Effects of intermittent feed deprivation, intermittent feed deprivation with ranitidine administration, and stall confinement with ad libitum access to hay on gastric ulceration in horses

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Objectives—To determine the effect of decreasing gastric acidity in a feed-deprivation protocol on induction of gastric ulcers, and to determine whether stall confinement may be a factor contributing to gastric ulceration in horses.

Animals—8 adult horses, 4 geldings and 4 mares, 3 to 8 years old, and 7 adult horses, 5 geldings and 2 mares, 4 to 11 years old.

Procedure—Gastric ulceration was induced in horses by alternating 24-hour periods of feed deprivation and ad libitum access to hay, for a total of 96 hours' feed deprivation. This protocol was repeated with the horses receiving the histamine type-2 receptor (H_2) antagonist ranitidine (6.6 mg/kg of body weight, PO, q 8 h). In another group of horses, severity of gastric lesions was compared after 7 days' pasture turnout and 7 days' stall confinement with ad libitum access to hay. Gastroscopy was performed after each feed-deprivation protocol was completed, and total lesion area in the gastric squamous epithelial mucosa was measured. Gastroscopy was performed at the beginning and end of 7 days' pasture turnout and 7 days' stall confinement.

Results—Alternating periods of feed deprivation resulted in erosion and ulceration of the gastric squamous epithelial mucosa of each horse. Concurrent treatment with ranitidine resulted in significantly ($P < 0.05$) less area of ulceration in the gastric squamous epithelial mucosa. After 7 days' stall confinement, 6 of 7 horses had ulceration in the gastric squamous epithelial mucosa, and 1 horse had a lesion in the glandular mucosa, whereas after 7 days' pasture turnout, 2 horses had reddening of the gastric squamous mucosa along the lesser curvature ($P < 0.05$).

Conclusions and Clinical Relevance—Severe ulceration of the gastric squamous epithelial mucosa, caused by excess acidity, can develop rapidly in horses deprived of feed or not consuming feed. Suppression of gastric acidity with the histamine type-2 receptor antagonist ranitidine effectively minimized the area of ulceration caused by feed deprivation. Compared with being turned out to pasture, stall confinement alone appears to be an important factor in the development of gastric ulcers in horses, probably as a result of altered eating behavior. (*Am J Vet Res* 1996;57:1599–1603)

Gastric ulceration is a highly prevalent disorder in foals[1-3] and adult horses.[4,5] In adult horses, most gastric ulcers develop in the squamous epithelial mucosal lining, presumably as a result of that mucosa's limited processes that protect against peptic injury. This mucosa is a stratified squamous epithelial mucosa that lacks an apparent mucus layer,[6] such as that which covers and protects the gastric glandular mucosa from peptic injury.[7,8] The equine gastric mucosa is exposed periodically to highly acidic conditions, particularly when horses are not eating. Feed deprivation for 24 hours resulted in median gastric pH of 1.6, compared with median 24-hour pH of 3.1 when horses had ad libitum access to hay.[9] Using a protocol that alternated periods of feed deprivation with ad libitum access to hay, progressive ulceration of the gastric squamous epithelial mucosa was induced in horses.[10] This is the first reported, to the authors' knowledge, model of inducing gastric ulcers in horses that did not use a chemical or pharmacologic agent to induce ulcers. Thus, it may be considered to be a physiologic model that creates conditions which mimic naturally acquired gastric ulcers in horses.

We have hypothesized that the cause of the ulcers induced in the feed-deprivation protocol is excess acidity. To verify this hypothesis, we examined the effect of treatment with the histamine type-2 receptor antagonist rantidine[a] during the feed-deprivation protocol on the degree of induced ulceration. The effects of ranitidine on gastric pH in feed-deprived horses[9,11] and in horses with ad libitum access to hay[9] have been reported, and results of those studies have indicated that administration of 6.6 mg ranitidine/kg of body weight effectively increases gastric pH.

We also have hypothesized that stall confinement, compared with maintenance on pasture, may influence gastric ulceration by alteration of eating behavior. We found that horses maintained on pasture typically have normal-appearing gastric mucosa. Therefore, we investigated the effect of stall confinement with ad libitum access to hay on the gastric mucosa of horses.

