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Comparison of Gastrointestinal pH in Cystic Fibrosis and Healthy Subjects

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The primary objective of this study was to define the pH conditions under which supplemental pancreatic enzyme preparations must function in the upper gastrointestinal tract. The hypothesis was that normal or greater gastric acid output in patients with cystic fibrosis (CF), combined with low pancreatic bicarbonate output, results in an acidic duodenal pH, compromising both dosage-form performance and enzyme activity. Gastrointestinal pH profiles were obtained in 10 CF and 10 healthy volunteers under fasting and postprandial conditions. A radiotelemetric monitoring method, the Heidelberg capsule, was used to continuously monitor pH. Postprandial duodenal pH was lower in CF than in healthy subjects, especially in the first postprandial hour (mean time greater than pH 6 was 5 min in CF, 11 min in healthy subjects, $P < 0.05$). Based on the dissolution pH profiles of current enteric-coated pancreatic enzyme products, the duodenal postprandial pH in CF subjects may be too acidic to permit rapid dissolution of current enteric-coated dosage forms. However, the pH was above 4 more than 90% of the time on the average, suggesting that irreversible lipase inactivation in the duodenum is not likely to be a significant limitation to enzyme efficacy. Overall results suggest that slow dissolution of pH-sensitive coatings, rather than enzyme inactivation, may contribute to the failure of enteric-coated enzyme supplements to normalize fat absorption.

KEY WORDS: cystic fibrosis; gastrointestinal pH; pancreatic therapy enzyme.

In 80–85% of patients with cystic fibrosis (CF), there is sufficient loss of pancreatic exocrine function to produce clinically evident malabsorption (1). It has been suggested that the degree of pancreatic insufficiency may be important to the overall prognosis in CF patients (2). For example, patients with uncorrected malabsorption have altered serum lipid profiles (3, 4). Moreover, normal fat absorption appears to be correlated with better pulmonary function (5). Some authors have suggested that the development of pancreatic insufficiency is the basic defect in CF, with other manifestations of CF resulting from secondary malnutrition (6). Successful correction of malabsorption in CF patients may therefore be an important therapeutic goal.

Enzyme supplements constitute the primary approach to treating pancreatic insufficiency. Although these supplements substantially reduce fat

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excretion, they usually fail to bring stool fat levels within the normal range (7–19). Inactivation by gastric acid is a major limitation to enzyme efficacy (20, 21) unless the dosage form is enteric-coated. The limited data available (19, 22, 23) suggest that the duodenum is more acidic in CF than healthy subjects. At least two aspects of enzyme replacement therapy could be detrimentally affected by low duodenal pH. First, enzyme release may be prevented by failure of the enteric coating to dissolve. Polymers used to enteric-coat dosage forms have dissolution times which are highly pH-sensitive. Time to dissolve varies from virtually infinity at low pH (1–2) to just a few minutes at neutral pH. The exact crossover pH from slow to fast dissolution depends on the pK_a of the polymer used. If the duodenal/jejunal pH is lower than the crossover pH, the coating may take a long time to dissolve, preventing enzyme release during a major portion of the small intestinal transit. The second potential problem resides with changes in enzyme activity as a function of pH.

The present study was undertaken to compare the gastrointestinal pH profiles of CF and healthy subjects. Our aim was to determine the extent to which low duodenal pH in CF subjects may limit the efficacy of currently available enzyme supplements, by comparing postprandial duodenal pH with (1) the pH profile for enteric coating dissolution and (2) the pH dependency of enzyme activity.

MATERIALS AND METHODS

Subject Selection. The study was carried out in the Clinical Research Center of The University of Michigan Hospitals on an outpatient basis, with approval of the Human Subject Review Committee. All participants gave written informed consent (parental consent in the case of minors).

