EQUINE HERPES VIRUS
A Challenging Foe

by Heather Smith Thomas

The herpes virus has evolved to where it can live within the horse for the lifetime of the animal by using the strategy of latency.

Heather Smith Thomas resides on a ranch near Salmon, Idaho. As a freelance writer for many years, her equine health and management articles are a regular feature in Speedhorse Magazine.

The herpes virus has evolved to where it can live within the horse for the lifetime of the animal by using the strategy of latency.

To date, at least 9 different herpes viruses are known to infect horses, according to Dr. Frank Cook, Research Associate Professor at the Maxwell Gluck Equine Research Center, University of Kentucky. "Although some of these viruses, such as the gamma-herpesviruses - equine herpesvirus 2 and 5 (EHV-2 and EHV-5) - have been associated with eye infection and respiratory disease, these associations remain controversial," he says.

"These gamma-herpesviruses are isolated from cases of disease, but they can also be isolated from clinically normal horses. Therefore, if they are associated with disease, it is a more complex situation than the simple presence of virus. It is very likely that host genetics and/or environmental factors play an important role in determining the potential pathogenic consequences of exposure to EHV-2 and EHV-5. In contrast, EHV-4 and particularly EHV-1 (two members of the alpha-herpes group) are known to pose a definite threat to equine health and well being."

Cook says the unfortunate thing about herpes viruses is that they are probably transmitted at a very early age. "EHV-1 and EHV-4 tend to be transmitted from mare to foal or from animal to animal within the same group of horses," he says. By 2 years of age, almost all horses have antibodies to EHV-1 and EHV-4, demonstrating that they have been exposed to these viruses.

"As a result of this almost ubiquitous infection rate, these viruses are difficult to control by good management practices, compared to viruses that have a much lower incidence of infection, such as Equine Infectious Anemia. Once a horse has been infected, it tends to remain infected because equine herpesviruses (in common with many other types of herpesviruses) use stealth tactics including a dormant state to avoid being eliminated by the powerful immune responses unleashed by the body," says Cook.

These viruses can then be reactivated at some future time, such as when the horse undergoes stress. "Unfortunately, effective immune responses to EHV-1 are relatively short-lived. Once they have declined, the horse is susceptible to re-infection with different strains of the virus," he says.

Viruses have evolved many strategies to survive within the host. These strategies vary, depending on the type of virus. The lentiviruses - such as the one that causes Equine Infectious Anemia in horses, or HIV in humans - have developed numerous mechanisms to persist in the body by resisting the effects of the immune system.

"For example, the host produces neutralizing antibodies that block viral infections by binding to those areas on the viral surface proteins responsible for attachment to the host cell. In lentiviruses, these sensitive areas are for a majority of the time buried deep within the structure of the surface protein, making them inaccessible to most neutralizing antibodies," explains Cook.

By contrast, the herpes viruses can avoid immune response by becoming latent. "Equine herpes viruses, such as EHV-1, can enter white blood cells or nerve cells and hide by becoming almost completely inactive," he says.

In this latent stage, they are not making viral structural components and the immune system cannot detect them. "As a by-product of replication, small fragments of viral proteins are transported to the host cell membrane and presented to the outside world by Major Histocompatibility Complex class 1 (MHC-1) molecules. When foreign protein fragments are bound to MHC-1 molecules, they serve as a distress signal that prompts the immune system to initiate an attack to destroy what in effect is a virus production factory."

If a herpes virus is shut down within the cell, however, there is nothing there to alert the immune system to its existence.

"Herpes viruses are big, complicated viruses and encode a large number of proteins. Some of those proteins have the effect of interfering with immune responses. This is an intensive area of research right now; trying to find out how the different herpes viruses fool the immune system," says Cook.

"The immune system has two components: an initial non-specific or innate response involving the production of antimicrobial molecules, some of which are responsible for symptoms of disease such as fever or inflammation; and a highly specific or adaptive response, EHV-1 appears to interfere with both responses by producing proteins that slow production of certain antimicrobial molecules and other proteins that partially inhibit the binding of viral protein fragments to MHC-1," he explains.