Materials and Methods

Experimental design: Comparison of gastric mucosa after feed deprivation protocol with and without concurrent treatment with ranitidine—Eight adult horses, 4 geldings and 4 mares, 3 to 8 years old, were maintained on pasture for at least 1 month before inclusion in experiments. During the experiments, horses were housed in box stalls with water available at all times.

Horses had ad libitum access to Timothy grass hay for 24 hours. Horses were then muzzled to prevent eating, but not drinking from a water bucket, for 24 hours. Horses were alternately deprived of feed for 24 hours, then provided ad libitum access to Timothy grass hay for 24 hours. The protocol continued until horses had been deprived of feed for a total of 96 hours.

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Figure 1—Caliper passed through the biopsy channel of the endoscope applied to the gastric mucosal surface adjacent to an ulcer.

To determine whether excess acidity is a predominant factor in induction of gastric ulcers by intermittent feed deprivation, the protocol was performed for each horse, the horses were turned out on pasture for at least 60 days, then the protocol was repeated, with each horse receiving ranitidine[a] (6.6 mg/kg, PO, q 8 h) during the protocol. Normal gastric mucosa was confirmed by gastroscopy at the beginning of each phase of the study, and gastroscopy was repeated after 48 and 96 hours of cumulative feed deprivation.

Horses and experimental design: Comparison of gastric mucosa after pasture turnout and 7 days of stall confinement—Seven adult horses, 5 geldings and 2 mares, 4 to 11 years old, were maintained on pasture for at least 60 days before inclusion in the experiment. Gastroscopy was performed to confirm normal gastric mucosa, the horses were returned to pasture for 7 days, then were re-examined by endoscopy. For comparison, each horse had gastroscopy performed to confirm normal gastric mucosa after pasture turnout, was confined to a stall with continuous access to Timothy hay and water for 7 days, then was re-examined by endoscopy.

Gastroscopy—Feed was withheld for 6 to 8 hours prior to gastroscopy, except after 48 and 96 hours of cumulative feed deprivation, at which time feed had been withheld for 24 hours prior to gastroscopy. Each horse was sedated with xylazine (0.5 mg/kg, IV) prior to gastroscopy by use of a 2-m-long video endoscope.[b] Images were captured and digitized during the examination, using a personal computer with a 16-bit Targa board.[c] Images were taken of the gastric squamous epithelium from the **right side of the stomach along the margo plicatus (MPRT)**, the dorsal part of the fundus, the **greater curvature along the margo plicatus (MPGC)**, the **lesser curvature along the margo plicatus (MPLC)**, and the glandular mucosa along the greater curvature.

Lesion measurement—Lesion areas were measured after 96 hours in both feed-deprivation protocols (ranitidine/no ranitidine). During gastroscopy, a caliper was passed through the endoscope biopsy channel, was applied to the gastric mucosa, and an image that included the caliper and a selected lesion was captured. The caliper had red, green, and blue bars on it, and each bar had an area of 6.2 mm^2 as viewed through the endoscope (Fig 1). Endoscopic images were imported into an image analysis software program[d] and the area of the colored bars on the caliper was used to calibrate the program to measure lesion area. All lesions in the gastric squamous epithelial mucosa were measured in this manner after 96 hours' cumulative feed deprivation.

Lesion scoring—Lesion scores were assigned to compare the degree of erosion/ulceration at each site in the stomach of horses after pasture turnout and after 7 days' stall confinement with continuous access to hay. Lesion scores ranged from 0 to 4, with 0 = intact epithelium, 1 = generalized reddening or hyperkeratosis, 2 = small single or multifocal lesions, 3 = large single or multifocal lesions or extensive superficial lesions, and 4 = extensive lesions with areas of apparent deep ulceration. This scoring system was developed as a collaborative effort between the first author (MJM) and 2 colleagues.[e]

Statistical analysis—The areas of ulcerated mucosa at sites MPRT, MPGC, and MPLC in the gastric squamous epithelium after 96 hours' cumulative feed deprivation were compared for treatment with ranitidine and no treatment by use of a paired *t*-test. Lesion scores after 7 days of pasture turnout were compared with lesion scores after 7 days of stall confinement and ad libitum access to Timothy hay by use of Wilcoxon's signed rank test. Significance was set at $P < 0.05$.

