

Zweig

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A report from the Harry M. Zweig Memorial Fund for Equine Research at the College of Veterinary Medicine at Cornell University



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Heaves results from an inflammatory reaction within the lower airway that is triggered when horses inhale dust and other environmental allergens from hay or bedding.

Does Heaves Adversely Influence the Immune Response?

Heaves—the common name for recurrent airway obstruction (RAO) or chronic obstructive pulmonary disease (COPD)—is one of the most common reasons horses are referred to the Cornell University Hospital for Animals. Primarily afflicting middle-aged and older horses, heaves is an inflammatory condition in the lungs that severely limits the athletic performance of horses.



Heaves

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"We need to know more about the immune response in heavey horses not only because it is such a common condition afflicting the health and performance of a large percentage of mature horses but also because we don't know if conventional vaccines might adversely affect the airway obstruction in horses whose immune systems have already been challenged by allergens."

—Dorothy Ainsworth

"Much like asthma in humans, the condition causes a chronic cough, a nasal discharge composed of mucus and inflammatory cells, an accentuated abdominal breathing effort, and exercise intolerance," says Dorothy Ainsworth DVM, MS, PhD, Dipl ACVIM, a large-animal pulmonologist and associate professor of medicine in the Department of Clinical Sciences.

Heaves is triggered when susceptible horses inhale hay dust and other environmental allergens from hay or bedding and develop an inflammatory reaction within the lower airway, similar to asthma in humans. The horse becomes hypersensitive to the inhaled allergens and launches an inflammatory response in defense.

With a new grant from the Harry M. Zweig Memorial Fund, Ainsworth, in collaboration with Judith Appleton MS, PhD, and Douglas Antczak

DVM, PhD, is building on her previous Zweig- and USDA-funded research evaluating the immuno-pathogenesis of heaves. In the past she's explored how the immune systems of symptomatic heavey horses exposed to a foreign antigen respond and produce antibodies.

With this new grant, Ainsworth seeks to find out whether a horse that is asymptomatic but prone to the development of heaves will be biased in its immune response to an inhaled vaccine or antigen, as compared to a healthy horse.

"We need to know more about the immune response in heavey horses not only because it is such a common condition afflicting the health and performance of a large percentage of mature horses but also because we don't know if conventional vaccines might adversely affect the airway obstruction in horses whose immune systems have already been challenged by allergens," says Ainsworth. "We just don't know whether the inflammatory condition of heaves might prevent an adequate immune response from developing if we try to vaccinate the horse."

Understanding better whether a horse that already has, or is prone to, heaves has a different sort of immune response to an antigen than a healthy horse is important not only for recurrent airway obstruction but also for other kinds of diseases as well.

For example, consider the case of a young foal infected with intestinal roundworms, says Ainsworth. As part of their life cycle, these parasites migrate through the foal's lungs, establishing a type of immune response known as a T helper cell 2 or Th-2 reaction. This kind of response drives the allergic responses, which are a feature of human asthma. This response is differentiated from another kind of T helper cell known as a Th-1 that protects against bacterial and viral infections within body cells (cellular immunity) and are pro-inflammatory.

What happens if the young foal responds with Th-2 immune response during a roundworm infection (the lung environment is biased toward a Th-2 reaction) and the animal is then challenged by either a bacterial or viral infection?

"The dominating Th-2 environment might attenuate the foal's response to the microbial infection and compromise its ability to clear the secondary bacterial or viral invader," says Ainsworth. "This has been documented in mice, rats, and guinea pigs, not in the horse. The net result is that the Th-2 environment has a negative impact on the pulmonary and systemic health of the foal."

Ultimately Ainsworth's results should benefit not only heaves-affected horses but improve the overall understanding of the equine immune response.

At present, COPD has no cure. Corticosteroids are often prescribed to reduce airway inflammation and relax bronchial constriction, and bronchodilators may be used to relieve respiratory distress.

Once a horse has COPD, it will likely continue to be oversensitive to airborne allergens. A variety of horse management changes can help minimize the horse's exposure to hay dust. Keep the horse outside as much as possible. In the barn, use shavings instead of straw to bed the horse and pellets, alfalfa cubes, and grass silage instead of hay for feed. Managing adjacent stalls in the same way also helps keep hay dust low in the general area. Ventilating the barn via open windows and doors or installing a ventilating system, and storing hay far from the vulnerable horse, also can go a long way in keeping the horse's exposure to the airborne allergens down.

