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The Equine Stomach: A Personal Perspective (1963-2003) (21-Nov-2003)

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1. State of the Art in 1963

It was in 1963 that I received my DVM from Cornell University. Developing a specialty in equine gastroenterology was the furthest thing from my mind. I was planning to be a cow doctor. Perhaps it was because of that bias, or because my memory is failing, that I remember virtually nothing that we might have been taught about equine gastrointestinal (GI) problems, except that surgical correction of a colic was a last resort that rarely had a favorable outcome. J.D. Wheat demonstrated the incorrectness of that maxim, however, during my internship the next year at the University of California at Davis.

I no longer have the notes I took in veterinary school that document what I should have remembered, but I have had another look at some of the texts of that era, which now reside in the dank and cobwebbed lower depths of the Marston Science Library at the University of Florida. Those texts, and what they include with respect to the equine stomach are the following.

***The Physiology of Domestic Animals*, 7th ed. H.H. Dukes, 1955 [1].**

Some very important basic aspects of equine gastric function were discussed in this text. First, the Russian researchers Ergerov and Cheredcov had actually cannulated the equine stomach (in 1933!) and collected gastric contents [2]. They reported that gastric acid was secreted continuously, and that the rate at which the contents flowed out of the empty stomach via the cannula would amount to 10 - 30 L/d. They noted that these contents contained not only acid, but also swallowed saliva and, at times, regurgitated intestinal contents. The feat was repeated in three yearlings by another Russian, Troitskii, in 1940, who also reported that fasting gastric secretion was continuous, but showing some "irregular undulations" in volume [3]. Second, stratification within the stomach of ingested contents as determined by meal consistency and order of ingestion is described in some detail. Some of the researchers actually used colored-coded feeds and water, followed by timed euthanasia, to make their observations. One of the most interesting findings was that ingested water appeared to have moved primarily around a stratified mass of relatively coarse ingesta and left the stomach quite quickly. What we now call "receptive relaxation" in response to meal ingestion was also briefly touched upon. Third, Dukes speculated that some microbial fermentation of ingested plant fiber and soluble carbohydrates should probably occur in the equine stomach, but he wondered, based upon his knowledge of ruminant forestomach function, whether the gastric acid might inhibit this process in the horse. Finally, the section on gastric motility is remarkably extensive. Quite a bit was known about gastric motility in general, starting with the pioneering roentgenographic studies in dogs and cats by Walter Cannon in the early part of the 20th century. With respect to the horse, roentgenographic, or cine-radiographic, studies were out of the question, but a number of *in vivo* studies, using balloons passed into the stomach of both conscious and anesthetized animals, and *in vitro* work with strips of gastric wall, had been performed; some of the best studies were executed by Prof. Frank Alexander at the University of Edinburgh [5]. However, the only thing to come from most of these studies was the inconsistency of results and the conclusion that, "The excised stomach of the horse does not show good motor activity". Dukes indicated that Alexander did make one interesting observation (that was "rediscovered" in more recent years): good motility could be recorded from the stomach of unanesthetized horses so long as the nasogastric tube was "of small diameter," whereas a tube of "large diameter" inhibited motility. No reference was listed for this information, however.

Dukes also very nicely reviewed the current knowledge of the control of gastric acid secretion, which was very basic according to our present understanding. Essentially, there was evidence for both neural (via the vagus) and hormonal stimulation of acid secretion, and the term "gastrin" for the hormonal component had been coined. But this edition of Dukes' book antedated the isolation of the gastrin peptide by Gregory and Tracy in 1964 [6].

Veterinary Pathology, 2nd ed. H.A. Smith and T.C. Jones, 1961 [7].

A total of two pages is devoted to equine gastric pathology other than that associated with parasitic infestation; "gastritis" and "hemorrhages," with no mention of the equine stomach, take up most of the discussion. A small section on "Impaction" specifically refers to the horse, and is attributed to "rapid ingestion of an excessive amount of ground feed or heavy grains," wherein signs of "circulatory derangement and shock may be fatal in a number of hours or may cause laminitis". There is not a word about gastric ulcers. Finally, under "Neoplasms" it indicates that carcinomas rarely may be found in the equine stomach, but there is no mention as to whether these arise from the glandular or squamous mucosa.

With respect to parasites, there is a relatively extensive section covering *Gastrophilus* species and their life cycle, with a short section on gastric habronemiasis, which states that "severe infections may interfere with gastric function, but a few parasites rarely have any significant clinical effect".

Equine Medicine and Surgery, 1st ed. J.F. Bone, E.J. Catcott, A.A. Gabel, L.E. Johnson, W.F. Riley, eds., 1963 [8].

The lone section on the stomach is titled "Gastric Dilatation," and was written by R.C. Herschler and H.E. Amstutz. The cause is attributed to either "impaction, flatulence, or excessive consumption of water". As with Smith and Jones, they ascribe the main cause of impaction to excessive grain ingestion, with acute flatulence, also due to ingestion of highly fermentable feedstuffs, as a secondary form. Chronic flatulence is attributed to cribbing. The clinical signs of the acute syndrome that are described in this section are familiar to any practitioner who has seen a case of excessive grain ingestion or, more commonly, a severe case of duodenitis - proximal jejunitis (anterior enteritis). It is implied that gastric rupture is a common sequella, in contrast to our experience today, when the lifesaving value of maintaining good gastric decompression is well recognized. In all fairness to Drs. Herschler and Amstutz, they did point out that passage of a nasogastric tube could provide relief for the acute "flatulent" form of the syndrome, which I do not think was taken much notice of at that time. They also recommend follow-up administration of a carminative, such as capsicum or turpentine, which was a common practice at that time for attempting to suppress further GI gas formation in horses and ruminants.

Finally, both *Gastrophilus* and *Habronema* infestation of the stomach are briefly discussed in a chapter entitled, "Metazoal Diseases," with a mention that the latter "may produce severe gastritis and one species initiates tumor-like abscesses". No clinical signs or treatment strategies are discussed for any of these problems.

While I will not deny that other contemporary texts contain other bits of useful information regarding equine gastric function and disease that we consider as common knowledge today, I think it is fair to generalize that most of the medical concerns of that time revolved around the acute gastric dilatation syndrome and its sequelae.

2. Ontogeny of Knowledge of Physiology and Pharmacology since 1963

2.1 Intra-gastric Microbial Digestive Activity

Ruminants, not monogastrics, readily come to mind when one mentions foregut fermentation of ingesta. Based on the classic studies performed in monogastric carnivores, the stomach has generally been considered too hostile an environment for meaningful microbial fermentative activity. This is definitely not the case for monogastric omnivores and herbivores, however, as represented by swine and horses, respectively (humans do not count because most of the food we eat is relatively sterile). It is true that most fermentative microorganisms do not like low pH any more than they like oxygen, and pigs and horses certainly can secrete plenty of gastric acid (see below). Yet intra-gastric fermentation of ingested carbohydrates can be considerable in both these species under certain dietary conditions. Though this was first recognized in the 1940's, it was a 1963 paper by Alexander and Davies that serves as the basis of the present outlook on this subject [9].

So, what about intra-gastric fermentation in the horse? It probably works like this. First of all, there are some fermenting microbes, such as *Lactobacillus acidophilus*, that survive quite well in a relatively acidic environment; the byproduct of *Lactobacillus* fermentation is lactic acid, a large quantity of which can be generated within a horse's stomach if there is a high proportion of soluble carbohydrates in the meal [9,10]. On the other hand, those microbes that convert ingested carbohydrates to volatile fatty acids (VFA) are more acid-sensitive, but they are also present and active within the equine stomach. I suggest that they colonize within the coarser fibrous ingesta, which collects towards the top of the stratified mat of gastric contents, where the pH of the contents is more to their liking because the mat has not been fully penetrated by gastric acid (Fig. 1). This higher pH is augmented by swallowed parotid saliva, which amounts to 10 - 12 L/D in an adult horse and has a bicarbonate concentration about twice that of plasma [11].



Figure 1. Representation of gastric fill and contents composition in a horse allowed free access to forage. Note that the fill line does not go much above the lower esophageal sphincter and that, just as in the rumen, the coarser contents layer at the top and the finer particulate components filter to the bottom. The upper, coarser mat, being the furthest away from the acid-secreting mucosa and more accessible to swallowed saliva, has a notably higher pH than the more liquid contents at the bottom. - To view this

image in full size go to the IVIS website at www.ivis.org . -

This pH/VFA production connection was first reported in a classic paper by Argenzio et al., in 1974 [10]. The regional pH variation was more recently and elegantly demonstrated by Baker and Gerring, who recorded a progressive drop in value as a nasogastrically introduced weighted pH probe slowly sank through the gastric contents toward the bottom of the stomach, where the most acidic components collect (Fig. 2) [12].

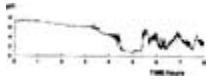


Figure 2. Continuous intragastric pH recording from a weighted probe passed nasogastrically in a pony at T = 0 as it descended through the stomach. The irregular increases in pH between 5.5 and 8 h is probably caused by a combination of exposure to contents from the upper part of the stomach passing by and by occasional duodenal reflux [12]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Argenzio et al., found that, in contrast to what happens in the ruminant forestomachs, the VFA produced within the equine stomach are not absorbed from the stomach into the bloodstream [10]. They indicated that the normal nonglandular (squamous) mucosa is particularly resistant to VFA penetration. This latter observation has important implications with respect to lesion formation within the squamous mucosa, as will be discussed in more detail later in this review.

2.2 Intra-gastric Nonmicrobial Digestive Activity

The two digestive enzymes of note secreted by the equine stomach are pepsin and lipase, which is in concordance with most other mammalian species. Pepsin is proteolytic in an acid medium. The primary secretion by the zymogen (chief) cells found within fundic and pyloric mucosae is pepsinogen, which is converted to pepsin when the pH of the medium is <4. More than one biochemical form of equine pepsinogen exists, but the functional significance of this, with respect to intra-gastric proteolysis, is not known [13-16]. We really know nothing about the extent to which pepsin contributes to the digestion of ingested dietary protein in the horse. Equine gastric lipase, which has a peak activity at pH 4, is also produced by zymogen cells, primarily in the fundic mucosa [17]. Horses produce a large amount of gastric lipase but, as with pepsin, nothing is known about its role in the processing of ingesta. Of related interest is that, on a relative basis, the equine pancreas produces much more lipase than any of the other digestive enzymes produced by this organ [a]. Also, recent studies have shown that horses can effectively assimilate quite large amounts of dietary fat [18,19].

2.3 Acid Secretion

As indicated in the "State of the Art in 1963" section, the Russians Egorov and Cheredcov successfully cannulated the stomach of a horse 70 years ago and reported that acid was secreted continually, even when the stomach was empty, and that its secretory rate appeared to be up-regulated by food intake. The significance of this interesting finding (to say nothing of the successful cannulation itself!) was totally unappreciated at the time. Only now do we appreciate it, in light of recognition of the involvement of gastric acid in the equine gastric ulcer syndrome (EGUS).

