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Department of Veterinary Science

LLOYD'S

COMMENTARY

THE OLD SAYING "AN OUNCE OF PREVENTION is worth a pound of cure" certainly applies to the current practice of vaccination in order to prevent infectious disease. Most horse owners recognize that it is much easier and less expensive to protect their animals through vaccination than it is to treat them once they become infected. For vaccination to be effective, however, it must be administered correctly and at the proper time. In terms of the adult horse, this means administering the proper dosage(s) well in advance of exposure to the infectious agent. This timing is particularly necessary for primary immunizations, since full protection may not be obtained until a month or more post-vaccination. More rapid protection will be seen following administration of a booster to a previously immunized horse, though even in that case complete protective immunity may not be in place until several days post-vaccination.

The need to vaccinate foals in order to protect them from infectious disease is also widely appreciated; however, the timing of the initial series of vaccinations is a contentious issue. Foal vaccination is complicated both by the immature status of the foal's immune system and by the presence of maternal antibodies obtained through the ingestion of colostrum. The newborn foal, like its human counterpart, possesses a fully functional but naïve immune system. The neonate is thus capable of responding to a vaccine or infectious agent, but because this represents a primary immune response, it may take a month or more for protective immunity to develop. This delay of protective immunity post-vaccination is why colostral transfer of maternal antibodies is so important to the foal. The maternal antibodies provide the foal with protection for several months and allow time for the foal's immune system to develop its own protective responses. Ironically, these antibodies can also inhibit the foal's ability to respond to vaccination by eliminating the antigens in the vaccine before an immune response has the opportunity to develop. This is particularly true in the case of modified live vaccines in which the infectious agents can be neutralized by maternal antibodies. This phenomenon of "maternal interference" is well recognized in puppies and kittens and is only now being recognized as a significant issue in foal vaccination. In light of these findings, it is now recommended that no vaccine be administered to foals before 4 months of age. The concentration of maternal antibodies in the foal's blood diminishes by approximately 50% every month of the foal's life, and by four months the levels should be low enough so that maternal interference is no longer a problem. It may also be necessary to administer at least three doses of vaccine in the primary series for foals in order to give the foal's immune system adequate stimulation with the antigen. Vaccination prior to 4 months of age will likely be ineffective in inducing protective immunity in the foal and could potentially interfere with the immune system's ability to respond later to the same antigens. A better strategy is to enhance the quality of colostral antibodies by vaccinating the mare four to six weeks prior to foaling.

CONTACT: Dr. David Horohov, (859) 257-4757, david.horohov@uky.edu, Department of Veterinary Science, University of Kentucky, Lexington, Kentucky.

INTERNATIONAL

Third Quarter 2003

THE INTERNATIONAL COLLATING CENTRE, Newmarket, and other sources reported the following disease outbreaks:

An outbreak of equine herpes virus (EHV) abortion attributable to EHV-1 occurred among 20 non-vaccinated Thoroughbred mares on one premise in Argentina during July and August. Sporadic cases of the neurological form were reported from the United Kingdom, and an outbreak among 20 riding horses also occurred on two premises in Oregon, USA. Respiratory disease caused by EHV was reported on one premise in Argentina and several premises among various breeds in France.

Equine arteritis virus (EAV) asymptomatic infection was diagnosed on a stud farm in Ireland involving 16 mares and a first-season unvaccinated Thoroughbred stallion. The outbreak was identified when the stallion was being prepared for shuttling duties to the Southern Hemisphere. The stallion was considered not to be shedding the virus and was permitted to travel.

Influenza was reported from several locations in France, Sweden, and one location in the United Kingdom. Four cases of Grass Sickness were reported on a premise in Switzerland that had reported similar cases in 2002. The first case of Japanese Encephalitis to be reported in Japan in 18 years was confirmed in an unvaccinated non-Thoroughbred. A mild outbreak of diarrhea due to rotavirus infection was diagnosed on a farm in Argentina involving foals of mares that had been vaccinated in late gestation.

Sporadic cases of salmonellosis were diagnosed in Ireland, and cases of strangles were reported from Australia, Ireland, Italy, Sweden, Switzerland, and the United Kingdom.

Cases of West Nile viral disease were diagnosed in the Var district of southern France among humans and horses during August and September.

Horse Genomics Research Update

SOUTH AFRICA'S KRUGER NATIONAL PARK WAS the center of the horse genome project as the Fifth International Equine Gene Mapping workshop was convened by the Dorothy Russell Havemeyer Foundation from August 11-14, 2003. Previous meetings have been held in Lexington, Kentucky (1995); San Diego, California (1997); Uppsala, Sweden (1999); and Brisbane, Australia (2001). Thirty-five scientists from Australia, New Zealand, Japan, Korea, California, Texas, Kentucky, New York, the United Kingdom, France, Norway, Poland, the Czech Republic, Italy, and South Africa presented their research and discussed ways to develop and use the gene map for the benefit of the horse.

