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Neurology Is Not a Euphemism for Necropsy: A Review of Selected Neurological Diseases Affecting Horses

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1. Introduction

Disorders of the nervous system are serious and often debilitating problems affecting horses. Reference to equine neurological diseases can be found as early as 1860 when Dr. E. Mayhew described a condition of partial paralysis in *The Illustrated Horse Doctor*. Dr. Mayhew wrote that "with few exceptions a permanent neurologic gait deficit renders a horse unsuitable for use." Although this is still at least partially correct today, there would be little need to go further with today's lecture if not for the fact that much progress has been made in our understanding of how to better diagnose and treat neurological disorders affecting horses. However, our knowledge of these disorders as well as our ability to diagnose and treat the conditions remain incomplete. My goals for equine practitioners are to be able to perform a neurological examination, to arrive at a neuroanatomic localization, and to use diagnostic tests to help determine the cause of the clinical signs in the affected horse. It is important to recognize that treating horses with neurological conditions, even serious ones, can often result in successful outcomes, including useful athletic lives.

An increased level of understanding about the causes and management of equine neurological diseases during the past 30 yr has resulted in considerably less fear on the part of owners and veterinarians when faced with the statement that "your horse is ataxic." This increased awareness and knowledge about causes of ataxia in horses has made it routine for most equine veterinarians to include some level of neurological testing as part of their physical examination. One need not look too hard to identify articles on the role of the neurological examination as a part of the purchase, lameness, and even exercise evaluation in horses. There are even articles on use of force plates and videography for differentiation of lameness from neurological disease.

Possible causes of neurological diseases in horses include developmental problems, trauma, and infectious diseases. Some diseases that affect horses can also affect humans as well as other species and may have important biosecurity or zoonotic implications. Examples of these disorders include West Nile virus, equine herpes myeloencephalopathy, rabies, and other encephalidaties. Conditions such as cervical vertebral malformation, equine protozoal myeloencephalitis, and equine herpes myeloen-

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cephalopathy are very common problems facing horse owners and veterinarians. Other important problems include head and spinal cord trauma, vestibular and cerebellar disorders, seizures, behavioral abnormalities, environmental, and chemical or drug toxicities.

This Milne lecture will emphasize the importance of the neurological examination as the best tool available to the equine practitioner who is faced with a horse suffering from neurological disease. It will review how to perform the examination on a horse and discuss some examples of diseases that can result in the clinical signs that are observed. The second part of the lecture will focus on the diagnosis and treatment of three neurological disorders that have been problematic for many veterinarians: cervical vertebral stenotic myelopathy, equine protozoal encephalomyelitis, and equine herpesvirus-1 myeloencephalopathy.

2. Neurologic Examination

One very helpful and simple advancement in equine neurology was to stop calling every horse with neurological disease a "wobbler" and instead, identifying the specific disease or disorder that was responsible for the clinical signs. As it has been said, giving different things the same name may seem innocuous, but it slows progress in the field. In evaluating horses with suspected neurological disease, the most important step is to establish the neuroanatomic localization of the disease. To accomplish this, one needs to begin with a careful neurological examination. The goals of the neurological examination are to differentiate the problem from musculoskeletal disorders and to identify the neuroanatomic location of the lesion(s). After determining the location(s), further diagnostic testing and/or a course of therapy must be chosen. In addition, the examiner should take advantage of ancillary diagnostic aids for horses with neurological diseases such as examination of cerebrospinal fluid, radiography, ultrasonography, electroencephalography, electromyography, myelography, computed tomography, magnetic resonance imaging, and other techniques such as auditory and visual evoked response testing, nerve conduction velocity, and other procedures.

The neurological examination should be included as a part of the physical examination of all equine patients. Understanding neurological disease and recognizing the clinical features that result from neurological disease in horses can result in early detection of potentially serious and sometimes fatal diseases. If left untreated, many disorders of the nervous system of horses can result in permanent disability, and the eventual outcome may be euthanasia for either humane or safety reasons.

Separating neurological from musculoskeletal disease is sometimes difficult but always important when evaluating gait abnormalities of horses. Many neurological diseases result in gait deficits that are sometimes difficult to distinguish from a musculoskeletal problem, and therefore, a lameness examination should be included as part of the neurological assessment.

The signalment and history are often useful pieces of information and should be obtained before the examination whenever possible. An accurate history can sometimes help narrow the list of differential diagnoses, especially when there has been a traumatic episode or the horse has been exposed to a specific disease or toxic substance. The signalment aids the examiner, because various breeds, sexes, and ages tend to present with specific disorders. For example, young Arabians will sometimes present with an absence of the menace and blink response along with a hypermetric gait as a result of cerebellar abiotrophy,[1] whereas a young Thoroughbred or Tennessee Walking Horse with no evidence of brain, brainstem, or cranial nerve abnormalities showing symmetric ataxia most severe in the pelvic limbs may be suffering from cervical vertebral stenotic myelopathy.[2]

It is important to record all information at the time of the examination to avoid it being lost or forgotten and to be sure no part of the examination is missed. It is helpful to have a neurological examination form that follows the format for easy recording and to ensure that nothing is left out of the exam. Regardless of the form used, the most important factors are that the examiner is comfortable with it and that it is easy to complete on a routine basis.

The examiner should carefully observe all parts of the examination and be cognizant of specific signs or abnormalities in the nervous system including subtle cranial nerve deficits or asymmetries in muscle size and/or in the movement of the horse. Some horses with obscure lameness of the pelvic limbs are often difficult to distinguish from horses with spinal ataxia. This is especially difficult and often requires significant time for examination when the clinical signs are subtle or when very mild ataxia is present. When one reaches an incorrect diagnosis, it may delay the initiation of appropriate therapy. This may lead to a worse prognosis, result in the potential use of an expensive but unnecessary medication, or in the case of a purchase examination, result in an inappropriate purchase or decline of what would have been a useful animal.

The neurological examination should be performed in a systematic fashion moving from the head to the tail and is generally divided into five parts: head and neck, trunk, tail and anus (perineum), gait, and posture. The examination should begin with careful observation of the horse including behavior, mental awareness, head posture and coordination, limb position, and symmetry of the muscles of the head, neck, and body. During the observation portion of the exam, one should detect unusual head or neck positioning, abnormal behavior, head tilt or tremor, muscle fasciculations, or

excessive yawning. Included in this part of the examination is evaluation of the cranial nerves and cervicofacial reflexes.[3–5]

Head and neck posture are influenced by the cerebellar and vestibular systems. Normal alert horses hold the head and neck upright and move with smooth directed motions. Coaxing a horse to turn the head and neck in all directions can often be done by use of grain or other desirable feedstuff. Horses with cerebellar disease often show fine resting tremors of the head that become exaggerated by intentional movements. Other clinical features of cerebellar disease include lack of a menace response and failure to blink in bright light as well as walking with stiff and spastic limb movements.

The level of consciousness can be evaluated as alert, depressed (reacting inappropriately to its environment or unresponsive), stuporous (appearing sleepy until stimulated by pain, light, etc.), semicomatose, or comatose. The response of an animal to its environment is controlled by the cerebrum and brainstem. The normal horse should appear alert and responsive to external stimuli. Lesions of the cerebral hemispheres can result in comatose or semicomatose animals, whereas severe systemic illnesses can produce depression. Horses with cerebral disease may show inappropriate behavior, head pressing, or compulsive walking and circling. Recumbent horses with spinal cord disease often appear bright and alert during the early stages of the problem.

Horses with vestibular disease will have a head tilt in which the poll is deviated toward the side of the lesion. There will be weakness on this side as well as increased tone on the opposite side, which often results in circling toward the side of the lesion. The vestibular system is responsible for maintaining balance as well as dictating the animal's response to gravitational forces. An additional observation that can be made during the general portion of the neurological examination is recognition of muscle fasciculation. Muscle fasciculation can be of either myogenic or neurogenic origin. Primary muscle conditions such as myotonia and hyperkalemic periodic paralysis, metabolic disturbances such as with electrolyte disturbances, and infectious causes such as botulism can all lead to fasciculations. Neurogenic causes of muscle fasciculations include focal nerve damage, shivers, myoclonus, ear ticks, and toxicities such as white snakeroot. Yawning may also be a signal of neurological disease. A typical scenario would be a horse with hepatoencephalopathy; however, horses with hepatic encephalopathy will more commonly show signs of subtle forebrain disturbances, such as behavior changes, episodic drowsiness, constant walking, or inappropriate response to stimuli and depression.

3. Head and Neck

A complete evaluation of the cranial nerves should be completed next. Cranial nerve analysis includes evaluation of the horse's sight, hearing, swallow reflex, breathing, facial symmetry and expression, sensation, jaw tone, larynx, and pharynx. A careful cranial nerve examination can help localize a problem in horses with neurological disease along the brainstem.

Deficits of the olfactory nerve (CN I) are very rarely observed in the horse, but having the horse smell the examiner's hand (holding grain or something that would attract the horse's attention by smell) can test it to some degree.

The optic nerve (CN II) extends to the retina as a continuation of the central nervous system. The CN II courses from the eye to the optic chiasm where a significant number of the fibers cross over to the contralateral side (~80%). From the optic chiasm, the fibers travel to the pretectal nucleus in the midbrain and from there, to the edinger westphal nucleus in the brainstem that provides input to the oculomotor nerve (CN III) and ciliary ganglia. In similar fashion, evaluation of visual perception is often tested by menace response. It requires input starting at the retina and moving from the CN II to the optic chiasm where it crosses over and continues along the optic tract to the lateral geniculate nucleus in the midbrain. From this point, information follows the optic radiation along the brainstem to the occipital cortex. The fibers seem to course from the brainstem through tracts in the cerebellum to the occipital cortex of the brain. Horses with cerebellar abiotrophy fail to blink in bright light and do not have a menace response. Evaluation of vision is very important, and to do so, one can place the horse in a maze or strange environment and observe its activity. Other tests that are helpful in evaluating vision include evaluation of menace response, pupil size, position, and pupillary light response (PLR). The menace response can be evaluated by making a menacing gesture toward the eye and observing a blink and the horse moving the head away from the examiner. It is important to avoid touching the eye or generating excessive air currents while performing this test. The blink response relies on both cranial nerves II and VII for a normal response.

The PLR provides information about cranial nerves II and III. The pupil is under the control of the CN III. Parasympathetic fibers in this nerve are responsible for pupil constriction, whereas the opposing pupillary dilation is under the influence of the sympathetic nervous system. When evaluating the pupils, one should initially examine for size and symmetry. When pupils of unequal size (anisocoria) are recognized, it is important to determine the one with the abnormality. If an animal is placed in dark light and one pupil fails to dilate, this is an indication of damage to the sympathetic system.

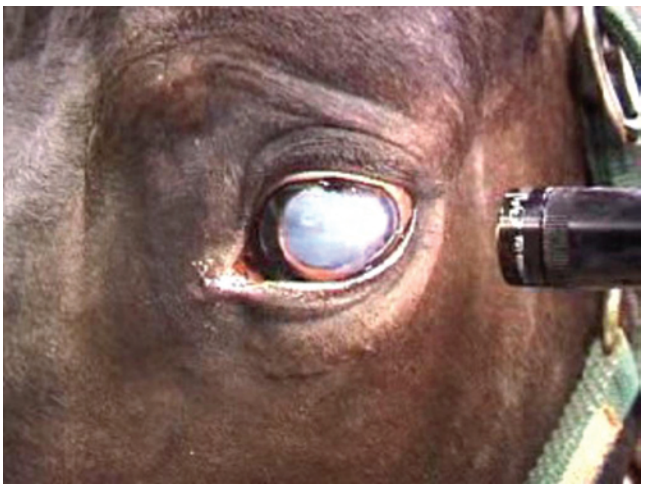

Fig. 1. The horse pictured has absolutely no PLR response in this eye. Loss of the PLR occurred ~2 wk after a traumatic head injury.

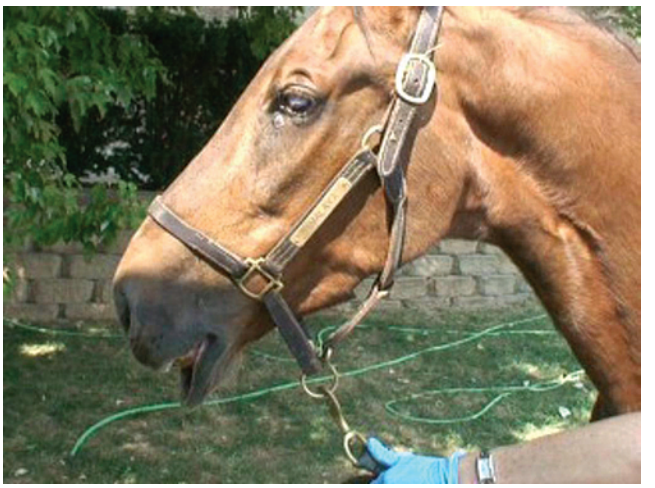

Fig. 2. The horse pictured has signs consistent with damage to CN V: both severe atrophy of masseter musculature and dropped jaw. The mare also exhibits loss of CN VII function, because she is unable to blink her left eyelid or produce adequate tears.

When the animal is placed in bright light, the pupil that fails to constrict is indicative of damage to the oculomotor nerve. It is important to use a bright light when evaluating pupillary response (Fig. 1). When a bright light is initially shined into a normal eye, the animal will blink; this is referred to as a dazzle response. When bright light is directed into one eye, constriction of the ipsilateral (direct PLR) as well as the contralateral pupil (consensual PLR) is observed in normal horses. It is often difficult to observe the consensual response, and therefore, a swinging light test has been described.[5] In the direct PLR, light is directed into one eye and travels along the CN II to the optic chiasm where crossing occurs. From here, the impulse follows the optic tract to the pretectal nucleus in the midbrain and then to the oculomotor nucleus. The signal is sent along the CN III to the ciliary ganglion and pupil where constriction occurs. The indirect PLR is a result of crossing of the fibers between the eye to the optic cortex. In most large animal species, ~90% of the fibers cross over. Thus, lesions of the eye or CN II often result with an abnormal light response of the pupil, whereas lesions along the optic tract present as blindness in both eyes.

Evaluation of normal vestibular nystagmus provides information about cranial nerves III, IV, and VI as well as the vestibular system. A normal response evaluates the extraocular muscles as well as the connections along the medial longitudinal fasciculus in the brainstem. Clinical features that result from damage to the oculomotor (CN III), trochlear (CN IV), or abducent (CN VI) nerves are strabismus, an abnormal positioning of the eye within the orbit, and enopthalamus.

The trigeminal nerve (CN V) contains both motor and sensory fibers. Clinical features associated with damage or abnormalities of this nerve may include decreased sensation to the skin and mucous membranes of the head and atrophy of the masseter muscle (Fig. 2). Sensory function can be evaluated by palpation of the ears and eyelids as well as local response along the face and inside the nares. Most normal horses respond with a flick of the ear, blink, or dilation of the nostril along with a cerebral response. Loss of innervation to the masseter muscles will cause a dropping of the jaw and drooling of saliva.

Damage to the facial nerve (CN VII) and vestibulocochlear nerve (CN VIII) are two of the most commonly recognized abnormalities of the cranial nerves seen in horses. Injury to these nerves may result from head trauma or infection (protozoal, fungal, or bacterial) or can be associated with temporohyoid osteoarthropathy. CN VII contains branches to the ears, eyelids, and muzzle. Unilateral damage to the seventh cranial nerve will result in deviation of the muzzle to the unaffected side as well as an inability to blink the eyelid and deviation of the ear (Fig. 3). This nerve contains parasympathetic fibers that control part of the tear production; thus, injury to this nerve results in a lack of ability to blink along with a loss of normal tear production in the affected eye. The salivary and lachrymal glands may also be affected on the damaged side, which causes a drying of the eye and mouth. Subtle paresis can be identified by observing the lips during eating and the nostrils during inspiration.