It is probably safe to say that the dawn of the current era of study of equine gastric secretion was the development of a cannulation technique in our lab by Martha Campbell-Thompson. The paper that signaled the application of that technique appeared in 1987 and concerned the effect of IV injection of the histamine-2 receptor antagonist ranitidine on acid secretion in young adult horses [20]. Although that report was important in that it showed that endogenous histamine was involved in the stimulation of acid secretion in the horse, as had been shown already in other species, the major focus of our investigation at that time was on gathering basic information that would be essential to our understanding of both normal function and diseases of the equine stomach. Much of the impetus for the work, and for that of others as well at that time some of whom were utilizing our cannulation technique was a rapidly growing realization that gastric ulcer disease could have serious consequences in all ages of horses. What have we learned about gastric acid secretory control in the horse during the last 16 years? Let us first review what is known in general about the subject, from studies performed primarily in mice, rats, and dogs, and then see how these relate to the horse.

As indicated in the anatomical review, acid is secreted by the parietal cells, which are located within the gastric glands of the fundic mucosa. Like any other bodily function, control of secretion involves a complex interaction between stimulatory and inhibitory signals. From the most elemental standpoint, our view of stimulatory input has not changed much since 1963. That is, the primary neural component involves vagally released acetylcholine, and the primary hormonal component is the peptide gastrin, which is produced by G-cells located within pyloric mucosa. However, this simple concept has now become much more complex in light of continuing discoveries. Acetylcholine and gastrin are still important players, but their stimulatory effect on the parietal cell is probably more indirect than direct, and is modulated by various feedback loops that are, in themselves, responsive to numerous factors, including intra-gastric pH and ingesta composition. Once the biochemical isolation of gastrin was accomplished by Gregory and Tracy in 1964 [6], isolation of other well-known peptides involved in GI tract control, such as secretin, cholecystokinin (CCK), somatostatin (SST), and gastrin-releasing peptide (GRP), followed

(the specific molecular structure of equine gastrin was not characterized, however, until 1998) [21,22]. With such peptide characterizations, effects of administration of whole molecules and their active fragments could be defined, and radioimmunoassays eventually were developed to measure their concentration in blood and tissues. All of these developments were crucial to bringing us to the level of understanding we possess today.

Although exogenous histamine has been known for a long time to be a very effective acid secretagogue, until comparatively recently the role of endogenous histamine remained elusive [23]. The inability of first-generation antihistamines, now regarded as H₁-receptor antagonists, to block the effect of exogenous histamine sustained the confusion. The development of what are now called histamine-2 (H₂) receptor antagonists showed that more than one type of histamine receptor exists and cleared the way for major advances in our knowledge of parietal cell secretory control [24].

Some essential components of this control, based on current knowledge and what I believe to be the most important clinical implications for equine medicine, are schematized in Fig. 3.

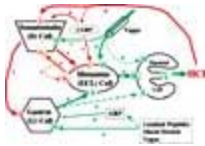


Figure 3. Schema of the major mechanisms involved in endogenous control of gastric acid secretion. The green arrows indicate those pathways that ultimately stimulate the parietal cell; the red arrows indicate the inhibitory pathways. The size of the arrows suggests the relative importance of the respective pathways in this activity. Note the suggested central role played by the enterochromaffin-like cell, which elaborates histamine, in this schema. - To view this image in full size go to the IVIS website at

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According to this schema, the major players in parietal cell secretory control are vagus nerve (acetylcholine), gastrin, and somatostatin, with minor roles played by calcitonin gene related peptide and gastrin-releasing peptide. It attempts to emphasize the contemporary thinking concerning the importance of the enterochromaffin-like (ECL) cells, which secrete histamine, found within the fundic mucosa, as the major pathway through which the stimulants of the parietal cell are transduced [25,26]. Understanding this makes it much clearer why H₂-receptor antagonists are so effective in suppressing acid secretion. The schema also illustrates the modulatory role of somatostatin (SST), which is elaborated by so-called D-cells that can be found in both fundic and pyloric mucosae. SST's effect is more paracrine than endocrine in this respect; that is, the close proximity of the D-cells to its various effector cells allows for a direct action that circumvents the need for delivery via the bloodstream. This is not to say that SST is not released into the blood (for it surely is), it just means that many of its gastric-related activities are paracrine. One of the most illustrative of these interrelations is within the pyloric gland mucosa, where the G-cells that produce gastrin and the D-cells, both of which are continually sampling the intra-luminal contents, are in close proximity (Fig. 4). If intra-luminal pH drops too low, especially below 4, SST release is up-regulated to down-regulate gastrin release [27]. Likewise, within the fundic mucosa, there is an ongoing, albeit somewhat complicated, mutually negative feedback paracrine interaction between ECL and D-cells that determines how much histamine will be released [28,29]. Thus, the stomach acts, in a sense, as its own pH meter.

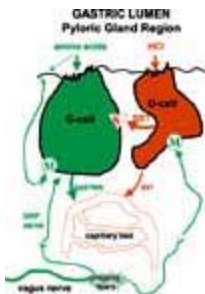


Figure 4. Representation of interaction within the antral mucosa between the G cells that produce gastrin and the D cells that produce somatostatin. As shown, both cells are constantly sampling antral contents for their respective agonists; certain nutrient components of the ingesta in the case of the G cell, and acid concentration with respect to the D cell. This mechanism represents an important system for control of antral gastrin release, and indicates how the stomach acts as its own pH meter [27]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Over the last 25 years, there has been an outstanding expansion of knowledge of how the parietal cell elaborates acid secretion, much of it coming from the laboratory of George Sachs [30]. This research has centered around characterization of the H,K-ATPase-induced proton pump mechanism at the secretory membrane of the cell that is responsible for the acid secretion. Essentially, the known stimulants of parietal cell secretion gastrin, acetylcholine, and histamine provoke tubovesicular H,K-ATPase within the cytoplasm to migrate to the secretory membrane of the cell and activate the H⁺/K⁺ exchange mechanism. This exchange is limited, however, by the amount of available K⁺ within the fluid close to the cell membrane. This K⁺ is cell-derived and moves from cytoplasm to luminal surface down a concentration gradient via channels through the cell membrane (Fig. 5). Likewise, the Cl⁻ moves passively via channels through the secretory membrane, pulled by the electrochemical gradient created by the active secretion of the H⁺ [30]. Thus, the H⁺ ions are secreted at a pH of 0.8, whereas that of the cytosol of the parietal cell ranges between 7.1 and 7.8, resulting in an H⁺ concentration gradient of 2.5 million fold across the secretory membrane! The acid is, obviously, greatly diluted as it moves through the parietal cell canaliculae and gastric gland up into the gastric lumen. The HCl concentration in primary secretion during maximal

stimulation, just as it emerges from the gastric gland, is 160 mEq/L at most. Still, this requires that the glandular mucosa maintain a number of important mechanisms to protect itself from self-destruction by the acid (see below).

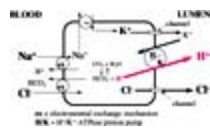


Figure 5. Mechanism of acid secretion by the parietal cell. The critical factor in sustenance of the H⁺/K⁺-ATPase proton pump that elaborates the acid is the ready availability of K⁺ within the parietal cell canalicular lumen. This K⁺ moves out of the parietal cell, as does the Cl⁻, down a concentration gradient through specific channels in the mucosal membrane. - To view this image in full size go to the IVIS website at www.ivis.org . -

Are the mechanisms of control of gastric acid secretion described above, which have been primarily worked out in rodents and dogs, present in the horse? The evidence to date says "yes". But this is a qualified "yes," because of the limited number of studies that have been done.

This evidence includes:

1. The stimulation of secretion by histamine, pentagastrin, the active terminal 5-amino acid sequence of gastrin, and bethanechol, an acetylcholine analogue;
2. The suppression of secretion by the SST analogue octreotide, and;
3. The inhibition of secretion by atropine, the H₂-receptor antagonists, and H,K-ATPase proton pump inhibitors (PPIs).

It should be kept in mind that much of this information has been obtained by using gastrically cannulated horses from which food has been withheld in order to easily collect the gastric contents through the cannula. This is a rather unnatural condition because healthy adult equids are rarely, if ever, without some food in their stomach. Nevertheless, this allows us to gather important fundamental physiological information that we can then apply to other, more natural, conditions. It must be remembered that what is collected from a simple gastric cannula is made up of a continually changing relative mixture of saliva, gastric secretions and duodenal reflux. Within this context, it is important to review what has been learned about how horses compare and contrast with other species:

- As indicated, we have confirmed that horses, like most other species, secrete some gastric acid even when the stomach is empty; only the carnivora are not "interdigestive secretors", probably because of their defined meal-feeding behavior in the wild. When equine gastric contents are continually collected over a period of time, the acid concentration, and thus pH, is quite spontaneously variable (Fig. 6) [31-39]. It appears, in the adult horse at least, that duodenal reflux is more responsible for this variability than is saliva (see below). This idea is supported by the endoscopic observation that the pyloric sphincter region of the horse is open most of the time (Fig. 7). There is some evidence that the reflux is more profound during that part of the so-called "migrating motility complex" of the GI tract when the antral motility is momentarily suppressed [40]. It is reasonable to assume that this backflow is less when the stomach is full, and the general gradient of contents movement is more aborad, but this remains to be determined. Nevertheless, these observations during the fasted state have important clinical implications with respect to the potential for ulcerogenesis in horses that have empty stomachs, either because of illness-related anorexia or human-imposed management conditions. This will be discussed in more detail in the EGUS section of this review.

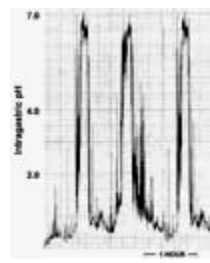


Figure 6. Continuous recording over a 3-h period of the pH of the gastric contents of a fasted horse. The pH probe has been introduced through a cannula in the most ventral part of the greater curvature of the stomach and sits ~3 cm within the gastric lumen. The periodic large increases in contents pH are most likely caused by reflux of duodenal contents coincident with phase I of the duodenal migrating motility complex. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 7. Endoscopic view of the pyloric sphincter region (yellow arrow) in its commonly seen open state. This allows for ready reflux of duodenal contents back into the stomach. - To view this image in full size go to the IVIS website at www.ivis.org . -