Results

All horses tolerated the feed-deprivation protocol. There were no signs of discomfort or other untoward effects. All horses had normal-appearing gastric mucosa at the time of initial endoscopy. The intermittent feed-deprivation protocol resulted in progressive ulceration of the gastric squamous epithelial mucosa in all horses, as has been reported.[10]

Lesions, mostly appearing to be erosions, were present in each horse after 48 hours' cumulative feed deprivation. Deep, ulcerative-appearing lesions were present in 3 horses after 48 hours' feed deprivation. After 96 hours' feed deprivation, lesions typically appeared deeper, ulcer margins appeared more delineated and had become thick, and the surrounding epithelium appeared thick, compared with lesions after 48 hours (Fig 2). Each horse had at least 1 moderate to severe area of ulceration in the gastric squamous epithelial mucosa after 96 hours' feed deprivation (Table 1). Lesions typically were most severe adjacent to the MPLC, and were least severe or absent along the MPGC. Lesions were not present in the dorsal portion of the fundus. No lesions were seen in the gastric glandular mucosa, of which approximately 40% could be seen in each horse.

When the ulcer induction protocol was repeated with concurrent administration of ranitidine (Table 1), lesion areas were significantly less ($P < 0.05$) along the MPRT (Fig 3; no ranitidine, 961 ± 967 mm^2; ranitidine, 7.6 ± 20.2 mm^2) and MPLC (no ranitidine, 1,638 ± 1,738 mm^2; ranitidine, 187 ± 182 mm^2). Along the MPGC, 4 horses had lesions after the ulcer induction protocol without ranitidine and only 1 horse had lesions after the ulcer induction protocol with ranitidine. Overall, with concurrent treatment with ranitidine, 2 horses had normal mucosa, 1 horse had mild hyperkeratosis of the squamous epithelium, 4 horses had small lesions in the squamous epithelium, and 1 horse had moderate squamous mucosal ulceration. In each horse, lesion area was less than when ranitidine was not administered.

Horses turned out on pasture had normal gastric mucosa when initially examined by endoscopy, except

