CEREBELLAR DISEASE IN THE ARABIAN HORSE

by

Margaret Turner Beatty
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College of Veterinary Medicine
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Approved by:

Major Professor

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DEDICATION

This thesis is dedicated to my parents, Col. and Mrs. Robert Turner, whose inexhaustible love and endless encouragement allows me to pursue life and learning with exuberance, perseverance and objectivity.

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INTRODUCTION

Equine cerebellar disease is observed primarily in the Arabian breed. An inherited mode of transmission has been assumed based on breed predisposition and familial relationships between affected animals. Yet, no controlled breeding trials have been reported to support this assumption.

Clinical signs are characteristic for cerebellar disease, reflecting proprioceptive and motor inadequacies. The time of onset, progression, and degree of severity are variable among affected individuals. Laboratory analyses have not been reported to elucidate any particular trends specific for or indicative of cerebellar disease, and electroencephalographic evaluation has not been made of horses with the condition.

Histopathologic abnormalities are consistently found in the cerebellum and variably identified in other regions of the central nervous system. The degree of severity of the cerebellar lesions is relatively constant despite the variable severity of gait deficit displayed clinically.

The objectives of this study were as follows:

1. Thorough evaluation of a group of Arabian horses showing signs of cerebellar disease. Assessment methodology employed clinical neurologic examination, hematology, blood chemistry, viral isolation, electroencephalography, radiology, and histopathology.
2. Comparison of the data collected to enable visualization of similarities among the animals studied.
3. Further definition of the clinical and histopathologic abnormalities considered characteristic for Arabian cerebellar disease.

REVIEW OF LITERATURE

INTRODUCTION

A brief review of cerebellar development and anatomy, and the histopathologic changes which are characteristic of nervous tissue, is required for a basic understanding of cerebellar pathology. Following a general overview, a breakdown of the cerebellar disorders of the domestic animal species will provide a basis for comparison to that which is seen in the Arabian horse.

The format used to abstract the literature was taken from an article by Alexander de Lahunta.[20] Cerebellar disorders are divided into prenatal and postnatal categories. Subdivisions of the prenatal group include infectious, malformations, and degenerations. Postnatal cerebellar disease is usually degenerative and is distinct from prenatal cerebellar disease in that a period of apparent normalcy preceeds the onset of clinical signs.

DEVELOPMENT

The cerebellum develops from the alar plate in the metencephalic region of the fetal brain. Each dorsolateral portion of the plate bends medially to form the rhombic lips which approach each other on the midline and become compressed in a rostro-caudal direction to become the cerebellar plate. The midline of the plate gives rise to the cerebellar vermis while the more lateral portions become hemispheres. A transverse fissure divides the flocculo-nodular lobe from the body of the cerebellum early in development. This small caudal lobe is the most primitive part of the cerebellum and is connected with the vestibular system.

The cerebellar plate is composed of three layers in laminar arrangement from ventral to dorsal. The neuroepithelial layer is most

ventral and adjoins the roof of the fourth ventricle. The mantle layer contains neuroblasts whose processes constitute the most dorsal marginal layer.

Neuroblasts from the mantle lose their ability to divide early, but continue to mature into Purkinje neurons and neurons of the deep cerebellar nuclei. Purkinje cell formation is generally complete by mid-gestation. In the bovine mature Purkinje cells are established by about 100 days of gestation.[23] In the ovine, however, they do not become recognizible until 85 days.[39]

A population of germinal cells migrate to the surface of the rhombic lip where they continue to divide as folia are formed. This cell layer is referred to as the external germinal layer (EGL). When the cells reach a thickness of about 10-12 layers the innermost cells begin to lose mitotic capabilities. These differentiated cells migrate through the Purkinje cells and take residence just deep to them forming the granular cell layer. Eventually the entire EGL is lost as the cells migrate into the cerebellar substance. A few neurons remain in the outer molecular layer as superficial stellate and basket cells.

The external germinal layer is active later in gestation than the internal germinal layer from which mantle cells arise. The stage of EGL activity, and consequently, the extent of neonatal cerebellar development, correlates with the degree of motor coordination immediately following parturition. In the feline and canine the external germinal layer has not even reached maximum thickness at birth. It does so by one week postpartum and begins to decrease in size after two weeks. However, it has been known to persist to 84 days in the kitten and 75 days in the pup.[23] Accordingly, the formation of the granular cell

layer in these species may continue growth through the tenth postnatal week.[63,70] Species such as the bovine and equine, in which immediate postnatal ambulation is imperative for survival, display a full thickness EGL prior to birth. In the calf this stage occurs at 183 days of gestation. By parturition the granular layer is almost complete and the germinal cells are markedly reduced. At six months of age the external germinal layer is no longer detectable in the bovine.[23] Formation of the granular layer continues for two to four weeks postnatally in the lamb.[39]

GROSS ANATOMY

The cerebellum lies in the posterior cranial vault caudal to the cerebrum, from which it is separated by the transverse fissure. It covers the fourth ventricle and is attached to the brain stem by fiber tracts referred to as cerebellar peduncles.

The core, or medulla, of the cerebellum is composed of white matter which extends many branching processes, the arbor vitae, toward the calvarium. These are covered superficially by a grey matter cortex and are collectively referred to folia.

The equine cerebellum is slightly flattened rostro-caudally so that its greatest diameter is in the transverse plane.[55] Along this axis distinction can be made between the centrally located elongate vermis and the lateral hemispheres. In a longitudinal plane the cerebellum can be divided into a large cranial body and a much smaller caudal flocculonodular lobe. The body is further subdivided by the primary fissure into anterior and posterior lobes which are themselves composed of smaller sections referrable to both vermis and lateral hemispheres.

The rostral lobe of the vermis consists of (from cranial to caudal) five lobules referred to by the numbers I-V, or as the lingula and the central and culmen lobules which are both divided into two parts. Corresponding hemispheric lobules are designated HI-HV. The caudal lobe of the body is composed of the vermal declive, folium, tuber, pyramid, and uvula lobules with respective hemispheric simplex, ansiform, paramedian, and dorsal and ventral paraflocculars lobules. The most caudal portion of the cerebellum, the flocculonodular lobe, consists of a median nodulus and two lateral flocculi. This lobe is closely integrated with the vestibular system.

Deep in the medullary white matter are three bilaterally symmetrical cerebellar nuclei. Arranged from medial to lateral they are the fastigial, interposital, and dentate.

Fiber tracts leaving and entering the cerebellum do so via three peduncular attachments to the brain stem. Anatomically these are located from medial to lateral, but nomenclature designates them cranial, middle, and caudal. The caudal cerebellar peduncle carries afferent input from the spinal cord and medulla oblongata. The middle peduncle is an extension of the transverse fibers of the pons and is also afferent to the cerebellum. The rostral peduncle connects the mesencephalon with the cerebellum and is primarily composed of efferent fibers which leave the cerebellum and course toward the cerebrum.

HISTOLOGY

Cortex

Cerebellar lobules are a series of transversely oriented folia covered by cortical grey matter. The cortex is composed of three

distinct layers. The outer molecular layer is largely devoid of cells, but consists primarily of neuronal fibers originating in the underlying layers. The few cells present in this layer are referred to as stellate cells and may be superficially or deeply placed. Their axons generally follow the folial plane, but collaterals of the more deeply placed neurons arborize around underlying Purkinje cells. Thus, the deeper stellate cells are called "basket cells".

Immediately adjacent to the molecular layer is a stratum of single large pyriform cell bodies which constitute the Purkinje cell layer.

The third layer is comprised of the small neuronal cell bodies of granular cells and the less numerous golgi cells.

Fibers and Projection

The fibrous arrangement of the molecular layer has been likened to telephone wires coursing from pole to pole.[23] The Purkinje dendrites which extend into this layer are oriented along the transverse axis of the folia (the telephone poles). Granular cell axons course longitudinally along the folia synapsing with numerous Purkinje dendrites.

Superficial stellate and basket cells of the molecular layer act as interneurons between granule and Purkinje neurons. Golgi neurons in the granular layer receive input from the molecular layer and in turn act on granular cells.

Purkinje cell axons are the only efferent fibers from the cerebellar cortex. They project primarily to the deep cerebellar nuclei. A few axons from the flocculonodular lobe bypass the nuclei and course to the vestibular nuclei by way of the caudal cerebellar peduncle.

The two major cerebellar afferent fiber types are mossy and climbing fibers. Mossy fibers originate in the brain stem and spinal cord and project into the cerebellum via the middle and caudal cerebellar peduncles. The fibers traverse the medulla and, after sending collateral branches to the deep cerebellar nuclei, they terminate on granular and Golgi cell dendrites.

Climbing fibers are the axons of olivary neurons which ultimately synapse with Purkinje cells. They enter the cerebellum via the caudal cerebellar peduncle on the side opposite that from which they originate. Collateral processes are given off to the deep cerebellar nuclei as they course through the medulla.

Actions

In general, information coming into the cerebellar cortex is facilitated at synapses. That coming from the cortex is modified by the inhibitory influence of interneurons and Purkinje cells. Mossy and climbing fibers facilitate granular neurons and Purkinje cells, respectively. Granular cells have a positive influence on Purkinje neurons. Interneurons of the molecular layer (stellate cells) inhibit Purkinje cells which, in turn, exert an inhibitory influence over the deep cerebellar nuclei or vestibular nuclei. Golgi neurons of the granular layer have a negative effect on granular cells.