This workshop was unique in the series because it was the first in which a majority of the presentations dealt with applications of genomics to health problems. Presentation topics included inflammatory diseases, developmental bone diseases, arthritis, respiratory disease, exercise-induced pulmonary hemorrhage, male infertility, sarcoid tumors, and immunity. Specific inherited traits also discussed included the angiotensin-converting enzyme (ACE) gene for performance, lavender foal syndrome, hereditary equine regional dermal asthenia (HERDA), degenerative suspensory ligament desmitis, and mapping the gene for Appaloosa coat color patterns. In a broad sense, the topics of the workshop included hereditary and non-hereditary conditions that are influenced by altered gene expression. Indeed, the legitimate topics of the workshop include performance, fertility, and health.

Colic and laminitis are important diseases of horses that are characterized by inflammation. The research group from the University of Georgia directed by Jim Moore is characterizing thousands of genes expressed in leukocytes with special emphasis on those expressed in response to lipopolysaccharides, a mediator of inflammation. Immunology is also a popular target of research. Petr Horin (Czech Republic), Loren Skow and Ashley Gustafson (Texas A&M), and Doug Antczak (Cornell University) reported characterizing gene expression as well as hereditary variants and genomic structure of the immune system. Joie Watson (UC Davis) reported studies on the gene IL4R and its possible relationship to recurrent obstructive airway disease in horses, and Cindy Harper (University of Pretoria, South

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Editors
Roberta Dwyer
David Powell
Neil Williams

Staff
Diane Furry

Correspondence should be addressed to the editors, Department of Veterinary Science, Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, Kentucky USA, 40546-0099
Telephone (859) 257-4757
Fax (859) 257-8542

Internet address:
http://www.uky.edu/Agriculture/VetScience/gluck1.htm

Africa) reported a large epidemiological study on exercise-induced pulmonary hemorrhage in Thoroughbred horses. Jamie MacLeod (University of Kentucky) reported on functional genomic approaches to studying musculoskeletal diseases. These complex studies are beginning to show results but will benefit greatly from further development of genomic tools for the horse.

Other studies focused on specific traits or specific candidate genes. Work continues to map and find the genes for lavender foal syndrome of Arabian horses (Broad at Brisbane, Australia/Antczak at Cornell/Penedo at UC Davis), suspensory ligament desmitis of Peruvian Pasos (Cothran at Kentucky), and HERDA (Bannasch at UC Davis). Work was reported by Natasha Ellis of Sydney, Australia, on performance and the ACE gene. Genetic variants had been found but so far none associated with improved performance. Bhanu Chowdhary and Terje Raudsepp (Texas A&M) and Gabriella Lindgren (Stanford University and Uppsala University, Sweden) described studies on the horse Y chromosome with the goals of identifying effects on male infertility. Work in Kentucky (Rebecca Terry, University of Tampa) led to mapping the gene for Appaloosa coat color to horse chromosome 1. The specific gene responsible for the color trait remains to be identified.

A recurrent theme within these reports was the need for improved genomic tools in order to achieve goals effectively and more rapidly and economically. In this connection, three comprehensive maps were unveiled during the meeting. Matthew Binns and June Swinburne (Animal Health Trust, United Kingdom) reported progress towards a linkage map with more than 700 markers covering all horse chromosomes. Domenico Bernoco (Stormont Labs and UC Davis) demonstrated that the linkage maps produced in different studies could be joined together in a comprehensive single map. Bhanu Chowdhary and Terje Raudsepp (Texas A&M) presented a framework map of 750 markers based on a radiation hybrid panel. Other scientists reported the addition of microsatellite markers to linkage and radiation hybrid maps (most participants), creation of new markers (Hasegawa, Japan), mapping markers to chromosomes (Teri Lear, Kentucky/Chowdhary and Raudsepp, Texas A&M) and projects to construct comprehensive maps using large insert DNA clones (Gerard Guerin, INRA, France/Tosso Leeb, Germany) preparatory for whole genome sequencing.

Workshop participants set new goals for the next two years that included tripling the number of mapped genes and DNA markers, creating new tools to investigate gene expression, and building a scaffold for whole genome sequencing of the horse.

So when will the map be completed? It is. We are using it while continuing to improve its resolution and usefulness.

A Web site describing the workshop activities and the accomplishments in detail can be found at http://www.uky.edu/AG/Horsemap.

CONTACT: Dr. Ernie Bailey, (859) 257-4757, ebailey@uky.edu, Department of Veterinary Science, University of Kentucky, Lexington, Kentucky.