"In addition, we have recently found that EHV-1 infects cells by initially binding to MHC-1, Therefore, a molecule that plays a pivotal role in defending the body against attacks from micro-organisms also
makes horses susceptible to infection by this herpesvirus. This is just one more example of how devious viruses can be," he says.

"The immune system is extremely powerful and capable of causing tremendous damage to the body, as evidenced by diseases such as lupus in humans, when it is not tightly controlled. A persistence strategy employed by EHV-2, a gamma-herpesvirus related to Epstein Barr virus in humans, is that it encodes a protein closely resembling one of the major host proteins (interleukin 10 or IL-10) involved in limiting or controlling immune responses once a pathogen has been eliminated."

The use of newer diagnostic techniques designed to detect viral genetic material directly, in clinical samples, has shown that in addition to the alpha-herpesviruses (EHV-1, EHV-4), large numbers of gamma-herpesviruses (EHV-2, EHV-5) may also be present during disease episodes. "Such associations cannot be observed using conventional virus isolation techniques because the alpha-herpesviruses replicate much faster in the cell cultures used for laboratory diagnosis than do gamma-herpesviruses. Although the presence of both types of virus could be purely coincidental, it is possible that EHV-1 or EHV-4 could benefit by the presence of EHV-2 and its ability to produce an immunosuppressive protein similar to IL-10. These potential relationships need to be investigated in the future," says Cook.

Fortunately, the strategies employed by herpesvirus to undermine immune responses are not 100 percent effective. "The immune systems of most EHV-1 infected horses eventually bring viral replication under control. The only viruses that survive are the ones that achieve latency," he explains.

Unfortunately, the latent herpes viruses can come out of hiding and cause disease. "We don’t know exactly what enables them to do this, but the common things seem to be stress, transport, racing, etc. Then we see a recurrence of disease, at which point the horse becomes sick and can infect other horses via nasal secretions," says Cook. When the virus is hiding, the risk for transmission is much lower.

"An analogy would be Herpes Simplex Virus-1 (HSV-1) that causes cold sores in humans. If a mother with an active infection on her lip kisses a child, the virus can be transmitted to the child, causing a localized skin lesion on the child. Although the child’s immune system will respond, some viruses escape, entering nearby nerves and migrating to a group of nerve cells (neuroganglion) at the base of the skull, where they become inactive and hide. If something activates them, the virus travels down the nerve and can cause disease again," says Cook.

Another example occurs with Varicella-Zoster Virus (VZV). "This virus causes chickenpox (varicella) and later in life can reactivate to induce bouts of shingles (herpes zoster). However, while many people have had chickenpox, not all of them get shingles," he says.

"It’s the same with horses - disease can crop up again later. The two herpes viruses that have the most impact on performance in horses are EHV-1 and EHV-4. Although both infect the respiratory tract, EHV-1 is probably the most dangerous in that it can cause a high incidence of abortion - a phenomenon that rarely occurs with EHV-4. This is why most horse breeders vaccinate their mares against EHV-1."

Some variants of EHV-1 can also cause severe neurological paralysis. "The paralysis can be anything from mild ataxia in the hind legs to total recumbency, with the horse unable to get up, depending on the severity of the lesion and where it is in the central nervous system," says Cook.

"We think EHV-1 is mainly a respiratory infection. In some cases, however, it can get from the lungs into the blood stream. When it does this, it infects the bloodstream, including capillaries in the spinal cord. It infects those tiny capillaries and then travels down because of all the dead cells and inflammation. This starves the neural tissue for oxygen."

EHV-1 does not actually infect neural cells of the horse, but has this indirect effect by shutting down the tiny capillaries. "This is what causes damage to the spinal cord, or sometimes the brain," explains Cook. The outcome can be quite variable when a horse becomes infected with EHV-1.

"The strain of virus makes a difference, as does the individual horse’s response. Some horses seem much more susceptible. The risk factors are also variable. One of the main risk factors for developing neurologic disease is old age. The older horse is more at risk than a horse in the prime of life," he says. The older horse seems to lose some ability to fight off disease, and there’s a reduction in effectiveness of immune responses.