FUNCTION

The cerebellum functions as a modulator of motor activity. It regulates and coordinates movement, maintains equilibrium, and preserves postural and spatial integrity. Feedback circuits between other aspects

of the central nervous system and the cerebellum allow it to keep constant awareness of changing position and exert its stabalizing influence.

Upper motor neurons (UMNs) from the cerebral motor cortex project information to the cerebellum concerning initiation of voluntary activity, postural maintainence, and antigravitational body tone. The connection between extra-pyramidal pathways and cerebellar afferents is primarily made at the caudal olive. Afferents from the olive enter the contralateral caudal cerebellar peduncle and continue as climbing fibers to synapse with Purkinje cells. These in turn exert their inhibitory effect over the lateral (dentate) nucleus from which fibers return to the motor cortex via the thalamic nuclei. The pontine nucleus is also a relay center for incoming cerebrocortical information. Cerebellar influence over upper motor neurons allows indirect control over lower motor neuron activity.

Knowledge of the body in space is relayed to the cerebellum by general and special proprioceptive pathways. The spinocerebellar, cuneocerebellar, and vestibulocerebellar tracts enter the caudal peduncle and project to vermal and paravermal folia. Vestibular feedback is communicated to the vestibular nuclei directly via Purkinje cells and indirectly via the fastigial nucleus.

Tectocerebellar processes carry auditory and visual stimuli to the head of the vermis by way of the rosral cerebellar peduncle.

Cerebellar nuclei are continually facilitory to brain stem nuclei. It is Purkinje inhibition which actually subdues the range and force of motion. The degree of inhibition exerted is dictated by the influence of mossy and climbing fibers.

PATHOLOGY

Clinical signs

When the regulation and control of motor activity are disrupted by diffuse cerebellar disease movement becomes exaggerated and erratic. Inability to control the rate, range, or force of movement is referred to as dysmetria. With cerebellar disease an overreaching stride or hypermetria is common. An example of dysmetria, unrelated to gait, is the so-called rebound phenomenon. If the head is extended and quickly released it will bob ventrally past its normal position and rebound dorsally before coming to rest. This delayed cessation of movement is due to lack of Purkinje inhibition.

The term ataxia is also applicable in describing poor coordination of the limbs and body. It is characterized by a swaying motion in the hips or entire trunk and the tendency to over adduct or abduct the limbs, especially when circling. Ataxia is an indication of proprioceptive loss.

Delayed protraction is yet another common manifestation of cerebellar disease. A moments hesitation prior to lifting the limb followed by exaggerated flexion and prolonged aerial phase (hypermetria) is typical.

The gait deficits which accompany cerebellar disease are generally bilaterally symmetrical. However, in the rare instance that only one side of the structure is affected, the ataxia may be unilateral and would indicate a lesion on the same side.

Broad based stance is a typical reaction to loss of postural stability. Often a trunkal sway or trunkal ataxia is displayed. As the animal loses his center of gravity he may shift his weight which inevitably results in overcompensation and appears as alternating jerk-sway motion.

A characteristic sign of cerebellar disease is the intentional head tremor; so called because intended movement causes it to be exaggerated. The tremor may be in a horizontal or vertical direction and is often in both planes. De Lahunta describes the intention tremor as a form of dysmetria.[23]

There is no paresis or loss of strength associated with cerebellar dysfunction. Reflexes remain intact and may even be hyperactive. Severly affected animals may reach a state of lateral recumbancy and exhibit opsthotonus. Even ambulatory individuals may seem to have increased muscle tone.

Vestibular disturbances result in loss of equilibrium and abnormal nystagmus, but these signs do not always accompany those of generalized cerebellar disease.

The lack of a menace (or blink) reflex despite normal visual responses has been an interesting finding in animals with cerebellar problems. The explanation for this phenomenon is that visual pathways, once past the optic radiation, course through the cerebellum prior to their connection with the facial nucleus. It is thought that these tracts are part of the corticopontocerebellar pathway.

Histopathology

The cerebellum reacts to injury in a manner typical of nervous tissue. Neuronal cell bodies and processes are the immediate foci of necrosis, while glial cells first react to surrounding degenerating structures, and then themselves undergo necrosis.

The cerebellar Purkinje neurons are uniquely susceptible to insult, be it traumatic, metabolic, chemical, or anoxic. Hypoglycemia and hyperthermia are noted causes of Purkinje cell death.[13]

The first sign of neuronal necrosis is chromatolysis. This refers to a dispersal of the Nissle substance normally present in the perikaryon. Nissle loss may be apparent centrally surrounding the nucleus or peripherally, with the exception of the area of the axon hillock where the substance is not normally found. Chromatolysis is a relatively immediate (within a few hours), nonspecific and reversible change. Occasionally neurons are lost with no evidence of chromatolysis. Peripheral axonal injury is held responsible for this degeneration labeled simple atrophy.[74]

Nuclear swelling and displacement follow chromatolysis. Eccentric repositioning of the nucleus accompanies its eventual lysis and dissolution. Past the point of reversibility, the swollen cell begins to shrink and take on deeper staining properties until finally it is lost. This process is referred to as Gudden's atrophy and may run its course in a matter of two days.[71]

Glial reactions to dying neurons is carried out in the two stage process of satellitosis and neuronophagia. This phenomenon is indicative of true necrosis and differentiates it from postmortem autolysis. Minutes after anoxic injury oligodendroglia or microglia surround the injured neuronal cell body in preparation for phagocytosis. This reversible change is called satellitosis. The actual engulfment of cellular substance takes place within a few hours of injury. At this stage the glial cells are termed neuronophages.

Astrocytes react to disruption within the central nervous system by increasing their numbers and/or size.[42] Edema is a primary stimulus for their amitotic activity, indeed. Nervous system edema is characteristically intra-astrocytic.[43] Swollen, hypertrophied astrocytes are

called gemistocytes. In white matter astrocytes aggregate to wall off focally inflammed or degenerative areas leaving a residual cavity. Blood vessels and pia matter may contribute scarring components to similar defects in grey matter.

Axonal damage often initiates the death of the perikaryon. However, axonal degeneration is, of itself, an entirely separate phenomenon. Initially the axon swells and increases its basophilic staining characteristics.[43] Swollen axons, termed spheroids, may be granular or homogeneous. Swollen Purkinje axons of the cerebellum are referred to as torpedos.

Concurrently myelin becomes fragmented and begins to degrade to neutral fat. So called digestion chambers of fatty myelin breakdown products and axonal debris are formed. The role of myelin in axonal degeneration is not apparent with hematoxylin and eosin staining due to the dissolution of that substance during fixation. Phagocytic glial cells are attracted by the necrotizing process and engulf the fat and debris to become known as "gitter cells". Wallerian degeneration occurs both in a proximal and distal direction from the point of injury to the extent that the cell body may eventually be destroyed.

Axonal degeneration and demyelination occur slowly in the central nervous system when compared to the peripheral nervous system.[43]

Vacuolations in the white matter may give an overall "moth eaten" appearance indicating axonal loss. Within the empty spaces lipid laden gitter cells may be observed. Myelin stains such as luxol fast blue will identify areas of demyelination as a generalized decrease in staining intensity. The Marchi stain for degenerating myelin is used as a direct assessment of myelin degeneration.

TERMINOLOGY

The terminology used to describe cerebellar pathology often leads to some confusion. In several of the inherited cerebellar degenerations it has not been definitively established whether the process begins before or after complete development has taken place.

The underdeveloped cerebellum requires its own descriptive designation. Hypoplasia is the term utilized in the case of tissue which has never completed normal growth. It can be used on both a macroscopic and microscopic level.

Atrophy describes a degenerative process which occurs after complete normal development of a tissue. It often signifies a reduction in tissue size due to shrinkage or loss of cellular components. Atrophy may be due to inadequate nutrition or innervation, cellular necrosis, or disuse.[77] It is nonspecific with regard to inciting cause of cell death and encompasses both endogenous and exogenous sources of insult.[20]

Abiotrophy is a term introduced by Sir William Gowers in 1902 at a lecture delivered to the National Hospital for the Paralysed and Epileptic in London.[32] Gowers used the word to describe an intrinsic lack of vitality among body parts distinct from the loss of general somatic life. The application was made to certain groups of neurons which differed both in function and rate of decay.[30] Such an endogenous defect suggested a hereditary, but not congenital, etiology.[28] Further definition of abiotrophy as a premature degeneration (of intrinsic metabolic error) distinguished it from atrophy.[20]

SUMMARY OF CEREBELLAR DISEASE IN DOMESTIC ANIMALS

I. CANINE -- PRENATAL

a. Infectious-Viral

To date there has been no report of in-utero virally induced cerebellar disease in the neonatal pup. However, newborns which contract systemic Herpes virus infection and survive may occasionally be left with residual cerebellar damage.[62]

b. Malformation-Cerebellar Hypoplasia

Wire-haired Fox Terrier and Irish Setter

Cerebellar hypoplasia accompanied by cerebral lissencephaly has been reported in two of three pups in a litter of wire-haired fox terriers and three of ten puppies in a litter of Irish setters. The animals displayed symmetrical dysmetria and head tremor which were nonprogressive in nature. One fox terrier which was kept for a period of time began having seizures after one year of age, presumably due to the cerebral defect.

Both breeds exhibited gross hypoplasia of the cerebellum with lack of cortical formation. Histologically cortical and Purkinje cells were randomly distributed.