- Ingestion of food naturally has a significant impact on intra-gastric pH. In the neonatal foal, where the gastric contents are uniformly liquid, the pH value measured by an intra-gastric recording electrode is reasonably representative of all the contents therein. Such studies have shown that milk ingestion causes a rapid and marked increase in value that lasts for less than 1 h [36,39]. However, as indicated in the "Intra-gastric Microbial Digestive Activity" section above, the pH of intragastric contents in the free-feeding adult horse is anything but uniform (see Fig. 1).
- Campbell-Thompson's studies established that the maximal acid secretory dose of pentagastrin in the horse is 6 µg/kg/h IV, which is within a reasonable range for what has been found in other species [32]. This conclusively demonstrated that a gastrin responsive mechanism was indeed present in equidae, although one would have predicted it thanks to the 1975 report of Olowo-Okorun of gastrin isolation from donkey antrum [41], and the subsequent measurement by others of gastrin activity in equine antrum and plasma [42-46]. More recently, Johnsen et al., have identified the molecular structure of equine gastrin collected from antral tissue and found that, in contrast to other species, both the G-17 and G-34 forms are virtually non-sulfated, and Sandin et al., showed that the maximal acid response to the purified equine G-17 was similar to that induced by pentagastrin [21,22]. The establishment of a maximal acid secretory dose of pentagastrin is important primarily because it forms a gold standard against which other stimulants of gastric acid secretion can be compared. Another finding from Campbell-Thompson's studies that is equally, if not more, important is that pentagastrin infusion also causes an increased appearance of "non-parietal" components of high Na content in the collected gastric contents [32]. Kitchen et al., subsequently showed that the appearance of these components could be significantly reduced by proximal duodenal obstruction, indicating their duodenal, rather than gastric, origin [47]. There are strong indications that their primary duodenal source is pancreatic secretion which, in the horse in contrast to other species, appears to be up-regulated by gastrin [48,49]. These findings reaffirmed earlier impressions that duodenal contents can readily reflux into the stomach of the horse, especially when the stomach is empty. Because of the high Na and substantial bicarbonate concentration of those contents, they provide an additional buffer of the gastric acid, and thus could potentially provide some protection for the gastric mucosa.
- It was important to verify that histamine infusion could stimulate gastric acid secretion in horses as it does in other species, and to a maximal level that was similar to that induced by pentagastrin [50]. Moreover, these studies showed that, in contrast to gastrin, histamine does not simultaneously stimulate the pancreatic water and electrolyte secretion. Also, it takes less histamine (15 µg/kg/h) to induce maximal acid secretion in the horse than in humans and other domestic animal species. This is consistent with the results of some earlier *in vitro* studies of isolated equine parietal cells conducted by Campbell-Thompson, indicating that equine parietal cells are much more sensitive to histamine than to gastrin, which is just the opposite for canine parietal cells [51]. This is of particular interest to GI pharmacologists and might, in part, explain why horses require such large doses of H₂-receptor antagonists, relative to other species, to effectively inhibit gastric acid secretion (see EGUS treatment).
- In 1992, Sojka et al., showed that SC administration of the SST analogue octreotide caused a sustained significant increase in the pH of fasting gastric contents of ponies when compared to nontreated controls [52]. We subsequently found in some unpublished studies performed in our laboratory that octreotide could markedly inhibit both basal- and pentagastrin induced acid secretion in adult horses. These findings provide further indication that the mechanisms of endogenous acid secretory control, as schematized in Fig. 3, are intact in equidae. It is most likely that the exogenous SST analogue used in the studies described above exerted its effect through suppression of histamine release by the ECL cells, which would be consistent with the notion that much of the effect of gastrin in horses, whether exogenous or endogenous in origin, is via stimulation of the ECL cells rather than directly on the parietal cells. The clinical implications of this reside in the concern expressed in human medicine that long-term gastric acid suppression, such as that provided by persistent PPI therapy, takes away the stimulation of local SST production and results in secondary hypergastrinemia which, in turn, leads to hyperplasia (carcinoid), and potentially to neoplasia, of the ECL cells [53]. The implications of this with respect to horses remains to be determined, especially as the PPIs are used more extensively to control equine gastric ulcer syndromes.
- In addition to the original study of Campbell-Thompson and Merritt mentioned above [20], the involvement of H₂ receptors in the elaboration of gastric acid secretion, even in foals as young as 2 d, has been well demonstrated in the horse by other researchers, using cannula collection, contents aspiration, and continuous pH measurement techniques (Fig. 8) [31,33,39]. There is a growing impression, through recent studies performed in rodents and dogs, that gastrin may exert some, if not all, of its parietal stimulatory effects through H₂ receptors [26]. This may be the case in the horse as well [13].



Figure 8. Site of action of the histamine-2 receptor antagonist drugs, indicating where they exert their inhibitory effect. - To view this image in full size go to the IVIS website at www.ivis.org . -

- There now exist a number of reports concerning the antisecretory efficacy of the PPI omeprazole (OME) on both basal and pentagastrin-induced acid secretion in the horse [34,49,54-58]. As with the H₂-receptor antagonists, the acceptable effective dose of OME for the horse is considerably higher than that required in other species, especially when given orally. Here, the problem may have more to do with the vagaries of the equine GI tract - for example, the horse cannot absorb a number of antibiotics that are readily absorbable in other species - than a species-specific variation in endogenous mechanisms of control of acid secretion. But it could also be caused in part by differences in acid production at the parietal cell membrane, because the drug needs to be acidified on the spot before it can bind to the proton pump [59]. This is somewhat of a paradox in that every effort must be made to protect OME and the other substituted benzimidazole PPIs from exposure to gastric acid *before* their absorption, because such exposure followed by alkalization within the small intestine renders the compounds inactive [59].

2.4 Endogenous Mucosal Protective Mechanisms

The glandular mucosa of the stomach has a complex mechanism of protecting itself from corrosive agents such as acid, pepsin, and certain bile salts. The essence of this mucosal barrier is a combination of mucus and bicarbonate that is produced by cells of the gastric glands, and through which secreted acid and pepsinogen can easily move from mucosa into gastric lumen, but not vice versa [60]. Thus, under normal conditions, the pH of the medium just adjacent to the mucosal surface is biologically neutral. As is well known, one of the most important inducers of mucosal protective mechanisms is prostaglandin-E₂ (PGE₂), which is up-regulated by the cyclo-oxygenase-1 arm of the arachidonic acid cycle [61,62]. Probably one of the most important systems by which PGE₂ and other mediators involved in promoting mucosal protection are modulated is the so-called "gastric neural emergency system" (Fig. 9) [63]. This is a component of the enteric nervous system within the stomach, which is essentially a reflex arc, the afferent arm of which is constantly sampling the pH at the mucosal surface. A sufficient drop in pH results in the neural reflex up-regulation of PGE₂ expression, along with that of other mediators of protection, such as calcitonin gene related peptide and constitutive nitric oxide synthase.



Figure 9. Representation of the major components of the gastric neural emergency system that is critical to maintaining mucosal defense of the glandular mucosa against the corrosive effects of gastric acid. This is an intrinsic component of the enteric nervous system, the afferent arm of which is responsive to acid concentration at the mucosal surface. - To view this image in full size go to the IVIS website at www.ivis.org . -

Another mucosal protective effect of PGE₂ is the direct inhibition of acid secretion by the parietal cell [61]. A small study performed in our lab with four gastrically cannulated ponies illustrates the point. It was work performed in humans and rats that demonstrated the ability of dietary supplementation with arachidonic precursors, such as linoleic acid, to increase endogenous PGE production [64,65]. We performed gastric secretory studies on the ponies before and during the fifth week of oral daily dosing of 20 ml/kg body weight of corn oil, which contains ~40% linoleic acid. We found that the corn oil treatment significantly increased PGE₂ and reduced gastric acid output, both before and during IV pentagastrin infusion (Fig. 10) [66]. The importance of PGE₂ in the protection of the equine glandular mucosa has been indirectly recognized for many years through the ulcerogenic effects of non-steroidal anti-inflammatory drugs (NSAIDs) [62]. Thus, the corn oil supplementation of horses that need to be on long-term NSAID therapy because of a chronic musculoskeletal problem, for example, is worth contemplating (see EGUS treatment).

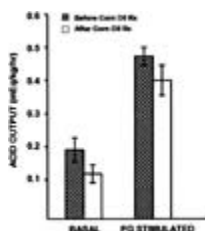


Figure 10. Mean basal and pentagastrin-stimulated gastric acid output from 4 ponies before and after oral administration of 40 ml/d of corn oil for 30 d. The values after corn oil treatment are significantly lower than those before treatment at every time point. This is strongly indicative of up-regulation of PGE₂ within the fundic glandular mucosa induced by the corn oil treatment [12]. - To view this image in full size go to the IVIS website at www.ivis.org . -

There is no evidence, however, that any of the mechanisms discussed above are operative in the squamous gastric mucosa.

2.5 Motility

The physiology and pharmacology of GI motility received a major kick-start in the late 1960's with the developmental use of electrodes surgically implanted onto the serosa of the bowel to record smooth-muscle myoelectrical activity. These are usually chronic preparations lasting for months that allow for the recording of activity over many hours from conscious,

lightly restrained animals. Yves Ruckebusch was a pioneer in the application of this technology to the equine GI tract; I had the pleasure of spending a year in his laboratory during 1984 - 1985. One of the most important discoveries from this technique was the so-called "slow wave" (SW), a persistent undulation of the resting membrane potential that is characteristic of GI smooth muscle [67,68]. When strain gauges, which record tissue deformation, are applied along with electrodes, it is seen that there is no significant motility associated with the SW activity. Contraction occurs only when there is an action potential that signals complete depolarization of the muscle [68,69]. And because an action potential can occur only in association with a SW, the *maximal* rate of contractile events for a respective region of the GI tract is limited by the SW frequency in that region. The SW frequency is ~3/min in the equine stomach, which puts it on a par with humans, and is about half the rate of that in carnivora and swine (Fig. 11) [70]. The clinical implications of this difference, if any, have yet to be defined. However, SW dysrhythmias have been recorded by clinically applicable transcutaneous methods during various GI disturbances in both dogs and humans [71-73].



Figure 11. Antroduodenal myoelectrical activity in a horse. The red brackets on the antral and duodenal traces, respectively, designate a period when only SW activity is present, which indicates a temporary cessation of motility. On the duodenum, this quiescent period is referred to as phase I of the migrating motility complex. - To view this image in full size go to the IVIS website at www.ivis.org . -

Unfortunately, the current techniques for this cannot be used in the horse due to the distance of the stomach from the body wall. The motile events of the equine stomach that are important to consider within the context of this presentation are those associated with the reception and emptying of ingesta:

- If the stomach cannot relax to receive an ingested meal, then the volume that can be ingested is very limited, and there is risk of rupture if an attempt is made to exceed the limit. The state-of-the-art technique for evaluating changes in gastric wall compliance involves the electronic barostat. This has provided a way to accurately evaluate gastric relaxation that was heretofore unavailable. What it involves is the intra-gastric placement of a plastic bag of appropriate volume that has no elastic recoil, with a flexible tube running from the bag to a computer-controlled instrument that rapidly responds to any change in preset intra-bag pressure by either injecting or withdrawing air [74]. That is, when the intra-gastric pressure drops, as the stomach relaxes, for example, air is injected into the bag and vice versa. These volume changes are continuously recorded over the time of the experiment. For evaluating the response of the stomach to a meal, the intrabag pressure is usually maintained at a low 4 or 6 mmHg, which provides for a rapid response to changes in intra-gastric pressure without distending the organ. Most of the studies performed to date in humans and dogs have employed a liquid meal, which results in a monophasic "receptive relaxation" volume response curve [75-78]. In our lab, Lorenzo-Figueras et al., looked at the response to two different sizes of either a hay or grain meal given to horses, which provided some interesting results. Basically, in contrast to the monophasic relaxation episode seen in humans and dogs after a liquid meal, we saw a distinct biphasic response to the ingestion of the solid meals. The first occurred during active ingestion, which we regarded as true "receptive relaxation," and the second, more prolonged phase, which we referred to as "accommodation", followed the active ingestion (Fig. 12). As seen in the figure, the duration of the receptive relaxation phase was directly related to the time it took to eat the meal, and was most distinct during ingestion of the "large" (1 g/kg body weight) hay meal. The only significant degree of accommodation (relaxation) above baseline during the second phase was after the large hay meal [79]. We have suggested that the first phase is mainly induced by mechanosensors within the pharynx and/or esophagus, whereas the second phase is more under the feedback control of sensors within the duodenum that are triggered by food entering from the stomach. These studies represent only the tip of the iceberg of what needs to be done in horses, particularly in view of the dietary manipulations fostered on them these days! Nevertheless, the results certainly suggest that, within reason, the equine stomach is fully capable of adjusting to the size of meal ingested.

