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Back-Diffusion of CO_2 and Its Influence on the Intramural pH in Gastric Mucosa

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We have examined the back-diffusion of CO_2 generated by buffering HCl with $NaHCO_3$ 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 $NaHCO_3$ (12.5 meq) to generate 12.5 meq CO_2 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 pCO_2. The intramural pH of the gastric wall was measured by hollow viscus tonometry. The pCO_2 in gastric juice rose to 1184 ± 139 mm Hg upon the generation of CO_2 in the stomach. The $t_{1/2}$ of the CO_2 generated by the buffering of acid was 32 ± 4 min and of the pCO_2 was 18.7 ± 0.7 min. The $t_{1/2}$ of an equimolar amount of HCl was 2 hr 42 min ± 40 min. The disappearance of the CO_2 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 (H_2CO_3) with a pK_a of 6.1. The dissociation of this weak acid yields CO_2 and induces a rise in pCO_2 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 CO_2. Isotopic studies using ^{14}C-labeled bicarbonate have shown that 95% of the CO_2 formed by the buffering of gastric acid is disposed 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 (CO_2) 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 (CO_2).

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-

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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 exceed 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 50 meq/liter. In the remaining three dogs the test fluid consisted of 35 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 CO_2. Five other dogs were used to determine the rate at which CO_2 diffused from the stomach. In each of these dogs 12.5 meq HCl and 12.5 meq $NaHCO_3$ were introduced simultaneously into the stomach to give a final volume of 250 ml and to generate 12.5 meq CO_2 in the stomach and a maximum *in vitro* CO_2 concentration of 50 meq/liter in an acidic environment.

4. Diffusion of CO_2 in stomach vs duodenum. The permeability of gastric mucosa to CO_2 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 canulated. 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% O_2 for 30 min to raise the pCO_2 in the arterial blood. The dogs were allowed to breathe spontaneously again for the last hour.

Measurement of pH and pCO_2

The pH and pCO_2 in samples of arterial blood and the pCO_2 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_a^+] to hydrogen ion concentration [H_c^+] 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 (pH_I) 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 ± 0.03 in 16 dogs and in the duodenum to be 7.33 ± 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).

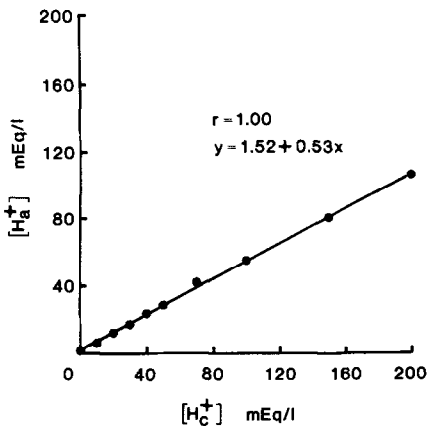

FIG. 1. Comparison between hydrogen ion activity [H_a^+], calculated from the measured pH, and the hydrogen ion concentration [H_c^+] induced by adding known amounts of HCl to 250 ml of normal saline that have been incubated in an isolated canine stomach.

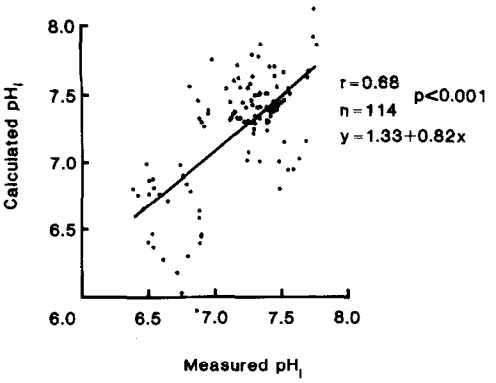

FIG. 2. Comparison between intramural pH (pH_I) in submucosal space, measured directly with a micro-pH probe, and that calculated from the pCO_2 in luminal fluid and [HCO_3^-] in arterial blood. Similar relationships existed in the stomach (n = 40, r = 0.76), small bowel (r = 0.65), and colon (r = 0.91).