Hearing and balance are controlled by the CN VIII. Horses with lesions of this nerve will present with a head tilt toward the affected side along with atypical positioning of the limbs and eyes and nystagmus with the fast phase directed away from the side of the lesion (Fig. 4). A head tilt needs to be differentiated from abnormalities of head turning/

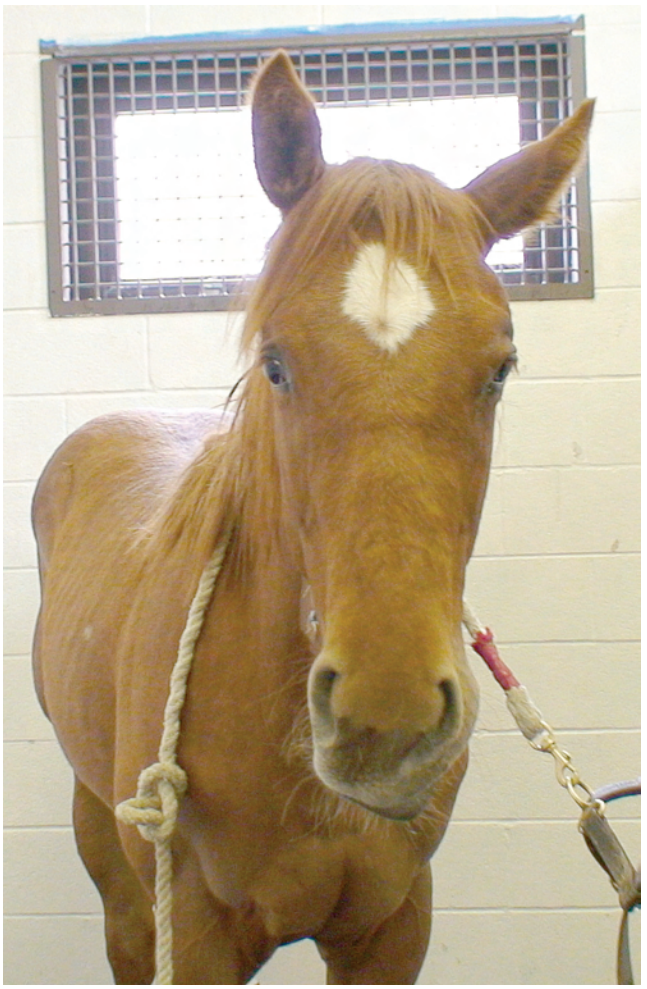

Fig. 3. The yearling pictured has a right-sided muzzle deviation, drooping of the left ear, and ptosis of the left eyelid. These changes are indicative of damage to the left CN VII with subsequent muzzle deviation toward the unaffected side.

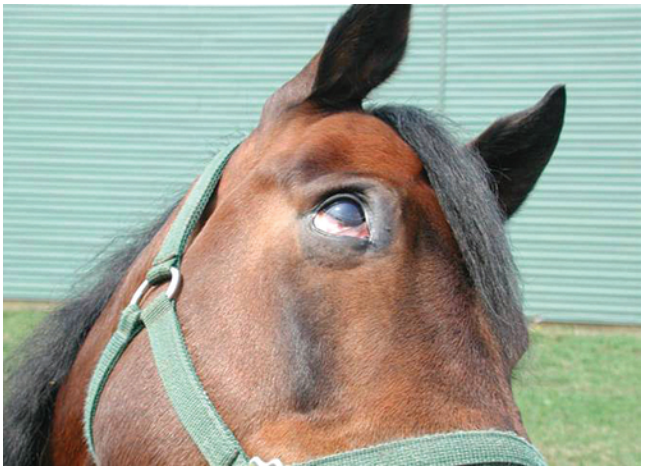

Fig. 4. Head tilt and strabismus. The colt pictured suffered acute head trauma with a basilar skull fracture.

posturing, because fractures or malformation of the cervical vertebrae and damage to dorsal gray columns have been reported with aberrant parasite migration.[6] Central damage to the vestibular nucleus will cause the nystagmus to be irregular and dependent on the positioning of the head. With central vestibular disease, the horses will often have gait deficits of ipsilateral weakness and contralateral hyperextension.

Laryngeal and pharyngeal paralysis can be caused by lesions located in the glossopharyngeal (CN IX), vagus (CN X), or spinal accessory (CN XI) nerves that originate in the medulla. These nerves contain both motor and sensory fibers for the pharynx, larynx, and esophagus. Damage to these nerves may occur as a result of guttural pouch disease or injury, temporohyoid osteopathy, protozoal infection of the brainstem, or secondary to head trauma. A horse with guttural pouch disease may present with dysphagia because of involvement of the peripheral nerves. However, dysphagia can also be seen in conditions such as rabies, yellow star thistle toxicity, or even botulism. Laryngeal paralysis will present as a horse making upper respiratory noise. Pharyngeal paralysis will present as a horse with difficulty swallowing food, water, or a stomach tube. Food or water may also be seen coming out of the nose. Endoscopic evaluation of the guttural pouches provides a means for examination of the peripheral portion of these cranial nerves. In addition, one can visualize the upper airway function as well as other structures in the pharynx by use of an endoscope. While visualizing structures in the pharynx, water can be squirted onto the structures to visualize swallowing. In addition, the performance of a slap test with the endoscope in place allows direct visualization of the adduction of the arytenoid cartilages.

Loss of motor function to the tongue indicates damage to CN XII. Evaluation of this nerve can be aided by direct visualization of the tongue. In addition, grasping the tongue and trying to pull it out of the horse's mouth will usually cause the animal to retract its tongue. The horse should resist its tongue being pulled out. This checks for lesions of the hypoglossal nerve (CN XII).

If the horse presents with a raised temperature of the face, asymmetric facial sweating, congestion of the nasal and conjunctival membranes, prolapsing third eyelid, or irregularly responding pupils, then Horner's syndrome should be considered (Fig. 5). This disease may be from a severe guttural pouch infection, cervical lesions, a perivascular injection, or damage (possibly from a tumor) to the vagosympathetic trunk that supplies the sympathetic innervation for the eye and blood vessels of the head.

Several reflexes may be helpful to localize a lesion, including the local cervical and cervicofacial responses. When pressure is applied with a sharp object along the side of the neck down to the level of about the third cervical vertebrae, there is a re-

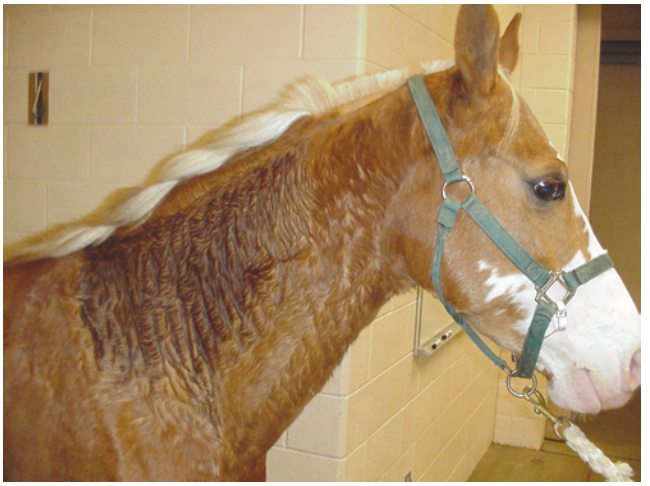

Fig. 5. This horse shows the localized sweating pattern associated with Horner's syndrome. It is often accompanied by unilateral ptosis, miosis, enophthalmos, and protrusion of the nictitans.

sponse in which a smile is initiated in the corner of the mouth on the affected side. Caudal to this level, there is a local response of the skin and muscles along the side of the neck. Abnormalities of these reflexes have been noted in horses with cervical spinal cord disease.[7]

4. Trunk

Beyond the level of the cervical vertebrae, one can evaluate the cutaneous trunci reflex. Pressure applied with either the thumb or an instrument to the skin on the side of the body locally sends an afferent impulse to the spinal cord where it ascends in tracts to the brainstem. Then, the efferent or motor response (contracture of the cutaneous trunci muscles) occurs along the entire side of the body. One should look for muscle asymmetry and decreased responses caudally along the body. The finding of muscle asymmetry is an indication of either primary muscle damage or damage to the lower motor neuron portion of the nervous system, because nerves are an trophic influence on muscle and loss of nerve supply results in muscle atrophy. Muscle atrophy is typically seen in horses with peripheral nerve injury and can sometimes be seen in horses with equine protozoal myeloencephalitis (Figs. 6 and 7).

5. Tail and Anus

Having reached the tail and anus, the tail position should be noted. Normally, a horse will carry its tail straight down, and it should have a free range of movement. Stimulation of the anus should cause the anal sphincter and tail to clamp down. Damage to the sacrococcygeal spinal cord segments can result in loss of the normal response of tail and anal tone as well as loss of sensation in the region of the perineum. In some horses, damage to these nerves may also result in urinary or fecal incontinence.

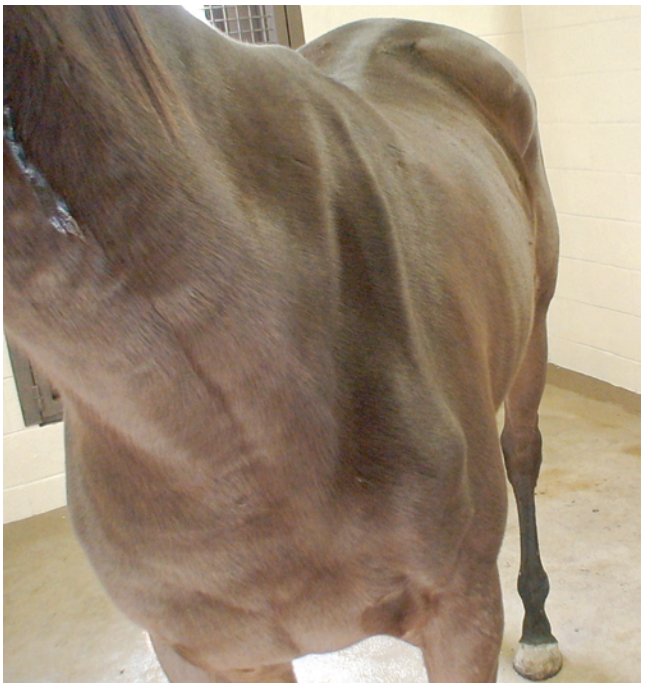

Fig. 6. Sweeney. The muscle atrophy over this horse's shoulder indicates damage to the suprascapular nerve. Although easy to identify in this chronic state, an acute case can be difficult to discern because of trauma-related swelling. Often, damage to the suprascapular nerve will also cause a gait deficit of outward "bowing" of the shoulder.

6. Gait

Lameness is the most common gait abnormality in horses of all ages. However, ataxia associated with neurological diseases, especially spinal cord diseases, is also a common cause of gait deficits in horses. Differentiating between mild pelvic limb lameness and subtle ataxia is often a difficult task. Most often, ataxia in horses is the result of spinal cord disease, usually involving the cervical spinal cord; thus, clinical signs are most apparent in the pelvic limbs. As a result of the difficulty in distinguishing between some musculoskeletal and neurological conditions, owners and horse are subject to extensive testing that can be both very expensive and time consuming. One difficulty when evaluating horses for spinal ataxia is establishment of a scoring system that is accurate and not affected by observer bias. The scoring system used by most examiners was established by Mayhew[5] in the mid-1970s, and some modifications have been made. Attempts to establish a more objective scoring system have been described.[8,9] Although the initial publications show that an objective system to evaluate the degree of ataxia in a given horse can be accomplished at this time, the methodology for performing these procedures would require application of force plate and/or videography equipment. The benefit of these procedures would be to provide an

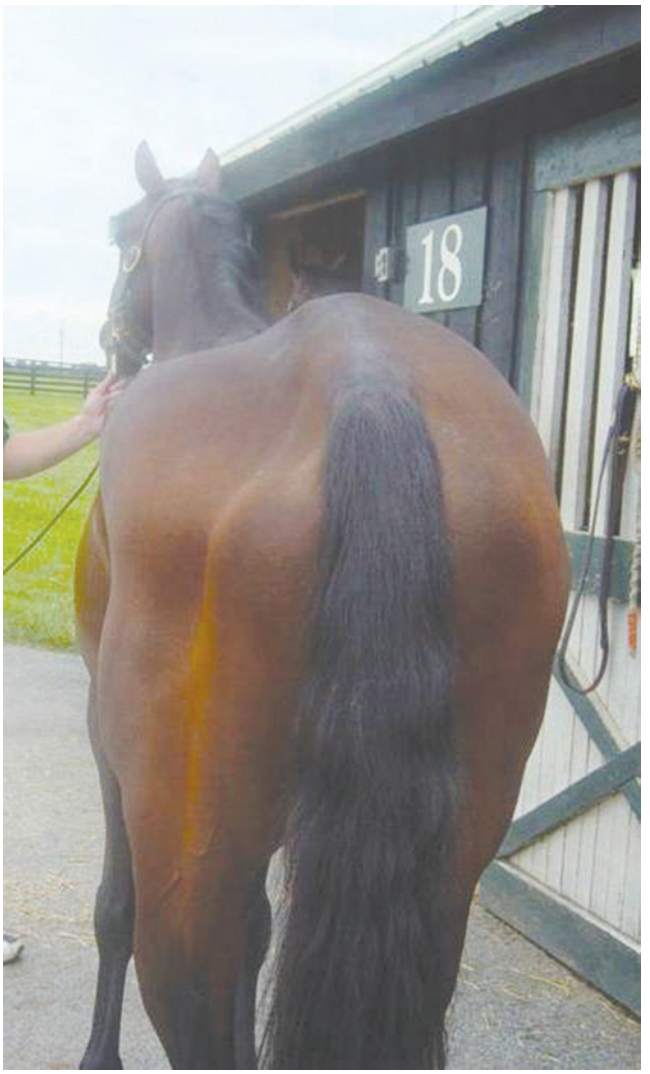

Fig. 7. This horse shows severe unilateral pelvic muscle atrophy. This is consistent with a lumbar spinal cord lesion or multi-focal lesion such as EPM.

accurate diagnostic tool to differentiate hindlimb lameness from ataxia.

The Mayhew scale ranges from 0 to 4 with grade 0 being normal and grade 4 being a horse that falls or nearly falls at normal gaits. Grade 5 has been used to describe a recumbent horse. A grade 1 abnormality will involve very subtle gait abnormalities that may be slightly more distinguishable when the head is elevated. Grade 2 deficits are moderate abnormalities that can be noted at a walk by most observers. Grade 3 deficits are easily recognizable and are much worse when the animal is negotiating obstacles or when its head is elevated. A horse with grade 4 deficits is very easily diagnosed, because the horse will fall or very nearly fall when negotiating normal gaits and activities. Evaluation of gait is very important for distinguishing musculoskeletal diseases from neurological diseases. A helpful difference is that a horse exhibiting musculoskeletal deficits will be consistent in its mistakes, whereas neurological deficits should be fairly irregular.

The animal should be examined for ataxia, paresis, spasticity, and hypermetria. Ataxia (a proprioceptive abnormality) will be exhibited by an increased swaying of the trunk while in motion, a prolonged pelvic limb stride, a waving of the limbs in the air before placement, abduction and crossing of the limbs under the body, and stepping on the opposite limbs. Ataxia is often accompanied by pacing, which produces a pronounced truncal sway caused by the limbs on the same side of the body hitting the ground at the same time. It is often indicative of a neurologic disease, except in selected breeds. Ataxic horse also often circumduct the outside pelvic limbs when walking in small circles. Circumduction is a circular movement of the limb and can be observed in any limb. It may sometimes be noted while going forward and backward, although it is most obvious when the horse is moving in a small circle. Horses with paresis or weakness will knuckle, stumble, drag their limbs, drop their trunk when bearing weight, and have a lower arc length when walking. Spasticity is seen as a stiff, short stride and a lack of joint flexion, whereas hypermetria is exaggerated joint flexion. When the horse is observed in motion, the examiner should evaluate each limb individually.

Gait evaluation includes observing the horse at a walk and then a trot. It is helpful for the observer to walk along beside the horse to get a better idea of its hoof placement and stride length. Additional obstacles and tests can be included, such as walking the horse over inclinations or curbs, walking the horse with its head elevated, and walking the horse with its head elevated over the obstacles.