Ten subjects (five female, five male) with documented cystic fibrosis were selected from the population attending the University of Michigan Cystic Fibrosis Clinic. Age ranged from 10.5 to 20 years with a mean of 13.2 years. All participants were prescribed pancreatic enzymes at the time of the study. The study was restricted to patients with Shwachman scores of over 40. Patients with clinical or laboratory evidence of cardiac disorders, diabetes mellitus, and hepatobiliary, renal, or other gastrointestinal disease were excluded. Pulmonary function was stable with varying severity among the selected participants. None were taking antacids or H_2-receptor antagonists or receiving oxygen therapy. Other medications were recorded for each participant. A summary of CF subject data is given in Table 1. Ten healthy volunteers (five female, five male adults), mean age 24 years (range 21–29 years) were selected to serve as controls. None of the healthy participants had historic, clinical, or laboratory evidence of gastrointestinal disease, nor were any on chronic medication. Smoking, alcohol, and caffeine were disallowed three days prior to and throughout the study. A 500-mg dose of bentiromide (*N*-benzolyl-L-tyrosyl *para*-aminobenzoic acid) was administered to each subject to assess pancreatic function (24–27). All healthy subjects excreted at least 50% PABA, indicating pancreatic sufficiency with respect to chymotrypsin. The 10 CF subjects had less than 50% PABA excretion, indicating pancreatic insufficiency.

pH Measurement. Continuous determination of pH with time was accomplished using a radiotelemetric device, the Heidelberg capsule (28–33). The device consists of a battery-powered high-frequency radio transmitter and a pH electrode housed in a nondigestible acrylic capsule 7 mm in diameter and 20 mm in length. The frequency of transmission changes with the pH of the capsule's environment and can be calibrated using standard buffer solutions. The subject wears an antenna

TABLE 1. CYSTIC FIBROSIS SUBJECT DATA

Subject	*Age (years)*	*Weight percentile*	*Height percentile*	*Shwachman score*	*Enzyme therapy and capsules per meal**	*Chymex® (% excretion)*
Females						
K.Y.	14	<3	7	60	C/6	14
S.M.	11	25	34	73	P/3	20
Rh.G.	12	20	25	66	C/3	17
Ro.G.	10.5	10	3	70	C/5	29
S.W.	15	15	7	64	C/4	35
Males						
J.W.	20	86	25	71	C/2	47
J.D.	16	<3	8	65	P/4–5	18
B.B.	16	44	30	72	P/3	46
R.V.	13	<3	3	48	P/4	38
D.T.	15	<3	<3	57	C/6–8	37

*C = Cotazym-S; P = Pancrease.
†Used normal weight percentiles for 18 years olds.

strapped around the midriff to receive the radio signal, which is converted back to pH and recorded as a function of time.

A modified calibration procedure was used to ensure the desired accuracy of ±0.5 pH units throughout the study period. Capsules were activated the evening prior to the study and calibrated just before being administered to the subject. *In vitro* studies were conducted at 37° C to confirm that this calibration procedure resulted in ±0.5 pH unit accuracy over an 8-hr study period. Readings in pH 1 and 7 buffer solutions maintained at 37° C were taken at 2-hr intervals for 8 hr, and recorded pH was compared with actual buffer pH to confirm that the capsule maintained the desired accuracy. At the end of each tethered capsule study, the capsule was recovered and its response to pH 1 and 7 buffers checked against the prestudy values.

Study Design. The participants fasted for at least 12 hr before swallowing a tethered Heidelberg capsule. Gastric pH was monitored until the capsule emptied into the small intestine, an event marked by a rapid, unreversed elevation in pH. After the capsule emptied from the stomach, it was allowed to travel approximately 10 cm further (ie, to the mid to distal portion of the duodenum), then the position was fixed by taping the tether thread (Braunamid surgical thread) to the subject's cheek. This procedure resulted in a tether length of 60–70 cm from the teeth in the younger CF subjects and 70–80 cm in adult CF and healthy subjects. In a separate study, the correspondence of this tethering procedure to a mid/distal duodenal location was verified by fluoroscopy. Fasting pH in the duodenum was recorded for 30 min, then a standard meal consisting of 6 oz of hamburger, 2 slices of bread, 2 oz of hash brown potatos, 1 tablespoon ketchup, 1 oz each of tomato and lettuce, 1 tablespoon of mayonnaise, and 8 oz of milk (for a total of 1000 calories) was given. CF subjects were permitted to take their usual enzyme supplements with the meal. Postprandial pH in the duodenum was monitored for 4 hr.