Use of steroids may also create risk. "Steroids are often utilized to treat an inflammatory problem, but they also knock down the immune system. They hinder all the immune responses and not just the ones you don’t want, such as fever, swelling and inflammation. Steroids reduce the body’s responses to viruses like herpes or EIA."

Steroids can be used short term, but if a person is treating a chronic pulmonary disease, they can have the side effect of allowing some of these viruses to escape control.

"This applies to all types of infection. If the animal is on an immunosuppressant like steroids, there is always a chance this will make that animal susceptible to other diseases - whether bacterial, viral or fungal. Ordinarily, the veterinarian will try to give a compromise dose - just enough to limit the clinical signs, but still allow the immune system enough force to function. It’s wise to not use steroids for very long," says Cook.
EHV-1 is one of the more serious diseases of horses in that it causes respiratory illness, abortion, and in some instances neurological disease. This year, cases of EHV-1 have again shown up around various parts of the country.

THE DISEASE

EHV-1 and EHV-4 are part of a large group of viruses - the alphaherpesviruses - that cause potentially serious disease in horses and other species, including humans. “EHV-1 and EHV-4 both induce similar respiratory diseases - such as cough, clear nasal discharge and fever - that usually permits secondary bacterial infections to occur - with characteristic thick nasal discharge containing mucus and pus,” says Cook, who has been studying these viruses for many years. “However, EHV-4 is not as efficient at getting into the bloodstream and infecting other cell types. Therefore, it is less likely to cause abortion or neurologic disease,” he says.

EHV-1, often called “thinovirus” even though it is not related to the type of viruses that cause the common cold in humans, is probably the most important for horse owners to know about. Like EHV-4, this virus causes respiratory disease - rhinopneumonitis, but has a higher propensity to infect white blood cells, thus enabling it to be transported around the body to the uterus and capillaries supplying the central nervous system.

“Although almost all EHV-1 strains are capable of inducing abortion, only some variants can produce neurologic problems. Recent outbreaks that have caused concern involve the respiratory/neurologic form. Epidemics of all 3 clinical entities - respiratory, abortion, neurologic - may occur separately or at the same time within any horse population.

“We think that whatever may be associated with the neurovirulent type seems to increasing in recent years. The USDA in 2007 classified herpervirus myelonecephalopathy (neurologic disease) as a potentially emerging disease of the horse,” says Cook.

There’s a lot of research in progress, looking at herpes virus in cattle, chickens and humans. “There is also research being done to learn more about what constitutes a neuropathogenic virus, and why some strains are neuropathogenic while others are not. There have been mutations identified in at least one herpes virus gene that seems to be associated with that neuroviral type,” he says.

“One mutation that shows some correlation with neurologic disease is in the gene that encodes the viral DNA polymerase. This enzyme is one component of the so-called ‘elongation complex’ and is absolutely essential for producing copies of the EHV-1 genome ready for assembly in progeny virus particles.” This mutation consists of a substitution and a resulting change. Lab tests have been designed that can distinguish between these two virus types, designating one of them as non-virulent and the other as neuroviral.

Viruses, and the immune system, are tremendously complex. “They have co-existed for a long time, each one trying to out-do the other,” says Cook. The herpes virus has evolved to where it can live within horses for the lifetime of an animal by using the strategy of latency. Up to half of any horse population may serve as a reservoir for EHV-1, with certain horses latently infected and intermittently shedding the virus.

One of the challenges of doing research on EHV-1 is that it is virtually impossible to find seronegative horses. Almost all horses have been exposed to EHV-1 and EHV-4 by the time they are 2 years old. Almost all horses are latently infected, perhaps by multiple strains of EHV-1 and 4.

The virus also has the potential to increase its virulence. “Viruses can increase in virulence. However, we and other labs have shown that horses can be simultaneously latently infected with ‘neuroviral’ and ‘non-neuroviral’ forms of EHV-1,” explains Cook.