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

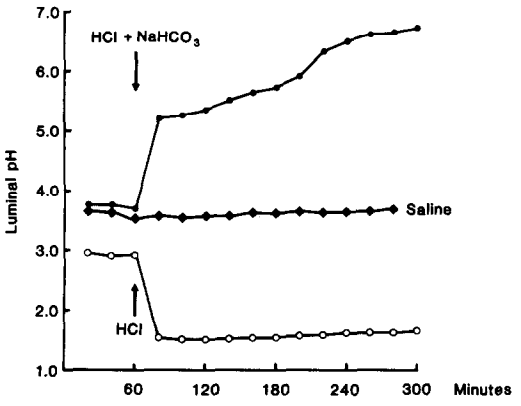

FIG. 3. Mean intraluminal pH measured in the stomach during exposure to 250 ml normal saline (n = 5), and to 12.5 meq HCl (n = 4) and 12.5 meq HCl plus 12.5 meq $NaHCO_3$ (n = 5) each diluted in 250 ml saline.

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 $[H_c^+]$, 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 pCO_2 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 $[H_c^+]$ 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 CO_2*

The pH in the lumen of the stomach rose rapidly toward neutrality following the introduction of HCl and $NaHCO_3$ into the stomach (Fig. 3). At the same time the pCO_2 in the lumen of the stomach rose to unre-

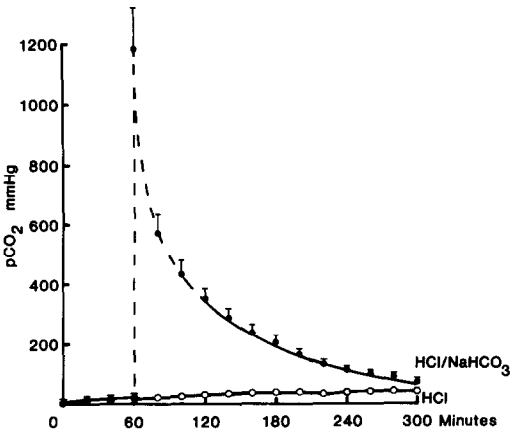

FIG. 4. Intraluminal pCO_2 in the stomach measured during exposure to 250 ml normal saline (n = 5), and to 12.5 meq HCl (n = 4) and 12.5 meq NCl plus 12.5 meq $NaHCO_3$ (n = 5) each diluted in 250 ml saline. Values obtained during exposure to saline and HCl were identical. Values obtained during the initial exposure to HCl and $NaHCO_3$ were too high to measure directly. Values above 280 mm Hg were extrapolated from the regression equations in Table 2.

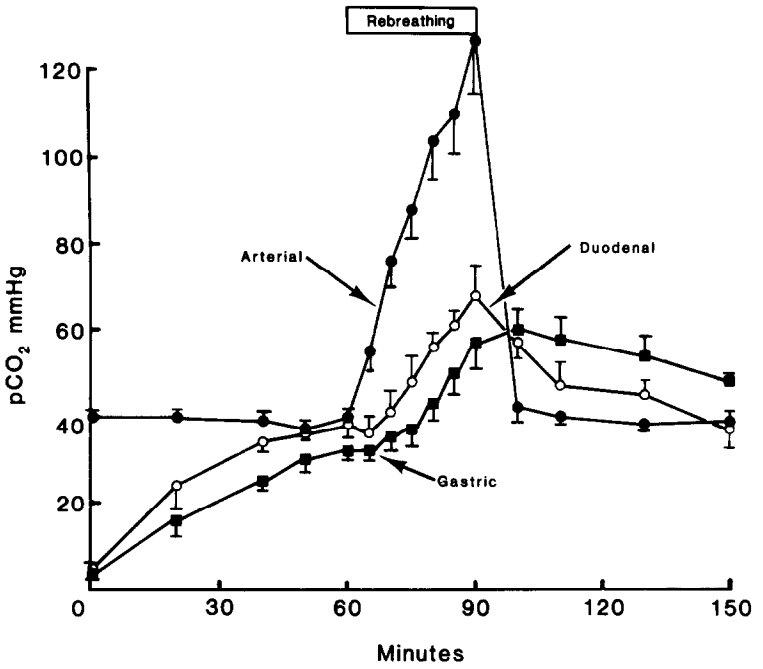

FIG. 5. Influence of rebreathing into a bag containing 100% O_2 on pCO_2 in arterial blood, duodenal fluid, and gastric fluid in five anesthetized dogs.