Further experiments were conducted in the same subjects to determine pH over the entire length of the small intestine. Subjects fasted for at least 12 hr, then swallowed an untethered, calibrated Heidelberg capsule. pH was continuously monitored for at least 7 hr as the capsule passed through the gastrointestinal tract under the auspices of natural motility.

Dosage-Form Evaluation. United States Pharmacopeia (USP) (34) disintegration apparatus was used to test two enteric-coated multiparticulate enzyme preparations, Cotazym-S and Pancrease. The USP test consists of visually following the disintegration (break-up into fine particles) of the dosage form on wire screens attached to the bottom of Plexiglas columns. Six dosage forms are tested per experiment, each dosage form in a separate column. The columns are mechanically moved up and down 30 times per minute in a fluid medium. This process is quite vigorous, so the times observed using the USP apparatus probably represent minimum times required for disintegration. The endpoint is taken as the time required for all the dosage form material to pass through the screen. Note that for an enteric-coated dosage form, the disintegration requires two steps. First, the coating must dissolve, then the spherule must break up into a fine powder. Citrate/phosphate buffers were used to adjust the disintegration medium to the desired pH. Disintegration testing was carried out at 37° C at pH 5.2 through pH 7.0. We were thus able to determine the minimum pH required for rapid coating dissolution, disintegration of the spherules, and subsequent enzyme release for both Cotazym-S and Pancrease.

Data Analysis. The pH and time values were sampled directly from the gastrointestinal pH profiles, and data analyzed using CLINFO (35) software. Descriptive statistics are reported as mean values ± SEM. Student's *t* tests (two sample and paired) were used to investigate differences in gastric emptying times and fasting gastrointestinal pH values between the healthy and CF groups. The postprandial data is reported as the percentage of time in each postprandial hour spent above pH 4, 5, 5.5, and 6. Time above the pH of interest was measured for each hour, divided by 60 min (total time), and multiplied by 100 to calculate percent time. Statistical postprandial differences between the CF and healthy groups were determined using a nonpaired Wilcoxon rank sum test.

RESULTS

Twenty-two of the 23 capsules used remained within calibration when recovered at the end of the tethered capsule study. Mean readings were 1.0 ± 0.05 and 6.9 ± 0.05 in the pH 1 and 7 buffers, respectively. The pH profile from the study day on which the capsule failed to maintain accuracy was excluded from data analysis.

In the tethered capsule study, fasting gastric pH ranged between 1 and 5 for all subjects. For 18 of the 20 subjects, the pH was predominantly between pH 1 and 2. In some subjects the pH became more variable close to gastric emptying of the capsule. Representative gastroduodenal pH profiles are shown in Figure 1. Typical gastric pH and gastric emptying times (time between swallowing the Heidelberg capsule and its passage into the duodenum) are given in Table 2. No significant differences were seen between CF and healthy subjects in either gastric pH or gastric emptying time of the capsule.

Results for postprandial duodenal pH are summarized for all subjects in Figure 2. Examination of fasting duodenal profiles (first half hour after the capsule emptied from the stomach) indicated that there was wider fluctuation of pH in CF subjects (an average of 3.1 units between minimum and maximum value observed in the 30-min period) than in healthy subjects (average of 1.8 units minimum to maximum). Nine of 10 CF subjects experienced a variation of greater than 2 units compared to three of 10 healthy subjects ($P < 0.01$).