Historically, the neurologic form of the disease has been rare. But in recent years we’ve seen significant increase in outbreaks in North America, Europe and other parts of the world. A few years ago there were several outbreaks at racetracks in Kentucky, followed by cases in New Jersey, Florida and California, and the disease drew a lot of attention.

“We have recently completed analysis of EHV-1 strains from Kentucky, isolated over a period of almost 60 years. Strains containing the mutation were present as early as the 1950’s, so they are not new. However, the incidence at which they occur increased from 3.6% in the 1960’s to 13.3% in the 1990’s. The incidence from 2000 to 2006 was 19%, suggesting that viruses with that mutation are still increasing in prevalence,” says Cook.

“It is important to realize, however, that not all viruses containing the mutation are associated with neurological disease and that many viruses without the mutation have been isolated from cases of paralysis. The only consensus observation is that EHV-1 isolates with the neuroviral genotype are more likely to be isolated in situations where there are multiple cases of neurologic disease on the same farm,” he says.

Unfortunately, there are many factors that contribute to myelonecephalopathy - ataxia and potential paralysis - triggered by EHV-1, and many of these factors are not yet known or understood. “For example, at the Gluck Center we have recently observed that an EHV-1 modified live vaccine strain contains the mutated virus. But in the many years of widespread usage, this virus has never been associated with neurologic disease. We think this is because the vaccine virus contains additional mutations that mitigate its affects,” he says.

A new lab test called the EHV-1 Allelic Discrimination Assay has been designed that can distinguish between the two virus types - the non-virulent and the neurovirulent form of EHV-1, and is becoming more common in major diagnostic laboratories. “But if an owner or veterinarian receives a result from this test indicating the presence of the non-virulent genotype, they should not relax and breathe a sigh of relief. EHV-1 is potentially a very dangerous pathogen, regardless, and both types should be subjected to the same precautions and levels of bio-security,” explains Cook.

The herpes virus is spread primarily through direct contact between horses - nose to nose, and by humans carrying the virus from one horse to another on hands and equipment, or by using the same equipment for more than one horse, such as water and feed tubs, bits and tack, clippers, grooming cloths, “snot rags”, etc. Practicing good hygiene can often help prevent transmission.

This virus can also be spread if a susceptible horse comes into contact with an aborted fetus or placental tissues. These can contain high levels of virus. “If another mare comes in contact with this material, she should be placed under strict quarantine. I was involved in an investigation of an EHV-1 outbreak on a large stud farm in England where mares were moved after coming into contact with an aborted fetus. As a result of this contact, there were 22 abortions or infected foals that did not survive,” says Cook.

Some researchers think that for a short time after the horse develops fever he can also spread...
the virus through aerosolization when coughing. You may be able to reduce the risks for transmis-
sion of EHV-1 by keeping horses separated.

This virus is primarily transmitted by direct
nose-to-nose contact. If your horse is in a stall
next to another horse or standing in line by
another horse, close contact could put your horse
at risk. Incubation period once a horse is exposed
can vary, depending on the clinical form of dis-
case. Signs of respiratory disease usually appear
between 3 and 6 days following exposure to the
virus. Abortion, however, may take place 7 days
to several months later. The long time periods
between exposure and abortion are usually due
to reactivation of the virus following latency.

The neurologic form of the disease may
appear within 2 weeks following respiratory tract
exposure to the virus. Horses that have experi-
enced prior infection may be at greater risk for
developing neurological manifestations, since
they are likely to harbor latent viruses. “However,
immune responses generated by a recent infec-
tion tend to have a protective effect, at least for
several months. For example, research has shown
that horses are more resistant to the development
of neurologic disease following exposure to a
neuroviral strain if they have experienced a
recent EHV-1 outbreak,” explains Cook.

After first signs of illness, such as fever, the
sick horse may shed the virus for 7 to 10 days,
and sometimes up to 28 days. Some horses that
have no symptoms and are clinically normal, can
shed the virus. Horses with the neurological form
shed much higher numbers of the virus than
aborting mares or horses with respiratory illness.