Instead of searching for a cure, Ainsworth's focus is to learn how to best develop vaccines or immunotherapies not only for healthy horses but also for susceptible horses that are already sick and will need continuing treatment. ■

Effective Drug Therapy for Postoperative Ileus Remains Elusive

When horses show signs of intestinal distress or colic, they may have potentially fatal bowel lesions. Thanks to modern advances in anesthetic and surgical techniques, these lesions usually can be corrected. Postoperative complications, however, put horses at high risk: the cause of as many as 90 percent of equine deaths after abdominal surgery is postoperative ileus, the loss of adequate intestinal motility.

Intestinal motility is a series of coordinated movements of the smooth muscle in the bowel wall that are regulated by nerves and muscles in the intestinal tract. Intestinal motility is critical for proper digestion—to get the digestive enzymes mixed into the food to break it down, to stir up the nutrients and push them to the intestinal wall where they are absorbed, and then to propel the contents of the intestines through the digestive tract.

Even though there is such a high risk of postoperative ileus, the development of drugs to treat the condition in horses is not a priority for pharmaceutical companies because the potential market is too small to warrant the high costs of research and development, explains Robert J. Gilmour, PhD, a professor of physiology.

“Thus, veterinarians may turn to drugs that increase intestinal motility in humans,” Gilmour says, “but whether these medications are safe and effective for horses is uncertain because the dietary requirements and the GI anatomy of horses are vastly different. Furthermore, so-called prokinetic drugs that increase intestinal motility have been shown to work via different mechanisms of action in different regions of the intestinal tract and in different species.”

To further confound the problem, researchers don't know whether the



David Lynch-Benjamin

Loss of intestinal motility is the leading cause of equine deaths following abdominal surgery.

equine gut has the same drug receptors (drug targets) as other mammals. Thus, even if a drug works well in humans or guinea pigs, for example, there is no way of knowing at the present time if the drug is appropriate for horses.

With a new grant from the Harry M. Zweig Memorial Fund, Gilmour plans to learn more about two drugs that have been shown to be effective for postoperative ileus, even though neither one is currently available in the United States. One of them—cisapride—has been withdrawn from the market because of its high incidence of toxicity to the heart in humans. The other—domperidone (Motilium)—also carries some risk to hearts and is still under investigation in this country.

Gilmour seeks to understand the mechanisms by which these drugs increase intestinal motility. Preliminary studies by Gilmour and his colleagues suggest that the same mechanism that damages the heart

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—Robert J. Gilmour

could be exactly what is therapeutic for improving the coordinated contractions in the horse intestines.

“In other words, we know that these drugs are toxic to cardiac muscle because they block what are called ERG channels (a class of ion channels) and by doing so don't allow potassium to exit the muscle cells,” Gilmour explains. ▶

Drug Therapy for Postop

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Gilmour, in collaboration with Drs. Lisa Freeman and James Lillich at Kansas State University, has recently shown that similar potassium channels are expressed in the equine intestine and drugs that specifically block the cardiac channels increase coordinated contraction in isolated pieces of horse intestine. As a result, Gilmour hypothesizes that blocking these ERG channels may be an important mechanism of cisapride and domperidone in enhancing the motility of the GI smooth muscle.

"If this is the case, ongoing efforts to find drugs that prevent or cure postoperative ileus without blocking ERG channels will be unsuccessful until new drug paradigms are designed that selectively target the potassium channels in the equine GI smooth muscle but not the smooth muscle in the heart," he says.

Along with assistant professor of large animal surgery J. Brett Woodie, Gilmour will study the interactions of cisapride and domperidone with ion channels in equine GI smooth muscle. They'll also perform a series of experiments to determine other potential mechanisms of these drugs. Depending on what he learns, Gilmour may compare the ERG potassium channels in the equine gut with those in the heart to see if a drug might target one without affecting the other. He also will seek to identify if there are other important receptors used by these two drugs that help relieve postoperative ileus.

"In either case, the information we gain will help veterinarians make rational choices about treating postoperative ileus with medications currently available for human use as well as drugs currently under development," Gilmour concludes. ■

Can Dietary Changes Prevent Cribbing?



Cribbing horses damage themselves, too, by wearing down their teeth and overdeveloping their neck muscles.

Cribbing is an abnormal behavior that affects about 300,000 horses in this country, including about 2.5 percent of all Thoroughbreds. A cribbing horse will grip a stall door, partition, fence post, bucket rim, or other object with its incisors then arch its neck and pull back. In doing so, the horse typically tenses up the muscles in its neck and face, retracts its voice box, and gulps down air into the esophagus.

"Little of the air is swallowed, and few horses actually develop colic, but owners dislike cribbing because of the damage it causes to fences and buckets when the horse pulls them," says Katherine A. Houpt, VMD, PhD, Dipl ACVB, director of the college's Animal Behavior Clinic. Cribbing should be distinguished from wood chewing in which wood is actually consumed and fence rails and barn walls must be replaced. Nevertheless, cribbing can wear down the horse's teeth, overdevelop

its neck muscles, and in some cases be associated with weight loss.

