



Respiratory System Priorities for Research
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This is a report of a group meeting held in conjunction with the World Equine Airway Symposium at Cornell University (July 19-22, 2005). The group addressed the questions provided by Nat White, DVM. Infectious and non-infectious diseases were considered separately. In each section of the report, there is a statement of issues and then a list of research priorities.

Infectious Diseases

Infectious respiratory diseases constitute one of the major economic threats to the horse industry and therefore need to be a high priority for research into rapid diagnostic and preventive measures. This requires development of some new tools, and standardization of methods among laboratories. Development of these tools will require more knowledge about pathogenesis of some of these diseases. There is also a need for effective in vitro methods to determine vaccine efficacy so that challenge methods that use whole animals can be reduced or even eliminated. In the case of some infectious diseases (e.g., influenza), development of educational programs to disseminate existing knowledge about rational use of effective vaccines could reduce the risk of outbreaks. Research into treatment of infectious diseases is of low priority.

Priorities

- 1) Develop effective diagnostic tools that are rapid, reliable, and standardized among laboratories.
- 2) Determine measures that correlate with effective protection against infectious diseases. Serology would be easiest but it may be necessary to develop other tools based on cytotoxic and mucosal immune responses.
- 3) Investigate disease pathogenesis in order to find candidates for new diagnostic tools and indicators of protection.
- 4) Develop methods to evaluate vaccines by indirect methods in order to reduce or eliminate challenge methods that use animals.

Specific infectious diseases***Influenza***

- 1) The highest priority is education of veterinarians and horse owners on effective prevention strategies with currently available EFFECTIVE vaccines.

Herpesvirus 1 and 4

- 1) Investigate how to resolve the difficult problem of latent infection. Latency is a central issue in herpes infections in all species and its elimination may be very difficult.

Rhodococcus equi

- 1) Prevention of infection, which will require more understanding of the foal's immune response.

Strep. Equi and Zooepidemicus

- 1) Prevention by effective genetically manipulated vaccines
- 2) Investigation of pathogenesis to develop ways to stimulate the immune response to streptococcal infections.
- 3) Detection and elimination of the carrier state.
- 4) Investigation of pathogenesis and treatment of bastard strangles and purpura hemorrhagica
- 5) Education of veterinarians and the public about known prevention strategies.

Non-infectious lower airway diseases***Chronic airway disease (COPD)***

Because the term COPD was being used to describe a collection of syndromes, it has been replaced with two terms. Heaves, also known as recurrent airway obstruction (RAO), is the syndrome of severe, intermittent, environmentally induced airway obstruction of older horses. The airway mucus accumulation and inflammation that occurs in young racehorses is known as inflammatory airway disease (IAD).

Heaves

Heaves is airway inflammation that is induced by exposure of susceptible animals to organic dusts that contains allergens and other inflammagens. Bronchospasm, airway wall thickening, and accumulation of mucoid secretions in the airways accompany the inflammation. The disease is not curable, but exacerbations can be prevented or controlled by environmental control and use of corticosteroids and bronchodilators. Initiation of treatment at the earliest stage of disease is essential to prevent airway remodeling.

- 1) Because the syndrome is well understood, the highest priority is development of educational materials for horse owners and veterinarians. These recommendations should be endorsed by the AAEP.
- 2) Development of cost-effective inhaled medications and inhalation therapy devices that limit the side effects of corticosteroid therapy.
- 3) Determine if airway remodeling is reversible with treatment.
- 4) Continuing investigation of genetics and pathogenesis to identify a marker of disease susceptibility.

- 5) Develop field tests of airway obstruction to identify horses in early stages of disease.

Inflammatory airway disease

Young racehorses develop bouts of airway inflammation when first introduced to the training environment (racetrack in the USA). Evidence from the UK and Australia suggest that viral infections are not important, but recurrent streptococcal infections may be part of the cause. However, many of these horses do not have active infections. The environment of stables is rich in particulates, endotoxin, and other inflammogens that could be participating in the pathogenesis of the condition.

- 1) Investigate role of streptococcal infections in IAD in the USA.
- 2) Investigate relationship between IAD and stable environment.
- 3) Investigate mucosal immune responses to particulates.
- 4) Investigate connections between IAD and heaves

Bleeders (EIPH)

Most racehorses bleed during some if not all intense bouts of exercise. Horses in other competitive events of high intensity also bleed. It is unlikely that bleeding can be eliminated because it is a consequence of the cardiopulmonary function that allows the high levels of oxygen consumption. There is still a need for more complete understanding of pathogenesis, especially why horses bleed from the caudodorsal lung region. The consequences of bleeding need to be understood so that any potential lung injury can be appropriately treated. Practical quantitative measures of the severity of bleeding are needed to know when to institute treatment.