VACCINATION

There are several vaccines for immunizing
horses against EHV-1 and these are generally
recommended for horses that might be at risk.
“We are concerned about the effectiveness of
vaccines, however. They are not 100% effec-
tive,” says Cook.

“The herpes viruses are difficult to vaccinate
fully against. A great deal of research is currently
being done to see if we can develop more effec-
tive vaccines. We are beginning to understand
more about how herpes viruses work. Some of
them have ways of inhibiting immune responses.
We must develop vaccines that can overcome
some of the ways these viruses reduce the effec-
tiveness of the immune response,” he says.

Some veterinarians recommend that horses
exposed to a sick one should not be vaccinated
due to possibility of immunization-induced
exacerbation of neurological symptoms, but
this worry is controversial. “There is no conclu-
sive evidence suggesting vaccine-enhancement
of disease. However, the commercial vaccines
are ineffective in preventing development of
neurologic disease,” he says.

“The consensus about currently available
inactivated and modified live vaccines is that they
can reduce severity of respiratory disease and may
decrease the period of viral shedding. In addition,
appropriate vaccination of pregnant mares can
decrease the incidence of abortion. However,
to quote one researcher, Dr. N. Osterrieder, the
incidence of neurologic disease is “mockingly
unmitigated by vaccination” says Cook.

PREVENTION AND TREATMENT

Recommendations a few years ago by Dr.
David G. Powell, then at the Gluck Equine
Research Center, University of Kentucky, are
still pertinent and appropriate for horsemen
today. “At the race tracks, we encourage tak-
ing horses’ temperatures. A lot of people are
starting to do this, especially when there’s an
outbreak, and are taking horses’ temperatures
once a day and even twice a day if they’ve been
in contact with horses that have shown disease.
Even on an everyday basis it is a very sound
management policy to take a horse’s tempera-
ture daily. This means that whoever is taking
the horse’s temperature is around the animal
and observing it for a few minutes. They could
determine not only if it has a temperature, but
also if it is not as active as it usually is, or if it
is not eating or drinking. This is a very basic,
commonsense procedure, which could help
improve the overall standards of the health and
welfare of the horse,” according to Powell.

Isolation of horses when they come back
from a race is a good way to minimize risks
for exposing the other horses on the farm or
in the barn or shed row, in case the horse brings
back a virus. “This is a very good manage-
ment practice, but not all farms or facilities
have an isolation area. Sometimes, all you can
do is just put the horse in a stall at the far end
of the barn. A lot of breeding farms do have a
separate facility for horses coming in or coming
back, where horses are put for awhile routinely;
whether the horse goes to a sale and comes back
and has not been sold, or comes back from a
veterinary clinic. Many farms, particularly in
Kentucky, will put that horse in an isolation
barn for a period of 14 days, but not everyone
has this kind of facility.”

DEALING WITH A SICK HORSE

A horse with the neurological form of her-
pesvirus will usually be dull and uncoordinated.
“The horse doesn’t look quite right and initially
may appear to be lame,” according to Powell.
With the neurological form, the signs prog-
ress rapidly. The incoordination and lameness
develop very quickly over 48 to 72 hours. From
a clinical point of view, this will differentiate it
from a lot of other neurological conditions, like
EPM, that do not progress that quickly.

There is no specific treatment for the viral
ilness, and no drug to actually combat the
infection. “Supportive care is what we empha-
size. Based on experience, we find that if the
animal’s condition deteriorates rapidly and it
becomes recumbent, the prognosis is not as
good as if it doesn’t become recumbent. Many
of the horses that have died or been euthanized
are the ones that become recumbent quickly.
If the horse does not develop those signs, the
prognosis is much better,” he says.

Trying to keep the horse on its feet is
always a good idea, but not always easy to do.
“In some cases people have tried using slings
to support the horse, but that involves heroic
efforts and intensive care. It demands a great
deal of care. If it is possible to do that, the out-
come has sometimes been favorable, but it’s no
guarantee that the horse will recover.” 