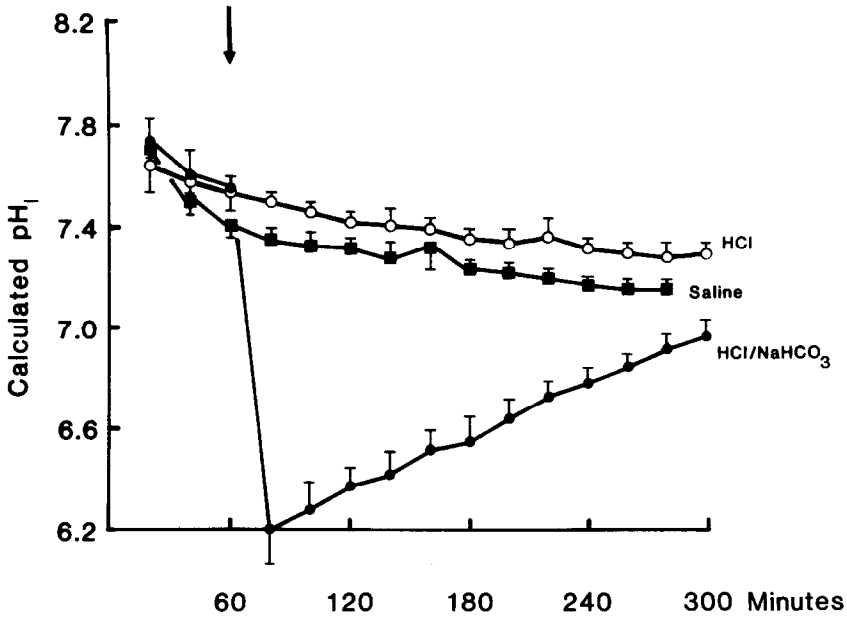

FIG. 6. Intramural pH, calculated from pCO_2 in gastric fluid and $[HCO_3^-]$ in arterial blood, during luminal exposure to 250 ml saline (n = 5), and to either 12.5 meq or 35 meq HCl (n = 7) and 12.5 meq HCl plus 12.5 meq $NaHCO_3$ (n = 5) each diluted in 250 ml of normal saline. Values obtained during exposure to HCl and $NaHCO_3$ were significantly lower than those obtained during exposure to either saline or HCl ($P < 0.001$).

TABLE 1

H^+ LOG REGRESSION EQUATIONS[a]

r	a	b	$t_{1/2}$
0.71	15.83	−1.53	2 hr 56 min
0.95	11.56	−1.31	1 hr 23 min
0.73	11.99	−1.07	4 hr 27 min
0.87	17.08	−1.26	2 hr 2 min
$\bar{x}$ ± SEM	12.87 ± 1.0		2 hr 42 min ± 40 min

[a] The H^+ log regression equations observed during exposure to 12.5 meq H^+ diluted in 250 ml saline and the calculated $t_{1/2}$ of H^+ in the stomach.

cordable levels due to the generation of CO_2 (Fig. 4). The pCO_2 in luminal fluid measured thereafter fell with the passage of time. By extrapolation from the regression equations, the pCO_2 present in the lumen immediately after the introduction of 12.5 meq HCl and 12.5 meq $NaHCO_3$ was 1184 ± 139 mm Hg. The $t_{1/2}$ of the pCO_2 was 18.5 ± 0.7 min (Table 2).