An inherited cause was suspected.[23]

Boston Bull Terriers

Partial agenesis of the cerebellum has been reported in this breed in conjuction with hydrocephalus.[24]

Chow Chow

Cerebellar hypoplasia in six of fourteen related Chow puppies has been hypothesized to be autosomal recessive in that breed. Signs were

apparent at 24 days of age when the pups displayed ataxia and hypermetria primarily in the rear limbs. Elevation of the head resulted in bobbing of both head and trunk. The syndrome was nonprogressive. Indeed, one related adult animal which was presented with clinical signs at ten months appeared normal when necropsied at nine years of age. Histopathic lesions, however, were consistent with those seen in the pups.

At necropsy gross hypoplasia was variable. Light microscopy revealed decreased numbers and heterotopy of Purkinje cells, but no degenerative changes in neuronal cell bodies. Granular cells were also less numerous. Localized vacuolization was random throughout the central nervous system.[48]

c. Degeneration

Samoyed

Evidence of cerebellar degeneration which was nonprogressive in nature was exhibited in three litters of Samoyed puppies. Present at first ambulation, the signs were ataxia and hypermetria of marked severity in the pelvic limbs with milder dysfunction of the thoracic limbs. The spastic rear legs were carried forward under the body. Falling to the side or backward was not uncommon. Vision was normal, but the menace reflex was poor. There was no intention head tremor.

The prominent histopathologic lesion was degeneration of Purkinje cell axons with little to no degeneration of cell bodies. Myelin degeneration and axonal damage were indicative of Wallerian degeneration.[20]

Beagle

Two of a litter of six beagles were affected with a macroscopically different type of cerebellar degeneration, present at first ambulation. The dogs displayed severe ataxia of the limbs and trunk, head tremor, and a hypermetric gait.

The cerebellum showed Purkinje cell degeneration as diffuse decrease in their numbers and swollen axons in the granular layer. Granule cell nuclei were also depleted. Myelin degeneration and axonal lesions were interpreted as Wallerian degeneration.

The presence of swollen axons of Purkinje cells is a nonspecific change indicative of neuronal degeneration. Such a finding would not be present if the neuron had failed to develop.[20] It is therefore used as a criterion for usage of the descriptive terminology, cerebellar degeneration rather than hypoplasia.

Dachshund Cross-breed

A part Dachshund mix breed puppy displayed abnormal gait and head tremor at three weeks of age.[53] By eight weeks signs had progressed to severe ataxia, dysmetria, base-wide stance, and frequent falling over. The vertical and horizontal intention tremor had increased in severity and extent to involve the trunk.

Central nervous system abnormalities were limited to the cerebellar cortex where degenerative changes were observed in virtually all Purkinje cells. These ranged from chromatolysis and vacuolization to shrinkage and hyperchromasia, eventually leading to empty basket formation as cell death occurred. The granular layer was attenuated and contained swollen axonal torpedos. Focal gliosis was present at the granular-molecular junction.

It was postulated that the abnormality in this case could be due to perinatal hypoxia. Purkinje neurons are easily damaged under hypoxic conditions.[39] This individual, the sole affected pup of a litter, was found to have a patent ductus arteriosus. Under normal circumstances that fetal bypass system obtains functional closure via high postpartem circulating oxygen levels. Thus, hypoxia was the common denominator behind both abnormalities.

Irish Setter

An autosomal recessive cerebellar degeneration has been reported in Irish Setters.[61] The dogs were born blind and were never able to ambulate. They displayed tremors, nystagmus, and "fits".

Gross lesions were not evident. Light microscopic findings revealed cerebellar cortical degeneration. There was a substantial deficit of Purkinje cells and those remaining were necrotic. Astrocytes infiltrated the Purkinje cell layer. Vacuolation and swelling of neuronal cell processes was evident among a depleted granular layer.

No explanation could be made for the amblyopia given solely cerebellar lesions.

Bern Running Dog

Some Bern Running dogs have displayed cerebellar ataxia from birth. Loss of Purkinje cells and symmetric olivary nuclear degeneration characterize the disease for which a genetic basis has been suggested.

II. CANINE -- POSTNATAL

a. Neuraxonal dystrophy

Collie Sheep Dog

A cerebellar axonal degeneration which spares Purkinje neuronal cell bodies has been documented in Collie sheep dogs from New Zealand and Australia.[14] Onset of clinical signs was at two to four months of age. The animals exhibited ataxia, hypermetria and difficulty balancing which resulted in a base-wide stance.

Swollen axons, termed spheroids, were the primary abnormality witnessed in the cerebellar folia and peduncles extending into the lateral vestibular nuclei. The lesions extended rostrally to involve the substantia nigra, rostral colliculi and cerebrum and caudally via the gracil nucleus into spinal cord grey matter. In these regions, however, it was of milder nature. Accompanying the axonal dystrophy in the cerebellum and vestibular nuclei was a diffuse gliosis. Vacuolations containing gitter cells were scattered throughout the cerebellar white matter characterizing a mild Wallerian degeneration. Purkinje and other neuronal perikarya were unaffected.

Axonal changes independent of soma degeneration and coincident with minimal demyelination suggested a primary defect in axoplasmic metabolism.

Smooth Coated Fox Terrier

An hereditary progressive ataxia was reported in Smooth coated fox terriers.[10] The dogs demonstrated ataxia beginning at ten to sixteen weeks of age which became slowly progressive.

Microscopic lesions were confined to the spinal cord, specifically the spinocerebellar tracts.

b. Cerebellar Degeneration

Rough Coated Collie

Thirty-nine of sixty known affected Rough coated collies were presented to the University of Sidney for necropsy due to cerebellar ataxia.[35] The pups began to show posterior incoordination at four to eight weeks of age. Later they became markedly hypermetric with base-wide stance and trunkal ataxia. Intention tremors of the head were present. Nystagmus, opisthotonus, and convulsions were not seen. Excited animals were inclined to fall forward or sideways.

On gross examination of the cerebellum the anterior vermal lobules displayed a reduction in size. In processed sagittal sections staining intensity of the granular layer in the anterior folia was greatly reduced due to extensive granular cellular loss. The variability in extent of the lesions from pup to pup suggested a cranial to caudal spread from lingula through central, culmen, and declive lobules, occasionally including part of the nodulus. Lateral spread accompanied the advancing vermal lesion.

Histopathology demonstrated degeneration and loss of preformed granular and Purkinje cells. The authors emphasized that necrosis of preformed granular cells might implicate those neurons as primary in the degenerative process. Axonal torpedos were occasionally present in the granular layer. In advanced cases Wallerian degeneration was extensive from the cerebellar folia to the brain stem and into the spinal cord. Myelin stains showed further evidence of demyelination at all levels of the cord including all but the dorsal funiculi. Minimal glial reaction was noted.

This syndrome was concluded to be of autosomal recessive inheritance.

Border Collie

A syndrome similar to that seen in Rough coated collies has been documented in two of a litter of four Border collies.[29] Communication with the breeder revealed that a previous litter borne to a related dam experienced three out of four affected pups. The condition was deemed familial.

At approximately two months of age the pups displayed ataxia. Later they became hypermetric and developed a head tremor.

Post mortem and histopathologic examinations showed cerebellar lesions characteristic of inherited cerebellar degeneration in Rough coats. The anterior cerebellar vermis was flattened grossly. Microscopically granule and Purkinje degeneration loss were apparent.

Kerry Blue Terrier

An autosomal recessive abiotrophy in Kerry Blue terriers has been documented by several authors.[52,22,18] The initial signs in two to four month pups were pelvic limb stiffness and head tremor. The dogs retained normal strength but became dysmetric and hypermetric in all four limbs to the extent that by one year of age they were unable to stand. Trunkal ataxia and base-wide stance were characteristic. Nystagmus has not been observed.

No gross pathology was evident on post mortem examination. Histologically cerebellar cortical degeneration was manifest first as Purkinje cell necrosis and depletion, followed by loss of granular cells. Over a six month time frame the degenerative process involved the olivary nuclei, substantia nigra, and caudate nuclei.

A similar temporal sequence of events characterizes olivopontocerebellar degeneration in man and has been described as transsynaptic

retrograde chain degeneration. The condition in Kerry Blues differs in that it did not include pontine nuclear degeneration. Mettler and Goss used the term striocerebellar degeneration in the first citing of this syndrome. The extensive involvement of extrapyramidal nuclei was evident even at that time. Deforest included axonal swelling and astrogliosis surrounding the deep cerebellar nuclei in his microscopic findings.[18]

Gordon Setter

Cerebellar abiotrophy in Gordon Setters was first reported by de Lahunta et al. in 1980 as being of autosomal recessive inheritance.[23] At that time a breeding colony was established at Johns Hopkins University under the direction of L. C. Cork to further study the degenerative phenomenon. In 1981 Steinberg added the findings of the Johns Hopkins team to the literature.[73]

Onset of clinical signs ranged from six to twenty-four months of age, with a more narrow span of six to ten months described in the later publication. Initially, a base-wide stance and a stiff hypermetric gait in the thoracic limbs were observed. As the disease slowly progressed the pups showed trunkal ataxia and delayed protraction. Strength and proprioception remained normal. Nystagmus and head tremor were reportedly absent in the animals examined by de Lahunta et al. Cork's group, however, found these abnormalities to be part of the clinical picture. Both articles cited an increase in tendon reflexes.

Post mortem evaluation of the cerebellum revealed a grossly smaller structure which weighed less than normal. Thinning of the folia allowed wider sulci to be evident.

