amount of HCl (2 hr 42 min ± 40 min) administered in the preceding experiments. This difference was statistically significant (t = 3.94, P < 0.001).

The rate at which CO₂ left the stomach during each 20-min test period after the first hour’s exposure to HCl and NaHCO₃ was linearly related to the average pCO₂ gradient present between the lumen and blood at the beginning and end of each 20-min test period (Figs. 7 and 8). The positive intercept of this regression equation (0.03 meq/hr) was a reflection of the basal rate of acid se-

TABLE 2

pCO₂ LOG REGRESSION EQUATIONa

<table>
<thead>
<tr>
<th>r</th>
<th>a</th>
<th>b</th>
<th>t₁/₂</th>
</tr>
</thead>
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<tr>
<td>0.97</td>
<td>1203</td>
<td>-203.3</td>
<td>19.3</td>
</tr>
<tr>
<td>0.99</td>
<td>1020</td>
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<td>17.8</td>
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<td>-276.3</td>
<td>17.6</td>
</tr>
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<td>0.997</td>
<td>1347</td>
<td>-238.3</td>
<td>16.9</td>
</tr>
<tr>
<td>0.98</td>
<td>769</td>
<td>-126.7</td>
<td>20.8</td>
</tr>
<tr>
<td>x ± SEM</td>
<td>1185 ± 139</td>
<td></td>
<td>18.5 ± 0.7</td>
</tr>
</tbody>
</table>

a pCO₂ log regression equation occurring during exposure to 12.5 meq HCl and 12.5 meq NaHCO₃ diluted in 250 ml of saline and the calculated t₁/₂ for the pCO₂ in the stomach.

![Image of a graph showing the relationship between log rate of H⁺ loss and log pH gradient.](image-url)
cretion, and of the same order as that observed in the first hour of each experiment in these five dogs (0.05 ± 0.2 meq/hr) and as that observed in the seven dogs exposed to HCl alone (0.01 ± 0.8 meq/hr). The slope of this regression equation (0.24) provided a measure of the gastric mucosal permeability to CO₂ in the five dogs studied. The permeability to CO₂ was 5.0 times greater than that to H+ alone (0.048). This difference between the slopes was statistically significant (P < 0.05).

4. Intramural pH

The back-diffusion of H+ occurring following the addition of 12.5 meq and also of 35 meq HCl to the stomach did not reduce the intramural pH significantly below control values (Fig. 6). The back-diffusion of CO₂ occurring following the addition of 12.5 meq of HCl and 12.5 meq of NaHCO₃ with the generation of CO₁ did reduce the intramural pH below control values and below those observed with HCl alone. The intramural pH returned toward control values as the experiments progressed.

5. pCO₂ in Stomach vs CO₂ in Duodenum

The pCO₂ in gastric and duodenal fluid rose in parallel during the first hour toward that observed in arterial blood (Fig. 5). The

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tbody>
<tr>
<td>TCO₂ LOG REGRESSION EQUATION*</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>r</th>
<th>a</th>
<th>b</th>
<th>t₁/₂ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.95</td>
<td>15.9</td>
<td>-2.36</td>
<td>29.5</td>
</tr>
<tr>
<td>0.97</td>
<td>13.4</td>
<td>-1.79</td>
<td>43.0</td>
</tr>
<tr>
<td>0.996</td>
<td>23.1</td>
<td>-3.67</td>
<td>23.5</td>
</tr>
<tr>
<td>0.72</td>
<td>3.6</td>
<td>-0.49</td>
<td>39.8</td>
</tr>
<tr>
<td>0.98</td>
<td>11.9</td>
<td>-1.89</td>
<td>23.3</td>
</tr>
</tbody>
</table>

$x ± SEM \quad 13.6 ± 3.2 \quad 31.8 ± 4.1$

* TCO₂ log regression equation occurring during exposure to 12.5 meq HCl and 12.5 meq NaHCO₃ diluted in 250 ml of saline and the calculated t₁/₂ of the TCO₂ in the stomach.

pCO₂ in the stomach and duodenum rose further in parallel and then returned toward basal values as the dogs were made to re-breathe and then allowed to breathe spontaneously again. The pCO₂ in the stomach measured at each moment in the experiment was linearly related to that measured in the duodenum ($r = 0.77, P < 0.001$) the slope of the regression equation being 0.8.