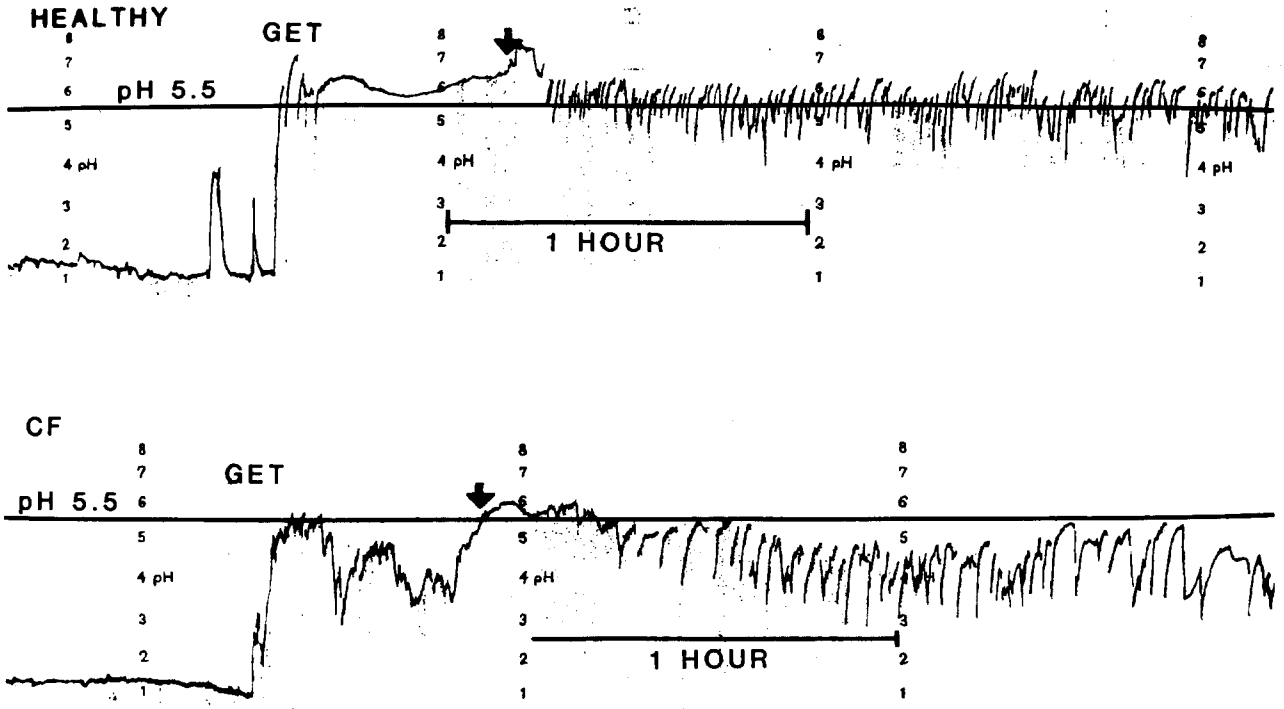

Fig 1. Typical pH profiles recorded in the study. GET corresponds to gastric emptying of the capsule. Thirty minutes elapsed between tethering the Heidelberg capsule in the duodenum and giving a standard meal (indicated by arrow).

In eight of 10 healthy subjects there was a rise of 0.5 to 1 pH unit in the duodenum as the subject started to eat. In one of the remaining two subjects, the pH was already greater than 7. It is postulated that the initial rise corresponds to the cephalic phase of pancreatic secretion, including bicarbonate. After this brief phase (5–10 min), acid deflections began to occur, continuing throughout the postprandial period. These occurred at a frequency of one every minute or so, although the rate was highly variable. The decrease in pH during the deflection often exceeded 1 pH unit, corresponding to a 10-fold or higher increase in hydrogen ion concentration, but quickly reverted to the predeflection level. Over the 4-hr postprandial period, there was an overall trend for the duodenal pH to decrease.

Postprandial pH in duodena of CF subjects followed a qualitatively similar pattern to that of healthy subjects, in that the pH fluctuated repeatedly after eating and that there was a tendency for pH to decrease with time. However, two key departures were noted. First, in CF subjects the initial rise in duodenal pH in response to meal intake was absent in all but one pH profile. Second, postprandial pH tended to be lower in CF than healthy subjects in all 4 hr, with the difference significant in the first hour at a 95% confidence level (mean time greater than pH 6 was 5 min in CF, 11 min in healthy subjects) (see Table 4 below). The trend toward more acidic pH with time was seen in CF as well as healthy subjects. For example, an average of 21% of the time was spent above pH 5.5 in the first hour in CF subjects; by the fourth hour only 9% of the time was spent at pH above 5.5.