Backing the horse and circling it can also produce important information. A normal horse should place its feet down in a coordinated fashion, whereas a neurological horse will often back into a base-wide position or may be very reluctant to move. When circling, the horse should be started in wide, slowly tightening circles until the horse is almost pivoting around the handler. Circumduction of the limbs will be exaggerated.

Crossing the animal's limbs will aid the examiner in determining if the animal is capable of realizing where its limbs are (conscious proprioception) and if the animal is able to move them back to the normal position in a timely fashion. Holding one of the horse's limbs in the air and forcing it to hop on the opposite limb is also a good check of the animal's awareness and balance (Fig. 8).

Two easy tests to perform to check the animal's strength and stability are the sway test and the tail pull. The sway test is performed with the animal at rest. The examiner should push on the horse at various locations on its body. The normal horse will respond to the pressure by pushing back on the examiner and keeping its balance. Eventually,

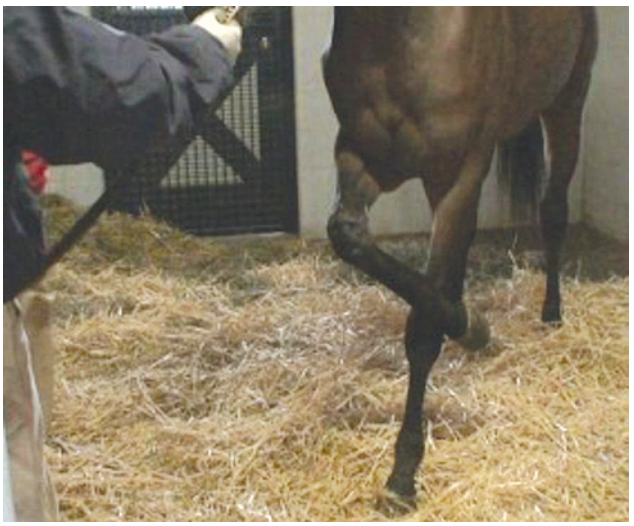

Fig. 8. Proprioceptive deficits. The horse pictured both allowed crossing of her thoracic limbs and had difficulty uncrossing the limbs. This is consistent with decreased conscious proprioception.

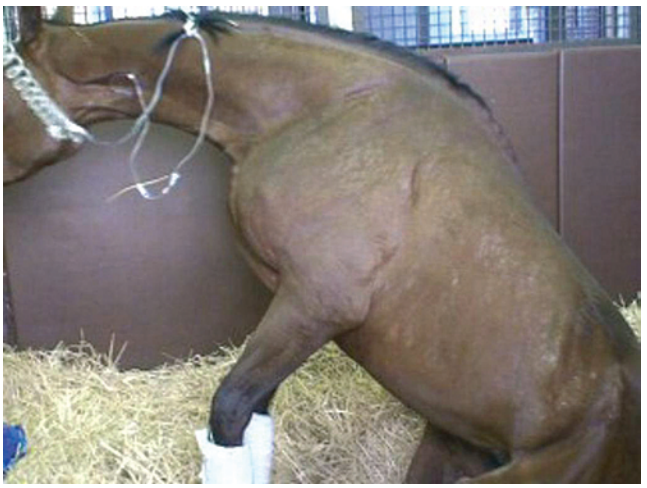

Fig. 10. "Dog sitting." This horse was able to reach this position with encouragement but unable to stand unassisted. This is consistent with a lesion caudal to T_2.

with continuous pressure, the horse will take a step with the opposite limb.

The tail pull should be performed while the animal is in motion. The examiner should walk alongside the horse and pull its tail at various times during the horse's stride. It should respond by resisting the pull and maintaining its balance. One other technique for testing strength is to apply pressure on the back and sacral muscles. The horse should respond by flexing its back upward against the pressure, but a horse with weakness in the pelvic limbs may be unable to endure the pressure (Fig. 9).

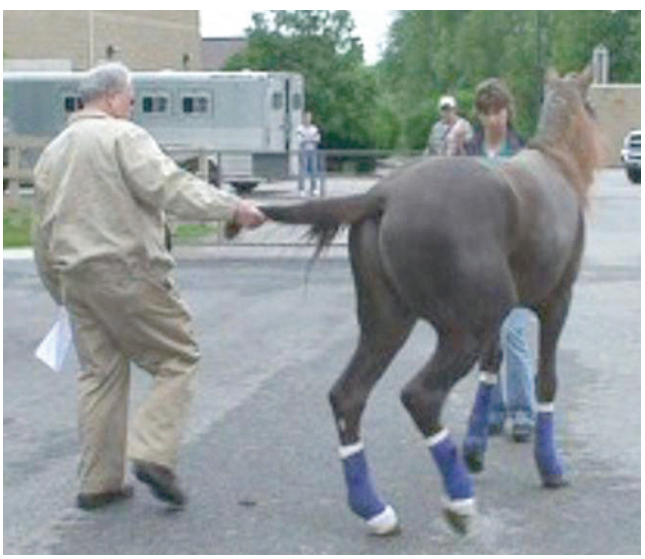

Fig. 9. This photo shows a "tail pull" to evaluate the patient for pelvic limb weakness. If tolerated, the horse should be tested bilaterally as well as at the halt and walk.

7. Anatomic Localization

After conclusion of the neurological examination and grading of the gait deficits, the examiner needs to be able to use the findings to determine whether or not a lesion is present and if so, where the lesion is located.

Localizing the lesion is the primary goal of the examination. If the horse exhibits no signs of brain, brainstem, or cranial nerve abnormalities, the lesion must be caudal to the foramen magnum. If the horse exhibits signs of proprioceptive and gait abnormalities in all four limbs, the lesion is most likely located within the cervical spinal cord. Gait deficits involving only the pelvic limbs indicate the lesion is caudal to the second thoracic vertebra (Fig. 10). Weakness or focal muscle atrophy along with areas of sensory loss indicates either focal peripheral nerve damage, generalized lower motor neuron disease, or polyneuritis equi. Some musculoskeletal diseases can be difficult to distinguish from a neurological disease. If a question exists as to whether or not the problem is musculoskeletal or neurological in nature, nerve blocks with subsequent re-examination or response to treatment with anti-inflammatory drugs are two routes that may help to make that determination.

After localization of the lesion, it is important to explain the findings to the owner and to recommend appropriate diagnostic procedures to help determine the underlying cause of the clinical signs. It is important to consider the owner's intended use of the animal when discussing the prognosis. It is helpful to explain to owners that many horses are able to continue to perform their activities with grade 1 or 2 neurologic deficits and that broodmares and stallions can often maintain the ability to function as useful breeding animals even with deficits of a grade 3. However, when a horse that has grade 3 neuro-

logic gait deficits is able to perform, clients sometimes have difficulty believing that a problem is present. This can lead to increased risk for the rider and handlers and often results in increased expense for the owner as a result of poor performance or later treatment costs. Furthermore, the examiner must also keep in mind that the anatomic diagnosis provides only the location of the lesion and narrows the differential diagnosis list. Thus, a diagnostic plan to pursue the specific cause of the neurological disease should be agreed on.

8. Cervical Vertebral Stenotic Myelopathy

Cervical vertebral malformation is often referred to by many names including cervical vertebral stenotic myelopathy, spinal ataxia, cervical stenotic myelopathy, and "wobbler's" syndrome. Cervical vertebral malformation is one of the most common causes of neurologic disease in horses worldwide. The most important feature of this condition is a narrowed or stenotic vertebral canal as a result of abnormal vertebral development. This results in compression of the spinal cord. Typically, the narrowing is identified between the third and seventh cervical vertebra, although it can occur at any site from C1 to T2. The disorder seems to be a multifactorial disease, although the underlying cause is not fully known. At this time, the problem is thought to be a developmental disorder that begins very early in life, perhaps even in utero.[10] It is more prevalent in young male horses, especially among Thoroughbred and Quarter Horse breeds.[2]

Stenosis of the vertebral canal may result from abnormal bone development, vertebral instability, degenerative changes, or soft tissue hypertrophy within the vertebral canal, which leads to a narrowed canal and injury to the spinal cord. The pathogenesis of this syndrome is not fully understood; however, there seems to be a role of genetics (multiple allele mode of inheritance) predisposing the horse to have a narrow spinal canal, and the problem can then be aggravated by other environmental factors such as diet, rate of growth, and gender. Trauma may speed up the appearance of the clinical signs, but when this occurs, the problem is a pre-existing one.

Many investigators have suggested osteochondrosis of the cervical vertebrae as contributing to or as the sole underlying problem in this disease process.[4,10–12] Osteochondrosis is described as a disturbance in endochondral ossification in rapidly growing animal species and humans (Fig. 11). Many factors have been suspected to play a role in the development of this condition in the appendicular as well as the axial skeleton of the horse. Included among these factors are genetic predisposition, endocrine dysfunction, dietary or nutritional imbalances, biomechanical stress, and rate of growth. The underlying abnormalities associated with osteochondrosis result in abnormal bone metabolism as well as damage to cartilage.

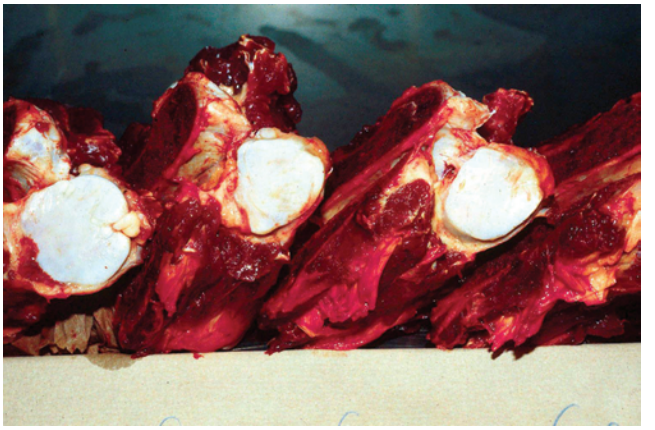

Fig. 11. The specimen pictured shows an osteochondrosis lesion of the vertebral facet in a young horse. The lesion is best seen in the left-most facet.

One dietary feature of interest is the effect of copper supplementation on the prevalence of cartilage lesions in foals. Several investigations compared farms with apparent high incidence of developmental orthopedic disease in foals to farms that did not have similar problems. From this survey of farms in central Kentucky, a difference in the dietary levels of copper was identified.[13] This information was used as the basis of several prospective research projects on the role of dietary copper on cartilage lesions in foals. In this experiment, 21 mares were divided into two groups and fed rations containing 13 parts per million (ppm) of copper (control) or 32 ppm of copper (supplemented) in the diet during the last 3–6 mo of gestation and the first 3 mo of lactation. The foals were fed pelleted concentrate containing 15 ppm (control) or 55 ppm (supplemented) copper. At 90 days of life, five control and five supplemented foals were euthanized, and at 180 days, six control and five supplemented foals were euthanized. In the post-mortem examinations of the foals euthanized at 90 days, more than twice as many osteochondrosis lesions and more than four times as many articular lesions of osteophyte formation or thinning were identified in the copper control versus the copper supplemented group. Interestingly, in the foals euthanized at 90 days, the predominant cause for the difference was the presence of many lesions in one control foal.

In the foals euthanized at 180 days of life, there were seven times more articular lesions of osteophyte formation or thinning, twice as many osteochondrosis lesions in the physis, and more than five times as many osteochondrosis lesions in the articular-epiphyseal complex in the six foals on the low copper diet. In many of the foals with osteochondrosis of the articular-epiphyseal complex, there was separation of the thickened cartilage from the subchondral bone, including nine foals showing subchondral fibrosis. The work from this study was

very significant, because it resulted in further investigation regarding the role of nutrition in developmental problems of cartilage and bone in foals. The work was examined and critiqued by many veterinarians, nutritionists, and biochemists, and it led to changes in the way that horses are fed today.[14]

After the nutritional investigations of Knight et al.,[13,14] application of this information to the investigation of examples of developmental bone disease was performed. The first study at The Ohio State University examined the frequency and severity of osteochondrosis in horses with cervical vertebral stenotic myelopathy. The most significant finding of the work by Stewart et al.[12] in 1991 was the identification of a generalized narrowing of the vertebral canal of horses with cervical vertebral stenotic myelopathy compared with clinically normal horses. This finding corroborated the work of several other investigators.[4,15,16] The finding of a smaller minimum sagittal diameter throughout the vertebral canal rather than only at the site of compression indicates that this problem is related to a general failure of vertebral canal development and is not simply a focal malformation caused by arthritis or some biomechanical disorder. Therefore, in any horse with a narrow vertebral canal, development of arthritic changes of the articular processes or abnormalities of the growth plates of the vertebral bodies may lead to further stenosis and additionally, may contribute to the onset of clinical signs.[12] Subsequent to the work of Mayhew[5] and Stewart et al.[12], many investigators have sought to understand the underlying pathology.

Stewart et al.[12] found that both osteochondrosis and non-osteochondrosis lesions were more severe at sites of compression than at sites of non-compression, although compression was also identified at sites with no lesions of the articular processes. In this study, an increased frequency and severity of osteochondrosis was noted in the appendicular skeleton of horses affected with cervical vertebral stenotic myelopathy. An increased severity of osteochondrosis of the cervical vertebrae was noted over the control group, yet the incidence of non-osteochondrosis lesions was equal between control and affected groups. These findings support the notion that the underlying problem in horses affected with cervical vertebral stenotic myelopathy is a failure of normal bone and cartilage development and maturation.

In some horses, the site of spinal cord compression is at a location different from where osteochondrosis lesions occur, although these lesions are more severe on articular processes (facets) at sites of compression than at non-compressed sites. It is noted that compression was also observed at sites with no articular process lesions. This work indicates that osteochondrosis dissecans (OCD) does not directly cause cervical vertebral stenotic myelopathy. However, the work of Stewart et al.[12] strongly suggests that OCD, cervical stenotic myelopathy (CSM), and spinal-canal stenosis may all be manifestations of an underlying inability to develop normal bone and cartilage in these horses.

Horses with cervical vertebral malformation (CVM) will present with symmetric ataxia, paresis, and spasticity that is delegated almost entirely to the hindlimbs. Toe dragging, stumbling, and circumduction of the hindlimbs will also be apparent. These signs tend to be exaggerated when the horse moves with its head elevated. The horse may also stand base wide when at rest. Clinical signs in horses are often observed in the first year of life and may sometimes be identified as early as before 3 mo of age.[10,12,17–19] The onset of clinical signs often appears quite acute, despite the fact that the signs may have been present and slowly progressing for several months. In some horses, the onset may follow a traumatic episode or a day of very hard playing while turned out. CVM manifests itself as both a loss of awareness of the limbs along with weakness and ataxia while walking.

The most valuable test to diagnose cervical vertebral malformation is to identify stenosis of the vertebral canal. Lateral views of the cervical vertebral column are often an informative ancillary diagnostic test when searching for a compressive site or lesion. Lateral views can be performed without the need for anesthetics, unless one has a very unruly animal.

The horse should be positioned with the head and neck in its natural position with the cassette on one side and the X-ray tube centered on the cassette on the other side of the horse. For recumbent horses, pads and wedges should be placed under the animal's neck and head for the cervical spine to be parallel to the ground. Placing the cassettes under the recumbent horse's neck may be difficult unless a bucky tray is used. A three-image series is generally adequate to image the entire cervical spine. The most cranial radiographs should be made with the tube centered on C_1-C_2, centered on C_4 for the middle radiograph, and on C_6 for the most caudal radiograph. These views will provide some overlapping. Lead markers on the neck can be useful to assist the viewer with the exact location of the radiograph. With experience, the viewer will become familiar with the anatomy and will readily identify the location based on anatomic features such as the size of dorsal spine, the size and shape of the facets, or the length of the vertebral body.