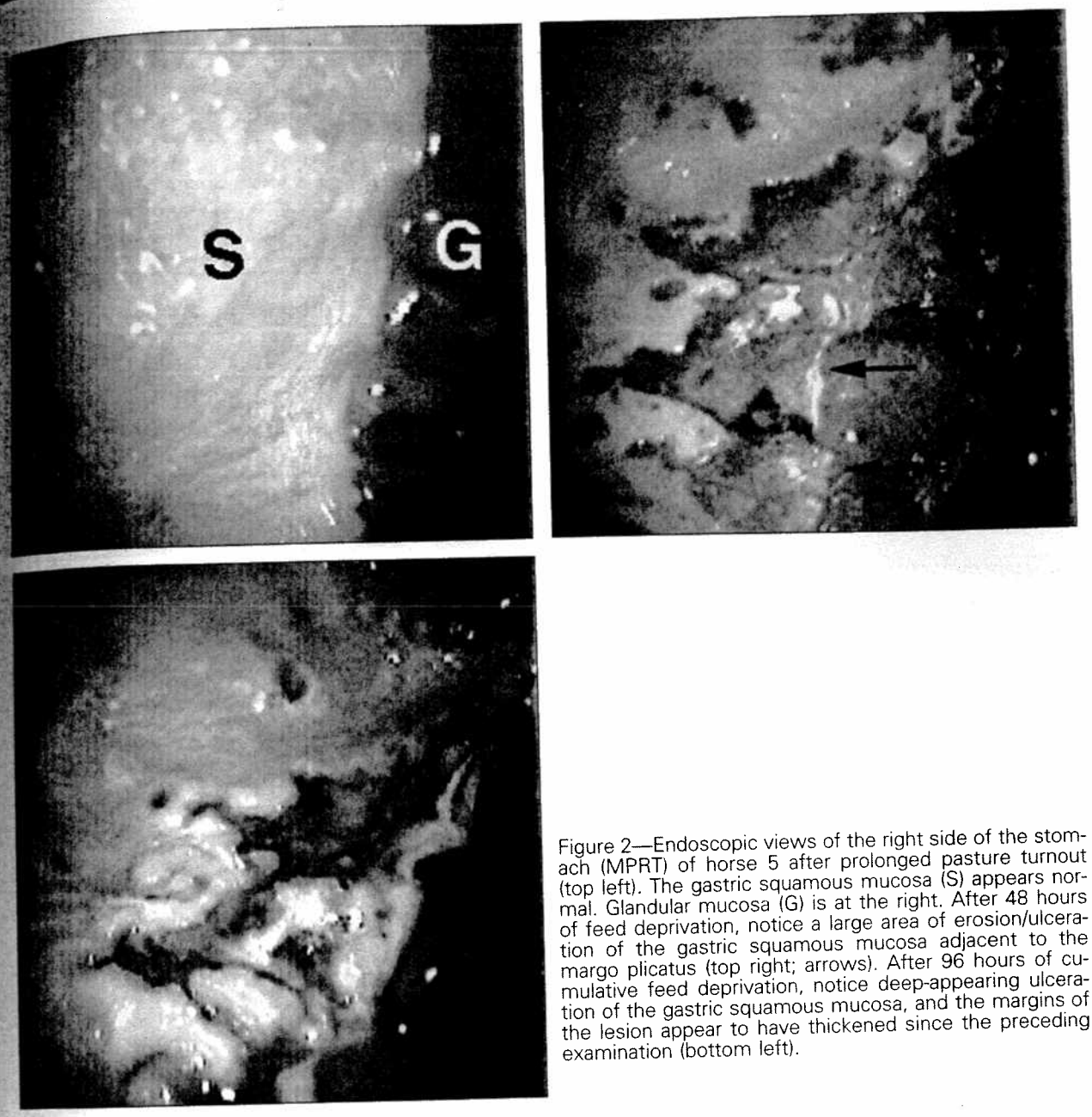

Figure 2—Endoscopic views of the right side of the stomach (MPRT) of horse 5 after prolonged pasture turnout (top left). The gastric squamous mucosa (S) appears normal. Glandular mucosa (G) is at the right. After 48 hours of feed deprivation, notice a large area of erosion/ulceration of the gastric squamous mucosa adjacent to the margo plicatus (top right; arrows). After 96 hours of cumulative feed deprivation, notice deep-appearing ulceration of the gastric squamous mucosa, and the margins of the lesion appear to have thickened since the preceding examination (bottom left).

3 horses had reddening or mild erosive lesions in the squamous mucosa along the lesser curvature. After 7 additional days of pasture turnout, only 1 horse had mild redness of the squamous mucosa along the lesser curvature. After 7 days of stall confinement, 2 horses had grade-4 lesions along the lesser curvature (Table 2), 3 horses had grade-3 lesions (Fig 4), 5 horses had grade-2 lesions, and only 1 horse had no lesions in the gastric squamous mucosa. Lesion scores were significantly ($P < 0.05$) worse for horses in stall confinement, compared with horses on pasture. One horse (with the most severe squamous lesions) had an apparent erosion in the glandular mucosa after 7 days' stall confinement.

Discussion

The equine gastric squamous epithelial mucosa is highly susceptible to peptic injury, because it has minimal intrinsic mucosal protective properties and is frequently exposed to a highly acidic environment.[9,12] The feed-deprivation protocol consistently and rapidly induced ulceration of the gastric squamous epithelial mucosa in adult horses. Because feed deprivation results in increased gastric acidity,[9] and because acid suppression significantly attenuated the extent and severity of ulceration in our study, excess acidity can be considered to be the principal pathophysiologic mechanism for inducing gastric squamous epithelial ulceration in adult horses. Gastric lesions were present within 48 hours of cumulative feed deprivation, indicating how rapidly gastric squamous epithelial lesions can form.

Administration of ranitidine did not completely inhibit gastric squamous epithelial lesion formation in all horses, but at a dosage of 6.6 mg/kg, the degree and duration of acid suppression varies between horses.[11] Additionally, the degree and duration of suppression of gastric acidity may be affected by feed consumption.[9] We presume that acid secretion was not inhibited continuously in each horse, and that there were periods of increased acidity between doses. Indeed, 3 horses in-

Table 1—Comparison of the number of horses with lesions and mean ± SD lesion areas, by site in the gastric squamous epithelial mucosa, in horses after 96 hours' cumulative feed deprivation with or without concurrent administration of ranitidine (6.6 mg/kg of body weight, PO, q 8 h)

Site in stomach	MPRT	MPGC	MPLC
No ranitidine			
No. with lesions	7	4	8
Lesion area (mm^2) ± SD	961 ± 967	265 ± 429	1,638 ± 1,738
Ranitidine			
No. with lesions	4	1	7
Lesion area (mm^2) ± SD	7.6 ± 20.2[a]	8.4 ± 22.2[b]	187 ± 182[a]

[a] $P < 0.05$; [b] $P = 0.08$.