DISCUSSION

This study has confirmed that both H+ [6] and CO₂ [17] can diffuse from the lumen of the stomach. It has also shown in dogs that the stomach is 5.0 times more permeable to CO₂ than to H+ and that CO₂ diffuses 5.1 times more rapidly from the stomach than an equimolar amount of H+. Gastric mucosa appeared also to be as permeable to CO₂ as duodenal mucosa. In contrast to the relatively slow back-diffusion of H+, which was not accompanied by any appreciable increase in the pH of gastric luminal fluid or by any appreciable fall in intramural pH below control values, the more rapid back-diffusion of CO₂ was accompanied by the neutralization of gastric luminal fluid and by a fall in intramural pH below
control values and below that encountered with the exposure to H⁺ alone. The findings are consistent with the hypothesis that the neutralization of acid by bicarbonate in the stomach increases gastric mucosal permeability to acid by transforming acid present in a relatively impermeable form (H⁺) to acid present in a more permeable form (CO₂).

As in other studies the rate at which H⁺ diffused from the stomach was linearly related to the [H⁺] gradient across the stomach [14]. It was, by extrapolation from the regression equation in Fig. 7, 7.1 meq/hr when applied in a concentration of 160 meq/liter. This rate of H⁺ back-diffusion compares favorably with the rates observed in healthy dogs [27] and human subjects [11, 25] during exposure to 160 meq/liter of HCl alone. The basal rate of acid secretion observed in our experiments was very low and, in the control experiments, remained constant for the duration of each 4-hr experiment. The basal rate of acid secretion was too small to have caused any significant underestimation in the rate of H⁺ back-diffusion.

The pCO₂ in luminal fluid rose to an estimated 1185 ± 139 mm Hg immediately following the introduction of 12.5 meq of HCl and 12.5 meq of NaHCO₃ into the stomach. This level approaches that calculated with the Henderson-Hasselbach equation to have been achieved following the generation 12.5 meq of CO₂ in 250 ml of fluid at low pH (1629 mm Hg). A pCO₂ approaching 1000 mm Hg has been found by direct measurement in luminal fluid in dogs [24] and in man [16, 25, 29]. The pCO₂ in luminal fluid fell rapidly from this high level with the diffusion of CO₂ from the stomach and the formation of bicarbonate in luminal fluid. As in other studies the rate of CO₂ diffusion was linearly related to the pCO₂ gradient present [15, 30]. It was, by extrapolation from the regression equation in Fig. 8, 12.5 meq/liter at the estimated pCO₂ gradient present immediately following the addition of HCl and HCO₃ to the stomach. This rate of back-diffusion was 5.0 times greater than that (2.5 meq/hr) at the estimated [H⁺] gradient present immediately following the introduction of 12.5 meq HCl into the stomach. It was twice as great as the rate of H⁺ back-diffusion, calculated by extrapolation from the regression equation in Fig. 7, to occur during exposure to 160 meq/liter of HCl (7.1 meq/hr), and approximately of the same order as that expected from the addition of bile to 160 meq/liter of HCl—an agent known to increase the mucosal permeability to H⁺ and to cause acute gastric mucosal injury [7, 9, 11, 22]. The back-diffusion of CO₂ that occurred following the buffering of acid by exogenous bicarbonate was also accompanied by the neutralization of luminal fluid and by a transient fall in the intramural pH to values shown in other studies to be associated with the development of acute gastric mucosal injury [13]. The fall in intramural pH occurring with the back-diffusion of CO₂ was presumably facilitated by the abundance of carbonic anhydrase in gastric mucosa [5].