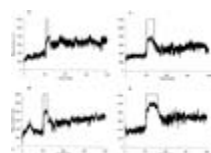


Figure 12. Mean volume of a barostat bag within the proximal stomach of 6 horses that tracks the response to ingestion of each of 4 diets: A, 0.5 g grain/kg BW; B, 1 g grain/kg BW; C, 0.5 g hay/kg BW; D, 1 g hay/kg BW. An increase in volume, indicating a decrease in gastric tone, was seen shortly after the beginning of intake for all of the diets. There was an initial peak response associated with the period of active ingestion (box), which was followed by a lower, sustained response that endured until the end of the experiment [80]. - To view this image in full size go to the IVIS website at www.ivis.org . -

- Gastric motor events that affect emptying can be essentially divided into two major components: 1) *increased tone* of the proximal half that affects primarily movement of fluid contents; and 2) *peristaltic contractions* that begin in the fundic region and migrate aborally with increasing speed and force to expel the more solid contents, along with any

liquid present, forcefully across the pyloric area and into the duodenum, which is an action often referred to as "antral systole" (Fig. 13). The maximal occurrence frequency and propagation rate of those contractions is determined by the underlying SW activity. This scenario is based upon what has been observed to date in humans, dogs, and swine, but there is little doubt that it also applies to horses, albeit with some species specific nuances that remain to be determined. The antral contractions also serve to break down, or "triturate," larger food masses into smaller components that can pass more easily across the pyloric sphincter region.

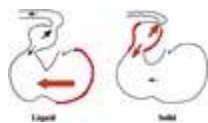


Figure 13. Diagrammatic representation of the relationship between the type of gastric motility and the subsequent emptying of liquid versus solid contents. The major determinant of liquid emptying (left) is directly related to the degree of proximal gastric tone, whereas the major determinant of solid emptying is directly related to degree of antral peristaltic activity ("antral systole"). - To view this image in full size

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- Initial attempts at evaluating gastric emptying in equids involved intra-gastric instillation of a radio-opaque substance, usually barium, and subsequent periodic x-rays; equipment limitations confined such studies primarily to foals [80,81]. This provided useful crude clinical information; for example, if the image taken at 1 h post-instillation was similar to that taken immediately after instillation, gastric emptying was delayed, but no kinetics could be applied to the process. The application of reliable methods for quantitative measurement of gastric emptying rate in horses began in the early 1990's. Baker and Gerring used a phenol red-marked liquid meal, a method first described by Hunt in the 1950's for use in humans [82], to evaluate the effect of meal composition and cisapride treatment on gastric emptying in foals [83]. Sosa Leon et al., also used this method to evaluate the gastric emptying rate of an isotonic electrolyte/glucose solution in adult horses before and after exercise [84]. The technique requires periodic naso-gastric intubation post-instillation to collect a sample for phenol red concentration, which clearly builds considerable artifact into the system. Nonetheless, Baker and Gerring noted that their liquid meals emptied rapidly from the foals' stomach, with milk the slowest [82]. Sosa Leon et al., found that 90% of the 8 L of fluid instilled left the stomach within 15 min of administration, whether the horses had been exercised or not [83].
- Both solid and liquid gastric emptying rates that provided time values for emptying one half of the administered marker (T-50) were first measured in the horse by gamma scintigraphy, using radioactively labeled meals that were quite artificial in their makeup with respect to what horses normally eat. Thus, they had to be administered by nasogastric tube, but avoided many of the artifacts associated with using the nonradioactive markers discussed above. The results showed distinct differences according to meal consistency, with the liquid meal being emptied more quickly, which would be in line with what has been seen in other species [85,86]. This technique provided for an evaluation of gastric emptying rate in horses, and for a way to test the efficacy of putative prokinetic drugs, that would prove to be clinically useful, as will be discussed later. With respect to the prokinetic agents, Ringger et al., reported a significant increase in the emptying rate of a "solid" (⁹⁹Tc fried into egg white) meal in normal horses after treatment with both low dose erythromycin lactobionate (0.1 mg/kg IV) and bethanechol (0.025 mg/kg IV) [85].
- Subsequently, a number of studies have been performed on the chemical manipulation of equine gastric emptying by using absorption characteristics, as assessed by sequential blood sampling, of intra-gastrically administered acetomenophin as the marker [86-89]. This technique looks only at liquid emptying, the normal values of which are similar to those obtained by scintigraphy [86], but has provided some useful clinical information nonetheless, which will be referred to later in the discussion of ileus.
- Finally, the recent application of the ¹³C-octanoate breath test technique for assessing gastric emptying rate in the horse has opened up a much more natural method of analysis [90-92]. For example, the results of a recent study using this technique confirmed earlier impressions that treatment with the commonly used α_2 -agonists and butorphanol, alone or in combination, significantly delays emptying [91]. Although this method has its detractors [19], it still provides the best way to date to evaluate emptying characteristics of foodstuffs that horses naturally eat. Thus, it not only has value in pharmacological studies, but also will be very useful in evaluating differences between various formulations of feedstuffs [92].

3. Ontogeny of Knowledge of Disease States and Treatment Since 1963

3.1 Impaction

Fortunately, gastric impaction is not a common problem in the horse, for it is not easy to diagnose without an endoscope, or to resolve without surgical intervention. There is a form that appears to be caused by partial gastric outflow obstruction a collection of ingested persimmon pits has been documented in a few cases [93-95] and then there is a form to which no apparent physical obstruction can be attributed. The earliest case report of so-called "primary" gastric impaction that I can find is that of Jones et al., published in 1972 [96]. Interestingly, a number of the cases that have been reported in the literature

since then have been associated with progressive hepatocellular failure, with signs of liver disease being the presenting complaint and the impaction found secondarily [97-99]. This is a very curious connection for which it is difficult to find a ready explanation. Other "primary" cases have presented with colic of varying intensity, sometimes of a chronic recurrent nature. Thus, for those cases of gastric impaction where there is no evidence of physical obstruction of gastric emptying, pathophysiology is speculative at best. Luckily, this form responds well to surgical removal of the impacted mass, so long as there is no attendant serious disease process, such as hepatic failure [100,101].

3.2 Tumors

The term "tumors" is used in the heading for this section instead of neoplasia because strange growths can develop within the equine stomach that are inflammatory rather than neoplastic in nature [102,103]. By far the most common problem, however, is neoplastic, in the form of squamous cell carcinoma arising from the non-glandular part of the stomach. Although squamous cell carcinoma had been described in texts and reports as early as 1900, it was not until the early 1970's that case studies started to appear in the literature with any frequency [104-110]. Squamous cell carcinoma should always be considered in the initial rule-out list for chronic weight loss in horses >5 years of age, particularly those with progressive anorexia and anemia. Sometimes progressive ptyalism (drooling) is seen also, particularly if the tumor involves the lower esophageal sphincter and/or distal esophagus [111]. Occasionally, but certainly not with any consistency, metastases within the peritoneal cavity are extensive enough to be felt per rectum as irregular masses, or neoplastic cells can be found in peritoneal fluid [109,112]. Imaging of the tumor by ultrasound has also been described [109]. But by far the most direct way to make a definitive diagnosis is by endoscopy (Fig. 14) [111,112].

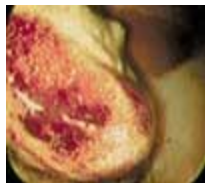


Figure 14. Endoscopic view of a gastric squamous cell carcinoma. Some reasonably normal-appearing squamous mucosa can be seen at the top center part of the view. - To view this image in full size go to the IVIS website at www.ivis.org . -

Other "tumors" involving the equine stomach, whether inflammatory or neoplastic, are extremely rare, with progressive weight loss and anorexia being the most consistent clinical signs [112,113]. Again, endoscopy is the most direct way to detect the presence of these lesions, although laparoscopy, laparotomy, or necropsy may be required for specific pathological definition.

3.3 Reflux

As indicated in my introductory remarks, when I graduated from veterinary school in 1963 the only medical problem of the equine stomach, outside of parasitism, that was routinely mentioned was "acute gastric dilatation," with the proviso that it was often fatal due to gastric rupture because "horses cannot vomit". While a number of texts extant at the time mentioned that relief could sometimes be provided by draining the gastric contents via nasogastric intubation, from my perspective it was not until the early 1970's that such intubation, not only once but repeatedly in some cases, started to become common practice when the problem was suspected [114,115]. It was quickly realized that just passing the tube into a dilated, fluid-filled stomach was usually not enough to initiate evacuation. Rather, persistent effort to create a siphon is usually required, even from some of the most fluid-filled stomachs. Another important trick readily learned was to fix the nasogastric tube in place for awhile in those patients that were difficult to intubate, or when there was a strong suspicion, because of the volume and/or appearance of the reflux, that frequently repeated decompression would be required. In spite of this knowledge, however, cases of gastric rupture continue to occur, often due to oversight, but sometimes in spite of a nasogastric tube being in place [116]. One epidemiological study indicated that horses on a diet of grass hay or grass/alfalfa hay were at higher risk for gastric rupture than were those fed grain [117].

Nowadays, nasogastric intubation with concerted effort to provoke drainage of gastric contents has become a routine part of the clinical evaluation of many cases of colic, particularly those that show any degree of attendant cardiovascular disturbance. The amount and character of the fluid obtained, *along with whether decompression provides pain relief or not*, have become important factors in the development of a definitive diagnosis and prognosis [118,119]. There is still not a consensus, however, regarding how much drained fluid is too much. Meyer and Hanson have suggested that repeat recovery of > 2 L of fluid at 1 - 2-h intervals constitutes excess [119], but it is not uncommon for us to drain 1 - 2 L of frothy, light yellow fluid from our cannulated horses that have been held off feed overnight, and then collect that volume or more over the next hour of drainage [32,47,50]. This normal fluid is composed of saliva, gastric secretions, and refluxed duodenal contents, with a pH that can range from 1.5 - 6.5, depending upon which of the sources is relatively predominant at the time of collection (see Fig. 6). *I would suggest that collection of 5 L or more of gastric contents from a horse that has not drunk water within the*

previous 2 h constitutes an excessive amount. Clearly, the appearance and odor of the contents must also be factored into this assessment; for instance, fluid that is reddish-colored and fetid, even if the collected volume is <5 L, should be considered abnormal.