When viewing the radiographic images, changes in vertebral body appearances should be closely examined. The normal equine vertebral canal in the cervical region should have a gentle curve. The spinal canal should be smooth with only the slightest changes at each intervertebral space. Normal articular processes (facets) should have joint spaces with smooth, rounded articular surfaces. One should look for irregular joint spaces, a lack of joint space, irregular surfaces, and decreased widths of the vertebral canal when searching for stenosis or other abnormalities of the vertebral canal. Flaring

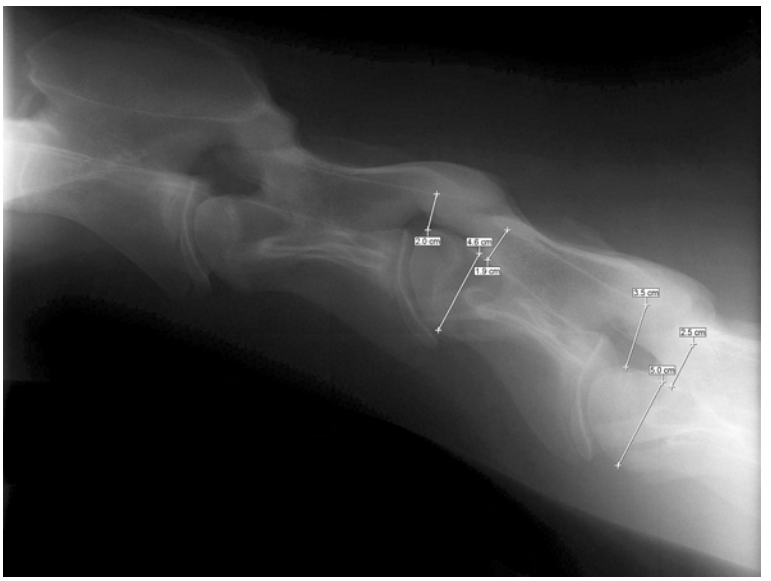

Fig. 12. Standing cervical spinal radiographs. This horse displays cervical canal stenosis suggestive of CVSM. The C_3-C_4 site is less than adequate in width based on the sagittal ratio.

of the caudal epiphyses, dorsal laminar extension, subluxation, degenerative joint disease, and abnormal ossification of the articular processes are all characteristic of CVM[2,4,17,20] (Figs. 12 and 13). However, identification of these findings alone may not be adequate to diagnose the exact location of spinal cord compression, and a myelogram may be required. The most important factor in the diagnosis of cervical vertebral stenotic myelopathy is the identification of cervical vertebral canal stenosis.[20–22] Objective testing is much more dependable than qualitative evaluation, and the sagittal ratio method should be used. Myelography is required to confirm the exact site for surgical intervention in horses diagnosed with cervical vertebral stenotic myelopathy.

Collection of cerebrospinal fluid (CSF) can sometimes be a useful diagnostic aid to determine the cause of ataxia in horses. Cerebrospinal fluid analysis is particularly helpful if the disease is suspected to be either inflammatory or infectious. However, it is important to remember that identification of normal cerebrospinal fluid does not necessarily negate any possibility of neurological disease and that it should be used as supportive evidence along with other findings and history.

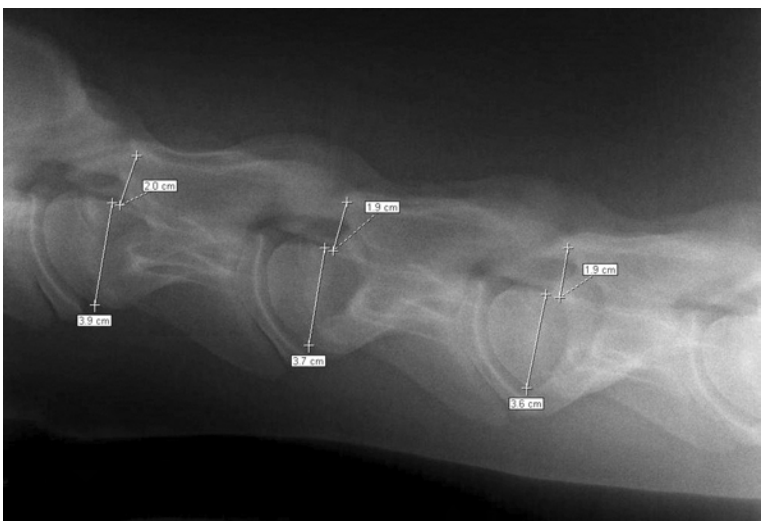

Fig. 13. Standing cervical spinal radiographs. The foal imaged here showed mild ataxia and proprioceptive deficits. Based on stenosis of the vertebral canal, the horse was managed conservatively with nutrition and limited exercise.

Cerebrospinal fluid is a clear, colorless fluid contained within the brain ventricular system, the central canal of the spinal cord, and the subarachnoid space. The majority of cerebrospinal fluid is produced by the ependymal lining of the ventricles and from the choroid plexus. A small amount of CSF is produced by brain and spinal cord blood vessels and leptomeninges. The CSF flows caudally to the subarachnoid space to bathe the cerebral hemispheres and the spinal cord. It is absorbed by microvilli located in the venous sinuses, collections of which are called arachnoid granulations. CSF is produced at a constant rate that is independent of the absorption rate by the venous sinuses. Because the production rate is constant and independent of intracranial pressure, the rate of absorption is the primary regulator of intracranial pressure.[23]

CSF functions to suspend and help nourish the brain and spinal cord, and it provides a degree of physical protection. It helps maintain the appropriate ionic and pH environment for the CNS and aids in regulation of the intracranial pressures.[23] Collection of spinal fluid is most likely to reflect the presence of a lesion when collected from a site nearest the lesion in the nervous system. If a lesion is suspected cranial to the second cervical vertebra, then CSF should be collected at the atlanto-occipital location. If a lesion is suspected caudal to C_2, then CSF should be collected at the lumbosacral space. If the neuroanatomic location of the lesion is unknown, collecting fluid from both sites and comparing their values may help. In most clinical cases, CSF is collected from the lumbosacral space, because it can be done on an awake, standing animal.[5]

Collection of spinal fluid from a sedated horse can be performed stall side in most cases. The procedure begins by identifying the landmarks for collection from the lumbosacral space on the horse and then clipping and scrubbing this site with the horse either unsedated or only very lightly sedated. The landmarks for the lumbosacral site include a depression on the midline above the lumbosacral space. This space is bordered by the cranial edge of the spine of S_2, the cranial edges of the left and right tuber sacrale, the caudal edge of the spine of L_6, and the caudal borders of the left and right tuber coxae. The site is blocked using lidocaine through a 20-gauge, 1- or 1.5-in needle. After the lidocaine has been instilled, the site is given a final sterile scrub, and at this time, the horse is sedated using either xylazine or detomidine. It has been my experience that if the horse is sedated for a prolonged period or if the horse is sedated too heavily, the head is difficult to elevate. As a result, the CSF pressure at the lumbosacral site is very low, which makes fluid collection difficult. Additionally, administering only a small volume of sedation very near the time of the procedure results in a greater likelihood that the horse will stand squarely, which facilitates palpation of the landmarks and makes it easier to locate the proper space. In some horses, the use of stocks and a nose twitch may help the handler in keeping the horse from moving.

The procedure should be performed in a sterile fashion using a 6-in, 18-gauge spinal needle advanced directly along the median plane. Reaching the subarachnoid space takes ~5 in. A distinct pop is often noted as one enters the lumbosacral space. This is often accompanied by the horse lifting the tail or mildly shifting its weight from one hindlimb to the other. However, if this is not felt, the needle can be slowly advanced until it hits the floor of the canal and then slightly withdrawn.

As one advances the needle, the arms and sometimes hands should rest comfortably on the animals back to insure the steadiness of the needle as it slowly advances. When checking to be sure one is in the correct location, the stylet can be removed, and a 5-ml syringe can be used to apply gentle suction if no CSF readily appears before trying again. Whenever advancing the needle, the stylet should be back in place. Sometimes, rotating the needle a small amount can be helpful to initiate the flow of CSF.

If the CSF is slightly pinkish, it is usually caused by a traumatic tap and should clear if allowed to flow or within 1–2 ml of aspirate. If contaminated with blood, the sample may not be suitable for performance of all testing, especially if examining for antibodies against a pathogen such as *Sarcocystis neurona*. Xanthochromic CSF may occasionally be collected from a horse that has elevated protein levels, that has had a recent hemorrhage, or that is infected with equine herpes virus (EHV)-1 myeloencephalopathy.[23,24] Cytologic counts should be performed to determine the cell type and number along with the quantification of the protein concentration.

CSF taps should be analyzed for normal values of total protein content, red and white blood cell counts, creatine kinase, glucose, and antibodies against *S. neurona* (protein = 10–120 mg/dl; red blood cells = 0; white blood cells = 0–5; and creatine kinase = 0–8 IU). Glucose levels normally range between 55 and 70 mg/dl or between 35% and 75% of the plasma levels, and creatine phosphokinase is normally <8 IU/dl.[25] Low glucose levels in CSF can be a result of several reasons, although the most common is associated with bacterial meningitis. Another change often observed with bacterial meningitis, Eastern Equine Encephalitis (EEE), head trauma, and brain abscessation is an increased level of lactic acid in CSF. One should always compare the results with the standard normal values of the specific laboratory running the CSF sample.

Protein levels can be increased for a variety of reasons. In horses with equine protozoal myeloencephalitis (EPM) or a parasitic infection, the protein may be increased by >70 mg/dl. Rabies virus and Western Equine Encephalomyelitis (WEE) produce a marked increase in small mononuclear cells. Acute CVM, a deep cerebral abscess, or vertebral osteomyelitis causes xanthochromia and increased protein lev-

els with the presence of a few mononuclear cells. The acute phase of EEE causes high levels of neutrophils with increases in protein content. Increased neutrophils can also be seen in horses with serous inflammations, and eosinophils are seen in rare situations of very severe inflammation or parasitism.[25]

Myelography is useful to confirm the diagnoses of cervical stenotic myelopathy and to determine the location of the lesion(s). This procedure is especially important when surgical intervention is anticipated. In my opinion, the performance of a myelogram on a horse is a safe procedure that can be used on even the most severely ataxic horses. Although this procedure is typically performed with the horse under general anesthesia, there have been at least two descriptions of the procedure in awake, sedated horses.[26,27] The procedure involves the performance of either an atlanto-occipital or lumbosacral CSF tap. Before anesthetizing a horse for a myelogram, a complete physical and neurological examination should be completed as well as an evaluation of standing radiographs of the cervical and occasionally, thoracic and lumbar vertebral column. Although some horses may transiently worsen after a myelogram because of manipulation of the cervical vertebral column while performing the study, in my experience (>1500 myelograms), it is rare for a horse to be unable to recover after this procedure. Whenever possible, it is best to avoid performing this procedure on horses with inflammatory or infectious causes of neurologic disease, and if a severe compression is suspected based on the findings observed on the standing radiographs, then minimal manipulation of the vertebral column and spinal cord are indicated.

In an effort to reduce the inflammatory changes associated with injection of a contrast agent along with manipulation of the vertebral column, horses are pre-medicated using phenylbutazone (4.4 mg/kg, IV) beginning the day before the myelogram and continuing daily for at least one day after the myelogram. After induction of general anesthesia, the horse is placed in lateral recumbency with appropriate padding under the shoulder and limbs. The area of the poll and the dorsal cranial neck should be clipped and scrubbed 6–8 in caudal to poll and 3–4 in on either side of the midline. The head and neck should be elevated using an incline board, and the head should be placed perpendicular to the median plane of the vertebrae. The landmarks for insertion of the 18- or 20-gauge, 3.5-in spinal needle are the intersecting lines between the cranial border of the axis and the dorsal median plane extending from the external occipital protuberance, and the insertion of the needle should be on the midline.

At insertion, the needle should be directed toward the lower jaw. Moving slowly and steadily, a pop will eventually be felt when the needle penetrates the dura mater and enters the subarachnoid space. At this point, the stylet can be removed, and clear CSF should appear. If not, rotate the needle a small amount and remove the stylet again. If no CSF appears, the stylet can then be replaced, and the needle can be moved further into the subarachnoid space. After the needle is properly positioned, collect ~30 ml of CSF and instill ~50 ml of a nonionic iodine-based radiographic contrast agent. At this time, the contrast agent of choice is either Iopamidole or Iohexol, although none have been federally approved for animal use. During the injection procedure, the head is maintained in an elevated position to prevent pooling of the contrast agent around the brain. This elevation increases the flow of the contrast agent caudally along the spinal cord. After instillation of the contrast agent, the head remains elevated for a few moments before removing the incline board. Radiographs should be taken of the cervical vertebrae in the normal, flexed, and extended positions with care taken not to overflex or overextend, because this can cause further damage to the cord. The X-ray tube should be positioned centrally on the vertebra as described earlier in the lecture.

Interpretation of cervical myelography is the subject of much debate, and several publications have appeared during the past 30 yr. To begin, it is the opinion of this author that no criteria can be used to determine whether or not a horse is a candidate for surgical correction using a ventral stabilization. Rather, it is important to consider all information that is known including the history, severity of the clinical signs, findings on the standing radiographs (perhaps most important after the neuroanatomic localization), and results of ancillary testing for other diseases such as EPM, equine herpesvirus myeloencephalopathy (EHM), or meningitis.

Interpretation of the height of the contrast column in cervical myelography has been considered the best ante mortem test for diagnosing extradural spinal cord compression in horses suspected to suffer from cervical vertebral stenotic myelopathy.[2,17,21,28–30] In our hospital, interpretation is generally based on reduction of the dorsal contrast column compared with the space ahead or behind this site, and a 50% attenuation considered abnormal. As means of allowing independent evaluation, the myelogram is generally performed by medicine clinicians and interpreted by those completing the study. The study is then examined independently by the responsible surgeon. After independent review, those clinicians that will perform the surgical correction as a team review and interpret the films together before contacting the owner and/or agent. This helps to insure that we have discussed all aspect of the clinical signs as well as the diagnostic testing before deciding on whether or not surgical intervention is to be recommended. If the myelogram is especially difficult to interpret, such as when the compression is very mild or there is suspicion that the spinal cord is swollen, then final recommendations will be reserved until additional results are obtained (e.g., Western blot for EPM).

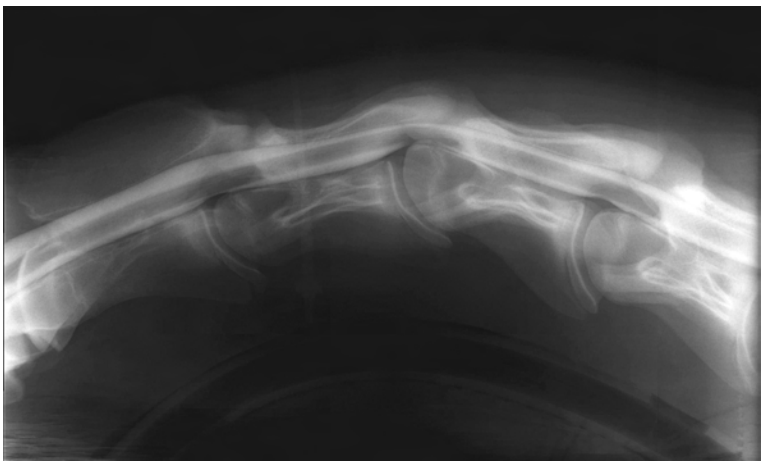

Fig. 14. The same horse imaged in figure 9 subsequently underwent a myelogram, and C_3-C_4 was confirmed as a compressive site. The horse underwent stabilization surgery for both the C_3-C_4 site and C_5-C_6.

Interpretation of the myelogram has been based at least in part on the subjective opinion of the individuals performing the studies. However, a recent review of the evaluation criteria used for interpretation of myelography indicated that the use of a reduction in height of the myelographic contrast column showed a low sensitivity and moderate specificity for diagnosing spinal cord compression caused by CVM.[21] These authors indicated that interpretation of myelography should be done with caution. This advice is important, and it is useful to make a decision for surgical intervention with the answers to these questions. Could the clinical signs in this horse be explained by a compressive lesion at that site, and are there other test results that indicate the presence of another disease process that could explain the clinical signs in this horse? The individuals performing the study read the myelogram, and this is followed by an independent reading by the surgeon. Finally, a combined review of the myelogram is performed. At this time, we use all published guidelines and criteria available from the literature, and we have chosen to err on the side of early surgery when a site only marginally meets the published criteria for surgical correction. This technique provides the best for the horse and the owner in our opinion, and because the horse is most important, we feel comfortable with this decision tree. In some cases, the myelogram will be referred to two or more surgeons or radiologists for additional opinions (Figs. 14–17).