MPRT = right side of the stomach along the margo plicaturs, MPGC = the greater curvature along the margo plicatus, and MPLC = the lesser curvature along the margo plicatus.

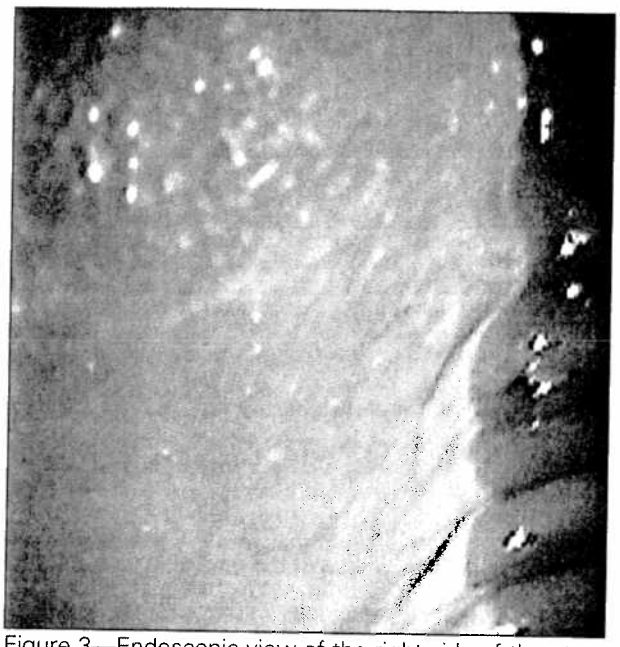

Figure 3—Endoscopic view of the right side of the stomach (MPRT) of horse 5 after 96 hours of cumulative feed deprivation and concurrent administration of ranitidine (6.6 mg/kg of body weight, PO, q 8 h). No lesions were present in the gastric squamous mucosa at this site, in contrast to results after 96 hours of cumulative feed deprivation without concurrent administration of ranitidine.

Table 2—Lesion scores from the 7 horses undergoing experimental conditions of 7 days' pasture turnout and 7 days' stall confinement

Condition	Horse	Gastroscopy 1			Gastroscopy 2		
		MPRT	MPGC	MPLC	MPRT	MPGC	MPLC
Pasture turnout	1	0	0	0	0	0	0
	2	0	0	2	0	0	1
	3	0	0	0	0	0	0
	4	0	0	2	0	0	0
	5	0	0	0	0	0	0
	6	0	0	2	0	0	1
	7	0	0	0	0	0	0
Stall confinement	1	0	0	0	0	0	0
	2	0	0	0	3	3	4
	3	0	0	0	2	2	3
	4	0	0	0	2	0	2
	5	0	0	0	2	2	2
	6	0	0	0	3	2	4
	7	0	0	0	1	1	0

Lesions were scored on a scale of 0 to 4.

cluded in our study previously had gastric pH monitored after administration of 6.6 mg of ranitidine/kg under fed and nonfed conditions. Administration of 6.6 mg ranitidine/kg after these horses had been deprived of feed for 18 hours resulted in increased gastric pH (> 5.0) for just 3 to 4 hours (unpublished data). Administration of ranitidine every 8 hours concurrent with ad libitum access to hay resulted in median 24-hour gastric pH of 5.5, 4.9, and 3.7, respectively, in these 3 horses.[9]

Because lesions tended to be most severe along the lesser curvature of the stomach, we believe that this mucosa must have the greatest exposure to acidic gastric secretions. Lesions were least severe adjacent to the MPGC, which is the most dorsal point along the margo plicatus, and, thus, probably receives the least exposure to peptic secretions.