NATIONAL

Insulin Resistance and Inflammatory Challenges

AN ASSOCIATION BETWEEN OBESITY AND THE development of insulin resistance in humans and laboratory animals has led to a marked interest in adipose tissue as a source of hormones and small proteins that function as signaling molecules. Of particular interest is the recognition that fat cells produce the inflammatory cytokine tumor necrosis factor-alpha (TNF-α). This cytokine plays a key role as a pro-inflammatory agent in inflammatory/immune challenges and is produced predominantly by circulating blood monocytes. However, in obese subjects, there is now compelling evidence that fat cells significantly contribute to increased circulating concentrations of TNF-α.

An initial response to an inflammatory challenge is the development of transient insulin resistance and thus redirection of available energy towards the immune system. The development of insulin resistance during inflammation and immune challenges is caused by TNF-α acting on the insulin receptor of target cells and leads to decreased glucose uptake by peripheral tissues. In obesity, circulating concentrations of TNF-α also are elevated, and there is growing support for the proposal that TNF-α plays

Figure 1.

States Reporting Equi
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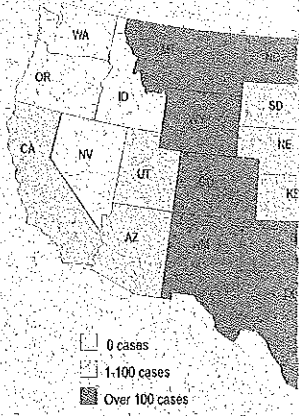

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a role in the development of insulin resistance associated with obesity. Indeed, the similarity of the mechanisms that lead to development of insulin resistance during an inflammatory challenge and obesity has led to proposal that the development of insulin resistance with obesity is representative of a mild inflammatory response.

Insulin resistance in the horse has been associated with the development of laminitis, osteochondrosis dissecans lesions (OCD), Cushing's disease, and hyperlipidemia. In previous studies we observed that equine adipose tissue is a source of TNF-α. Further, we proposed that this cytokine may play a key role in the development of insulin resistance associated with obesity. In consideration of the observation that in other species an inflammatory/immune challenge leads to profound insulin resistance, an investigation was undertaken to identify whether a similar relationship may exist for the horse. Insulin resistance was determined using the euglycemic hyperinsulinemic clamp procedure before and after administration of endotoxin to induce a mild inflammatory response. Within 24 hours after administration of endotoxin, profound insulin resistance was identified by a marked reduction in the ability of insulin to promote glucose uptake by peripheral tissues. The development of insulin resistance in the horse following administration of a bacterial endotoxin is similar to that found in other species, including humans. Insulin resistance also occurs in humans following sepsis, surgery, and hemorrhage. This injury/infection-induced resistance is often referred to as "stress diabetes." The development of insulin resistance in these stress conditions serves to ensure a high flow of glucose to the predominantly glucose-consuming cells, such as the wound, the inflammatory and immune cells, and all insulin-independent cells. On the other hand, an elevated circulating concentration of insulin, a characteristic feature of insulin resistance, promotes protein catabolism in muscle tissue and thus muscle wasting if the insulin-resistant state is maintained. The consequences of insulin resistance in the horse remain relatively unknown, but strong associations with particular diseases have long been proposed. A question arising from the plethora of perturbations leading to insulin resistance is whether these stressors predispose the animal to further pathological conditions, including the development of laminitis and OCD lesions.

CONTACT: Dr. Barry Fitzgerald, (859) 257-4757, bfitz@uky.edu, Department of Veterinary Science, University of Kentucky, Lexington, Kentucky.

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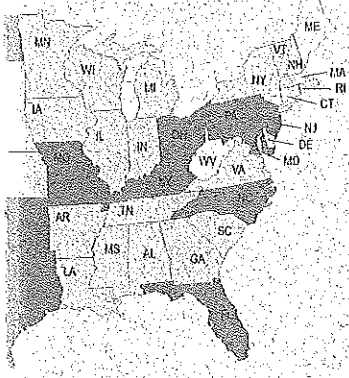

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West Nile Virus 2003

THE EPIDEMIC OF WEST NILE VIRUS (WNV) INfection continued its spread in a westerly direction across the United States during 2003. Only four states—Alaska, Hawaii, Nevada, and Oregon—are considered free of the disease. As of November 24, the USDA reported 4,426 equine cases in 41 states compared to 14,358 cases in 40 states reported during 2002 (Figure 1). The midwestern states of Colorado, Montana, New Mexico, and Wyoming reported 1,231 (28%) of the cases in 2003.

The number of human cases reported by the Centers for Disease Control (CDC) as of November 25 was 8,567—approximately double the number (4,156) reported in 2002. Of the reported cases this year, 737 were presumed WNV-viremic blood donors. The majority of total human cases (67%)—and 54% (107 out of 199) of fatalities—were recorded in Colorado, Nebraska, South Dakota, and Texas. These were primarily in rural areas, as distinct from more populated areas during previous years. The mosquito vector *Culex tarsalis* that predominates in farmland areas in the western states and is an efficient vector of the virus may well have contributed to this disease pattern.