Microscopic lesions were restricted to the cerebellar cortex. Purkinje and granular cells were degenerate and depleted. Astrocytes filled the void after Purkinje cell loss. Occasional swollen axons were observed. The molecular layer was thinner than normal. De Lahunta noted the presence of yellowish granular pigment in macrophages surrounding the cerebellar nuclei and, less frequently, in the meninges.

Unique aspects of this syndrome were the late onset and slow progression of signs and the exclusive involvement of the cerebellar cortex.

Schnauzer-Beagle Cross

Signs indicative of cerebellar degeneration became evident in a Schnauzer-Beagle cross of four and a half years when he began to display hind limb ataxia and forelimb hypermetria.[13] The hypermetria progressively involved all four legs. The dog developed a head tremor and later, trunkal ataxia. Wide-base stance was assumed when he was immobile. Though vision was not impaired, the menace reflex was diminished.

Computerized tomography and surgical exploration identified irregularity of the osseous tentorium cerebelli. Biopsy was made of the vermis and right cerebellar hemisphere to evaluate possible histologic change.

Microscopy showed degeneration of Purkinje and granule cells with thinning of the molecular layer. Some Purkinje cell bodies were displaced into the granular layer. Yellow granular pigment, which was neither PAS positive nor lipofuscin-like, was observed free and in glial cells among the Purkinje and granular cell layers. Morphologic diagnosis was chronic active neuronal necrosis.

At the time of this report (1983) the dog remained alive and healthy despite severe symptoms as described. This slowly degenerative process was thought to be associated with changes which took place in the osseous tentorium.

Airedale Terrier

In 1952 Cordy and Snelbaker described a cerebellar degeneration in Airedale terriers which seemed to be both a regressive and hypoplastic process.[15] The incidence of occurrence in several generations led to the belief that this was an inherited syndrome.

The pups became extremely ataxic, with hypermetria in the thoracic limbs and frequent falling by three to six months of age. Initial signs were evident at twelve weeks of age. While the dogs could hardly stand, they sat with relative ease, but exhibited swaying of the trunk and head. Opisthotonus and nystagmus were not witnessed and the disease seemed nonprogressive.

Gross pathology disclosed a small flattened cerebellum.

Histopathologically, lesions were confined to the cerebellum. Purkinje cells were markedly reduced in number and the few remaining were quite degenerate. Occasional empty baskets were seen among the proliferative glial cells in the Purkinje cell layer. Gliosis was also observed in the molecular stratum along with neuron-like cells identified as "neuroblasts". The white matter of the folia did not show demyelination but was randomly vacuolated. Mild chromatolysis of cerebellar nuclear neurons was apparent.

Others

Cerebellar degenerations of suggested genetic origin have been documented in Finnish Harriers[78] and observed by de Lahunta in Labrador and Golden retrievers, Great Danes, Cocker Spaniels, and Cairn terriers.[23]

III. FELINE -- PRENATAL

a. Infectious-Viral

Panleukopenia Virus

Feline cerebellar ataxia was first described by Rumpf in 1885. Since that time numerous cases have been documented. The syndrome was thought to be genetically transmitted by some authors but others suspected a viral etiology.[54] The latter supposition was proven to be correct by Kilham and Margolis when they were able to transmit the disease from affected kittens to normal kittens and ferrets by intracerebral inoculation of a cerebellar emulsion.[46] The organism was further defined as feline panleukopenia virus by Johnson[41] and confirmed as such by Csiza.[17]

Clinical signs were manifest as the kittens became ambulatory. They consisted of symmetrical ataxia, periodic falling, and head bob and were nonprogressive.

Gross pathology generally revealed a smaller than normal cerebellum.

Granuloprival cerebellar hypoplasia along with Purkinje neuronal degeneration were paramount among microscopic lesions. The virus' propensity for actively mitotic cells attract it to the granular layer which reaches its full thickness by one week post-partem and continues to mature for up to ten weeks in the kitten.[70] Purkinje destruction is

not as easily explained. It has been established that development of these cells is complete by midgestation in the bovine.[45]

If natural infection occurs while the cells of the external germinal layer are actively mitotic, then the preformed Purkinjes should not suffer. The fact that they do degenerate, and have been shown to contain feline panleukopenia particles by flourescent antibody testing[16] has lead to the proposition that this is not only a hypoplastic process, but a degenerative one as well.[19]

Other central nervous system abnormalities cited as part of this syndrome were spinal cord demyelination, glial nodule formation, and perivascular lymphocytic cuffing. Alterations in viability and numbers of cerebellar associated brain stem nuclei prompted one author to describe the process as olivopontocerebellar atrophy.[68] At that time feline panleukopenia virus had not been etiologically incriminated.

b. Degeneration

Siamese

Woodard presented evidence to substantiate an autosomal recessive pattern of inheritance for feline neuraxonal dystrophy in the Siamese cat.[83] The incidence of disease was associated with dilute coat color in that breed. Kittens showed signs of incoordination at birth which were progressive with age.

Cerebellar size was normal in young affected cats but mildly reduced in older animals.

Axonal degeneration was the most outstanding abnormality witnessed in the central nervous system. The lesion, characterized by swollen and ballooning axons, was pronounced in the olivary and lateral cuneate nuclei and was of a less severe nature in the brain stem, thalamus, and

cerebellar vermis. Neuronal degeneration accompanied the white matter lesion in the thalamus and olivary nuclei and was evidenced by reduction of Purkinje and granular cells in the cerebellum.

IV. BOVINE -- PRENATAL

a. Infectious-Viral

Bovine Viral Diarrhea (BVD)

The relationship between calves with cerebellar disorders and their BVD infected dams was observed by Kahrs et al. cited by de Lahunta, 1980. In time further investigation verified the association through epidemiologic and immunologic avenues.[45,1] Brown et al. produced the defect by innoculation of pregnant heifers at various days of gestation in order to establish a suseptability pattern.[11]

In utero viral infection results in several central nervous abnormalities which may accompany cerebellar hypoplasia. Hydranencephaly is most commonly encountered. Greene reported four incidences of the combination, but was unable to elucidate a cause.[33] Badman et al. described a relationship between BVD and the occurance of these two malformations, including hydrocephalus as a third abnormality.[3] The duo of cerebellar hypoplasia and hydrocephalus was also found to be related to BVD by Axthelm and Leipold.[2]

Calves demonstrated clinical signs from birth. Their ability to rise was impaired and in those which could stand the inability to gain equilibrium and coordinate movement was obvious. Recumbant animals paddled or exhibited opisthotonus. Occasionally abnormal nystagmus and/or head tremor were exhibited. Individuals with a concurrent hydrocephalus or hydranencephaly frequently showed doming of the forehead.

The cerebellums of affected calves were generally smaller than normal.

Histologic lesions varied with the age at infection in the work done by Brown et al.[11] Calves infected early in gestation (79 days) demonstrated uniform cerebellar granuloprival hypoplasia which was most dramatic in the lateral hemispheres. Those animals infected at a later gestational stage (up to 150 days) exhibited cavitation of the folial white matter and variable degrees of cortical destruction. Heterotopy and loss of Purkinje cells and reduction of the granular layer were intermittently mingled cortical abnormalities. Axonal torpedos were seen among the granule cells.

Scott et al. found that the most critical time for infection resulting in cerebellar hypoplasia was 146-150 days of gestation.[69] The development of the external granular layer (EGL) in the bovine occurs between 57 and 183 days.[21] It is reasonable, then, that viral intervention during this critical developmental period would result in delayed or arrested migration and differentiation of granule cells.

Brown and workers were of the opinion that the granuloprival destruction was the result of viral action on precurser cells and thus a hypoplastic process.[11] The marked cortical degeneration and white matter cavitation, however, were considered to be the result of a degenerative phenomenon. It was suggested that a virally induced vascular disturbance or coagulopathy gave rise to the cavitating lesion.

Cho and Leipold pointed out discreet differences in the lesions produced by genetically induced cerebellar hypoplasia as opposed to those of viral etiology.[12] In virally induced disease calves presented evidence of an inflammatory process, cavitation of cerebellar white

matter, and occasional ocular lesions. The genetic form of an often clinically identical syndrome was characterized by a generalized reduction in cerebellar size or parts thereof.

Akabane Virus

This insect born Arbovirus has been the cause of neonatal central nervous system anomalies in calves and lambs.[36] In utero infection resulted in cerebral malformations that were often accompanied by cerebellar hypoplasia.

Clinical signs were referable to the cerebral lesion, but could be amplified by cerebellar disturbance. Weakness, blindness, difficulty standing and walking, and variable doming of the forehead were typical manifestations of viral destruction of nervous tissue. Hydranencephaly was the most prominent cerebral malformation.

Greene considered the possibility of Akabane virus as the etiologic factor in a group of Holstein-Friesian calves with hydranencephaly and severe cerebellar hypoplasia.[33]

Bluetongue

In utero bluetongue infection is reported to cause hydranencephaly in calves and lambs.[51,64] As with Akabane virus, the cerebral lesion is primary and constitutes the major basis for clinical appearance of the disease.

b. Malformation-Cerebellar Hypoplasia

Hereford

Innes et al. first reported familial cerebellar hypoplasia and degeneration in Herefords.[38] Another autosomal recessive central nervous defect of Herefords was later described by Orman and Grace,[56] and Baker et al.[5] Cerebellar cortical dysplasia accompanied by cerebral

polymicrogyra and dilatation of the lateral ventricles due to hydrocephalus characterized this syndrome. Ocular defects were also common.