From collected clinical experience with sick animals and advances in the knowledge of normal GI function, we have made important strides over the last 30 yr in the diagnostic and therapeutic implications of reflux. I think it is safe to say that the source of large volumes (e.g., > 10 L) of fluid drained from the stomach at any given intubation of a sick horse, particularly if the pH is consistently > 6, is primarily duodenal in origin. The two main sources of this fluid would be duodenal and pancreatic secretions. This excess reflux could be caused either by a physical obstruction of the small-intestine aboral to the pancreatic duct opening, or by a functional obstruction due to shutdown of normal small-intestinal motility, commonly referred to as *adynamic ileus* [119-121]. In equine medicine, the latter is much more common, but either situation can result in reflux of very large volumes up to 100 L/d! When the problem is due either to physical obstruction or ileus with little attendant enteritis, the main source of the fluid could very well be pancreatic, because the horse normally secretes, even under fasting conditions, a large daily volume of pancreatic juice [48]. This fluid will be quite watery in appearance, and have little odor. In those cases, such as duodenitis/proximal jejunitis, where the cause of the ileus is due to the severe inflammation, the source of the fluid may be primarily due to intestinal hypersecretion, and is more likely (though not always) to be reddish and sometimes turbid in appearance, and have a fetid odor (Fig. 15) [122,123]. Those small-intestinal obstructions due to incarceration, volvulus, etc., can induce a refluxate with an appearance and odor that falls anywhere in between the two extremes described above. Finally, if the "reflux" has a pH that is consistently < 4, gastric outflow obstruction by a lesion oral to the pancreatic duct opening should be highly suspected [124]. In contrast to those cases where the excess fluid is of duodenal origin, the true gastric-outflow-obstruction patients will have some degree of gastric squamous, and perhaps even esophageal, mucosal ulceration (see EGUS section).



Figure 15. "Refluxing" the stomach of a horse. Note that the 18-L bucket is nearly full of the reddish-colored fluid that is typical of the duodenitis-proximal jejunitis (anterior enteritis) syndrome. - To view this image in full size go to the IVIS website at www.ivis.org . -

With respect to that group of equine patients described above that has a physical obstruction that causes collection of excessive fluid in the stomach, the most direct therapeutic approach is surgical, with either removal or bypass of the obstruction, depending upon its cause and/or site. Unfortunately, post-operative ileus (POI), with continuing reflux, may be a complication of such a manipulation [125-127]. As in humans, medical management of POI in horses requires a multipronged approach that includes continued decompression, IV fluids, and NSAIDs as the essential elements, along with a "prokinetic" drug to immediately jump-start GI motility [125,127,128]. As of yet, the ideal prokinetic drug remains to be found, and clinical trials of putative agents are sadly lacking, although testimony regarding the efficacy of one or another compound is plentiful. Drugs that have been investigated for use in horses have included neostigmine, yohimbine, bethanechol, naloxone, metoclopramide, cisapride, erythromycin, and lidocaine. An extensive review of these studies is beyond the scope of this paper. *If the POI is not complicated by persistent endotoxemia*, then IV lidocaine infusion would be my personal first choice, with the logic that it has been shown to have analgesic and anti-inflammatory properties that may down-regulate enteric nervous-system activity directed at inhibition of GI motility [129-133]. A secondary consideration for me would be low-dose erythromycin lactobionate (0.1 mg/kg IV), which we have shown to significantly increase the gastric emptying rate of both solid and liquid meals in normal horses (Fig. 16), and which Roussel et al., have shown to significantly increase ileal myoelectrical activity after electrode implantation surgery [85,134].

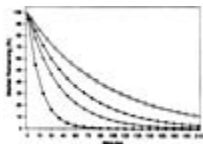


Figure 16. Power exponential gastric curves for a ^{99m}Tc-labelled solid meal derived from average values for time to 50% emptying (T-50), and slope describing the rate of change. N = 4 for each IV treatment group. White square = 0.9% NaCl solution; black circle = 0.025 mg/kg bethanechol; black triangle = 0.1 mg/kg erythromycin; white triangle = 1 mg/kg erythromycin [86]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Erythromycin acts by stimulating motilin receptors within the enteric nervous system; such receptors have recently been found in high numbers in the equine duodenum [135,136]. Finally, recent studies in rats strongly indicate that a leukocyte infiltration within the intestinal muscularis may be mediating POI; thus, judicious use of NSAIDs in cases of equine POI is worth considering [137]. *If endotoxemia appears to be at the bottom of the ileus*, such as with duodenitis/proximal jejunitis, I believe there is a good rationale for giving an α_2 -receptor antagonist, such as yohimbine (0.7 mg/kg IV) or tolazoline (1

mg/kg IV), along with the usual therapeutic armamentarium, including NSAIDs, directed at suppressing the multisystemic effects of the endotoxin [138,139]. There is some evidence that the indirect cholinergic agent cisapride can increase gastric emptying rate in the face of endotoxemia [140], but the removal of this agent from the human market in the U.S. removes it from further consideration. However, the 5-HT₄ agonist tegaserod may prove to be a worthy replacement for cisapride [141]. Finally, in those cases where the problem is partial physical obstruction of gastric outflow that results in only moderate gastric distention, and where surgical correction is not an immediate option, periodic administration of bethanechol (0.025 mg/kg SC) might be helpful, but this should not be considered a final solution to the problem [142,143].

3.4 Equine Gastric Ulcer Syndrome

The term "equine gastric ulcer syndrome" has been adopted in reference to a number of specifically unique problems that can manifest as mucosal erosion and ulceration within either the esophagus, stomach, or upper duodenum, or in some combination thereof [144]. The operative phrase here is "specifically unique problems" for enough is now known about ulcerative diseases of the equine upper GI tract to recognize that they represent more than one pathophysiological entity. Classification can be based currently upon signalment, management conditions, medical status, and/or primary lesion site. The latter takes into account the presence of a nonglandular, squamous-type mucosa lining the proximal half of the equine stomach and, from a personal perspective, is viewed accordingly: 1) primary squamous (non-glandular) lesions not associated with any apparent problem that could disrupt gastric emptying; 2) primary glandular and/or upper duodenal mucosal lesions that, if they cause sufficient mechanical or functional gastric outflow disruption, may cause secondary squamous lesions (even up into the esophagus); and 3) primary lesions within the cardiac gland mucosa of highly stressed neonates. This view could be amended at any time, subject to the results of ongoing research that includes the search for *Helicobacter* species within equine gastric tissue.

3.5 Currently Recognized EGUS In Adults 1 yr of Age, in Order of Decreasing Frequency

Primary Erosion and/or Ulceration of the Nonglandular (Squamous) Mucosa (Fig. 17) - The most common manifestation of this syndrome is in adult horses under intensive training programs, irrespective of breed or program. It can also be found incidentally in younger sedentary horses if they are subjected to gastric endoscopy for some specific reason.



Figure 17. Diagrammatic representation of primary squamous ulcer disease in horses, where there is no evidence lesions that could account for physical or functional disruption of gastric emptying. Suggested causes for this form of EGUS are listed at the lower right [214]. - To view this image in full size go to the IVIS website at www.ivis.org . -

The strong association between training and the presence of squamous lesions was most definitively brought to our attention by a seminal study, published in 1986 by Hammond et al., of thoroughbreds from the Royal Hong Kong Jockey Club that had been submitted for necropsy, mainly because they were "unsuitable for riding or chronically lame" [145]. Animals that were in active training right up to the time they were put down were compared to those that had been retired from training for varying periods of time. Lesions were scored as Type 1, 2, or 3, according to increasing severity. The Type 1 lesions were confined to a region near the *margo plicatus* that bordered the pyloric glandular mucosa, that is, right at the lesser curvature of the stomach where a small portion of the squamous mucosa lips around to the ventral side of the curvature. Type 2 lesions extended along the whole length of the *margo plicatus*, and Type 3 lesions were not only judged as more grossly and severely ulcerated but also extended in varying degrees up into the proximal part of the "pars oesophagea" the non-glandular squamous mucosa as well as that along the *margo plicatus*. While Type 1 lesions were found in 40 - 50% of horses, whether in training or retired, Type 2 lesions were found in ~30% of horses in training and in only 5% of those that had been retired. No Type 3 lesions were found in retired horses, but occurred in 10% of 2 - 8 year old horses, and in 29% of those that were 9 years and older and had been in training [145].

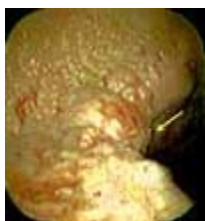


Figure 18. Endoscopic view of a severe case of primary squamous ulcer disease. The yellow arrow is pointing at the lesser curvature. Note the diffuse corrugated appearance of the mucosa interspersed with lines and fissures exposing the underlying submucosa. A particularly large patch of exposed submucosa is near the lesser curvature. - To view this image in full size go to the IVIS website at www.ivis.org . -

The dawn of modern equine clinical gastrology was heralded in 1985 by Brown et al., who presented the first endoscopic views of the adult equine stomach, obtained via a 2.75 m-long fiber optic instrument [146]. Coincident with the expanding

availability of endoscopes of 2 m and longer, a large number of publications have appeared over the last 10 yr indicating that up to 90% of horses in training, irrespective of breed and type of exercise, may have erosive and ulcerative lesions of the squamous mucosa of varying degrees of severity [147-156]. The lesions can be in the form of discrete ulcers of various sizes and depths, or can be strictly erosive (Fig. 18).

The milder lesions are, for the most part, confined to the region on the lesser curvature, near the *margo plicatus*, similar to the Type 1 lesions of Hammond et al., Murray et al., were the first to propose a scoring system for lesions viewed endoscopically [157], followed by one proposed by MacAllister and Andrews [158]. Finally, a consensus scoring system was presented by the EGUS Council, a group of academic clinicians and private practitioners assembled by Merial (Table 1) [144]. Such scoring systems are most useful to those evaluating the anti-ulcer potential of given chemical agents or following the progress of an individual case.

Interestingly, however, there is the clinical impression that there is a poor relationship between lesion score and severity of the "classical" clinical signs of squamous ulcer disease in the athletic horse, other than the disappearance of signs when the lesions totally subside. Common complaints by trainers include: 1) poor appetite, especially failure to finish grain; 2) reluctance to train/decreased performance; 3) poor body condition, e.g., rough hair coat; 4) low-grade colic, especially after grain ingestion [144,146,157,159].

Table 1. Equine Gastric Squamous Ulcer Disease	
Severity Scoring Proposed by EGUS Council [145].	
Grade 0	Epithelium is intact throughout; no hyperemia, no hyperkeratosis (yellowish color, sloughing)
Grade 1	Mucosa is intact but there are areas of hyperemia and/or hyperkeratosis
Grade 2	Small, single or multi-focal erosions or ulcers
Grade 3	Large, single or multi-focal ulcers, or extensive erosions and sloughing
Grade 4	Extensive ulcers, with areas of deep submucosal penetration

In view of the predilection of training-related squamous type gastric ulcers in horses, a question arises concerning the similarity between this problem and gastro-esophageal reflux disease (GERD) in humans. That is, are these horses suffering from what humans would complain of as "heartburn"? Clearly, there is a major anatomical difference between humans and horses in that the squamous epithelium in the former stops at the lower esophageal sphincter. Nevertheless, it is well accepted that the basic cause of GERD is excessive exposure of the esophageal mucosa to refluxed gastric contents. One of the most common reasons for GERD in humans is hiatal hernia and associated lower esophageal sphincter incompetence, which allows relatively free reflux to occur [160]. However, many other cases of GERD, either sporadic or recurrent, occur in the absence of hiatal hernia [160,161].