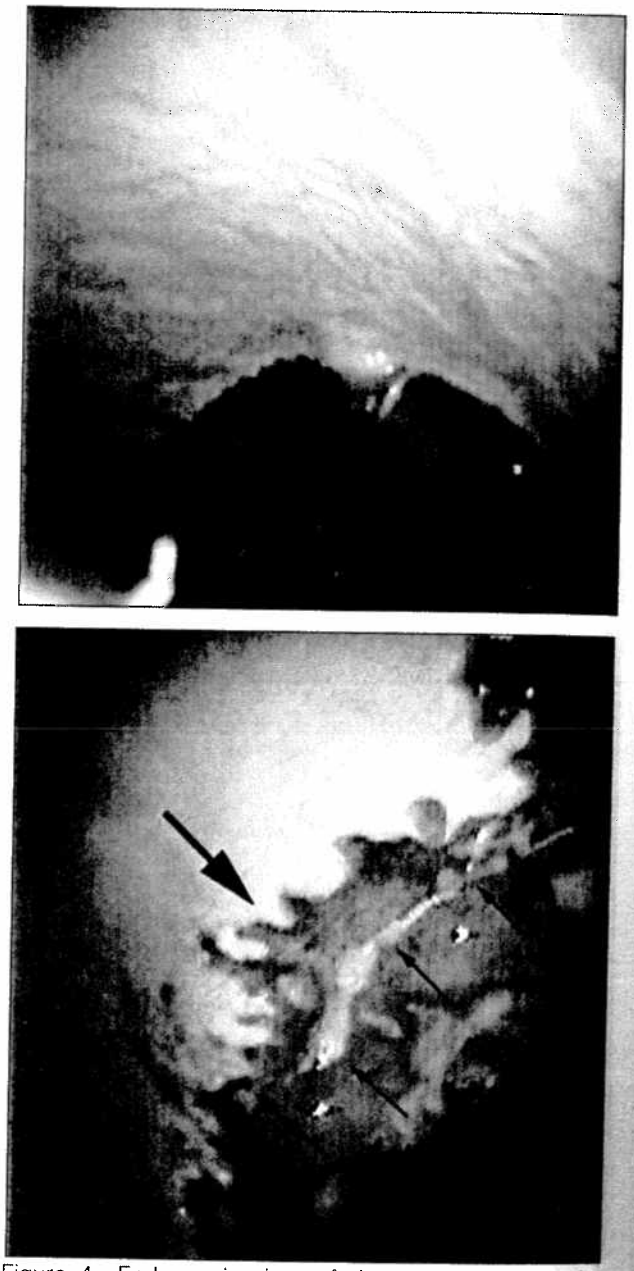

Figure 4—Endoscopic view of the stomach along the greater curvature (MPGC) of horse 2 after a period of prolonged pasture turnout (top). The gastric squamous mucosa appears normal. After 7 days of stall confinement with ad libitum access to Timothy hay, notice ulceration (large arrow) in the squamous mucosa adjacent to the margo plicatus (small arrows; bottom).

Our results confirm that, in some horses, stall confinement itself is an important factor in the pathogenesis of gastric ulceration. We did not measure hay consumption, but by having hay available at all times, we ensured that horses would have the same access to hay as they would to grass when turned out on pasture. We believe that the effect of stall confinement is an alteration in eating behavior (grazing), so that horses spend less time eating and subsequently undergo periods of increased gastric acidity. Previously,[9] we reported that, under similar conditions of stall confinement with ad libitum access to Timothy hay, median 24-hour gastric pH averaged 3.1. Gastric pH was < 2.0 for 30% of the pH readings during the 24-hour recording periods.

We cannot exclude the possibility that there may be a factor in grass, missing in cured hay, that may influence gastric acidity or mucosal resistance to acid. Also, we have not measured gastric pH in horses turned out on pasture. Yet, the cumulative evidence strongly supports our contention that lesions in the gastric squamous epithelial mucosa result from increased exposure to gastric hydrochloric acid, and that eating behavior influences gastric acidity and development of gastric mucosal lesions.

[a]Zantac, Glaxo, Research Triangle Park, NC.
[b]VideoEndoscope, Welch Allyn, Skaneateles Falls, NY.
[c]Targa-16, Truevision, Indianapolis, Ind.
[d]Horsepath, Loats Associates Inc, Westminster, Md.
[e]Andrews FM, University of Tennessee, Knoxville, Tenn, MacAllister CG, Oklahoma State University, Stillwater, Okla: Personal communication, 1996.

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