Congenital internal hydrocephalus and cerebellar hypoplasia has been reported recently in Polled Herefords.[2] Ectopic Purkinje and granule cells were noted within a grossly smaller cerebellum.

Clinical signs of the familial form of cerebellar hypoplasia reported by Innes were manifest at birth as inability to rise and rigid extension of the limbs and head. Often this progressed to opisthotonus. Periodic tremors of the head were exhibited. No seizure activity was observed and only one incidence of nystagmus was described.

Post mortem examination revealed gross cerebellar hypoplasia. Microscopic examination showed lesions limited to the cerebellar cortex. Typically, there was Purkinje cell degeneration and heterotopia accompanied by surrounding gliosis. These findings suggested a degenerative process. Thin molecular and granular layers had indistinct bounds. Large cells, described as neuroblasts, were found in the molecular layer and suggested a developmental defect. There was no involvement of the deep cerebellar nuclei or olivary nuclei and no demyelination.

Ayrshire

Cerebellar cortical atrophy was found in an Ayrshire calf in which the cerebellum appeared grossly hypoplastic.[40] The authors felt that microscopic lesions closely resembled those found in lambs affected with inherited cerebellar cortical atrophy (daft lamb disease).

Beginning at birth, seizure-like activity described as "fits" was exhibited. The seizures were described as clonic spasms followed by opisthotonus. During the interictum signs of ataxia and straddle-legged stance were evidence of loss of coordination. The syndrome did not progress in severity once the calf was under observation.

Histopathology was indicative of generalized cortical degeneration. The molecular layer was thin and bore foci of hypercellularity. The granular layer was thick with cells encroaching upon the white matter. Purkinje neurons were reduced in numbers and degenerate in appearance. Empty basket formation was evidence of their complete loss. There were no signs of demyelination.

c. Degeneration

Shorthorn

Initially Finnie and Leaver,[27] and later D'Sullivan and McPhee,[59] described an autosomal recessive cerebellar hypoplasia in Australian Shorthorn cattle.

Calves were affected at birth with a horizontal and vertical head bob and tendency toward base-wide stance. Severe ataxia and frequent falling were displayed when the animals were driven.

One of the four calves examined showed a macroscopic reduction in cerebellar size.

Microscopic changes consisted of thinning of the molecular layer and loss of Purkinje and granular cells. Heterotopic Purkinje cells were found in the granular cell layer. The spinal cord revealed Wallerian degeneration of the lateral and ventral funiculi.

Swan and Taylor[75] reported cerebellar hypoplasia in the same breed with identical clinical signs and microscopic lesions. The animals they examined did not have grossly hypoplastic cerebellums.

Angus

Note: This syndrome is of borderline nature with regard to prenatal-postnatal classification. Since the animals may be affected at birth or

as much as three months later, it would seem reasonable to suspect that the degenerative process is begun prenatally, regardless of the time of onset of clinical signs.

An hereditary cortical atrophy has been reported in Angus calves.[7] It is thought to be a dominant trait with incomplete penetrance.

The onset of clinical signs was at birth or, less commonly, at two to three months of age. Calves exhibited tetanic seizures which lasted for three to twelve hours and were either of two forms. The milder form was typified by an increase in muscle tone which was of such magnitude that it interfered with locomotion, giving a stilted appearance to the gait. The head was held high and showed a fine tremor. Sight was retained. The more severe seizures caused the calf to become recumbant and exhibit opisthotonus or paddling. Unlike the mild form, an increase in respiratory rate and temperature was sometimes manifest with severe seizure activity.

The seizures remissed to a residual ataxia which was exemplified by a goose-stepping gait, poor placing ability, and spasticity. Slow rhythmic lateral head movements were not uncommon. Seemingly complete recovery would accompany the conclusion of several months on pasture, but relapse was common when the animals were stressed or excited by handling.

Histopathology revealed cerebellar cortical degeneration limited almost exclusively to the Purkinje cells. Neuronal degeneration was characterized by swelling and vacuolation of the perikaryon. Nissle staining was diminished. Complete loss of Purkinje neurons was typified by empty basket formation, and it was common to find degenerative forms displaced among the granular cell layer. "Torpedos" or swollen axons

were observed in this region as well. There was no neuronophagia, no loss of mossy or climbing fibers, and only rare glial proliferation or deep cerebellar nuclei involvement.

The clinical and histologic aspects of this degenerative affliction are strikingly similar to those seen in a Charolais calf.[12]

V. BOVINE -- POSTNATAL

a. Spinocerebellar Degeneration

Brown Swiss

A genetically transmitted spinocerebellar degeneration in Brown Swiss cattle has been studied by Stuart and Leipold at Kansas State University.[74]

The onset of clinical signs ranged from five to eight months of age. Affected cattle displayed variable degrees of hind limb weakness and ataxia along with deficient proprioceptive reflexes. Sensory reflexes remained intact.

Macroscopic central nervous system abnormalities were limited to a reduction in spinal cord diameter.

Histopathologic studies indicated axonal degeneration and demyelination to be the primary lesions, the spinal cord being most strikingly affected. Cerebellar cortical change accompanied the myelopathy and was characterized by Purkinje cell degeneration and loss along with axonal torpedo formation in the granular layer.

b. Cerebellar Degeneration

Holstein

Cerebellar cortical atrophy of an inherited nature has been described in Holsteins.[81]

Calves, born normal, began to show signs at three to four months of age. These included gait deficits ranging from spastic dysmetria to total recumbancy, during which opisthotonus was often exhibited. All four limbs were affected symmetrically or assymmetrically and no loss of strength was apparent. Difficulty balancing was compensated for via base-wide stance and low head carriage with extended neck. Trunkal ataxia and intention tremor of the head were common. Though they were visual, calves had no menace reflex and inconsistently displayed abnormal nystagmus.

Necropsy findings revealed a cerebellum of normal size and appearance. Histologically the Purkinje cells were quantitatively and qualitatively deficient. This was exemplified by decreased Nissle staining and swollen neuronal processes in the molecular and granular layers. Bilaterally symmetrical vacuolization of the medulla in the region of the deep cerebellar nuclei was noted. No inflammation accompanied these changes. Electron microscopy of cerebellar sections revealed only non-specific neuronal degeneration. Randomly distributed degenerate nerve cell processes were found at variable levels of the spinal cord.

Charolais

Cho and Leipold cited an incidence of cerebellar cortical atrophy in a Charolais calf for which the etiology was obscure.[12] The owner reported several similarly affected calves in his herd, but the dam of this particular animal had borne six others, all normal.

The age of onset was six months, prior to which the calf had appeared normal. Initially, the animal became recumbant and unable to rise, but remained alert. Following spontaneous recovery seizures occurred, lasting from one to several minutes. These came at two to

three week intervals. The seizures eventually regressed to residual ataxia, but could be manifest as a result of excitement. During the interictal period the calf displayed ataxia, proprioceptive loss and a fine head tremor.

No gross cerebellar lesions were obvious at necropsy. Histopathologically there was evidence of cortical atrophy exclusive to the Purkinje cells. Neuronal swelling and vacuolation, as well as presence of empty baskets and torpedos characterized the degenerative process. There was no neuronophagia or glial proliferation.

The authors were inclined toward a genetic basis for the defect because of the absence of lesions typically seen with virally induced cerebellar disease. These would include medullary cavitation, ocular defects and inflammatory activity.[12]

VI. OVINE -- PRENATAL

a. Infectious-Viral

Bluetongue

Injection of bluetongue vaccine virus into fetal lambs has resulted in central nervous malformations which may include cerebellar hypoplasia.[58] Commonly hydranencephaly and porencephaly were presented. Lambs infected from 50 to 57 days of gestation exhibited partial or total cerebellar hypoplasia. Those innoculated at 75 to 78 days of gestation displayed small cerebellums with underdeveloped lateral lobes and cystic medullas by 63 days postinnoculation. The small folia of the lateral lobes showed variable loss of granular and Purkinje cells. Mild Purkinje heterotopia was observed in the vermis. Subependymal rosette formation, presumably due to destruction of subependymal stroma, was noted in the roof of the fourth ventricle.

In the sheep, the cerebellum matures primarily during the second half of gestation. Gyri formation begins in the lateral lobes at 70 days and cellular organization continues two to four weeks into the postnatal period.[39] It can be seen, then, how infection at or prior to this time may result in a hypoplastic process.

Border Disease

Pestivirus has been associated with cerebellar hypoplasia in several species, including sheep.[6] Osburn et al. duplicated the work of Australian and British researchers when they demonstrated the presence of serum neutralizing antibody to hog cholera and bovine viral diarrhea in lambs experimentally infected with border disease.[57]

Hydranencephaly and porencephaly were frequent accompaniments to cerebellar hypoplasia with in utero viral infection.

Affected lambs displayed some or all of the following signs: Abnormal body conformation -- short legs or domed head; hairy fleece; rhythmic muscular contractions or trembling; weakness or poor growth.

Barlow described two types of cerebellar malformation is lambs born of border disease or bovine viral diarrhea infected ewes.[6] The more mildly affected offspring showed small but normal cerebellar folia and cavitation of the folial white matter with a macrophagocytic cellular infiltrate. Those lambs more severely affected had only rudimentary development of the entire structure characterized microscopically as islands of germinal cells surrounded by rosettes of Purkinje and granular cells. The overall effect was one of cytolytic nature -- the virus on germinal cells.