Proposed causes of cribbing range from boredom and an equine version of obsessive-compulsive disorder (such as constant hand washing in humans) to the presence of ulcers, a genetic predisposition to chronic stress, a desire to nibble, and diet.

"We believe that cribbing may be caused by the perception of a sweet taste of concentrate rations, which leads to the release of opiates, which in turn leads to cribbing," says Houpt.

Cribbing does not seem to stimulate endorphin release, however, and the cribbing horse is actually more sensitive rather than less sensitive to pain. Thus, the release of opiates may cause cribbing, but cribbing does not cause a high.

"Another possible cause of cribbing is a horse's response to pain from acidic conditions in its stomach and/or large intestine caused by

“We believe that cribbing may be caused by the perception of a sweet taste of concentrate rations, which leads to the release of opiates and in turn, to cribbing.”

—Katherine A. Houpt

high-concentrate diets. The pain from the high acid levels also could result in opiate release, which could lead to cribbing,” she explains.

With a new grant from the Harry M. Zweig Memorial Fund, Houpt hopes to find a dietary treatment for cribbing that can easily be administered by horse owners and managers but still be a high-performance diet. She plans to test three experimental diets in different orders in six horses. Each diet will be administered for three weeks and then gradually tapered during the subsequent three-week period while the horse gradually adapts to the next diet. Then, the second diet will be given for a full three weeks before the next diet is slowly introduced. Using time-lapse video recordings of the horses, Houpt will be able to assess the effectiveness of each diet by measuring how much time the horses crib each day.

The baseline diet is Respond. The first experimental diet is Respond with Sweetness Reducing Factor (SRF). This diet blocks the sweet flavor of the grain and molasses mixture that is typically part of a high-performance equine test. The second experimental diet is a high fat diet in which half the carbohydrate calories are replaced with corn oil.

“This diet allows a horse to still perform at a high level but does not have as much sweet feed,” Houpt explains.

The third experimental diet is a concentrate diet with a nontherapeutic antibiotic virginiamycin added. Virginiamycin inhibits the acid-producing bacteria in a horse's large intestine.

Current management practices for horses that crib include muzzles, neck straps, and spiked and shock collars to prevent the horse from arching its neck or from reaching a surface to grasp with its teeth. These, however, can cause tissue damage and pain. Mechanical methods also may stress the horse and don't change its motivation to crib.

“It would be much more beneficial to horses for researchers to determine why a horse cribs and to remove the stimulus rather than punish the horse,” Houpt says.

In the meantime, cribbing may be controlled by keeping the horse on pasture with compatible companions as much as possible. Providing a padded bar on which the horse can crib will reduce wear on its teeth and should direct his behavior away from buckets and fence rails. Another strategy is to give the horse a stall toy that it can roll over to obtain a small quantity of feed.

Although certain medications can block opiates, they are too expensive to be practical. Surgical techniques, which have been used in the past, may have serious side effects and are ineffective over the long term; thus, they are no longer recommended. ■

Check Out the Zweig Memorial Fund Web Site



Where can you read all about current and past research sponsored by the Harry M. Zweig Memorial Fund for Equine Research? Or relive the history of the memorial fund, scan information about the 13 members of the Zweig Committee, review all the Zweig newsletters since 1997, and explore numerous equine-related links?

All of this and more is available through the new home page of the Zweig Memorial Fund.

In addition, the new web site has links to more than three dozen articles describing, in lay language, the equine research conducted in the past five years at Cornell. Among them are articles on ovary stimulation, immunotherapy for treating COPD, and gene therapy techniques for repairing equine cartilage damage, as well as those about equine leptospirosis, equine protozoal myeloencephalitis (EPM), and cardiac arrhythmia.

The site also offers quick access to equine organizations and societies and to numerous other equine resources, such as Equine Info (a gateway to numerous horse-related links), Equine Online, the Horse Interactive (an online guide to equine health care), and Horse Net (an internet community for horse people).

So, check it out:

www.vet.cornell.edu/public/research/zweig/

The Harry M. Zweig Memorial Fund for Equine Research honors the late Dr. Harry M. Zweig, a distinguished veterinarian, and his numerous contributions to the state's equine industry. In 1979, by amendment to the pari-mutuel revenue laws, the New York State legislature created the Harry M. Zweig Memorial Fund to promote equine research at the College of Veterinary Medicine, Cornell University. The Harry M. Zweig Committee is established for the purpose of administering the fund and is composed of individuals in specified state agencies and equine industry positions and others who represent equine breeders, owners, trainers, and veterinarians.

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