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 CO_2 (TCO_2) calculated from the pH and pCO_2 and from the calculated volume present in the stomach when each sample was taken, fell with the passage of time. The $t_{1/2}$ of the TCO_2 was 32 ± 4 min (Table 3). This $t_{1/2}$ was 5.1 times shorter than the $t_{1/2}$ 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 CO_2 left the stomach during each 20-min test period after the first hour's exposure to HCl and $NaHCO_3$ was linearly related to the average pCO_2 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-

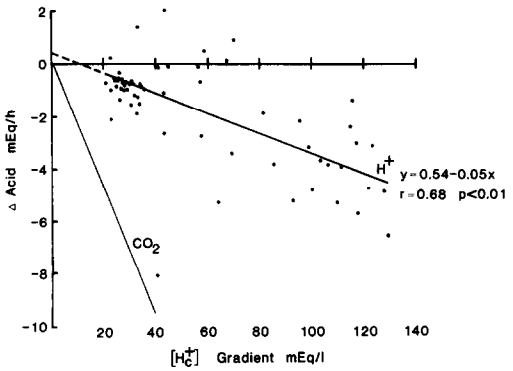

FIG. 7. Measured rate of H^+ loss from luminal fluid (ΔH^+) in each 20-min period in each of seven dogs compared with the average $[H_c^+]$ gradient between luminal fluid and arterial blood present at the beginning and the end of each 20-min test period. Comparison with CO_2 loss at different pCO_2 gradients (see Fig. 8).

TABLE 2

pCO_2 LOG REGRESSION EQUATION[a]

r	a	b	$t_{1/2}$
0.97	1203	−203.3	19.3
0.99	1020	−177.3	17.8
0.99	1585	−276.3	17.6
0.997	1347	−238.3	16.9
0.98	769	−126.7	20.8
$\bar{x}$ ± SEM	1185 ± 139		18.5 ± 0.7

[a] pCO_2 log regression equation occurring during exposure to 12.5 meq HCl and 12.5 meq $NaHCO_3$ diluted in 250 ml of saline and the calculated $t_{1/2}$ for the pCO_2 in the stomach.

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 CO_2 in the five dogs studied. The permeability to CO_2 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 CO_2 occurring following the addition of 12.5 meq of HCl and 12.5 meq of $NaHCO_3$ with the generation of CO_2 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. *pCO_2 in Stomach vs CO_2 in Duodenum*

The pCO_2 in gastric and duodenal fluid rose in parallel during the first hour toward that observed in arterial blood (Fig. 5). The

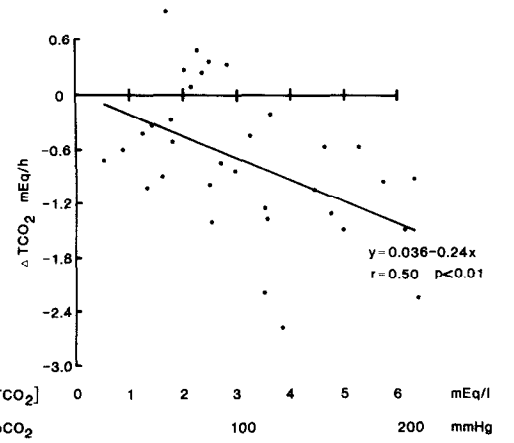

FIG. 8. Measured rate of CO_2 loss by back-diffusion (ΔTCO_2) during each 20-min test period in five dogs compared with the average CO_2 gradient measured at the beginning and end of each 20-min test period and expressed in both mm Hg and meq/liter.

pCO_2 in the stomach and duodenum rose further in parallel and then returned toward basal values as the dogs were made to rebreathe and then allowed to breathe spontaneously again. The pCO_2 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.

TABLE 3

TCO_2 LOG REGRESSION EQUATION[a]

r	a	b	$t_{1/2}$ (min)
0.95	15.9	−2.36	29.5
0.97	13.4	−1.79	43.0
0.996	23.1	−3.67	23.5
0.72	3.6	−0.49	39.8
0.98	11.9	−1.89	23.3
$\bar{x}$ ± SEM	13.6 ± 3.2		31.8 ± 4.1

[a] TCO_2 log regression equation occurring during exposure to 12.5 meq HCl and 12.5 meq $NaHCO_3$ diluted in 250 ml of saline and the calculated $t_{1/2}$ of the TCO_2 in the stomach.