Naturally occurring cases of border disease have been characterized by hypomyelination. Barlow and Storey suggested that viral influence on neuroblast cells diverted their formation from myelin producing oligodendroglia.[8]

Akabane

Akabane virus, a member of the Bunyaviridae, has been cited as a cause of bovine and ovine intracranial malformations, including cerebellar dysgenesis.[20,6]

b. Cerebellar Degeneration

Inherited Cerebellar Cortical Atrophy (Daft Lamb Disease)

A cerebellar degeneration on Welsh Mountain sheep was first recognized in 1945.[82] It has subsequently been reported in Corriedales.[37]

Clinical signs were present at birth. Gait deficit ranged from ataxia to inability to rise. Attempts at compensation for lack of equilibrium were characterized by base-wide stance. Trembling was also apparent. With maturation the signs seemed to regress.

On gross examination the cerebellum was of normal size. Microscopy showed loss of Purkinje cells with empty basket formation and astrogliosis. Granular cells were also degenerate and reduced in numbers. Some involvement of the deep cerebellar nuclei and olivary nuclei was evident.

A clinically identical syndrome was described in Border Leicester sheep.[76] There were, however, no cerebellar lesions found. Ultimately, this was thought to be a different form of the same disorder.

So called "Daft Lamb Disease" is presumed to be an inherited disease.

VII. PORCINE -- PRENATAL

a. Infectious-Viral

Hog Cholera Virus

This infectious disease of swine has been associated with cerebellar hypoplasia and hypomyelinogenesis in pigs farrowed from sows vaccinated against it during gestation.[26] Vannier et al. infected pregnant sows at 22, 43, and 72 days gestation with unmodified hog cholera virus and found cerebellar hypoplasia to be evidenced grossly, but not histopathologically, in piglets from the two earlier innoculums.[7g]

The clinical signs displayed by affected piglets were indistinguishable from congenital tremor syndrome. Indeed, HCV has been proposed as a cause for that multifarious disease.[34] Tremors, ataxia, and splayleggedness were typical.

Emerson and Delez reported grossly hypoplastic cerebellums which, on histopathologic examination, showed lack of a cortical organization.[26] Thinning of the molecular layer, heterotopy, and loss of Purkinje cells were characteristic. Reduction in myelination was also evident throughout the central nervous system. They hypothesized that vascular disturbance by the virus resulted in hypoxia which induced cerebellar malformation and that injured oligodendroglia contributed to hypomyelinogenesis.

VIII. PORCINE -- POSTNATAL

a. Cerebellar Degeneration

Yorkshire

Two different clinical manifestations of cerebellar degeneration have been described by de Lahunta in Yorkshire pigs.[20] Histologic findings were also dissimilar.

The first syndrome was typified by abnormal gait in the rear legs beginning (after a period of normalcy) at four to five weeks of age. The incoordination rapidly progressed to severe dysmetria and involvement of the thoracic limbs preceeding inability to stand. Although the pigs had normal strength and reflexes, they responded slowly or not at all to postural testing. Nystagmus and lack of menace reflex were noted. Head tremor was not present.

Microscopically Purkinje cell degeneration was the only lesion. The presence of axonal torpedos among the granular cells indicated axonal deterioration while only mildly degenerative signs were seen in the Purkinje perikarya.

Another related group of piglets became stiff and ataxic at one to four weeks of age. They, also, rapidly progressed to recumbancy. Histopathology revealed reduction in Purkinje and granular cells and complete absence of the external germinal layer. The lesion was most obvious in the vermal and paravermal folia.

Both syndromes, because of the breed predisposition and relation of litters were supposed to be inherited.

IX. EQUINE -- PRENATAL

a. Cerebellar Malformation

Thoroughbred

An atypical case of cerebellar hypoplasia was reported in a six year old thoroughbred gelding.[80] The animal, a jumper in training, exhibited no gait deficit but frequently reared and fell backward at the take-off. He was found to have bilaterally symmetrical defects in the lateral cerebellar hemispheres.

Microscopically the areas were devoid of cortical tissue and gave no indication of its pre-existence. The underlying white matter was unaffected.

Aspects of this case which make it unique are the breed of horse, the lack of observable gait abnormalities, and the gross cerebellar malformation.

Gotland Pony

Swedish Gotland ponies represent a borderline situation in regard to classification. Bjorck et al. reported a progressive ataxia which was noted soon after birth or four to six months later.[9a,b]

Macroscopic cerebellar hypoplasia was the manifestation of a reduction in cortical components. The molecular layer was thin, granular cells were diminished, and Purkinje degeneration was suspect. Glial proliferation was evident surrounding the Purkinje cell layer.

The authors postulated an inherited mode of transmission.

b. Cerebellar Degeneration

Note: It is very difficult to place reports of equine cerebellar disease into the category of prenatal cerebellar degeneration alone. Cases which present with clinical signs at birth have been cited, but are included with those in which onset is at a later date.[60,49,9a,b] Differences in pathology with respect to age at onset have not been discussed in the literature.

X. EQUINE -- POSTNATAL

a. Cerebellar Malformation

New Caldonian Horses

A chronic progressive neurologic disease of horses in a localized area of New Caldonia has been reported.[50] An environmental etiology was

suspected as normal horses entering the area also began showing signs. Soil in the region was known to contain a high content of heavy metals and affected individuals were frequently pastured prior to development of clinical signs.

Clinical signs were typical of cerebellar pathology. The minimum age at onset was one to two years. Initially a mild ataxia was apparent, primarily in the rear quarters. The inability to coordinate movement progressed until the horses were reluctant to move. When made to do so affected individuals would fall and rise with difficulty. The gait deficit was bilateral, but not always symmetrical. Dragging of feet and wide-base stance were characteristic. No nystagmus was observed.

Histopathology on six and seven year old animals revealed cerebellar cortical lesions. Thinning of the molecular layer accompanied the loss of Purkinje and granule cells. Neurons of the spinal cord and purkinje cell layer contained lipofuscin pigment. No evidence of demyelination was described.

b. Cerebellar Degeneration

Oldenberg

The first description of equine cerebellar disease was that of inherited spinocerebellar degeneration in Oldenbergs.[49] Although the primary focus of the lesion was in the spinal cord white matter, the Purkinje cells of the cerebellar cortex and semilunar ganglion of the trigeminal nerve showed selective degeneration.

Incoordination and ataxia were exhibited at three to four weeks of age and rapidly progressed to complete paralysis during the following two weeks. Death was inevitable prior to a year of age.

Arabian

In 1965 Dungworth and Fowler described cerebellar hypoplasia and degeneration in a six month Arabian foal.[25] Macroscopic lesions were not evident. Their report was followed by several others in which a very similar syndrome was recounted, and interestingly, it occurred in partial or full-blood Arabians.[28,72,60,4]

Fraser applied the term abiotrophy to the disease which indicated a postnatal degeneration of hereditary origin. This terminology was subsequently questioned on the basis that foals were occasionally affected at birth. The degenerative process would have therefore had to begin prenatally.[60]

The theory that Arabians were hereditarily disposed to cerebellar disease received additional support when Sponseller reported the syndrome in 21 horses, all but one Arabian.[72] Though the provided pedigree information which would partially substantiate the genetic etiology, no firm conclusions were made to that end. In fact, he suggested the possibility of a filterable agent or an interaction of the two. Baird and MacKenzie later reitterated the possibility of genetic predisposition to viral infection, citing the preponderance of Adenoviral infection among Arabians as an example.[4]

Despite failure to elucidate a definitive etiologic agent, cerebellar disease has continued to predominate in the Arabian breed.

In light of the relatively small number of reports concerning cerebellar disease in Arabs, the review of clinical signs and histopathologic lesions will be covered by article in chronological order.

The initial citing of cerebellar hypoplasia and degeneration by Dungworth and Fowler concerned a five and a half month Arabian foal which had developed incoordination and a slight head tremor at six weeks of age.[25] The signs had progressively deteriorated up until the date of examination. A slow, ataxia gait gave way to falling if the animal was led or startled. Base-wide stance was typical at rest. An inconsistent vertical head tremor was present, however, no nystagmus was displayed.

There were no gross lesions noted at necropsy. Microscopic lesions were limited to the cerebellum. An external granular layer of two to three cells thickness covered the cortex. This was considered to be normal in a five to six month foal. The molecular layer was thin and hypercellular. Angular neurons twice the size of a granular cell was predominant in this layer, accompanied by an increase in glial fibers. Purkinje cell loss and degeneration was striking. Empty baskets and glial proliferation were observed along this intermediate zone. Fibrillary gliosis and prominent Golgi cells were evidenced by mild granular layer depletion. No neuronal degeneration was apparent in this layer.

Throughout the white matter there was reduction of myelinated axons, but no evidence of demyelination. Neurons of the deep cerebellar nuclei and caudal olives were within normal limits. However, mild gliosis and decreased myelin density surrounded nuclear cell bodies. The cerebellar peduncles showed no abnormalities.

Lesions were most severe in the vermal declive and tuber lobules and the hemispheric lateral ansiform and paramedian lobules. Less severly affected were the nodulus, uvula, and median ansiform lobules.

The authors interpretation of clinical and histopathologic data was that the degenerative process began prior to complete cerebellar maturity, thereby causing both a lack of normal development and premature atrophy.

Fraser described two dissimilar cases of cerebellar disease in the horse in 1966.[28] One case involved a Thoroughbred colt who was subsequently diagnosed as having cerebellar nematodiasis. For obvious reasons, that particular incidence is not pertinent to this discussion.