The method of measuring intramural pH by hollow viscus tonometry depends in part upon the assumption that the pCO₂ in the lumen of the stomach equilibrates with that in the wall of the stomach, and in part upon the knowledge that the pCO₂ within the cellular cytosol is linearly related to the pCO₂ in the extracellular environment [23]. This method was validated by direct measurement in preliminary experiments incorporating 114 paired measurements in 16 dogs. The validity of measuring intraluminal pH by hollow viscus tonometry was, however, established for lower pCO₂ gradients than those encountered following the intragastric instillation of HCl and NaHCO₃. As a pCO₂ gradient exists between the superficial and deep layers of gastric mucosa, the magnitude of which is proportional to the pCO₂ gradient between the lumen and blood, only the pCO₂ in the superficial layers can justifiably be regarded as being accurately reflected by the pCO₂ in the lumen of the stomach [4]. Thus, the measurement of intramural pH by
hollow viscus tonometry, especially during the back-diffusion of CO₂ in our studies, was a more accurate reflection of the pH in the superficial layers than the deeper layers of stomach. The measurement of pH by hollow viscus tonometry depends also upon the assumption that the bicarbonate concentration in the wall in the stomach is the same as that being delivered to the stomach in arterial blood. It is conceivable, therefore, that the measurement of pH by hollow viscus tonometry may have been artifactually low during the generation of an alkaline tide by the secretion of acid [14]. Fortunately, the basal rate of acid secretion, and hence the generation of an alkaline tide, was negligible in our studies. It is also conceivable that the measurement of intramural pH by hollow viscus tonometry may have been artifactually high during the back-diffusion of H⁺. The measurement of pH by hollow viscus tonometry was, however, validated under circumstances including those in which endogenous acid had been placed into the stomach in the concentrations used in these experiments. Thus the measurement of intramural pH by hollow viscus tonometry is likely to have been an accurate reflection of the pH in the superficial layers of the stomach in the circumstances in which our experiments were conducted, especially in those samples collected after the pCO₂ in luminal fluid had had more than an hour to equilibrate with the pCO₂ in the mucosa.

The degree to which the appearance of endogenous bicarbonate in the stomach might increase the back-diffusion of acid, and hence influence the intermucosal pH, can be calculated from the gastric mucosal permeability to H⁺ and CO₂ and the [H⁺] and pCO₂ gradients generated by the buffering of acid in the stomach. The permeability of gastric mucosa to H⁺ and CO₂ was determined from our experiments. The [H⁺] gradient can be derived from the pH of gastric juice. The pCO₂ gradient can be calculated for the concentration of bicarbonate appearing in the stomach, upon its volume in proportion to the volume of gastric acid present in the stomach, and upon the proportion of bicarbonate existing as CO₂. The proportion of bicarbonate existing as CO₂ depends upon the equilibrium pH of gastric juice, and may be calculated from the Henderson–Hasselbach equation. Thus, if the values (0.048 and 0.24) derived from our experiments for the gastric mucosal permeability to H⁺ and to CO₂, respectively, are an accurate reflection of the values present in vivo when both the pylorus and esophago-gastric junction are open, and if the two component hypothesis for acid secretion is correct and acid is secreted in a constant concentration of 140 meq/liter, the effects which the appearance of physiological amounts of endogenous bicarbonate in the stomach might have on back-diffusion of acid are as illustrated in Fig. 9.

Figure 9 shows that the appearance of only modest amounts of endogenous bicarbonate (in the stomach) may increase the rate of back-diffusion of acid many times above that occurring during exposure to HCl alone in those concentrations usually encountered in the stomach, especially at the interface between acidic and alkaline secre-
tions where bicarbonate and acid are mixed in almost equal proportions. Direct measurements of $pCO_2$ [24, 29] and pH [20] in luminal fluid suggest that the interface between acidic and alkaline secretions, where the rate of back-diffusion is calculated to be greatest, is located in the duodenal bulb in healthy subjects and patients with duodenal ulcers, and in the stomach in patients with gastric ulcers [12]. If ulcers are indeed caused by the back-diffusion of acid and by a fall in the intramural pH, as recent experiments would suggest [14], then the effect which bicarbonate has on the back-diffusion of acid at the interface between acidic and alkaline secretions may explain why ulcers occur in areas where “acidity alternates with neutrality” rather than in areas exposed to either acid or bicarbonate alone [20].

REFERENCES

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