Numerous theories have been presented, some of which have been explored here, that might explain the relationship between training and the high occurrence of gastric squamous lesions in horses. The "stress" of training has been raised more than once, and has been reinforced by the fact that the lesions quickly decrease in severity, and often disappear, when the animal is taken out of training [152]. However, those protective mechanisms of glandular mucosa that may be susceptible to disruption by excessive corticoid release, changes in mucosal blood flow, etc., have not, to date, been found to be operative in squamous mucosa. Change in, or excessive exposure to, some constituent of acidic gastric contents is more likely. Thus, in horses, as in humans, gastric acid has to be the number one etiological candidate, especially because treatment with acid-suppressing drugs results in lesion regression, even in the face of continued training [162,163].

Certain foods are notorious for causing "heartburn" in humans, although the actual mechanism for this is still not well understood. Accordingly, based upon the findings of Argenzio and Eisemann, who showed an ulcerogenic effect of acetic acid in an acidic medium on the squamous portion of the porcine stomach [164]. Nadeau et al., have explored the possible etiologic role of volatile fatty acids (VFA) derived from intragastric fermentation of ingested soluble carbohydrate feedstuffs as the cause of squamous gastritis in horses [165]. This idea takes into account the common practice of feeding horses in training large amounts of feedstuffs that are high in soluble carbohydrates. They found a significant positive relationship between the presence of squamous lesions and the concentration of some of the longer chain fatty acids, but not acetic acid, within the gastric contents of their horses. They also found that feeding alfalfa hay resulted in an increased, rather than the

expected decrease, in post-feeding intragastric pH, which was attributed to the buffering effect of constituent calcium salts and protein. Thus, alfalfa-fed animals had fewer squamous lesions, in spite of more VFA production, than did horses fed bromegrass. More recent *in vitro* studies by this group support the idea that VFAs can add to the corrosive potential of acidic gastric contents, especially as their chain length increases [166]. While the role of diet in the pathogenesis of primary squamous ulceration cannot be ignored, there remains a great deal of work to be performed to elucidate what parts of the diet may be critical to the production of potentially corrosive properties.

Finally, with regard to gastric contents composition, certain bile acids refluxed from duodenum into the stomach have been shown to have corrosive potential for esophageal squamous mucosa [167]. Comparable studies with equine gastric tissue have produced mixed results, however [168,169]. Thus, while duodena-gastric reflux can easily occur in the horse, especially when the stomach is not very full [47], the actual ulcerogenic potential of this activity remains to be determined. What must be kept in mind, however, with regard to any possible relationship between constituents of gastric contents and pathogenesis of squamous gastritis, is that the horse never normally fills its stomach above the opening of the esophagus, thus presumably sparing most of the squamous mucosa from continuous contents exposure (see Fig. 1).

As indicated above, one cause of GERD in humans that has been well documented is strenuous exercise. Increased gastroesophageal reflux has been recorded by continuous measurement of lower esophageal pH during both running and cycling, with the former inducing more consistent and severe effects [170,171]. With this in mind, we devised a series of studies designed to look at some of the effects of treadmill exercise on equine intragastric status. We chose to first see if exercise had any effect on gastric wall compliance through the use of the barostat. Accordingly, we introduced a mylar balloon of ~1,600 ml maximum volume into the most proximal part of the horses' stomach via a nasogastric tube, and barostatically maintained the intraballloon pressure at 4 mmHg, which required 900 - 1,200 ml of air when the horse, from which feed had been withheld for 12 h, was standing or walking. As soon as the horse moved from a walk to a trot, the volume of air within the balloon started to rapidly decrease down to a point where it was virtually empty. The balloon remained deflated during a gallop as well, and did not refill to the original volume until the horse was brought back to a walk (Fig. 19) [172].

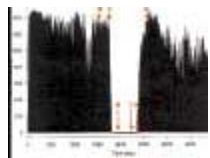


Figure 19. Typical volume tracing of a barostat bag maintained at an internal pressure of 6 mmHg within the proximal stomach of a horse before, during, and after being made to walk (W), trot (T), and gallop (G) on a treadmill. S = stop. Note that any gait faster than a walk tends to cause collapse of the bag, indicating that a $P > 6$ mmHg is being continuously exerted on it during that time. We have hypothesized that the source of this pressure is intra-abdominal, secondary to tension of the abdominal muscles during exercise. - To view this image in full size go to the IVIS website at www.ivis.org . -

The same thing happened in fed horses, although the initial volume of air in the bag was much less because of the presence of food in the stomach. This suggests that during movement at a gait faster than a walk, either the gastric wall of the horse becomes more rigid or some external pressure is being exerted on the stomach. To investigate the latter hypothesis, we inserted, under sterile conditions, a catheter into the abdominal cavity through the right dorsal flank to measure intra-abdominal pressure during the treadmill exercise sequence, while at the same time monitoring intra-gastric pressure with a solid-state pressure transducer. As soon as the horse moved from walk to trot, the mean intra-abdominal pressure increased by 12 - 15 mmHg, and remained there throughout the exercise protocol. Presumably, this was due to a tensing of the abdominal muscles during the faster gaits. The changes in intra-abdominal pressure were paralleled by changes in intra-gastric pressure, suggesting that the deflation of the intra-gastric barostat balloon described above was due to external pressure exerted upon the stomach by the increased intra-abdominal pressure. In fact, we could prevent balloon deflation by setting the barostat pressure at 15 mmHg rather than at the 4 mmHg level that we routinely used.

From the above results, we hypothesized that the increase in intra-abdominal pressure during exercise pushes gastric contents up into the squamous-lined proximal region of the stomach, exposing that mucosa to corrosive agents, most notably acid, within those contents (Fig. 20). As indicated above, the proximal, squamous lined portion is not normally filled, and most horses, if left to their own devices, spend the majority of a day standing or walking around, so this part of the stomach is not exposed to the contents, particularly the acidic components [173].



Figure 20. Changes in mean (\pm SEM) intra-gastric (diamond) and intra-abdominal (square) pressures during training sessions in three horses. Slope = tipping up the front of the treadmill to increase the amount of exertion [173]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Horses in training, on the other hand, spend a significantly larger part of their day moving at faster gaits, which could result in relatively prolonged exposure of the squamous epithelium to acidic gastric contents. To test this hypothesis, we inserted a pH electrode, via nasogastric tube, into the stomach just distal to the lower esophageal sphincter to continually monitor pH during

an exercise session. While a horse was standing or walking, the pH remained in the 5 - 6 range, but as it moved into a trot or faster, the pH began to drop rapidly, as far down as 1 in some cases, and remained very low until the animal was brought back to a halt (Fig. 21). The shape of the mean pH curve closely paralleled that of the mean volume change within the barostat balloon described above.

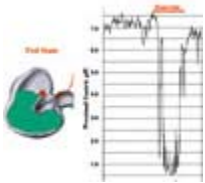


Figure 21. Continuous intragastric pH recording from just inside the lower esophageal sphincter. The pH probe, indicated in red on the drawing of the stomach, is held in place by snugging a small balloon (red circle) that is attached to the lead wire up against the lower esophageal sphincter. The period of exercise, in this case trotting only, is indicated in red at the top of the pH tracing on the right. - To view this image in full size go to the IVIS website at www.ivis.org . -

We feel this finding strongly supports our hypothesis. Furthermore, it is consistent with the following observations: 1) the lesions regress or disappear when a horse is taken out of training or is treated with an acid-suppressing drug; and 2) the lesions are most often found near the *margo plicatus* on the lesser curvature, where the squamous mucosa is most constantly in contact with acidic gastric contents, even in resting animals. Does it fit with Murray's model of producing squamous lesions by alternate-day feeding over a 5-d period [174]? The only way to test this would be to follow intra-gastric pH by our method, although it is interesting to note that we saw the most consistent and profound drops in pH during exercise in fasted rather than fed animals. Does it fit with Murray's observation that a large number of foals have significant squamous erosion and ulceration, even without showing any clinical signs of same [148]? We think so, considering that the younger horses have more liquid (milk) in their diet, and they frolic and lie down a lot more than adults do, resulting in more exposure of their squamous mucosa to acidic contents. In conclusion, we suggest that the high incidence of squamous (non-glandular) gastric mucosal ulcers in horses in training is primarily a mechanical phenomenon, due to an increased exposure of that region of the stomach to acidic gastric contents during the exercise sessions (Fig. 22).



Figure 22. Proposed way by which exercise in the horses causes a change in pH within the proximal part of the stomach, as is illustrated in (Fig. 20). The more liquid, highly acidic contents that reside in the lower, glandular part of the stomach during periods of inactivity are squeezed up around the overlying more solid contents by the increased intra-abdominal pressure (red arrows), created by tensing of the abdominal muscles that occurs as part of the movement at the faster gaits [214]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Primary Glandular Ulcer Disease (Fig. 23) - Since 1979, it has been well-known that NSAIDs can, if given in excess to horses, cause severe ulceration of the glandular mucosa, especially in the pyloric region (Fig. 24) [175-181].

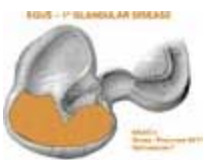


Figure 23. Diagrammatic representation of primary glandular disease. The classic cause of this form in the horse is NSAID toxicity (see Fig. 24), although this would be the region where lesions caused by "stress" or *Helicobacter* infection would occur. To date, *Helicobacter* infection of the equine stomach has not been confirmed. Sometimes, primary glandular lesions can become so severe that they cause disruption of gastric emptying and secondary squamous ulceration [214]. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 24. Multiple sites of glandular mucosal ulceration (yellow arrows) induced by NSAID toxicity. Note that the squamous mucosa (upper right) is lesion-free. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 25. Diagram representing the way NSAIDs such as phenylbutazone and flunixin interfere with normal gastric mucosal protective mechanisms. These non-steroidal agents not only inhibit cyclooxygenase-1, which results in down-regulation of local PGE₂ production, but also inhibit cyclooxygenase-2, which allows increased expression of tumor necrosis factor and, thus, the damaging effect of increased neutrophil adherence within gastric mucosal blood vessels. - To view this image in full size go to the IVIS website at www.ivis.org . -

They are considered to be ulcerogenic by causing down-regulation of PGE₂ production within the glandular mucosa and local

mucosal irritation (Fig. 25) [182,183]. As discussed in the physiology section of this review, major protective effects of PGE₂ include suppressing HCl and inducing mucosal bicarbonate and mucus secretion [60,61].

If the recommended dosages for the NSAIDs are followed, however, it is highly unlikely that this problem will occur, although I have the impression that certain horses appear to be overly sensitive to the GI tract damaging effects of NSAIDs and will develop lesions even when given recommended doses. MacAllister has shown that the order of gastric ulcerogenic potential in horses is as follows: phenylbutazone > flunixin > ketoprofen [184]. It should be stressed that the primary gastric lesions of NSAID toxicity in the horse occur within the glandular mucosa. Squamous lesions may be seen in some cases, but I suggest that these reflect a disruption of gastric motility and emptying rather than a primary effect of the drug.