The second report was that of a three month old Welsh Cob x Arabian who was initially stiff in the left foreleg at the gallop and became progressively ataxic in all four limbs by the age of six months.

When presented, the fillys giat was extremely stiff and protractive efforts resulted in abduction of the limbs. Extensor tone was further increased throughout the neck muscles.

Gross pathology showed no ruduction in cerebellar size. Histopathologic examination revealed cerebellar cortical changes, the most outstanding of which was the near complete loss of Purkinje neurons. Those remaining were both degenerate and normal in appearance. The molecular layer exhibited fibrillary gliosis and the granular layer was narrowed with prominent Golgi cells. No abnormalities of white matter were evident in the cerebellum, however, slight Wallerian degeneration was found in the ventral and lateral columns throughout the spinal cord.

Fraser, in essence, supported the theorized genetic transmission of cerebellar disease in the Arabian when he referred to this case as "progressive cerebellar cortical abiotrophy".[28]

Sponseller conducted an extensive study of 21 Arabian horses with cerebellar disease.[72] Seventeen animals were male, four were female.

Onset of gait deficit and head tremor varied from birth to three or four months of age. One foal was unable to rise for nursing without assistance, but eventually learned to do so. Hypermetria characterized the ataxic gait. Some animals had a tendency to rear and fall backward. No nystagmus was noted.

Gross cerebellar hypoplasia was not apparent on postmortem examination. Cerebellar cortical lesions were as follows: thin, hypercellular molecular layer; thin, hypocellular granular layer; depletion, degeneration and disarray of Purkinje cells. Gliosis gave the molecular layer its busy appearance.

Six Arabian foals with signs of cerebellar abnormality were studied by Palmer and Blakemore.[60] Head tremors and ataxia were noticed from birth to nine months of age and predominated in males. This sex predilection would agree with the preponderance of males cited by Sponseller.[72]

The ataxic individuals demonstrated a lurching, swaying, gait. Some animals were unable to rise. No nystagmus was present in any animal, but four of five tested had sluggish menace responses.

No significant macroscopic abnormalities were found. Cerebellar lesions were typical of those previously cited. Purkinje neuronal degeneration and loss predominated with concurrent thinning of the molecular and granular layers. Astrocytes and glial fibers had infiltrated the molecular layer. In those horses from which it was taken, the spinal cord was found to be free of any abnormalities.

The most recent report of cerebellar disease in the Arabian was that of the offspring of the same mix-breed mare and two different, but related, stallions.[4] Neither the sires nor the dam displayed signs indicative of cerebellar dysfunction.

The first colt was born of the mix-bred dam and an Arabian sire. The same mating had previously produced a normal male foal. The foal did not nurse for eight hours post-delivery. At four months he developed a horizontal head tremor, incoordinated gait and wide-base stance. The signs progressed to eleven months of age.

No reduction in cerebellar size was noted at necropsy. Eburnation and cartilage folding along the cervical vertebral facets were found. There was a decided difference in size and structure of the articular processes from side to side.

Histopathologic lesions were most obvious in the cerebellum. The molecular and granular layers were thin and the latter displayed a reduction in cell numbers and presence of swollen axons (torpedos). Ectopic Purkinje cells were also evident among the granular neurons. These cells appeared normal, as did those few which remained in the Purkinje cell layer. A pronounced reduction in the pyriform neurons was a most notable abnormality. Bergman glia were increased. Demyelination was observed in and around the dentate nucleus and spongy degeneration was evident at the level of the caudal olives. Both brain and cord showed mild perivascular lymphocytic cuffing.

The second case reported by Baird and MacKenzie was that of a male foal born to the same mare and a different Arabian sire. The colt became incoordinated and displayed wide-base stance and head tremor at six months of age. The signs were less severe than those in case 1.

Apparently the gross and microscopic findings concerning the cerebellum were similar to the previous case. The authors described the histopathologic lesions for both foals simultaneously.

A summary of the findings common to the preceding reports would implicate a three month old male Arabian foal as the most typical candidate for cerebellar disease. The most frequently found clinical signs were base-wide stance, head tremor, and incoordinated gait. These were also the initial complaints in several cases. Clinical abnormalities were characteristically progressive to a point. Abnormal nystagmus was not reported in any case.

No gross reduction in cerebellar size was observed. Cerebellar cortical degeneration was typified by diffuse, marked reduction in Purkinje cells. Most authors found those remaining to be degenerating. Baird and MacKenzie, however, described normal looking remainders, some of which were ectopically placed.[4] Thinning of the molecular and granular layers was often accompanied by glial proliferation.

Demyelination surrounding the dentate nuclei was observed by Baird and MacKenzie.[4] Decreased myelin density without gliosis was found in the folial white matter by Dungworth and Fowler.[25] The same authors noted reduction in myelin staining properties accompanied by glial proliferation around the deep cerebellar nuclei. Normal olivary nuclei described by Dungworth and Fowler were found to be surrounded by spongiosis and laden with PAS positive material by Baird and MacKenzie. Wallerian degeneration in the ventral and lateral spinal cord columns was reported by Fraser.[28]

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MATERIALS AND METHODS

CLINICAL STUDIES

Animals. Six Arabian horses, three male and three female, met the diagnostic criteria for cerebellar disease and were included in this study. Animals were transported to Kansas State University from various locations around the United States and retained by Animal Resource Facility on pasture until studies were made.

Clinical Evaluation.

1. History: Background information and pedigrees were obtained from the owners of each animal by mail. Standardized questionnaires also provided historical accounts (Appendix Fig. 1).

2. Diagnostic Criteria: Three criteria were utilized to substantiate a clinical diagnosis of cerebellar disease and establish candadacy for this project:

   a) Onset of ataxia prior to one year of age;

   b) Intention tremor of the head; and

   c) Member of the Arabian breed

3. Clinical Neurologic Examination: A standard format for clinical evaluation was employed by consistent examiners on each horse (Appendix Fig. 2). Qualitative observations were noted concerning head posture, cranial nerve function, neck flexability, gait abnormality, maintanence of equilibrium, back-line resistance. Reflexes were not evaluated due to the unpredictable nature of the subjects.

4. Additional Clinical Procedures: The horses were anesthetized so that the following procedures could be performed:

Electro-encephalography

Cerebro-spinal fluid tap

Blood Collection

Skull radiography

a) Anesthesia. Anesthetic induction was accomplished using intraveous xylazine[a] (0.5 mg/lb) and thiamylal sodium[b] (3 mg/lb of 2% sol'n). The animals were maintained on a surgical plane of anesthesia with halothane[c].

b) Electro-encephalography. Electroencephalograms (EEGs) were performed on a Grass electroencephalograph[d] using eight channels for encephalographic recording and one channel for electrocardiography (EKG). The EEGs were recorded with high and low electronic filters of 70 and 1 Hz respectively. A 60 Hz band was also used. The sensitivity employed for each EEG was 3 uv/mm and/or 5 uv/mm to give maximum visualization of the EEG without topping out the signal. All of the EEGs were recorded at a paper speed of 15 mm/sec, 30 mm/sec, and 60 mm/sec.

Fifteen Grass platnum subdermal needle electrodes[e] were placed subcutaneously to record the EEG and EKG (Appendix Fig. 3). The number 1 electrode was placed over the midline of the nose approximately midway between the infraorbital foramen and the medial canthus of the eye.

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[a]Rompun, Haver-Lockhart, Bayvet Division Cutter Laboratories, Inc., Shawnee, KS.

[b]Biotal, Bio-Ceutic Laboratories, Inc., St. Joseph, MO.

[c]Halothane, Halocarbon Laboratories, Inc., Hackensack, NJ.

[d]Grass Electroencephalograph, Model 8-10D, Grass Instrument Co., Quincy, MA.

[e]Grass Platnum Subdermal Electrodes, Type E2, Grass Instrument Co., Quincy, MA.

Electrodes 2 and 3 were frontal electrodes, 4 and 5 were temporal electrodes, 6 and 7 were parietal electrodes, and 8 and 9 were occipital electrodes. Each pair was placed over their representative regions of the brain. The number 11, 10, and 12 electrodes were placed on the midline at the level of the frontal, parietal, and occipital electrodes respectively. The EKG was recorded by placing one electrode over the cranial end of the jugular vein near its bifurcation into the linguofacial and maxillary veins. A second EKG electrode was placed either over the heart at the 5th interchondral space on the same side of the body or over the caudal end of the jugular vein near the thoracic inlet on the same side of the body as the first electrode. A ground electrode was placed on the side of the neck at the level of the wing of the atlas.

To reduce muscle artifact the auriculopalpebral nerves were blocked bilaterally with 6 ccs of 2% lidocaine[f] each and a total of 24 ccs of 2% lidocaine HCl was infused around each electrode. The recordings were made with the animals in lateral recumbancy. Horses 880 and 508 were in left lateral recumbancy while the remaining four animals were in right lateral recumbancy.

The EEG of each horse was recorded using six different montages. Appendix Table 1 lists the six montages and indicates the channels on which each pair of electrodes in the respective montages appeared. The numbers in the table correspond to the numbers of the electrodes given in Appendix Fig. 3.