The aim of medical management of horses with cervical vertebral stenotic myelopathy is to reduce swelling and inflammation of the spinal cord. When this problem is diagnosed in weanlings or horses <12 mo of age, then a conservative approach directed at management changes can be instituted. These changes include a reduced level of exercise and careful attention to the diet including avoidance of excess weight gain along with close observation for balance of macro minerals (calcium and phosphorous) as well as trace minerals such as copper, zinc, and manganese. We also often supplement young horses with vitamin E and selenium, especially when raised in a selenium-deficient area of the country. In mature horses with compressive lesions that are not candidates for surgical intervention, use of anti-inflammatory agents such as non-steroidal

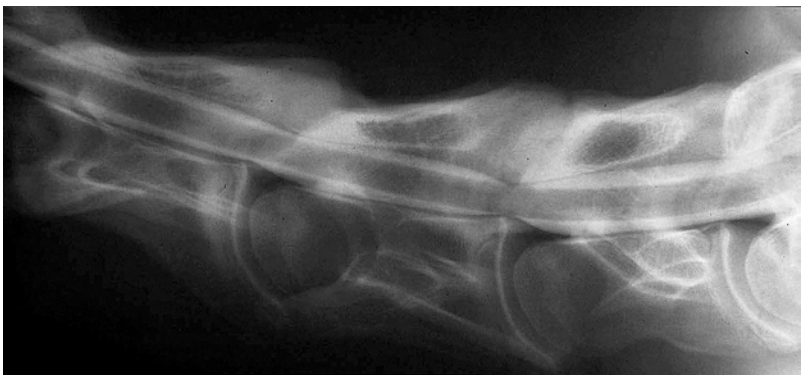

Fig. 15. The horse imaged in this myelogram has a caudal cervical compressive lesion that is indicative of stenosis at the site.

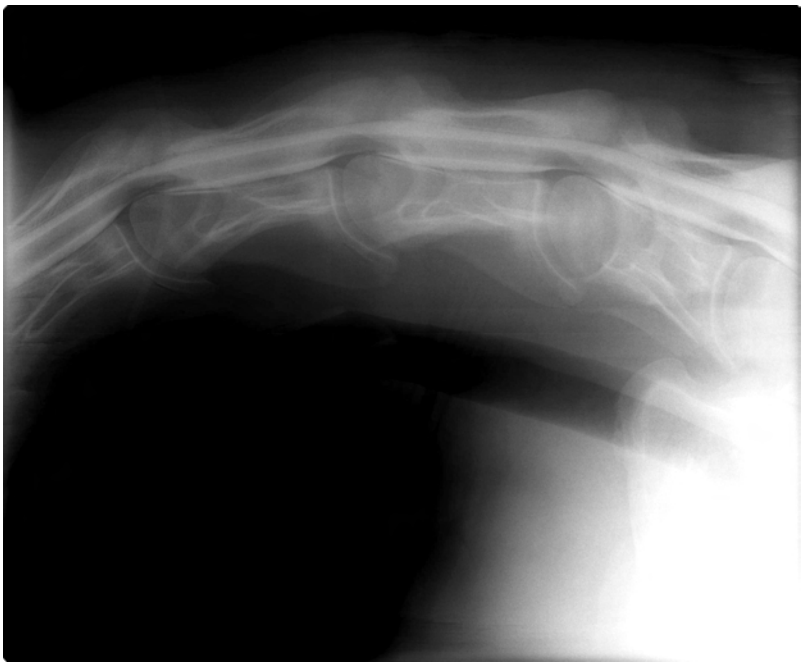

Fig. 16. This radiograph shows compression at both the C_3-C_4 and C_5-C_6. The C_3-C_4 site is less affected, whereas the C_5-C_6 site is markedly compressed.

medications as well as short-term use of corticosteroids combined with exercise limitations can sometimes result in a successful return to athletic use. In horses with arthritis of the articular process joints, intra-articular use of corticosteroids combined with medications to promote cartilage healing can be useful.

If surgical correction is desired, the best treatment is ventral interbody fusion. This treatment has been in use since 1979, but it continues to be somewhat controversial. Questions surrounding the multiple factors responsible for the development of this condition are part of the reason for this controversy. The role of genetics in the development of cervical vertebral stenotic myelopathy continues to be one important question. Investigations of the published literature beginning as far back as 1937 have failed to convincingly prove that this condition is inherited.[31] Work by Dimock,[32] published in 1950 in the *Journal of Heredity*, suggested a recessive nature of the defect, although breeding of affected horses failed to produce an affected foal. This was also the first work to show the occurrence of cervical vertebral stenosis to be three times more frequent in males over females. A study involving Thoroughbreds in Great Britain provided no evidence that affected horses are suffering from a genetically determined disease.[33] Additional concerns about surgical

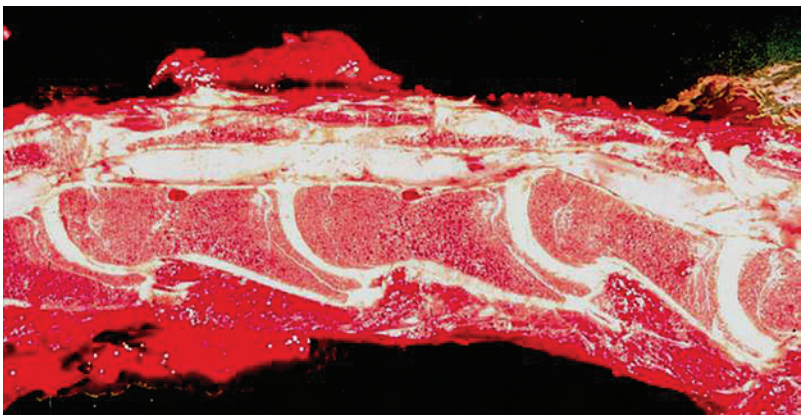

Fig. 17. Compressive lesion at necropsy. This specimen shows spinal cord compression at C_3-C_4 and C_5-C_6. The lesion is analogous to the horse imaged in Fig. 16.

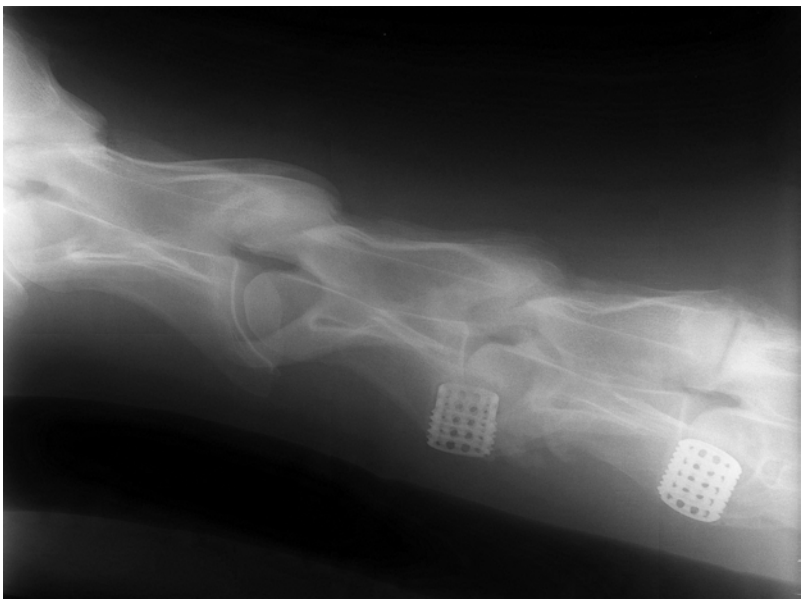

Fig. 18. Post-operative radiograph. This horse underwent surgical stabilization at C_4-C_5 and C_5-C_6. The radiograph was taken in the immediate post-operative period, and thus, the bony stabilization is ongoing.

correction of horses with spinal cord compression include safety, because the horses must recover sufficiently to return to some athletic or breeding use; however, some owners are content to allow the horse to live out its life as a pasture pet (Figs. 18 and 19).

In man, it has been shown that 80% of patients with vertebral canal stenosis similar to what is observed in horses improve after a laminectomy and posterior fusion,[34] and 80–90% of patient's damage caused by discogenic injury to the cord improves after ventral interbody fusion.[35] Similar studies in dogs with cervical arthropathy affecting the caudal vertebral bodies showed an 89% improvement,[36] and in a previous study in horses, 77% improved and 46% returned to athletic performance.[37] In a study by Nixon and Stashak[42] comparing use of ventral stabilization with dorsal laminectomy, there was a 56% return to normal in the ventral stabilization (n = 27) group with 37% showing only grade-1 deficits. After dorsal laminectomy (n = 30), there was a 57% returned to normal, and 27% showed only grade-1 deficits at 1 yr post-surgery. The technique used to perform ventral stabilization in horses has been described extensively.[37–42]

Patient selection is very important, and many factors are a part of the selection criteria including severity of clinical signs, duration of clinical signs, number of sites affected, age of the horse, commitment of the client and cost. In the experience of this author, horses with the best chance for a successful outcome have mild to moderate clinical signs and a relatively short time period from diagnosis to surgical correction. However, exceptions do exist, and several recent publications describe successful outcomes after surgical correction in horses with three sites of cervical cord compression.[43,44] Although all of these criteria are important, a successful outcome is also dependent on the skill of the surgeon and the

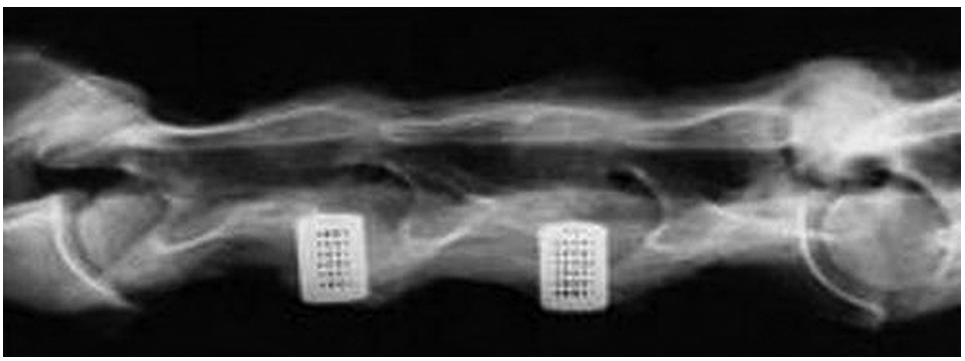

Fig. 19. Post-operative radiograph. This radiograph was taken 16 yr post-cervical stabilization. The articular processes of the operated vertebral joints have virtually fused in contrast to the articular process joints immediately caudal to the surgical site.

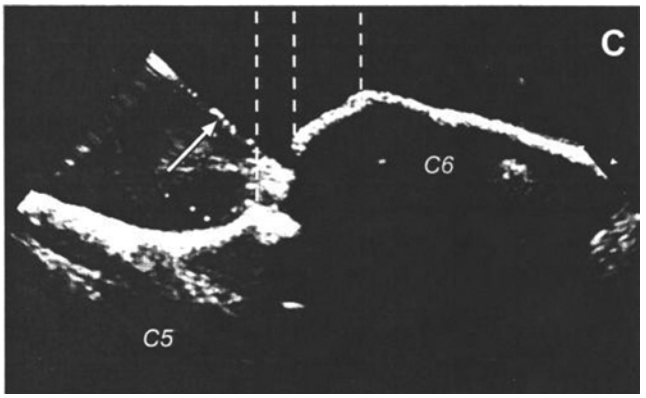

Fig. 20. Vertebral process ultrasound. This ultrasound image shows the appearance of a cervical vertebral process joint. This is referred to as the "chair sign" because of the curved appearance of the facets. The entrance to the process joint space is through this aperture. Reprinted with permission from Mattoon J, Drost W, and Reed S. Technique for equine cervical articular process joint injection. *Vet Radiol Ultrasound* 2004;45:238–240.

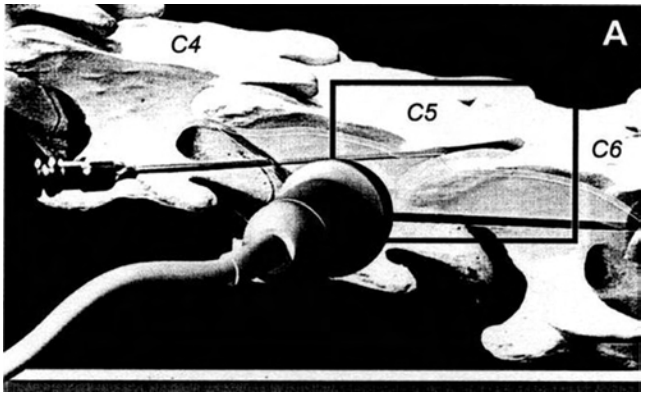

Fig. 21. Vertebral process skeleton. Skeletal mockup of the approach to the cervical vertebral process joints. Reprinted with permission from Mattoon J, Drost W, and Reed S. Technique for equine cervical articular process joint injection. *Vet Radiol Ultrasound* 2004;45:238–240.

commitment of the owner to take on a reasonably long-term period of rehabilitation, often up to 1 yr.

A technique that has been used on some horse with mild signs of spinal ataxia caused by cervical vertebral osteoarthropathy is injection of the articular process joints (often referred to as facets). This procedure is most indicated when the horses are showing signs of neck pain and stiffness and very little or no ataxia.[45–47] Furthermore, the procedure can be performed in awake, sedated horses. Arthrocentesis is performed for patients suffering from osteoarthritis and osteochondrosis of the cervical vertebral articulations.[47] Many of these horses will often present for obscure lameness rather than neurological disease.[48]

Ultrasonography is used throughout the entire procedure: first for location of the facet and then for accurate passage of the needle into the facets.[47,49] A 7.5-MHz microconvex probe is used to locate the joint. This probe provides the best image detail and adequate depth of field in most horses. The joint will be found dorsal to the caudal most extent of the transverse process of the cranial vertebra of the affected joint. The ultrasound beam is directed parallel to the joint space to show the space between the cranial facet of the caudal vertebra and the caudal facet of the cranial vertebra. The angles of entry and the depths for complete insertion of the needle will vary for each horse depending on the placement of the head, the age of the horse, and the size of the lesion. Some veterinarians prefer to use the biopsy guide, whereas others are more comfortable using a free-hand technique (Figs. 20 and 21).

A 6-in, 18-gauge spinal needle can be used for the facets of C_3-C_7, although occasionally a longer needle may be needed for C_6 or C_7. The needle should be inserted ~5 cm into the neck in the same plane as the ultrasound beam and cranioventral to it. Aspiration of synovial fluid will confirm correct location of the needle, although, in many instances, no fluid will be obtained. In these horses, it is helpful to leave the ultrasound probe in place, because you can often observe the fluid while it is injected and can determine if the material is entering the joint space or is being deposited near the joint. I use long-acting corticosteroids such as methylprednisolone[a] (80 mg per site) accompanied by amikacin (125 mg). We have injected as many as six sites on a single horse at one time.

9. EPM

EPM is an important neurological disease of horses in the Americas. The disease was first reported in 1970 in 52 horses from Kentucky and Pennsylvania, although some literature describing clinical cases dates in the late 1960s.[50,51] Within a few years, similar clinical findings were identified in horses from other regions. Confirmation that the disease was caused by a *Sarcocystis* organism was obtained by Simpson and Mayhew[52] in 1980. Based on the organism's structure, reproductive characteristics, and association with neurons, Dubey[53] proposed the name *Sarcocystis neurona* for this organism.