TABLE 2. GASTRIC pH AND EMPTYING TIME OF HEIDELBERG CAPSULE IN CF AND HEALTHY SUBJECTS

	CF	*Healthy*
Mean minimum gastric pH	0.9*	1.3
Mean maximum gastric pH	1.8	2.1
Range of gastric pH	<1–4.7	<1–3.2
Gastric emptying time of Heidelberg capsule	116 ± 25	77 ± 19 min

*This value must be regarded as approximate since the lower limit of calibration of the Heidelberg capsule is pH 1.

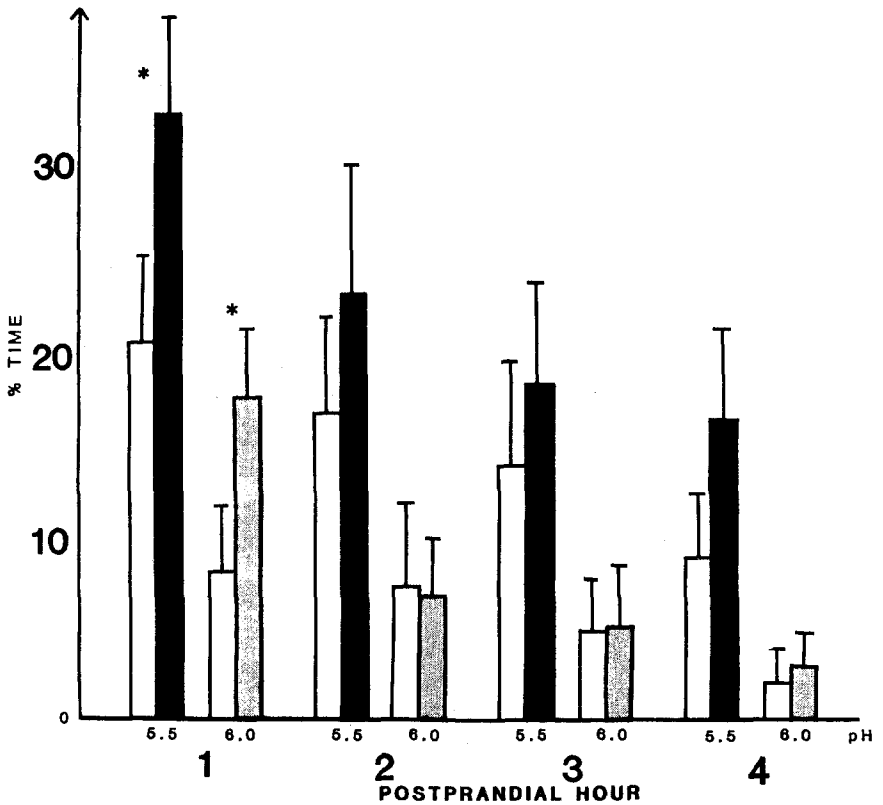

Fig 2. Percentage of time spent above pH 6.0 and pH 5.5 in each postprandial hour in the duodenum. Solid bars represent data from healthy volunteers, open bars represent data from CF subjects.

In the untethered capsule study, fasted pH in the small intestine of CF subjects (Figure 3) was significantly lower just after gastric emptying (upper small intestine) and again at 3 hr postemptying, than in healthy subjects. Moreover, the mean pH in CF subjects was always pH 6.0 or below, whereas in healthy subjects, mean intestinal pH climbed to pH 6.4 within 2.5 hr after the capsule was emptied from the stomach.

***In Vitro* Studies.** Disintegration times as a function of buffer pH for Cotazym-S and Pancrease are listed in Table 3. The enteric coating of Cotazym-S only dissolves rapidly, ie, within 15 min of exposure, at pH of 6.2 or higher, whereas rapid dissolution of the Pancrease coating occurs at pH 5.6 and above.