With the availability of longer endoscopes, combined with extra effort to remove all contents from the stomach during endoscopy, a form of EGUS in the horse that manifests as a primary ulceration of the pyloric glandular mucosa has been seen in adult horses [185]. The squamous mucosa is usually free of lesions. Clinical signs of the acute form of this problem can be as varied as those seen with primary squamous disease, however. Furthermore, if untreated in their early stages, lesions near or around the pyloric outflow may induce sufficient scarring to interfere with gastric emptying, which can end up causing secondary squamous ulceration and severe post-prandial distress to afflicted animals (see the Reflux section; Fig. 26). Of all the variations of EGUS discussed above, this form would qualify as that most likely to be caused by a *Helicobacter*-like organism. David Scott, working in Sachs' lab, has reported on finding the presence of the ure-I gene, which is involved in urease production by microbes such as *H. pylori* to protect themselves from acid, in equine gastric tissue [186].



Figure 26. Endoscopic view of severe gastritis around the opening to the pyloric canal. The pyloric sphincter is open. Note the marked edema, erythema, and irregularity of the mucosa. A region of mucosal erosion, indicated by the yellow arrow, can be seen at the lower left (contrast this with the normal appearance shown in Fig. 7). Lesions such as this can induce abnormal gastric motility and/or progress to a point where they begin to scar down, any of which can reduce gastric emptying and cause secondary squamous ulceration (see Fig. 27). - To view this image in full size go to the IVIS website at

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However, at present, no incriminating organism itself has been found within the equine stomach. Thus, at present, we do not know the cause of pyloric glandular form of EGUS.

Secondary Squamous Ulceration (Fig. 27) - This problem, where the primary lesion commonly occurs in the duodenum (see gastroduodenal ulcer disease [GDUD] discussion in foals), is virtually never seen in horses >1 yr of age. What is seen from time to time is the rather acute onset of gastric outflow obstruction caused by the formation of proximal duodenal stricture that has progressed to a critical point. It would be interesting to examine the medical history of these cases to see if they may have shown classical signs of GDUD when they were sucklings or weanlings, but this has not yet been done. At this point, this is a problem that requires surgical intervention for possible amelioration. The prognosis for a successful outcome is very guarded. Secondary squamous disease may be seen in adults as a result of any condition that might functionally or physically disrupt gastric motility, such as extensive glandular mucosal ulceration due to NSAID toxicity, upper duodenal stricture, or other currently unidentified causes.



Figure 27. Diagrammatic representation of secondary squamous disease. The most serious forms of this problem are those associated with the physical obstruction of gastric outflow, some causes of which are listed at the lower right. Secondary squamous disease can also sometimes occur as a consequence of severe primary glandular disease even when there is no apparent physical obstruction, suggesting that the glandular lesions are inducing a feedback inhibition of gastric emptying [214]. - To view this image in

full size go to the IVIS website at www.ivis.org . -

3.6 Currently Recognized Syndromes In Foals < 1 Yr of Age, in Order of Decreasing Frequency

Gastroduodenal Ulcer Disease - This problem is confined almost exclusively to sucklings and early weanlings. From a historical perspective, it is probably the first form of EGUS to be reported in the literature. The first pathological report that I know of was written by Rooney in 1964 [187]. In that report, Rooney reviewed 8 cases between 19 - 90 d of age, 5 of which all 30 d or older had lesions described as "multiple esophageal region ulcers," perforated at the *margo plicatus*, which would be consistent with either the peracute or advanced forms of GDUD (see below). Whether the duodenum was examined or not is not mentioned. Rooney attributed the lesions to either *Gastrophilus* infestation or to physical trauma from sharp solid material (e.g., sand) ingested by the foals, some of which he found in histological sections of the lesions. Not much was heard

about this condition again until the early 1980's, when a number of cases, sometimes in the form of herd outbreaks, exploded upon the scene [188-195]. The syndrome has continued to appear with varying frequency up to the present time [159,196]. Often the first, and sometimes the outstanding, clinical sign is watery diarrhea. Some foals refuse to suckle and show mild colic and/or teeth grinding. A few may be found dead without forewarning due to perforation of the non-glandular (squamous) lining of the stomach or the duodenum [159,195,196]. A definitive diagnosis usually can be made by endoscopy of the duodenum, where, early in the course, a diffuse duodenitis can be seen, characterized by a yellowish plaque of exudate overlying the mucosa (Fig. 28). Thus, we now recognize that the most severe, and probably primary, lesion is in the upper duodenum. There may be some mild to severe lesions in the squamous mucosa as well in this early stage. My impression is that the most fulminant form of the duodenal disease is that with the highest risk of either secondary gastric or duodenal perforation (Fig. 29). Thankfully, this is a rare occurrence.

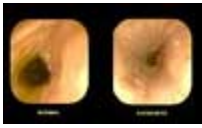


Figure 28. Endoscopic views of a normal foal duodenum (left) and one in the early stages of the GDUD syndrome showing a diffusely roughened mucosa covered with an exudative-appearing plaque. This is considered to be the primary lesion of the GDUD syndrome, and commonly causes some disruption of gastric emptying with varying degrees of secondary gastric squamous erosion and ulceration. At this stage, physical obstruction of gastric outflow is not of major concern. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 29. A case of peracute GDUD-like disease which was so fulminant that the squamous mucosal region (top) was denuded almost totally throughout its extent. At one spot, the damage was so severe that perforation occurred, killing the foal. The glandular mucosa, under the yellow, broken line indicating the site of the *margo plicatus*, was intact throughout. - To view this image in full size go to the IVIS website at www.ivis.org . -

Most afflicted animals survive and are back to normal within a week after some supportive or specific anti-ulcer therapy (how many may be asymptomatic and survive with no therapy is unknown). A few become progressively more ill despite treatment and develop the "classic" signs of this disease, which include drooling, teeth grinding, periodic bouts of colic, especially after suckling, and marked weight loss (Fig. 30). If these signs persist for more than a week, it is a strong indication that the duodenum has become severely constricted by inflammation-induced fibrous tissue and is mechanically obstructing gastric emptying (Fig. 31). Abdominal radiography will reveal a markedly enlarged gastric gas cap and prolonged retention of a standard barium meal, which normally should completely leave the stomach within 1 h. The major endoscopic findings are severe erosion and ulceration of the squamous mucosa of the stomach and lower esophagus (Fig. 32).



Figure 30. A suckling foal showing continuous salivation and tongue lolling that is typical of advanced GDUD when the duodenum has strictured to a point that gastric outflow is markedly obstructed. These patients often have not only severe, diffuse gastric squamous disease, but also severe reflux esophagitis. It may be the esophagitis that is causing most of these signs. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 31. Post-mortem finding of two distinct strictures of the duodenum (red arrows), which represents a serious consequence of the GDUD syndrome. Such an outcome would almost invariably cause the signs and lesions shown in Fig. 30 and Fig. 31. - To view this image in full size go to the IVIS website at www.ivis.org . -

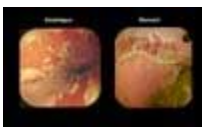


Figure 32. Endoscopic views of reflux esophagitis (left) and squamous gastritis (right) that commonly are seen in foals with chronic GDUD, such as that shown in Fig. 30. The lighter islands of tissue within the esophagus are the remnants of the normal mucosa. The broken, yellow line in the stomach view indicates the site of the *margo plicatus*, indicating that severe erosion and ulceration of the squamous mucosa has occurred above it, to the point where the junction between squamous and glandular mucosa is virtually obliterated. - To view this image in full size go to the IVIS website at www.ivis.org . -

This is the classic form of a secondary squamous disease. Occasionally, dilated bile ducts can be seen radiographically. If this occurs, the only relief is a gastrojejunostomy, which is an expensive procedure with a guarded prognosis. When this is performed, the squamous lesions quickly resolve.

The cause of GDUD in young horses is unknown. Epidemiological investigations dating back to the early 1980's have not provided a definitive answer. It may be due to a unique combination of factors. As indicated, the impression is that the development and extent of attendant erosions and ulcers of the squamous gastric and esophageal mucosae are dependent upon the degree and duration of gastric outflow obstruction secondary to the extent of the primary duodenitis. There has been considerable interest in its apparent relationship with outbreaks of rotaviral diarrhea, but there is no precedent for this agent causing duodenitis in other species in which its pathology is better understood. Also, it does occur in foals in which no rotavirus can be found. The possible interaction of a *Helicobacter*-type agent cannot be discounted at this time.

Primary Erosion and/or Ulceration of the Squamous Mucosa - Sometimes these lesions occur in association with some other more apparent disease problem; sometimes they are found when there is a complaint of unthriftiness or vague mild colic; or sometimes they are found in asymptomatic young animals that are being endoscoped routinely to check for the possible presence of ulcers or some other problem [148,149]. In contrast to indications that prolonged periods of exercise and attendant increase in intra-abdominal pressure may be the underlying cause of this problem in adult horses, the basis for the pathogenesis of this lesion in younger horses is unknown. I have suggested that a more liquid composition of gastric contents and the daily activity of foals versus adults are etiological factors to consider. However, partial obstruction of gastric outflow, as after a previously unrecognized bout of GDUD, must always be ruled out in any foal presenting with persisting severe squamous disease.

Stress-Related Disease - Classically, "stress-related" ulcer disease is attributed to a disruption of the circulation of the gastric mucosa. It may involve down-regulation of mucosal PGE₂ production, which implies reduction in normal mucosal circulation, as well as bicarbonate and mucus secretion, among other things. But it is probably more multifactorial than this. The most common occurrence of this problem is in foals that are suffering from a severe illness or trauma. Recent studies in septic rats indicate that an increased expression of inducible nitric oxide synthase (iNOS), combined with decreased expression of constitutive NOS (cNOS), could be an important etiologic factor [197]. The lesions in foals are primarily confined to the glandular mucosa just adjacent to the *margo plicatus* in the cardiac gland region, and they can be severe enough to cause a perforation (Fig. 33). Unfortunately, the afflicted animal usually shows no prodromal signs that this lesion is present. Thus, if perforation does occur, then it is too late to do much about it.



Figure 33. Erosion and ulceration of the cardiac gland mucosa of a very sick neonatal foal that succumbed to perforation of one of the lesions. This type of problem has become much less common as a result of major strides taken in the medical management of such patients. - To view this image in full size go to the IVIS website at www.ivis.org . -

Interestingly, 3 of the cases, between 19 - 37 d of age, that Rooney presented in 1964 had ulcers and perforation of the pyloric gland region; 2 of these cases had a history of being treated for "pyemia, arthritis" for 15 and 30 d, respectively [187]. It is primarily these kinds of problems that have provided the rationale for automatically including antacid drugs, mainly ranitidine to date, as part of the therapeutic regimen for very sick foals. Continuance of this practice has been sustained by the observation that very few sick foals are now struck down by perforating ulcer disease. As implied by studies of sepsis and stress on gastric mucosal protection mechanisms in other species, the critical factor in reducing the problem in sick foals may lie in generally improved methods of intensive care than in the inclusion of antacid drugs. As a result, some ENICUs have discontinued the practice without seeing a recrudescence of the problem [198].