The most common agent recognized that causes EPM is *Sarcocystis neurona*, an apicomplexan protozoan, but clinical signs in some horses are a result of *Neospora hughesi,* which causes a rare sporadic form of EPM. Less is known about the life cycle of *N. hughesi.* Most *Sarcocystis spp.* affect a single host, whereas *S. neurona* has the ability to affect a wide host range; this is similar to *Toxoplasma gondii* and *Neospora caninum. S. neurona* has been shown to have considerable antigenic diversity among its surface antigens (SAG) proteins.[54] Recognition of the major surface antigens has been used in the development of diagnostic testing modalities to evaluate the equine antibody response.[55,56]

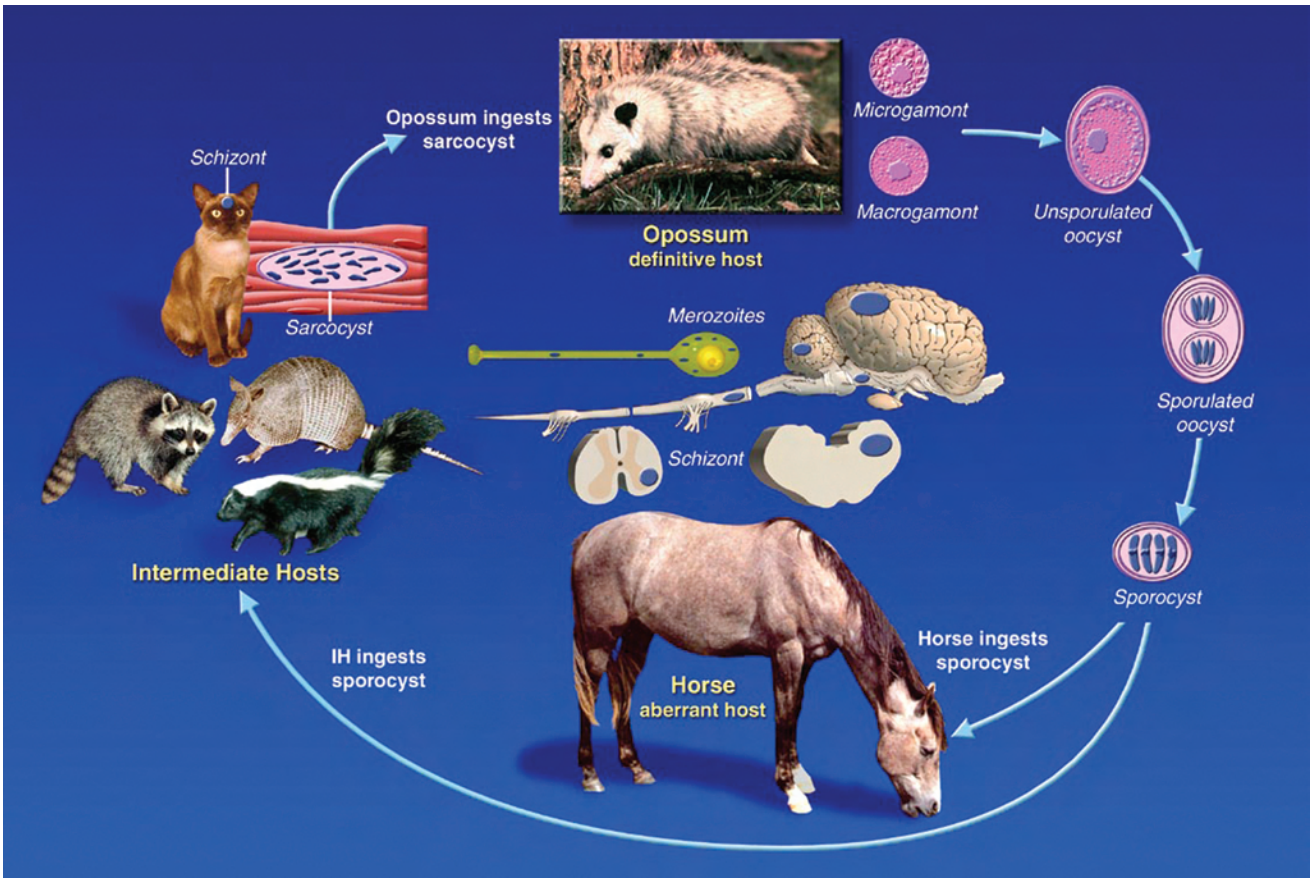

Fig. 22. Sarcocystis life cycle. Courtesy of The Ohio State University and Tim Vojt.

The life cycle of *S. neurona* involves two hosts: the opossum is the definitive host, and there are several intermediate hosts. Important questions about why the disease was seen only in the Americas or in horses that had been in the Americas were answered when the definitive host of the protozoan was determined using polymerase chain reaction (PCR) amplification of merozoites collected from the small intestine of the opossum (*Didelphis virginiana).* Later, *Didelphis albiventris* was also identified as a definitive host of this organism.[57] The prevalence of *S. neurona* in wild caught opossum is reported to be 18–25%.[58] The definitive host becomes infected by ingesting the muscles of an intermediate host that has encysted stages of the *S. neurona*. After it is inside the intestine of the definitive host, the organism undergoes sexual reproduction and ultimately, produces a large number of sporocysts. These are shed in the feces and are immediately infective to intermediate hosts. The duration of viability of the sporocysts in the environment is unknown, although an experimental infection of interferon γ knockout mice showed infectivity of 7 mo.[59] (Fig. 22).

Completion of the life cycle for *S. neurona* was initially performed in a laboratory using the domestic cat as the intermediate host.[60–62] Further investigation by this group showed antibodies in ~5% of domestic cats.[61] The infective stage for the definitive host is the sarcocyst. *S. neurona* sarcocysts have been identified in the muscles of raccoons, armadillos, sea otters, cats, harbor seals, and skunks.[60,62–65] Sarcocysts can be found in tissues of true intermediate hosts such as cats, skunks, raccoons, and armadillos. The intermediate host can develop clinical signs of disease if the organism invades the brain or spinal cord.[66–68] However, the encysted form in the muscle of the intermediate host is the source of infection for the opossum, and thus, animals that do not form sarcocysts, including horses, are aberrant intermediate hosts.

Sporocysts are the infective stage for the intermediate hosts. After the horse ingests the sporocysts, the organism passes into the small intestine. Then, it excysts, and sporozoites enter the blood stream. This stage of the life cycle may replicate in endothelial cells of blood vessels to produce tachyzoites, which can migrate to the central nervous system. Tachyzoites can asexually replicate in neurons and microglia cells and grow at a slow rate, which results in gradual destruction of nervous tissue. Ultimately, this damage to the nervous tissue results in ataxia, lack of coordination, and other signs of infection in the nervous tissue.

Initial work by Saville et al.[69] evaluated the exposure of horses to *S. neurona*. These studies showed that horses residing in states where the opossum is present within the United States have an exposure rate of 33–53%.[69–77] Recent studies conducted in South America showed a seroprevalence rate of ~35%.[78,79] The seroprevalence rate for *N. hughesi* seems to be quite low; however, in a study performed in California, the rate has been shown to be as high as 37% in one study and 1.7% per year of age in another study.[75,80]

Although a reasonably high percentage of horses show antibody titers in the blood, which indicates previous exposure to the causative organism of EPM, relatively few horses develop clinical signs. In studies conducted on animals examined at postmortem, the rate of disease is <1%. The reasons for the small percentage of infected horses is unknown, but it is likely related to the strain of the organism, the infective dose, the presence of concurrent infections, and the immune status of the horse. The lesions typically identified in horses that fail to survive infection with *S. neurona* are small foci of inflammatory cells in either grey or white matter. The cellular infiltration is often non-suppurative and characterized by monocytes, macrophages, and giant cells. This ultimately leads to axon swelling and degeneration.[81,82]

While developing a model of EPM in horses, stress was identified in association with the development of clinical signs in naïve horses.[83] In that study, it was noted that the parasite load was not the most important feature in development of histopathologic lesions in the spinal cord of experimentally infected horses. Nitric oxide concentrations in CSF were reduced in horses that were experimentally infected after transport stress.[84] Nitric oxide functions in the body in many ways, including as a neurotransmitter, vasodilator, and immune effector.[84] This agent is produced in response to many parasitic infections including *S. neurona* infection. In the transport-stress model, horses that developed the most severe clinical signs of ataxia showed the greatest reduction in nitric oxide concentrations measured in the CSF.[84] A similar finding was identified in naturally affected horses (i.e., horses with clinical signs of ataxia and positive for antibodies in the CSF) compared with unaffected horses (i.e., no clinical signs of ataxia but still positive for antibodies in the CSF). Horses that were allowed to acclimate to a new environment before infection and horses that were infected after treatment with dexamethasone had increased levels of nitric oxide in the CSF. Similar findings of lower levels of CSF nitric oxide were identified in naturally infected horses with EPM. In 2001, Tornquist et al.[85] showed reduced cell-mediated immune responses in horses with EPM. Furthermore, in 2004, Spencer et al.[86] showed that *S. neurona*-infected horses had markedly reduced levels of γIFN induction and cell-mediated immune responses to antigens of the parasite.

EPM is most often a sporadic disease on a farm; however, in a study conducted at The Ohio State University, several risk factors were identified, such as age (<5 and >13 yr), time of year (summer and spring was greater than winter), previous cases recognized on the home farm, presence of woods on the farm, and presence of opossums on the farm.[87] In this study, horses that were 3 yr of age were at the greatest risk, especially when they were traveling for showing or racing. The prevalence of the disease was reduced on farms where wildlife had little or no access to feed and if a creek or river was on the premises. Another study that examined only histologically confirmed cases of EPM noted that 33% of the horses were <2 yr of age and almost 62% were <4 yr of age.[88] Use of antibody concentration in blood as a means of determining exposure to *S. neurona* in foals <1 yr of age may be difficult; although all foals will be negative at birth, as many as 100% of foals whose dams have an antibody level will also show antibody after ingestion of colostrums. This may not wane for as long as 9 mo.[89] When comparing horses from farms with EPM to premises with no cases of EPM, one of the most important risk factors was age. Young horses (<5 yr) had a four time greater likelihood of developing EPM than did horses between 5 and 20 yr of age, and horses between 18 mo and 5 yr of age were twice as likely to develop EPM.[90] Factors that have been shown to be strongly associated with EPM occurrence include the number of horses in a given turnout area, the number of horses that were permanent residents of a given farm, the use of the resident horses, the presence of small wildlife such a skunks, raccoons, or opossums on a premises, and the proximity of a marsh.[90]

In final analysis, it seems that the likelihood of a horse on a given farm or operation to develop EPM is closely tied to any factor that increases the exposure of a horse to opossums, their feces, and their environment. Based on two published studies examining risk factors for developing EPM, other publications on infection studies, and retrospective reviews of cases with EPM, it seems that young horses used for intensive training for either racing or showing are at greatest risk to develop EPM, although it may be that managers of these horses are more likely to seek a definitive diagnosis and treatment than would a manager or farm where the horses are used for pleasure rather than work. Saville et al.[69] noted that environmental factors such as number of freezing days will impact the seroprevalence rate. Similar findings were identified by other investigators.[71–74,76,88,91]

To fully investigate *S. neurona* infection in horses, experimental reproduction of the disease was and continues to be important. Several investigators have attempted to reproduce the disease in healthy as well as in immunocompromised horses.[83,92–103] In addition, several investigators have examined small ani-

mal models of the disease using nude and interferon gamma knockout mice and raccoons.[59,104,105]

The earliest descriptions of the clinical syndrome now known to be EPM were published in the mid to late 1970s. The clinical signs may vary from acute to insidious onset of focal or multifocal signs of neurologic disease involving the brain, brainstem, spinal cord, or any combination of the areas of the central nervous system.[106–108] The early clinical signs of stumbling and frequent interference are often easily confused with a lameness of either the thoracic and/or the pelvic limbs. In many horses, the disease tends to have a gradual progression of clinical signs including ataxia, but in some horses, there may be mild clinical signs followed by a rapidly progressive course. Some horses affected with EPM may initially show abnormal upper airway function, unusual or atypical lameness, or even seizures.[109] In severe cases, the horse may have difficulty with standing, walking, or even swallowing, and the disease may progress very rapidly. In some horses, the disease seems to stabilize or remain static for a time period. Because the organism may affect spinal cord gray matter, focal muscle atrophy may be observed. Gait abnormalities are often a result of damage to the spinal cord and may be quite variable depending on the location and severity of the lesion. The variability of clinical signs is caused in part by the fact that the organism may attack randomly within the white and gray matter of the brain, brainstem, or spinal cord of the horse.

On physical examination, the vital signs are usually normal, although some horses may appear thin and mildly depressed. The neurological examination often reveals an asymmetric weakness, ataxia, and spasticity involving all four limbs. Frequently, areas of hypoalgesia or complete sensory loss may be noted. The most frequent brain or cranial nerve deficits observed in horses presented to The Ohio State Veterinary Teaching Hospital include head tilt, depression, facial nerve paralysis, and difficulty swallowing, although signs are not limited to these areas.[106] Most horses affected with EPM are bright and alert; however, any horse with signs of neurologic disease are candidates to have EPM. One of the most helpful clinical signs is that horses with EPM often present with evidence of asymmetric gait deficits with focal muscle atrophy. This can be a useful differentiating feature and may help distinguish EPM from some of the other neurological diseases.

Although the causative organism was identified in the early 1990s, EPM disease remains a challenge for veterinarians to accurately diagnose. At this time, there is no definitive test or group of tests that accurately diagnose EPM in all affected horses. The presence of clinical signs, positive serological testing, positive CSF testing with or without abnormal CSF cytological evaluation, response to treatment, and post-mortem examination have all been used to confirm a suspected case of EPM in a given horse. Currently, I diagnose EPM using a combination of neurological examination, blood and CSF testing for antibodies by immunoblot analysis, cytological examination of CSF, examination of cervical vertebral radiographs, and sometimes, a myelogram. In addition, assessing response to treatment can provide additional information, because many horses have been treated or are being treated at the time of presentation for referral or second opinion.

Development of a useful diagnostic test for many infectious diseases is sometimes difficult. This has indeed been the case with EPM where antemortem diagnosis is presumptive at best. Confirmation of infection can only be accomplished by post-mortem examination with demonstration of microscopic evidence of the organism or of histological changes compatible with EPM. There are several laboratories available to perform ante mortem testing for detection of EPM. The ability to produce consistent results with acceptable levels of standard errors over multiple trials is very important. There will always be variation between laboratories and between individual assays. Therefore, reporting of results as relative rather than absolute values would be best. Use of a percent positivity value over an absolute value would correct for inter-laboratory differences as well as background activity. The publications describing currently available tests, along with a brief discussion regarding how the tests were validated, were recently reviewed.[110]

At the present time, there are four published commercially offered tests to look for IgG antibodies against the causative organism *S. neurona* or in a few cases, *N. hughesi*.[56,101,102,111] These test formats are immunoblot (western blot), enzyme-linked immunosorbent assay (ELISA), and immunofluorescent antibody (IFA). PCR testing for *S. neurona* and *N. hughesi* DNA are also available from a number of labs, but they have poor clinical sensitivity; most samples test negative. CSF samples are most likely to test PCR positive when clinical signs are acute. In the United States, several studies have identified many horses that have been exposed to *S. neurona* and thus, carry antibodies against the organism in the blood stream; however, the disease incidence seems to be very low for *S. neurona* and even lower for *N. hughesi*.[75,112]

The most common ante mortem test used at this time is the standard western blot test on serum and CSF. This test detects *S. neurona*-specific IgG antibodies in blood and CSF. Based on the original validation data from ~300 necropsied horses with ~40% confirmed to be EPM, the standard immunoblot test has a specificity and sensitivity of 89%.[103] A modified western blot procedure with a claim of improved specificity has been described, but it was validated on just six necropsy positive cases.[113] The SAG1 ELISA detects the response to a single surface antigen of *S. neurona,* but there is much evidence that this antigen is absent from many strains of *S. neurona*.[114] The IFA serum test has a

reported specificity and sensitivity of 100%, but this was based on a small number of necropsied horses (from California) with a low frequency of EPM-confirmed cases.[115] This test also has a known cross reactivity in horses exposed to *Sarcocystis fayeri*, a species that infects horses but does not cause EPM.[99] The only reported direct comparison of all four tests was by Saville and Dubey.[116] In that study, ~20 sera from horses with characterized histories were submitted to four labs, representing the four test formats, and the results were summarized as follows. The modified western blot generated apparent false positives, whereas the SAG1 ELISA test generated apparent false negatives, including a necropsy-confirmed case. Although the IFA compared favorably with the standard western blot, it tested a pony experimentally infected with *S. fayeri* as positive.