The significant decrease in equine cases as compared to the increase in human cases during 2003 could well have been influenced by the extensive equine vaccination program using an inactivated vaccine that was undertaken in the United States during 2003.

KENTUCKY

Rotavirus Vaccination in Foals

THE EQUINE ROTAVIRUS VACCINE (FORT Dodge Animal Health) was first commercially available in 1996 for use in pregnant mares. As one of the few vaccines labeled for use in pregnant mares, it has significantly reduced the incidence and severity of rotaviral diarrhea in foals, not only in Central Kentucky, but also in other areas of concentrated horse breeding, such as Newmarket, England.

Before use of the vaccine, serious outbreaks of rotavirus had high morbidity and moderate mortality in foals less than 14 days of age. With use of the vaccine, protection is conferred via ingestion of colostrum from vaccinated mares, and decay of maternal antibody in foal blood over the first 60 days of life is expected. Also, as foals age, their gastrointestinal tract develops and is better able to mitigate a rotavirus infection, with foals beyond 90 days of age having mild or asymptomatic rotavirus infections.

Because of concerns among Kentucky veterinarians and farm managers of some foals developing mild rotaviral diarrhea around 60 days of age, a study was designed to determine if foals from vaccinated mares would respond to a rotavirus vaccine to boost immunity by age 60 days.

Two well-managed Central Kentucky Thoroughbred farms with 105 foals were included in the study. All of the pregnant mares on the farms had received the Equine Rotavirus Vaccine at 8, 9, and 10 months gestation, per label instructions. All foals born had greater than 800 mg/dl of immunoglobulin G (IgG), and none received any supplemental colostrum, plasma, or serum. Blood samples were obtained from foals at 24 hours of age and periodically through 75 days of age. Half of the foals were vaccinated with the Equine Rotavirus Vaccine at 30 and 45 days of age; the other age-matched foals served as controls. Foals were critically observed for signs of diarrhea, with appropriate diagnostic testing and treatment determined by the farm veterinarians.

Only one foal had a fever (103.1 F) after rotavirus vaccination; no other adverse reactions occurred. Serum samples from the foals were tested via serum neutralization to determine rotavirus antibody titers. Foals from both groups (vaccinates and controls) had high initial rotavirus antibody titers at birth, which decreased over time at the same rate through 75 days of age. There was no significant difference in the antibody titers between vaccinated and unvaccinated foals or between farms. No foals developed rotaviral diarrhea during the study, but five foals recovered from bacterial diarrheas.

The significance of this study is the confirmation again that high concentrations of maternal antibody will interfere with vaccination of young animals. No similar studies have been performed on the antibody response in foals from mares not vaccinated with the Equine Rotavirus Vaccine.

Also important to recognize is that proper farm management, routine disinfection, isolation/quarantine protocols, prevention of overcrowding, and other techniques are just as important as a proper vaccination program in the prevention of equine infectious diseases.

CONTACT: Dr. Roberta M. Dwyer (859-257-4757), rmdwyer@uky.edu, Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, Kentucky.

Bibliographies

THE MORRIS LIBRARY NOW HAS AVAILABLE A new bibliography of selected references on cryptorchidism in the horse. The bibliography is available on the Library's Web site (http://www.uky.edu/Agriculture/VetScience/morris.htm) or in print by contacting Gracie Hale (ghale@uky.edu).

Other recent bibliographies on contagious equine metritis, chronic obstructive pulmonary disease, laminitis, hyperkalemic periodic paralysis, and equine protozoal myeloencephalitis are also available. In addition, older bibliographies on exercise-induced pulmonary hemorrhage, poisonous plants, and colic are still available from the library.

A comprehensive bibliography on West Nile Virus, covering the years 1975 to 2003, may also be obtained.

Reprinting EDQ articles

ONE OF THE PRIMARY PURPOSES FOR THE PUBLIcation of the Equine Disease Quarterly is to disseminate factual health information to the equine and veterinary industries. The editors encourage other publications to reprint the articles that appear in the *Equine Disease Quarterly*, either directly from the printed publication or from the Web site. Permission to reprint articles is granted if the article is published in its entirety, the author(s) is/are cited, and the source is quoted as "Equine Disease Quarterly."

If space dictates that the entire article cannot be published, the article portion used shall be referenced to "http://www.uky.edu/Ag/VetScience under *Equine Disease Quarterly* to view the entire article." If editors have any questions regarding this policy, they are encouraged to contact either Dr. Powell or Dr. Dwyer.

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Department of Veterinary Science
Maxwell H. Gluck Equine Research Center
University of Kentucky
Lexington, Kentucky 40546-0099

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