DISCUSSION

Conventional dosage forms of pancreatin consist of enzyme powder, either packed in capsules or loose, and enzyme tablets. Although they reduce fat excretion, these preparations do not fully normalize fat absorption (7–19). The chief limitation to their efficiency is thought to be inactivation of enzymes by gastric acid. Secretion of gastric acid in response to meals has been studied in both healthy and CF subjects. In healthy subjects, the meal initially buffers and dilutes the gastric contents to a pH of 5 or so (36, 37). Postprandial gastric acid secretion quickly results in a lowering of the pH—below 3 within 60 min and returning to a baseline value of 2 or lower by the end of the second hour. Cameron et al (38) observed postprandial gastric pH profiles in CF subjects that were similar to those in healthy volunteers. Other groups (10, 39, 40) have also observed normal or higher acid output in CF subjects. Although we did not measure stimulated gastric acid response, our results for fasting gastric pH were similar in CF and healthy subjects and are therefore consistent with normal gastric acid function in CF subjects.

In the fasting state, with the capsule tethered in the duodenum, the pH was observed to fluctuate over a wider range ($P < 0.02$) in CF than healthy subjects, indicating poorer ability to regulate pH in

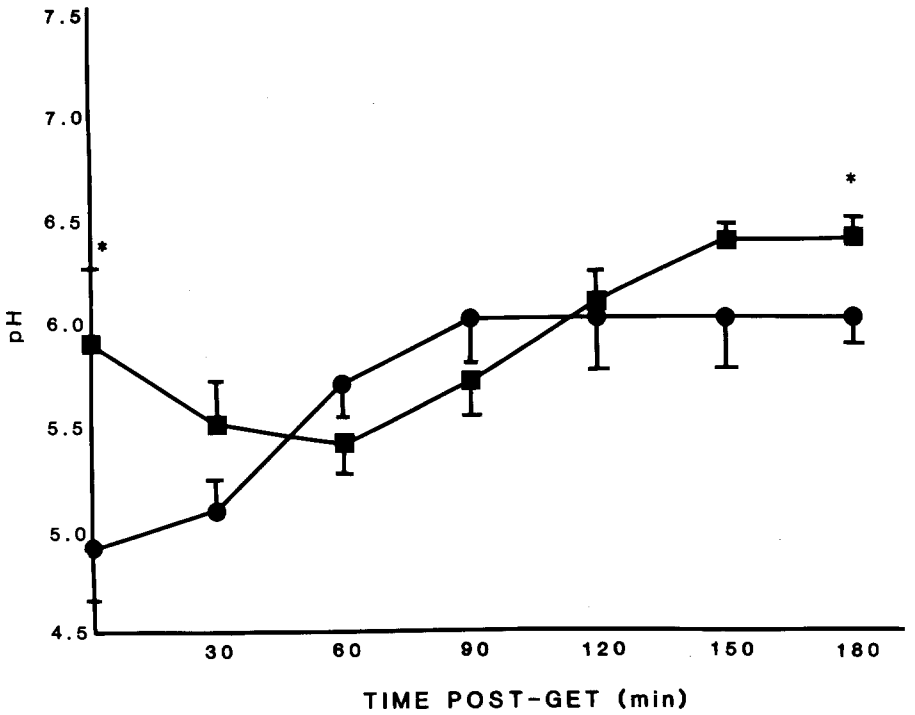

Fig 3. Summary of fasting small-intestinal pH data over a 3-hr period of intestinal transit. Squares represent mean pH ± SEM in the healthy subjects. Circles represent mean pH ± SEM in the CF subjects. *Statistical difference in pH between the healthy and CF subjects ($P < 0.05$).

CF. Fluctuations in duodenal pH in patients with pancreatic dysfunction have also been observed by Dutta et al (41) and Benn and Cooke (42). The mean and range of fasting duodenal pH in CF subjects ($\bar{X}$= 5.1, range 3.3–6.4 after 30 min in the duodenum) was in good agreement with data of Abrams et al (22) ($\bar{X}$ = 5.0, range 3–6.7) and Knauff and Adams (43) $\bar{X}$ = 4.8, range 2–6.9). Likewise, the fasting duodenal pH in healthy subjects ($\bar{X}$ = 5.7, range 5.0–6.9 after 30 min in the duodenum) was similar to previously reported results (37, 44, 45).