A positive CSF test means that the parasite has crossed the blood-brain barrier, and the IgG index and albumin quotients should be checked. With the apparent moderate to high seroprevalence of horses in many areas of the United States and other parts of North and South America, it is important to be able to distinguish exposed from infected horses. Negative IgG findings may not rule out EPM in the most acute stage of the disease. CSF can be re-evaluated in 2–3 wk for an ample incubation period. Some horses may never produce a clinically detectable level of the antibody but will still show signs of the disease.

Recognition of antibodies in the blood indicates that the horse has been exposed to the causative organism, and in the presence of signs of ataxia, the likelihood this horse has EPM is increased. Horses that show clinical signs of ataxia and have antibody titers both in blood as well as in CSF are even more likely to be infected with EPM. However, work by Furr[117] has shown that horses exposed to an antigen (ovalbumin) injected intramuscularly developed titers in the CSF. This study sought to answer the questions of if antibodies developed in the serum passively crossed the blood-brain barrier into the CSF or if the CSF titer did indicate intrathecal production. The study concluded that using a non-replicating protein antigen intramuscularly resulted in production of antibodies in serum and CSF without change in the immunoglobulin G $(IgG)_{index}$ or Ab_{index}. This outcome indicated that antibodies found in CSF likely passed through the blood-brain barrier rather than by intrathecal production.[117]

Another potentially useful EPM diagnostic tool is the detection of immunoglobulin M (IgM) in the early stages of infection. Murphy et al.[111] examined the IgM response after experimental exposure to *S. neurona*. In other apicomplexan parasites, a strong IgM response has been shown.[106,118–120] The specific aim of the study by Murphy et al.[111] was to develop an *S. neurona*-specific IgM capture ELISA and to evaluate its usefulness in detecting acute EPM infections in naïve individuals using either serum or CSF.[111] In this study, the authors were able to detect significant differences in serum neutralizing (Sn)-IgM concentrations between serum and CSF samples collected before and after inoculation with *S. neurona*. The serum concentrations of Sn-IgM were significantly increased 2 wk after inoculation, which is very similar to what happens after infection with other apicomplexan parasites.[111,119,120] This study showed a persistence of Sn-IgM antibody concentration over a 6-wk period and a return to normal by week 7; this is the expected normal waning of IgM in the serum of acutely infected animals. The persistence of IgM concentrations at a measurable level over a 30-day period would provide a clinically relevant result that should be quite useful to owners and veterinarians trying to determine if this is a recent or previous exposure to *S. neurona*. Therefore, it could be helpful to determine the likelihood of this organism as the cause for the clinical signs in the horse.

CSF concentrations of Sn-IgM were examined at two points in the study: before inoculation with *S. neurona* and at the time of euthanasia. The results showed low concentration of Sn-IgM before inoculation and higher concentrations at the time of euthanasia. Interestingly, the samples collected from horses euthanized 4 wk post-inoculation were higher than those at 7 wk post-inoculation. This likely indicates that intrathecal IgM antibody concentrations wane between 4 and 7 wk.[111] Similar findings have been described in other infectious types of encephalitis, specifically tick-born encephalitis.[121]

The test results of the CSF from horses suspected of having equine protozoal myelitis often come back normal. However, if the clinical signs persist, testing should be performed again in 2–3 wk to allow the antibodies to build up to a detectable level. A positive CSF may indicate (or perhaps suggest) that the parasite has penetrated the blood-brain barrier; IgG levels and the albumin quotient should be tested as well. The levels should be compared with those of the serum. If the IgG index and the albumin quotient are both increased, then parasites have crossed into the central nervous system with subsequent production of intrathecal antibody. Crossing of parasites is also indicated by a normal IgG index with an increased albumin quotient, because the albumin content of CSF should be much less than that of serum. Any increases would be from a leakage in the blood-brain barrier that is letting in blood or blood contents.

Previous authors have looked for changes in the complete blood count and serum chemistry profiles in horses with EPM, but no consistent abnormalities have been identified.[122,123] The results of this testing may be helpful to eliminate other disease conditions or primary muscle problems that might result in a horse showing an abnormal gait. In addition, several authors have examined CSF, and none have shown consistent changes in cell counts, total protein, antibody concentrations, or enzyme concentra-

tions in horses affected with EPM.[24,123–125] The article by Miller et al.[125] also showed the challenges of interpretation that can arise when peripheral blood contaminates CSF. Use of a ratio of the albumin concentration in the CSF to the albumin concentration in the serum has been shown to be useful in determining if the quality of the CSF sample is good. When there is an elevated albumin concentration in CSF or if one observes an elevated albumin quotient, the sample has either been accidentally contaminated by blood or the horse has increased blood-brain permeability.

Treatment of horses suspected to have EPM should be done as quickly as possible after clinical signs of the disease are recognized. Treatment seems to result in successful recovery in 70–75% of the affected horses. For many years, treatment was confined to the use of sulfa drugs and pyrimethamine.[51] Initially, this treatment was compounded, but more recently, a Food and Drug Administration (FDA)-approved formulation has come to market. The sulfonamide component competes with paraminobenzoic acid to decrease folate metabolism, whereas the pyrimethamine competes with dihydrofolate reductase, which reduces folate synthesis. The traditional therapy used to treat horses diagnosed with EPM was a prolonged course (up to 12 wk or longer) of pyrimethamine and sulfadiazine or a potentiated sulfonamide. The combination of sulfadiazine and pyrimethamine results in a sequential blockade of folic acid metabolism. The specific concentration of pyrimethamine required to achieve an anti-protozoal level for *S. neurona* is not known. However, it is known that *T. gondii* and *N. caninum* are susceptible at 1 μg/ml of pyrimethamine alone and 0.1 μg /ml when combined with sulfadiazine.[126,127] At this time, there is an FDA-approved formulation of the combination of these medications known as ReBalance.[b] Duration of treatment using ReBalance at 1 mg/kg of pyrimethamine and 20 mg/kg of sulfadiazine (or dose according to weight) can be as short as 30 days or as long as 120–150 days. Longer treatment is indicated if the CSF remains positive and/or the horse continues to shows clinical signs of neurological disease. Complications of anemia and/or leukopenia have been observed, especially when the dose of pyrimethamine is doubled, and in some horses, diarrhea has occurred.

When horses are treated using dihydrofolate-reductase inhibitors (sulfa drugs and pyrimethamine), folic acid deficiency and anemia may be side effects of the treatment. In humans, megaloblastic anemia is a common side effect of treatment with pyrimethamine. To combat this problem, frequently evaluate the complete blood count in horses while on treatment. Whenever there is evidence of anemia, the treatment should be discontinued, and supplementation of folic acid should be initiated. In humans, Leucovorin (folinic acid or 5-formyl-THF), a form of bioactive tetrahydrofolate, is used to combat the anemia. Folic acid cannot be used by the protozoan; however, administration of this product to the horse has two potential problems. The first is that the drug is poorly absorbed from the intestinal tract, and the second is that conversion of the folate to the active form of tetrahydrofolate requires dihydrofolate reductase, which is being inhibited by the treatment.

At the present time, veterinarians have several available and effective treatment choices for use in the horse, including ponazuril[c] and nitazoxanide.[d] The active ingredient in Marquis is ponazuril. Ponazuril is an anticoccidial triazine-based compound that is effective and approved for the treatment of naturally occurring EPM. Clinical trials were performed involving >100 horses randomly allocated to treatment with either a 5 or 10 mg/kg of body weight for 28 days using a 15% oral paste. Horses were evaluated clinically as well as by analysis of CSF and blood before and 18 and 28 days after the start of treatment. Clinical success was defined as either an improvement of at least one grade in the neurologic score or conversion to a negative status on the western blot for *S. neurona* antibodies by 90 days after treatment. Efficacy was shown to be quite good for this compound. The use of this drug has been shown to result in very few complications, and no significant elevations of serum chemistry values or changes of complete blood counts have been observed. The mechanism of action seems to be inhibition of the respiratory chain enzymes of the *S. neurona* apicomplex and mitochondria.[128–130]

The third medication for treatment of EPM in horses is nitazoxanide (NTZ). NTZ has broad-spectrum activity against bacteria, protozoa, and helminth parasites. NTZ is a member of the 5-nitrothiazol class of antimicrobials.[131] The drug is effective in killing *S. neurona* in cell culture and has been tested in a clinical field trial for the treatment of horses with EPM. This drug has antibacterial, antiprotozoal, and antiparasitic activity and is being investigated for effectiveness against *Rotavirus* in some species. The drug seems to have good oral absorption, although the concentration found in CSF after six clinical doses of 50 mg/kg was low. Safety studies indicated that a double dose for 1 wk caused horses to be lethargic and a four times dosing caused horses to appear ill; one horse died. An efficacy study of 70 horses showed that 63% of the horses improved one grade or more or became negative on western blot testing of CSF.[132] Dosing at this time is suggested to begin at 25 mg/kg daily orally for the first 7 days followed by 50 mg/kg for a total treatment time of 30 days.

Toltrazuril[e] is an anticoccidial drug used in several species. This is the parent compound of ponazuril and was previously used as treatment for some horses with EPM. The mechanism of action is to disrupt intracellular pathways important in energy metabolism as well as cell division. This drug seems to have good oral absorption and fairly long elimination time (48–72 h); however, with the approval of ponazuril, the use of this compound is no longer indicated, and the drug is difficult to obtain. Many veterinarians and owners believe that horses

respond better to this medication, because it is converted to the active ingredient ponazuril in the horse; thus, its use continues to be requested.

Diclazuril has received FDA approval but has not yet been brought to market for clinical use in horses. The medication was shown to be effective in clinical trials, and the drug may soon be available for use.[133] Investigation regarding the effectiveness of this mediation have been published.[134] This has been used as an alternative treatment for horses that have failed to respond to or developed complications using the traditional therapy. The drug is in the benzeneacetonitrile group and has been used as a prophylactic agent against coccidiosis in poultry and experimentally in the treatment of similar problems in rabbits. The drug has also been used to treat protozoal infections such as *Isospora* and *Cryptosporidia* in AIDS patients.[135–137]

Supplemental or ancillary treatments such as immune stimulants have been suggested as possible assistance in the treatment of horses with EPM. Drugs such as levamisole, thought to improve cell-mediated immunity, have been recommended as an adjunct to treatment for EPM.[133,138] We avoid corticosteroids in horses suspected to have EPM, because this may worsen the clinical signs. However, when faced with a rapidly deteriorating case, one or two doses of corticosteroids can be administered to help reduce the inflammatory process and allow time for the antiprotozoal medications to work. In addition, other anti-inflammatory/antioxidant drugs such as dimethyl sulfoxide and vitamin E should be administered to help decrease the inflammatory effect of rapid killing of the organism or to suppress inflammation that results from an exacerbation of the disease. Vitamin E can also be given throughout the treatment period to combat any further oxidant injury to the central nervous system.

Prevention of EPM has been the focus of much of the current research on this disease. Prevention has been investigated by use of vaccination and low-level daily or intermittent use of treatments. Although vaccination has not yet been shown to be effective, further investigation in the future seems likely. Recent publications have shown apparent success using frequent intermittent low-dose administration of several approved therapeutic medications. The use of NTZ at 25 mg/kg for 2 days a week had some benefit as did ponazuril at 20 mg/kg one time per week.[133,139,140] In a study by Furr et al.,[141] the use of ponazuril at both 2.5 mg/kg and 5.0 mg/kg reduced the incidence of infection with *S. neurona*. It does seem that protection of feed and bedding supplies from exposure to opossums or other small wildlife may very well help reduce the incidence of EPM on a premise. Furthermore, if small wildlife and/or wild cats are found on a premise, then removal of these animals or dead carcasses might further reduce the incidence of disease by reducing the exposure of wild opossums to the *S. neurona* sarcocysts.[133]

10. EHM

EHV-1, a member of the *Alphaherpesvirus* subfamily in the *Varicellovirus* genus, has a worldwide distribution and results in economic losses as well as various forms of infectious disease including mare abortions, respiratory disease, neonatal deaths, and myeloencephalopathy. Infection typically occurs early in life and is followed by the establishment of latent infection. The virus can then be reactivated after a stressful episode, which can result in onset of fever, respiratory disease, or neurological disease. Many horse, viral, and environmental factors are likely to have an impact on the incidence of recrudescence of EHV-1 in horses. Investigations to examine shedding in stressed horses have recently been published, and it is unclear what conditions are stressful enough to result in viral shedding.[142] In young horses, most typically horses <2 yr of age, the clinical signs include fever, loss of appetite, serous nasal discharge, and loss of training days. With this manifestation, the horse is usually out of work for 4–7 days and then will return to work with little or no apparent long-term consequences, although the horse may now be latently infected with EHV-1 virus. When the virus affects pregnant mares, abortions can occur, most commonly during the last trimester, but they can occur at any time. The third manifestation is the neurological form of the disease in which many horses on a premise can become infected. Some of the affected horses develop equine EHM with significant neurological signs of weakness and ataxia, often involving the pelvic limbs, but any part of the nervous system may be affected.

Virus transmission is usually from horse to horse by aerosol transmission through close contact, although fomite transmission should also be considered. Virus enters the respiratory epithelial cells and is transported to the regional lymph nodes, usually within 1–2 days. After the virus has established itself in the respiratory epithelium, it undergoes replication and may be infective for other horses for as long as 14 days. The recently recognized strain associated with EHM seems to have a replicative aggressiveness that results in higher numbers and a longer period of replication. The consequence is a greater concentration of virus for longer periods on nasal mucosal surfaces, which prolongs the period of infectivity.[143,144] The virus rapidly enters peripheral blood mononuclear cells (lymphocytes and monocytes) and circulates in the blood in what is described as a cell-associated viremia that can persist for up to 21 days.[145–147] After the virus is within the cell, it seems to be able to circulate without destruction, even in the face of high-circulating antibody titers. In this location, the virus can disseminate to other tissues, including the central nervous system. It is thought that the mononuclear cells contact the endothelial cell lining of the central nervous system, and the virus enters

into the endothelial cells through this close contact.[148,149] The damage that occurs as a result of this infection with EHV-1 is vasculitis followed by thrombosis and ischemia in the nervous tissue without direct viral infection. This results in a myelopathy rather than myelitis.[146–148,150] This cell-associated viremia is an important feature in the development of abortions as well as myeloencephalopathy and is an important target for stopping or blocking outbreaks of these problems in the horse.[148,150]

The first definitive association between EHV-1 and myeloencephalopathy was made after isolation of the virus from the brain and spinal cord of a horse in Norway in 1966.[151] Since that time, examples of similar cases have been shown to have a worldwide distribution. In most instances, the myeloencephalopathy occurs as an outbreak of cases, although sporadic disease can be observed.[143] In many situations, EHM occurs as an outbreak, often during the winter or spring. The outbreaks are typically associated with he congregation of horses in a somewhat closed environment with common airspace as well as common management system. There is often a history of recent introduction of new horses or a return home of horses that have been on the travel circuit. Horses that are most often involved are > 3 yr of age and engaged in frequent travel for racing, showing, or sales activity. The initial signs will usually be fever in one or more horses followed in 7–10 days by horses showing signs of neurological disease, such as poor tail tone, urinary incontinence, and pelvic limb weakness.