NSAID-Induced Glandular Ulcer Disease - See the discussion in the EGUS Adults section.

3.7 Anti-Ulcer Therapy

Strategies of antiulcer therapy currently applied to horses are those developed for humans. There are three basic approaches: 1) maintain an intragastric pH >4; 2) coat the ulcer with an acid-resisting agent; and 3) provide PGE₂, or stimulate its production by the gastric mucosa. Medical treatment of EGUS was recently reviewed by MacAllister [199].

3.8 Maintaining Intragastric pH > 4

The time-honored method of buffering gastric HCl with Al/Mg hydroxide preparations, though potentially the least expensive approach, does work in horses but requires considerable effort. Studies performed in our laboratory show that 240 ml of an extra-strength oral antacid product [b] will keep the intragastric pH of an average-sized horse above 4 for at least 2 h [38]. Clinical experience has indicated that administration of this dose QID has been effective in treating squamous ulcer disease in some patients. Clearly, however, this is a time-consuming process that some animals tolerate better than others. A few horses will actually eat a flavored product mixed in with a little grain. There is also a feed additive for horses [c], which is marketed with the claim of having effective acid-buffering properties that can eliminate the signs that we associate with squamous ulcer disease. To date, however, there are no intra-gastric pH data available showing that this feed additive meets these claims.

Acid secretory control can be accomplished in the horse by treating with a histamine-2 receptor antagonist; compounds that primarily have been used in horses to date include cimetidine [d] and ranitidine [e], although any of the compounds on the market should work because it is a question only of effective dose. Much larger doses than recommended for humans are needed to affect any reasonable increase in intra-gastric pH in the horse. The recommended dose of ranitidine is 6 - 7 mg/kg orally, or 2 mg/kg systemically, at least 3 times per day, which represents a significant expense in a 500-kg animal [39,144,200]. Fortunately, the oral form is much less expensive than it used to be because it can now be purchased over the counter as the generic compound. Good clinical trials of the efficacy of the H₂-receptor antagonists in controlling EGUS of any form are lacking. A recent study from the University of California at Davis indicates that cimetidine at 20 mg/kg TID per os is not effective in controlling squamous ulcer disease in horses in training [201]. These results were consistent with those of an earlier investigation by MacAllister et al., which used an experimental model of non-glandular ulcer disease in ponies [202].

The problem of what I have referred to as "stress related" disease in neonatal foals deserves special comment here. Sanchez et al., at the University of Florida showed that ranitidine is effective in suppressing gastric acid secretion in normal neonates, with 6.6 mg/kg given orally maintaining the mean intragastric pH > 4 for 6 - 8 h, whereas 2 mg/kg IV maintained a pH > 4 for only 4 h [39]. In critically ill neonates, however, they found that the response to IV ranitidine was highly variable, with some responding as expected, but also with a significant group of others not responding at all [203]. Also, it was discovered that, especially in those foals that were recumbent, the intragastric pH was often near neutral, suggesting that they either could not produce gastric acid or that there was a profuse and constant duodenal reflux that neutralized any acid that was present. This provides additional credence to the idea that anti-ulcer therapy is probably not routinely indicated in sick, young foals. The more effective approach to chemical suppression of gastric acid secretion in the horse is through use of a proton pump blocking agent, such as OME. This class of drugs works, as discussed previously, at the final step of elaboration of HCl secretion by the parietal cell by blocking a K⁺/H⁺-ATPase "pump" that involves an exchange at the secretory membrane (Fig. 34).

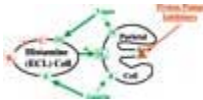


Figure 34. Diagrammatic representation of where PPI drugs (proton pump inhibitor) exert their pharmacologic action. - To view this image in full size go to the IVIS website at www.ivis.org . -

In the early development of OME for use in horses, various oral and IV preparations were evaluated for their effect on acid secretion and ulcer healing [34,55-58,204]. Ultimately, an orally administered paste formulation [f] (GastroGard[™]) was approved for horses. A number of clinical trials have shown that daily treatment with the recommended dose of GastroGard[™] (4 mg/kg SID) results in significant reduction of the severity and occurrence of primary squamous lesions in horses in training [162,205,206]. Numerous small pharmacies within the U.S. also formulate their own OME-based compounds. Recent studies performed in our laboratory and at the University of California at Davis have found that, in general, compounded preparations were distinctly inferior to GastroGard[™] with regard to the duration of maintenance of a satisfactorily high pH and to the efficacy in controlling development of squamous lesions, respectively [207,208]. We monitored intragastric pH with a probe inserted into the bottom of the stomach via the cannula during 24 h on the day before, and days 2 and 7 of, the treatment period and found that least 4 mg/kg orally QD of GastroGard[™] is needed to effectively keep the intragastric pH >4 for up to 15 h in adult Thoroughbred horses. In humans it is generally accepted that it takes 3 d of daily dosing to achieve maximum efficacy, whereas a study we recently completed indicates that it takes no more than 2 d in the horse. Based upon our findings discussed above concerning the pathophysiology of squamous ulcer disease in horses in training, our OME efficacy data would suggest that the best time to train would be somewhere between 2 - 8 h after giving the drug (Fig. 35). Furthermore, we recommend that a small grain meal be given right after treatment to maximize the drug's efficacy, because it is more rapidly taken up by parietal cells that have been stimulated to secrete acid.

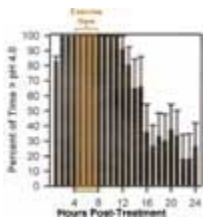


Figure 35. Mean intragastric pH in 6 horses, expressed as percent of time the pH > 4 for hourly segments during 24 h after oral treatment at T = 0 with 4 mg/kg OME (GastroGard[™]). The pH sensor is situated in the ventral, fundic part of the stomach very close to the mucosal surface. The horses were offered a grain meal within 30 min of the morning treatment, and again in mid-afternoon. They also had free-choice access to Bermuda hay throughout the recording time. This recording was made during the second day of a 7-d daily treatment regimen. In accordance with the hypothesis that primary squamous ulcer disease in athletically active horses is due to the pushing of acidic gastric contents up into the top part of the stomach, and a decision is made to try to control the problem through daily OME therapy, the best time to train might be within a 4 - 8-h post-treatment window (yellow shading) to assure the exercise occurs during maximum drug effect. - To view this image in full size go to the IVIS website at www.ivis.org . -

Efficacy trials of orally administered OME in neonatal foals remain to be done.

3.9 Coating the Ulcer

The compound available as an ulcer-coating agent is a polysulfated sugar, sucralfate [g]. In humans, it is recommended that it be given on an empty stomach, which is a pretty difficult recommendation for application to horses. Nevertheless, this compound is used quite freely in equine patients and many feel it is certainly helpful in controlling the severity of various ulcer diseases. An additional rationale for its use is its putative ability to induce mucosal protection by activating PGE₂ synthesis [209]. So far, however, clinical trials of its efficacy in treatment of experimental EGUS have not been very convincing [210,211]. In addition, animal experiments indicate that sucralfate binds to lesions best within an acid medium so that, ideally, it should not be given concomitantly with, or soon after, an H₂ antagonist [208].

3.10 Administering Exogenous or Up-regulating Endogenous Prostaglandin

The prostaglandin approach would be most indicated when there is some concern about the effects of NSAIDs, or when there is a recognized stress, as discussed above. One 1985 study indicated that prophylactic treatment with a synthetic PGE₂ compound might be useful in controlling phenylbutazone-induced gastric mucosal injury [180]. Unfortunately, commercially available synthetic prostaglandins are extremely expensive. Some studies performed in our laboratory found that feeding corn oil, which contains a large amount of the arachidonic acid precursor linoleic acid, at a dose of 20 ml/100 kg body weight to ponies, significantly increased the amount of PGE in the gastric contents, similar to what had been found earlier in rats and humans. This treatment also significantly decreased the amount of acid produced by the ponies' stomach, both before and after pentagastrin stimulation [66]. The true anti-ulcer potential of this approach still needs evaluation, but it would do no harm to supplement the diet of horses being treated with a NSAID with corn oil, and it might reduce the risk of NSAID-induced gastritis.

In summary, the proton-pump blockers are proving to be more effective and practical for treating adult EGUS, especially for controlling the development of squamous ulcer disease in horses in training. Prophylactically, future emphasis may perhaps shift away from the acid suppressors to agents that promote mucosal protection directly, although this may be more difficult to accomplish with respect to the squamous, as opposed to the glandular, mucosa. Furthermore, we should not overlook the idea that another very important component of prophylaxis, particularly with respect to training procedures, may lie as much in preventive management techniques as in any chemical means available.

4. Important Challenges for the Future

In my opinion, there are currently two major challenges on the table concerning EGUS. The first challenge is the determination of the specific cause of GDUD syndrome. This problem is in great need of a well-designed epidemiological investigation, as well as concerted attempts to identify an infectious agent as its cause. With respect to the latter, foals in the early stages of the disease are the ones that need to be studied most thoroughly. Endoscopes of sufficient length are now available to put them directly into the upper duodenum for observation and biopsy of the acute lesion. Collected tissue should be subjected to state-of-the-art histopathological and microbiological techniques to look for candidate etiologic bacterial or viral agents. If such an agent is found, then Koch's postulates must be satisfied. Delivery of an etiologic agent via the biliary system, whether it be microbiological or chemical, should be considered as well as the obvious oral route.

The second major challenge regarding EGUS is the development of nutritional and other management strategies to reduce the incidence of training-related squamous ulcer disease. Development of diets containing natural ingredients that either effectively buffer gastric acid and/or inhibit its secretion should be vigorously pursued. Nadeau and Andrews have effectively introduced this concept by demonstrating the greater buffering capacity of alfalfa over brome grass hay [165]. The practical and economic implications of this goal are obvious. An additional challenge to achieving the goal itself, which could involve a prescribed feeding/training relationship, may be convincing trainers to buy into a program that does not jibe with their specific ideas about how to manage an equine athlete. This should be a very interesting project.

Finally, I seriously wonder if the manner in which sport horses are kept between exercise periods does not also have a significant role in primary squamous ulcerogenesis. That is, I suggest that active animals that are housed in stalls are inherently more "tensed up," which includes more instill activity and associated contraction of abdominal musculature, than if turned out into a paddock or pasture. In experimental horses with the pH probe in place just inside the lower esophageal sphincter, we found that pH often started to drop as soon as the treadmill motor was turned on. That is, they were already starting to contract their abdominal muscles in anticipation of the exercise ahead.

Footnotes

[a] Merritt AM, Morisset J. Unpublished data, 2002.

[b] Maalox Maximum Strength®, Novartis Consumer, Somerville, NJ 08876.

[c] Neigh-Lox®, Kentucky Performance Products, Versailles, KY 40383.

[d] Tagamet®, GlaxoSmithKline, Research Triangle Park, NC 27709.

[e] Zantac®, GlaxoSmithKline, Research Triangle Park, NC 27709.

[f] GastroGard[™], Merial Limited, Duluth, GA 30096.
[g] Carafate[®], Aventis, Bridgewater, NJ 08807.

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