TABLE 3. DISINTEGRATION TIME AS A FUNCTION OF pH FOR COTAZYME-S. AND PANCREASE (AVERAGE OF SIX EXPERIMENTS)

	Time to Disintegrate (min)	
pH	*Cotazym-S*	*Pancrease*
5.2	>120	>120
5.4	>120	33 ± 5
5.5	*	40 ± 4
5.6	96 ± 30	10 ± 0.5
6.0	31 ± 23	10 ± 1
6.1	33 ± 26	*
6.2	12 ± 1	*
7.0	13 ± 1	*

*Not tested at given pH.

At the start of the meal, we observed a transient rise in duodenal pH in most healthy subjects but only in one CF subject. These observations would be consistent with a failure in CF subjects to secrete bicarbonate ion as part of the cephalic response to meal intake.

We observed consistently lower postprandial duodenal pH in CF compared with healthy subjects, in concurrence with three studies reported in the literature. Weber and Roy (19) observed postprandial pH lower than 4 in two CF subjects. Isenberg and Powell (23) observed pH of less than 5.1 in almost half the meal fractions aspirated from three CF subjects with steatorrhea. Abrams et al (22) found that the average basal duodenal pH in five adult male CF subjects was pH 5, with the pH dropping to 4.4 by the second postprandial hour. We also observed a trend for the pH to decrease with time during the postprandial period. This trend was observed for the healthy subjects as well, consistent with data reported by other groups (36, 42, 49, 50). However, the time spent above pH 5.5

as well as the overall pH was always lower in CF subjects in any given hour.

Three ways in which an acidic postprandial duodenal pH could compromise enzyme performance are (1) to reduce lipase activity and, at sufficiently low pH, to irreversibly inactivate lipase, (2) to cause bile acid precipitation, and (3) to prevent dissolution of the coating on enteric-coated formulations.

Apparent lipase activity is quite pH-dependent. Go et al (46) found a 10-fold decrease in activity between pH 6 and 3. Similarly, Dressman et al (47) reported a three- to fourfold decrease in lipase activity of commercial preparations when lipolysis was compared at pH 5 with pH 8, the optimal pH for the enzyme. Below pH 5, the efficiency of lipolysis is additionally compromised by bile acid precipitation (46, 48). At very acidic pHs (below 4), lipase is irreversibly inactivated (20, 21, 47). Comparing our pH data with these findings suggests that lipolysis would be somewhat less efficient in CF subjects.

From the mean data (Table 4), it appears that only a very short time was spent below pH 4 in either group of subjects. Appraisal of the data on an individual basis is somewhat more revealing. Three CF subjects had duodenal pH below 4 for substantial periods. Abrams et al (22) reported a similar incidence (two of five subjects). Overall, however, it appears, that irreversible lipase inactivation as a result of low duodenal pH is not a major limitation to enzyme activity—in most subjects the pH is not remarkably lower than in healthy subjects, and those that did exhibit low pH (S.W., J.W., B.B.) are not the most malnourished. A further point to note is that time below pH 5 was very similar for the two subject groups. This suggests that precipitation of bile acids occurs to about the same extent in CF and healthy subjects and is therefore probably not the limiting factor to lipolysis.

In both subject groups, the duodenal pH is below the pH for optimal lipase activity. This apparently does not present a problem in healthy subjects who secrete excess quantities of lipase in response to a meal. In CF subjects, however, the dose of enzymes administered may be insufficient or substantial degradation may occur in the stomach (eg, with conventional dosage forms). In such cases the low amount of lipase reaching the duodenum combined with suboptimal conditions for activity could result in incomplete fat digestion.

The third consideration is the ability of enteric-coated products to release their contents in the small intestine. Enteric coating is a favored approach to circumventing gastric inactivation of enzyme products. In this case a coating which is impervious to acid but dissolves at a more neutral pH is used to protect the enzymes against the high acid concentration in the stomach. *In vitro* tests have shown that uncoated preparations quickly lose activity at gastric pH, whereas enteric-coated products retain a high percentage of activity (51).