DISCUSSION

This study has confirmed that both H^+ [6] and CO_2 [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 CO_2 than to H^+ and that CO_2 diffuses 5.1 times more rapidly from the stomach than an equimolar amount of H^+. Gastric mucosa appeared also to be as permeable to CO_2 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 CO_2 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 (CO_2).

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 pCO_2 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 $NaHCO_3$ into the stomach. This level approaches that calculated with the Henderson–Hasselbach equation to have been achieved following the generation 12.5 meq of CO_2 in 250 ml of fluid at low pH (1629 mm Hg). A pCO_2 approaching 1000 mm Hg has been found by direct measurement in luminal fluid in dogs [24] and in man [16, 25, 29]. The pCO_2 in luminal fluid fell rapidly from this high level with the diffusion of CO_2 from the stomach and the formation of bicarbonate in luminal fluid. As in other studies the rate of CO_2 diffusion was linearly related to the pCO_2 gradient present [15, 30]. It was, by extrapolation from the regression equation in Fig. 8, 12.5 meq/liter at the estimated pCO_2 gradient present immediately following the addition of HCl and HCO_3 to the stomach. This rate of back-diffusion was 5.0 times greater than that (2.5 meq/hr) at the estimated $[H_c^+]$ 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 CO_2 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 CO_2 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 pCO_2 in the lumen of the stomach equilibrates with that in the wall of the stomach, and in part upon the knowledge that the pCO_2 within the cellular cytosol is linearly related to the pCO_2 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 pCO_2 gradients than those encountered following the intragastric instillation of HCl and $NaHCO_3$. As a pCO_2 gradient exists between the superficial and deep layers of gastric mucosa, the magnitude of which is proportional to the pCO_2 gradient between the lumen and blood, only the pCO_2 in the superficial layers can justifiably be regarded as being accurately reflected by the pCO_2 in the lumen of the stomach [4]. Thus, the measurement of intramural pH by

hollow viscus tonometry, especially during the back-diffusion of CO_2 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 exogenous 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 pCO_2 in luminal fluid had had more than an hour to equilibrate with the pCO_2 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 CO_2 and the $[H^+]$ and pCO_2 gradients generated by the buffering of acid in the stomach. The permeability of gastric mucosa to H^+ and CO_2 was determined from our experiments. The $[H^+]$ gradient can be derived from the pH of gastric juice. The pCO_2 gradient can be calculated for the concentration of bicarbonate appearing in the stomach, upon its volume in proportion to the volume of gastric acid

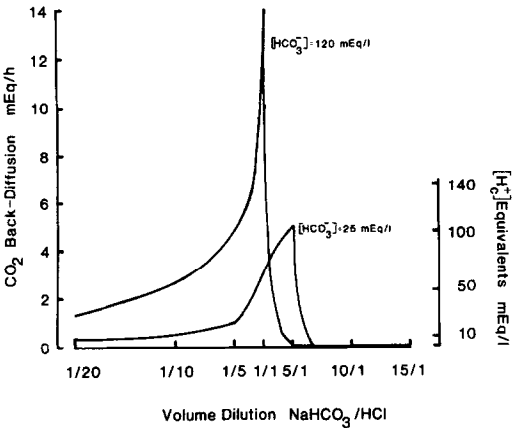

FIG. 9. Rate of acid back-diffusion calculated from Fig. 8 to occur as CO_2 when HCO_3, in concentrations of either 120 or 25 meq/liter (the range found in endogenous secretions) is mixed in different proportions with HCl in a concentration of 140 meq/liter. Comparison with rate of acid back-diffusion calculated from Fig. 7 to occur as H^+ with different concentrations of $[H_c^+]$.

present in the stomach, and upon the proportion of bicarbonate existing as CO_2. The proportion of bicarbonate existing as CO_2 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 CO_2, 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].

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