During the past 7 yr, several outbreaks of the neurologic manifestation of EHV-1 have been observed and/or described in the literature from around the world. In the United States, the United States Department of Agriculture: Animal and Plant Health Inspection Service (USDA:APHIS) with the Centers for Epidemiology and Animal Health determined in 2007 that this viral problem met the criteria for an emerging infectious disease. Careful examination of the outbreaks and particularly of the virus isolated from horses infected in these outbreaks indicated an apparent increase in virulence of the virus along with increased morbidity and increased mortality than previously described. Outbreaks of neurological disease associated with EHM have been described.[152–156] Beginning in 2000, there have been an increase in the number of epizootics of EHV-1 myeloencephalopathy in which the number of horses affected, the severity of the clinical signs, and the rapidity with which the virus spread through a group of horses seems dramatic compared with previously described outbreaks. A recent report from central Kentucky showed a number of horses harboring a particularly neuropathogenic strain of this virus.[157,158]

In most outbreaks, it is difficult to identify the horse that was the source of infection for other horses (i.e., index case); however, after the onset of signs, the resultant spread throughout the herd is similar. For purposes of discussion, I would like to focus on an outbreak with which I was particularly closely associated. In addition, I would like to dedicate this portion of the Milne Lecture to Dr. George Allen, who was constantly available to answer even the most seemingly mundane questions about this problem and who gave his time, energy, and knowledge to educate me about EHV-1. More importantly, his research has contributed much of the current knowledge available today, and he generously shared this with his colleagues worldwide. In doing so, he provided a great deal of help to horse owners and relieved much suffering for horses. Although his untimely death in 2008 was a very sad day for his family and friends around the world, his legacy remains through the many graduate students and colleagues he helped to train. Much of what I am able to present today regarding this disease was made possible by the kindness and generosity of this brilliant scientist and wonderful person. The study of outbreaks from around the world along with development of newer, more sophisticated diagnostic testing has helped us learn a great deal about this infection. Still, many questions remain unanswered about the virus, the pathogenesis of EHM, the mechanism of infection of endothelial cells, the recognition of a single nucleotide polymorphism in the DNA polymerase gene, the role of host and environmental factors, and their affect on the risk of development of this disease syndrome.

In 2003, after the introduction of five horses from an existing outbreak of EHM to a veterinary teaching hospital, several horses in the hospital that were exposed to these horses and/or the personnel managing the horses developed signs of neurological disease suspected to result from EHV-1. The initial response after recognition of onset of disease in apparently naïve horses was to identify owners of all horses that had been in the hospital during a wide temporal period surrounding the time the known affected horses had been in the hospital (January 3 through February 11, 2003).

Use of a broad range of dates assured the likelihood of identifying all horses that might have entered the hospital before January 18th and stayed beyond this date. It was well beyond the date when the last horse from the original outbreak had either died or left the hospital. During that period, 146 horses had been in the hospital as either inpatients or outpatients (single-day visit). Among those 146 horses, 9 developed fever without neurological deficits, although one horse had originally presented with neurological gait deficits as a result of cervical vertebral stenotic myelopathy. Seven of the horses subsequently tested negative for EHV-1 exposure based on paired serological testing as well as virus isolation and/or PCR testing of nasal swabs. One of the remaining two horses was PCR positive on nasal swab, positive for virus isolation in blood for EHV-1, and had an acute titer of 1:160 and a convalescent of

1:640. The final horse in this group was PCR positive on nasal swab but virus-isolation negative. This horse did seroconvert, showing an initial EHV-1 titer of 1:10 and a convalescent titer of 1:>640.

Four additional horses developed fever and a change in neurologic status. One horse initially presented for fever and cellulitis. This case was subsequently found to be virus isolation positive on nasal swab and developed clinical signs compatible with EHM. The horse progressed rapidly to recumbency and was subsequently euthanized. EHV-1 was isolated from the central nervous system in this horse. The second horse presented for fever, cellulites, and acute onset ataxia. This horse did not seroconvert, and subsequent diagnostic testing implicated cervical spinal cord compression as a result of degenerative changes as the cause of its ataxia. The third and fourth horses developed fever and neurologic disease within days of discharge from the hospital. One of these horses was maintained in a stall on the owner's property and had no contact with other resident horses. This horse progressed rapidly to recumbency and was euthanized. The horse was PCR and virus isolation positive on a buffy-coat sample. The final horse developed moderate ataxia but made a complete recovery. This horse was PCR and virus isolation negative; it did seroconvert and had an initial EHV-1 titer of 1:40 and a convalescent titer of 1:160. Unfortunately, this horse had a single pasture mate that subsequently developed fever and rapidly progressive neurologic disease, which resulted in euthanasia. The pasture mate was virus isolation positive on a buffy-coat sample.

Recognition of apparent lateral transmission of an infectious disease suggestive of EHM, which results in signs of ataxia, should signal any veterinary hospital or stable to immediately initiate an intensive investigation to determine the cause for the clinical signs. Additionally, any potential relationship between animals presented for this disease and new cases identified among patients in the hospital should be identified. After the recognition of apparent lateral transmission of an infectious disease, it is very important to protect horses remaining in one's hospital as well as new patients presenting to the hospital. To do so may require a period of closure of the hospital to accomplish thorough cleaning and disinfection. This should be followed by segregation of all remaining horses into a separate portion of the hospital, and no new horses should be admitted for a period of 21–28 days.

Whenever there is adequate space to allow separation of the hospital stalls as well as all hospital staff, the hospital may be divided. After appropriate disinfection, at least one portion of the hospital may be reopened for use. Before reopening, the hospital designated as clean should be closed, steam cleaned, disinfected, and allowed to dry for a period of 5–7 days. After the hospital is reopened, the horses, grooms, veterinarians, veterinary technicians, and all other personnel and owners should remain separated from those working around horses that were in the hospital during the time of the outbreak. No cross traffic of personnel, horses, or equipment should be allowed.

Using these guidelines, the epizootic was quickly brought under control, and most importantly, no additional horses became infected. The unfortunate part was the loss of several horses along with the suffering of several owners. Despite these disappointments, much was learned from this experience. At the local level, changes were made in the biosecurity systems used at the hospital, including additional questioning by personnel when talking to clients about potential admissions to the hospital. On a more general level, the outbreaks have stimulated further investigation regarding the virus and risk factors associated with the development of clinical signs in naïve horses, better diagnostic testing for use on horses involved in a suspected outbreak of EHM, and development of biosecurity strategies for prevention and control of outbreaks. Additional research is being focused on development of new vaccines and the study of medications useful to treat affected horses. Finally, several workshops on this virus have been held, and a consensus statement is being developed by the American College of Veterinary Internal Medicine (ACVIM) regarding this disease.

Information regarding the virus has been significantly impacted by the notion that strains of EHV-1 with variation in pathogenic capacity exist. This hypothesis was investigated by Nugent et al.,[159] who recognized that variation of a single amino acid of the DNA polymerase was strongly associated with differences in clinical signs (neurological versus non-neurological disease). The recognition of this amino acid variation in a highly conserved region of the herpesvirus DNA polymerase increased the likelihood of this having an important function in the pathogenicity of the virus. Investigation regarding the virus is ongoing and has generated some controversy amongst major researchers in the field as they attempt to determine more precisely when the mutation occurred. Some of what has been learned about this strain of EHV-1 is that the strain has enhanced replicative capacity, which results in a greater likelihood of neurologic morbidity and mortality.[143,159–162] This increased replication of the mutant strain results in increased levels of viral particles in the nasal mucosa of horses, which then increases the efficiency of spread from horse to horse. Recently, recognition of this virus in certain populations of horses has been shown.[157] The finding of this strain of the virus as latent EHV-1 DNA in the submandibular lymph nodes of Thoroughbred broodmares in central Kentucky provides evidence that the virus has a presence in certain equine populations.[157] These findings suggest that attention should be focused on development of vaccines capa-

ble of providing protection against this strain of the virus and that horses with this strain of the virus do not need to be treated differently than other EHV-1 survivors.

The importance of this virus to the equine industry is in part a result of the economic impact from multiple abortions, multiple cases of equine respiratory disease, and outbreaks of myeloencephalopathy. The respiratory and abortion outbreaks have resulted in a detailed tracking of this virus worldwide; through this surveillance, variations in the composition of the nucleic acid have been detected. The *Alphaherpesviruses* have a wide host range, short reproductive cycle, and most importantly, the capacity to establish latent infections. Use of genetic and biologic markers has helped to track the viruses and explain the changes in virulence of the virus. Also, they may partially explain the inability to predict when and why cases of neurological disease occur. In addition, the protective immune response after either natural infection or vaccination is quite short.[163–168]

The criteria that have been used for the diagnosis of the neurologic form have been described, but in general, a prospective diagnosis can be made based on clinical signs alone. To confirm the diagnosis, a history of antecedent or concurrent upper respiratory tract disease, xanthochromic CSF (containing increased quantity of protein), or a three- to fourfold rise in anti-EHV-1 neutralizing antibody titers are useful. In addition, histological evaluation of nervous tissue from an affected horse will show the classic vasculitis changes, and in some cases, virus isolation from the buffy coat, nasal swabs, or postmortem samples are helpful.

When an outbreak of EHM is suspected, it is very important to have available rapid testing that has both good sensitivity and specificity to guide the management to control the outbreak. The testing that yields the most rapid result is PCR. The samples of choice are nasal swabs and buffy-coat samples of blood collected from horses suspected to have this disease. A PCR test that distinguishes the mutation associated with EHM has been described.[162]

The natural spread of this disease is through inhalation and ingestion, primarily by nasal aerosols from infected horses. Infections first occur on the mucosal surface of the respiratory tract, although direct contact with infected aborted fetuses or placental tissues may also serve as a source of infection. Spread of infection may occur by direct cell-to-cell spread and hematogenously through infected peripheral blood monocytes. The virus is considered to be endotheliotropic and results in vasculitis.

Clinical signs include fever, inappetence, and depression combined with serous nasal discharge and cough. Neurological signs are often preceded by a fever or upper respiratory disease in the few days to weeks before onset of neurological signs. The clinical signs observed as a result of EHV-1 myelitis can be quite variable. In most affected horses, symmetric ataxia and weakness of the pelvic limbs, urinary incontinence, and loss of sensation and motor deficits around the tail and perineal area are typical.

The management of horses with suspected EHV-1 myelitis or myeloencephalopathy should be directed at achieving a safe environment and providing excellent nursing care. A horse with obvious bladder dysfunction should quickly and as frequently as possible have aseptic evacuation of the bladder. Prophylactic antibiotics are essential to combat the problems associated with the development of cystitis along with non-steroidal anti-inflammatory agents such as flunixin meglumine, phenylbutazone, ketoprofen, or firocoxib.[f] The daily water needs for an affected horse should be 60–80 ml/kg daily. Along with the water, it is important to feed a gruel or if the horse can eat, provide a highly palatable source of energy and protein daily.

Treatment with antiviral drugs is now becoming more common. Initial investigation looked at acyclovir;[g] however, results using this drug were very inconsistent, and despite good dosing, blood levels failed to be recognized. Most recently, use of valacyclovir[h] has been investigated in the horse. This compound is a prodrug of acyclovir and has much better absorption and good bioavailability from the gastrointestinal tract.[169]

Despite the fact that many available vaccines contain high titers of inactivated virus and are able to stimulate high titers of virus to neutralize antibodies in horses, none are able to provide protection against the most severe forms of the disease—abortion and myeloencephalopathy.[143,160,163,165,167,168,170–172] Still, the risk of viral shedding may be decreased in herds of vaccinated horses. Therefore, regular vaccination is still important. The ideal frequency of revaccination is unknown but may be two to three times per year.

At this time, it is unclear whether or not any of the current or new vaccines will be effective against the neurological form of EHV-1. Preliminary work by researchers at Cornell University suggested a benefit using a modified live vaccine; however, the data is not yet compelling enough to recommend changes in choice of vaccine.[172] Understanding the role of the various arms of the immune system against this agent, particularly with regard to abortions and development of neurological disease, is important as is an understanding of the role of the various vaccines and adjuvants used in the production of herpesvirus vaccines.[173–181]

A critical part in the prevention of both abortion and herpesvirus myeloencephalopathy is to reduce the duration of the cell-associated viremia. Reduction of the cell-associated viremia seems to be important in preventing abortion after challenge with live virus in previously vaccinated horses.[163,182] Although the specific role of increased numbers of cytotoxic lymphocytes in prevention of myeloencephalopathy is unknown, it is likely this will play a role in protection from EHM in horses.[163] In any case, having both a humoral and cell-mediated re-

sponse against EHV-1 seems to be important in prevention of this disease. Currently, much work is being devoted to the investigation of the role of cell-mediated immunity in EHV-1 as well as the level of protection afforded by currently available vaccines.[177–179,183,184]

Investigation regarding EHV-1 is currently focused on three areas: the development of reliable and quick diagnostic testing, the identification of the role of specific parts of the equine immune system active against this virus, especially the mutant strain that has "replicative aggressiveness," and the development of a live virus vaccine that is hoped will be fully protective against the neurological form of this disease.[147,157]

11. What Does the Future Hold?

Outcomes for horses with neurological diseases are improving, because many practitioners now recognize that including the neurological examination as a part of the routine physical examination leads to earlier diagnosis and treatment. In addition, newer rapid and quantitative testing for diseases that affect the nervous systems of horses means early recognition and accurate diagnosis, and ultimately, this leads to significant economic savings for owners and trainers. Over time, many veterinarians are going to have access to horse-side testing for infectious diseases as readily as they now have access to radiography.

Diagnostic Modalities

The start of this manuscript described the technique for performing neurological examination on a horse. At the same time, there was discussion about the difficulty that sometimes exists with evaluation of a subtle lameness and separation of this from a neurological problem. Regardless of what neurological examination technique one chooses to employ, a difficulty faced by the examiner is elimination of the subjectivity associated with assigning a severity grade to the degree of weakness, ataxia, spasticity, and/or dysmetria. In some texts, a lack of joint flexion is described as a hypometria, which could also indicate weakness,[5,23,185,186] whereas in others, a lack of joint flexion is used to describe "spasticity."[131,187] With the benefit of technology in the future, practitioners may be able to better evaluate subtle gait changes including weight bearing through the use of force plates and videography.[188–190] Techniques such as fuzzy clustering and kinetic gait analysis will likely become more common.[8,9,191] Using kinetic gait analysis, one is able to detect significantly higher lateral force peak and greater variation in vertical force peaks in ataxic horses over lame horses,[9] whereas use of fuzzy clustering shows a greater amount of uncertainty of movement in ataxic horses over lame horses.[8]

After the identification of an ataxic horse as well as the neuroanatomic localization of the lesion, use of more sophisticated techniques for ante mortem evaluation of the lesion are now available.[192] Techniques such as magnetic resonance imaging, computed tomography, and ultrasonography are currently becoming more popular. With continued publications regarding the benefit of these techniques, it is my belief that modification of existing equipment will occur such that these techniques will become applicable to all parts of the equine anatomy, including the entire vertebral canal of an adult horse.

Diagnostic Techniques

As research continues, more specific and medically relevant laboratory tests are likely to be developed. Newer techniques such as real-time PCR with its high specificity, speed, and ability to be quantitative are already facilitating infectious disease diagnoses. With a better understanding of the biology of these diseases, it may be possible to develop tests that identify genetic factors (host and organism), disease predispositions, or biomarkers that are clinically meaningful. Rapid and accurate recognition of clinical signs of disease, combined with a proper diagnosis of the cause for the signs, will have significant implications in improved treatment regimens for an individual horse as well as helping to prevent outbreaks of infectious diseases such as EHM, West Nile virus, or Eastern and Western encephalomyelitis. Older diseases such as rabies might also be less problematic for a horse and its owners and caretakers when a rapid, accurate diagnosis can be made.

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[a]Depomedrol, Pfizer, New York, NY 10017.
[b]ReBalance, Phoenix Scientific, St. Joseph, MO 64503.
[c]Marquis, Bayer, Shawnee Mission, KS 66201.
[d]Navigator, IDEXX Laboratories, Westbrook, ME 04092.
[e]Toltrazuril, Baycox 5% suspension, Bayer, Toronto, ON M9W 1G6. Canada.
[f]Equioxx, Merial, Duluth, GA 30096.
[g]Acyclovir, GlaxoSmithKline, Research Triangle Park, NC 27709.
[h]Valtrex, GlaxoSmithKline, Research Triangle Park, NC 27709.