Comparing postprandial duodenal pH data with pH dependency of disintegration times enabled us to assess the importance of pH limitations to enteric-coated dosage form performance. For instance, at pH 6.0, Cotazym-S takes 31 ± 23 min to disintegrate, yet during the first postprandial hour the duodenal pH in CF subjects is above 6 for an average of only 5 min. It should be noted that disintegration of the dosage form is just the first step in enzyme release; the enzymes must subsequently dissolve before becoming fully active. It is therefore unlikely that efficient release of enzymes from this dosage form would occur in the postprandial CF duodenum. Pancrease spherules disintegrate within 10 min at pH of 5.6 or higher. Since about 12 min/hr

TABLE 4. TIME SPENT IN VARIOUS pH RANGES IN HEALTHY (H) AND CF POSTPRANDIAL DUODENUM (MIN/HR ± SEM)

		pH range			
Hour		*>4.0*	*>5.0*	*>5.5*	*>6.0*
1	CF	58.9 ± 0.5	41.6 ± 3.7	12.6 ± 2.9	4.9 ± 2.2
	H	59.8 ± 0.2	45.0 ± 4.3	20.3 ± 3.2	10.7 ± 2.2
2	CF	56.7 ± 1.5	36.7 ± 4.4	10.2 ± 3.2	4.4 ± 2.7
	H	56.2 ± 2.0	31.8 ± 5.2	14.1 ± 4.4	4.0 ± 2.0
3	CF	52.3 ± 3.9	25.6 ± 5.7	8.5 ± 3.4	3.0 ± 1.7
	H	57.7 ± 0.9	33.6 ± 4.3	11.0 ± 3.5	3.1 ± 2.0
4	CF	52.2 ± 2.5	25.3 ± 5.3	5.4 ± 2.1	1.1 ± 0.5
	H	55.3 ± 1.6	28.8 ± 3.9	10.0 ± 3.0	1.7 ± 1.1

of the first two postprandial hours are spent at pH 5.5 or higher, spherules emptying during this period would take almost an hour to release their enzyme content. By the fourth postprandial hour, pH is above 5.5 for less than 10 min/hr, indicating that the coating may take longer than an hour to dissolve and release the enzymes. While the Pancrease disintegration/pH profile is more favorable than the Cotazym-S profile, it still may not provide for efficient digestion as there would be a lag time on the order of an hour between emptying of spherules from the stomach and onset of digestive action. Presumably both preparations would eventually release their enzyme content at more distal, higher-pH locations. Cameron et al (38), found that the mean proximal jejunal pH in four CF subjects ranged from pH 5.7 to 6.5 in a 90-min postprandial observation period.

In the second part of our study in CF subjects, fasting gastrointestinal pH was observed as a function of time following administration of an untethered Heidelberg capsule. It was found that the pH reached 6 at an average of 90 min after the capsule passed from the stomach into the small intestine. At pH 6, coating dissolution requires about 10–15 min, so the total time elapsed prior to enzyme release would be approximately 100 min. Comparing this release time to the usual small-intestine transit time of just under 200 min for an inert object of similar dimensions to the Heidelberg capsule (53), it appears that as much as half the available contact time between chyme and enzymes could be lost because of the high pH required to dissolve the coating. The reduced contact time might be insufficient for digestion to be completed prior to entry of the chyme into the colon. Recently published data for jejunal pH in pancreatic insufficient adults and healthy volunteers indicates that jejunal pH is the same or lower in the postprandial than the fasted state (Ovesen et al, Gastroenterology 90:958, 1986). Our estimates for contact time of enzymes with chyme after administration of enteric-coated dosage forms are based on fasted intestinal pH data and may therefore tend to overestimate available contact time in the fed state.

From the results presented here, it appears that prolonged coating dissolution time, possibly exacerbated by a suboptimal lipase activity–dose combination, provides a reasonable explanation for the inability of Cotazym-S and Pancrease to fully normalize absorption. A comparison of stool fat after direct perfusion of enzymes into the duodenum versus administering a comparable dose orally would be required to determine the extent of formulation limitations to enzyme performance.

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