- 1) Re-investigate pathogenesis of EIPH in order to understand why horses bleed from the caudodorsal region of the lung.
- 2) Investigate the consequences of single and repeated bleeding into the lung.
- 3) Develop methods to quantify the severity of bleeding.
- 4) Develop treatments to prevent the consequences of bleeding.

Upper airway diseases

A recent Havemeyer workshop on recurrent laryngeal neuropathy (laryngeal hemiplegia) recognized the lack of information on pathogenesis of the condition and the conflicting scoring systems used to evaluate horses. The optimal surgical methods to correct the airway obstruction and abnormal noise production have been evaluated only on treadmills and there is a need for investigations under field conditions. The pathogenesis of other obstructions such as dorsal displacement of the soft palate (DDSP) and pharyngeal collapse needs to be understood before rational therapies can be designed.

Recurrent laryngeal neuropathy

- 1) Investigate the pathogenesis of the recurrent laryngeal axonopathy. Such studies should include investigations of the status of neurons in the nucleus ambiguus and the molecular pathology of the condition.
- 2) Investigate the relationship between endoscopically visible movements of the larynx and the severity of lesions in laryngeal muscles.

- 3) Develop methods to evaluate laryngeal function during racing. These might include endoscopy, sound recording, and measurements of airway function.

DDSP and other obstructive disorders

- 1) Investigate the neuromuscular basis of DDSP and other pharyngeal obstructive conditions. This should involve studies of experimentally induced and naturally occurring disease.
- 2) Develop methods to diagnose airway obstructive disorders in racehorses exercising on the track at high speed.
- 3) Use the methods developed to investigate the efficacy of treatments.

Collaborations among laboratories

There is already considerable collaboration among laboratories both nationally and internationally. In infectious disease and immunology research, investigators share tools and reagents. The Havemeyer Foundation has had a leading role in sponsoring the development of immunological tools for equine research. The USDA recognizes the need for such tools and the AAEP should lobby in support of the USDA's efforts to develop a toolbox of reagents. Investigators of heaves already collaborate worldwide because different labs have different expertise. Investigators also are joining forces with their colleagues in human medicine and basic sciences. Discussions are underway to establish a bank of tissue for immunohistochemistry, and other samples for investigations of molecular pathways in heaves-susceptible horses exposed to a standard challenge protocol. This bank of material would be shared worldwide.

Costs of research

It is impossible to estimate the costs of the needed research in these horse diseases. Progress depends not only on the specific studies conducted in horses but to the greatest extent on progress in NIH-funded investigations of basic science and human disease.

Progress in equine research requires long-term consistent funding of laboratories dedicated to investigation of horse diseases. Without this, the best investigators seek NIH funding and that requires that they address questions that are not always those most pressing for understanding horse diseases. A productive laboratory requires technicians, graduate students, and postdoctoral fellows in addition to supplies and animals. At present costs, \$100,000 covers a graduate student, a technician, and supplies for one year; an annual budget of \$500,000 maintains an active laboratory that does state-of-the-art research.

Consistent long-term support is critical to attract the best individuals to a career in equine disease research. There are always eager young people who are interested in studying horse diseases. Once they get their PhD, they move away from horse disease research because the funding available does not allow them to develop a research career. If the pipeline of investigators is not kept flowing, horse disease research will be reduced.

What can AAEP and other foundations do?

- 1) Educate members and horse owners on the benefits and **realistic** costs of doing research into horse diseases.

- 2) Develop methods to provide long-term research and training support for individuals studying horse diseases.
- 3) Actively lobby at the federal and state level for more animal disease funding.
- 4) Facilitate access to racetracks and horses for research projects. Laboratory-based projects use horses that have been rejected from competition and may not be representative of the real world. Field investigations must be used to confirm laboratory-based results.
- 5) Do not make extravagant promises about what can be accomplished with relatively small amounts of money.
- 6) Stop worrying about research duplication. It is a necessary part of the search for truth. Without duplication of investigations, erroneous ideas are perpetuated for years.
- 7) Encourage AAEP members to stop using generic and compounded drugs. In the past, the pharmaceutical industry provided considerable research support. It is no longer developing drugs for horses because use of compounded drugs eliminates the possibility of making a profit. Consequently, the money the industry provides for research is decreasing.