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[f]Lidocaine HCl Injection, USP, Elkins-Sinn Inc., Cherry Hill, NJ.

c) Cerebro-spinal Fluid Tap. Surgical preparation was made of the area overlying the cysterna magna. Using aseptic technique a cerebro-spinal fluid tap was done with a 3.5 inch, 18 guage spinal needle. Samples were collected for cytologic and biochemical evaluation (to include creatinine phosphokinase levels), equine influenza and Herpes viral titres, and viral isolation.

d) Hematology. Sterile venapuncture was performed to obtain blood samples for a complete blood count and biochemical profile.

e) Radiography. Lateral skull radiographs were taken to rule out basilar skull fracture or malformation.

f) Euthanasia. Horses were euthanatized[g] while under anesthesia via intrajugular injection. Necropsy was immediately performed.

PATHOLOGY

Necropsy Procedure and Tissue Collection:

The animals were decapitated immediately following euthanasia. The calvarium was opened to expose the brain, which was carefully dissected free from cranial nerve attachments and removed. Gross evaluation for size and structural abnormalities was made at this time.

The cerebellum and brain stem were separated from the cerebrum and midbrain. Cerebellar and brainstem samples were collected for histopathologic studies from the following locations:

Caudal Cerebellar Lobe -- folium vermis
-- paramedian lobule right
-- paramedian lobule left

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[g]T-61 Euthanasia Solution, American Hoechst Corp., Animal Health Div., Somerville, NJ.

Cranial Cerebellar Lobe -- central lobule vermis
-- hemispheric lobule III right
-- hemispheric lobule III left

Nodulus
Flocculus -- right and left
Caudal Olivary Nuclei -- right and left
Pontine Nuclei -- right and left

Gross examination of the viscera was carried out as random samples were obtained for light microscopy. The eyes were retained to be evaluated for retinopathy. Random cerebrocortical diencephalic and midbrain specimens were collected at the time of necropsy. Later serial sections were taken of the diencephalon. All levels of spinal cord were evaluated.

Tissue Fixation and Processing

All tissues were fixed for histopathologic and ultrastructural study within 30 minutes from the time of euthanasia.

Tissue samples were fixed in 10% buffered neutral formalin (BNF). With the exception of eyes, the sections were further processed in an autotechnicon[h], embedded in paraffin, cut on a rotary microtome[i] to a thickness of 9 microns (CNS) or 6 microns (viscera), and stained with hematoxylin and eosin.

Selective stains employed on the cerebellum, brain stem, and spinal cord sections consisted of Luxol fast blue - cresyl echt violet for myelin and nerve cells, trichrome for astrocytes, and Periodic acid Schiff (PAS) for glycogen storage products. The latter 2 and Von Kossa were later employed on the diencephalon. These tissues were cut at 9 microns.

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[h]Autotechnicon Ultra II, Technicon Instruments Corp., Tarrytown, NY.

[i]Spencer Rotary Microtome, Model 820, American Optical Corp., Buffalo, NY.

Eyes were fixed for a minimum of 48 hours in 10% BNF, after which they were washed for 24 hours with cold running tap water. Two 24 hour alcohol baths followed; the first in a 50% solution and the second in a 60% solution. The tissues were stored in 60% alcohol until further processing. Embedding and cutting of eyes was accomplished using the same equipment and technique as described for other tissues. The sections were cut at 7 or 9 microns.

Further Diagnostic Procedures

Cerebral samples from four horses were tested for presence of Adenovirus by passage in primary equine kidney cell cultures a total of three times. Lung from three of the four was similarly evaluated. On a fifth animal cerebral samples were tested for viral presence by both passage in cell culture and flourescent antibody (FA) technique (for Herpes virus).

RESULTS

I. Clinical

Histories and Pedigrees

The horses used in this study were obtained from various parts of the country through unrelated sources. The animals developed signs indicative of cerebellar disease from a few days to several months of age, the majority ranging from one to six months. An equal number of both sexes were affected. Only one owner reported evidence of difficulty at parturition. Dams were not overtly ill during pregnancy. They received usual vaccines and worming medications during that time, none of which appeared to be associated with cerebellar dysfunction in their foals. Table 1 provides an historical summary.

The Arabian horse has been excessively inbred. Each animal evaluated could be traced to one or more common ancestors with others employed in the study. One specific stallion is present in the seventh or eighth generation removed from each affected foal (Appendix Figs. 1-5).

Neurologic Examination

The predominant clinical sign, as reported by owners, was intentional head tremor. Every animal examined displayed both horizontal and vertical tremor to approximately the same degree, although number 880 seemed more severe than the others. Trunkal sway or ataxia was exhibited by four to six animals examined.

Raising the head, approaching a threat to rear, was the typical response to trepidation or display of resistance exhibited by all subjects. Though a loss of equilibrium could be sensed at these

moments, if handling did not apply counter resistance rearing did not follow. Three of the animals did rear during the course of clinical evaluation, but did not fall backward.

Number 1307 had the most severely abnormal gait. He displayed exaggerated extensor tone which gave his gait a goose-stepping appearance. His attempts to walk up hill resulted in aerial pawing with the front limbs extended as his weight shifted backward and eventually pulled him over. Falling episodes in the other animals were rare and limited to periods of extreme excitement such as during unloading from a trailer.

Ataxia or incoordination best generally describes the gait deficit seen in the horses. The fore limbs were consistently more markedly affected than the rear. Limb involvement and degree of severity were bilaterally symmetrical. Proprioceptive inadequacies were reflected in a resting base wide stance, trunkal ataxia, tendency toward circumduction of the limbs and stepping on the opposite foot during circling, and variable knuckling over (Figs. 1-4). Motor ataxia was characterized by hypermetric dysmetria and delayed protraction.

None of the animals showed limb weakness, with the possible exception of 1307 whose gait was more accurately described as spastic (Figs. 5-7).

Some of the horses were reluctant to back and reacted to handlers attempts to elicit this maneuver by raising the head and threatening to rear (as previously described).

Abnormal nystagmus was not witnessed with or without an opthalmoscope. The menace reflex was depressed or absent in all but one horse. Table 2 provides a summary of neurologic findings.

Electroencephalography

The major electroencephalographic finding among Arabians in this study was an increase in synchrony. The synchrony was usually symmetrical between leads, but it was sometimes asymmetrical (Fig. 44). There was also an increase in the number of abrupt frequency changes (afc) elicited by the cerebellar animals (Figs. 44,45).

Table 3 lists the typical frequencies which displayed synchrony in the study subjects, and ranks the degree of synchrony observed. The duration of the synchronous recordings was typically one second and ranged from one half to two seconds. The three spectra most commonly seen were 2-4 Hz, 6-7 Hz, and 9-10 Hz. All of the affected horses showed synchrony in these spectra, but not to the same extent. Horse 910 showed the greatest degree of synchrony within the 9-10 Hz spectrum (Fig. 46). The same range was predominant in all the horses except horse 880, in which the 6-7 Hz spectrum was most often displayed, and horse 701 in which the 6-7 and 9-10 Hz frequencies were equally obvious. All the horses displayed increased 2-4 Hz frequencies less prominently than the 6-7 and 9-10 Hz frequencies. The amplitudes of the three main spectra ranged from 15 uv to 100 uv, with 30 to 60 uv being typical. Relatively large amplitudes made the spectra much more obvious than they are in the normal equine EEG. Characteristics of the normal equine EEG are represented in Fig. 43 and discussed.

Cerebrospinal Fluid Evaluation

The color and appearance of cerebrospinal fluid were normal for all subjects. Two animals (508, 880) had increased white blood cell counts (N = 0-6/ul). Cytology on 880 revealed one neutrophil and that of 508

contained four neutrophils and four mononuclear cells. Red blood cell elevation was found in five out of six horses with that of 880 being as high as 375/ul (N = 0/ul).

Trace turbidity was shown on Pandy testing in three horses (1307, 910, 880). Protein was outside the normal range (N = 20-85 mg/dl) on numbers 508, 880, and 701, where the average value was 226.3 mg/dl.

Glucose concentration fell within the normal range of 40-80 mg/dl on all animals.

Creatinine phosphokinase was high normal or elevated in every horse for which a value was obtained. Values ranged from 8 IU to 62 IU (N = 0-8 IU).

Viral titres were within normal limits for all subjects. Equine influenza was less than 1:10 and Herpes was less than 1:2.

Table 4 lists the findings on cerebrospinal fluid analysis.

Hematology

One animal had lowered hematocrit and hemoglobin values (508) among otherwise normal profiles. Numbers 987 and 701 were leukopenic with low normal and excessively low segmented neutrophil numbers, respectively. No band cells were observed. Lymphocytes for both animals were within the normal range. Horse number 880 had a high normal leukocyte count with increased segmented neutrophils and band cells.

Blood Chemistry Profiles

Serum glucose was significantly elevated in four out of six horses (1307, 880, 987, 701). Horse 880 had the highest value of 203 mg/dl (N = 70-110).

Serum alkaline phosphatase (SAP) was slightly increased in three animals (1307, 508, 880).

Serum creatinine phosphokinase was evaluated in only two animals and both had very high values of 732 IU (1307) and 296 IU (987) (N = less than 50 IU).

Phosphorus was high in every horse tested. Potassium was high normal in two animals (1307, 910) and elevated in one horse (987).

Tables 5 and 6 consolidate hematologic and blood chemistry information.

Radiography

Lateral skull radiographs did not reveal any abnormalities.

II. Pathology

Gross Pathology

There were no gross abnormalities found at necropsy of either central nervous system or other organ systems with the exception of those encountered in horse number 880 in which multiple cartilaginous outgrowths were present at various cartilage-bone junctions. Those bones involved included the ribs and virtually every bone in both pectoral and pelvic limbs.

Histopathology

Skeletal System (880): Light microscopy findings from boney outgrowths revealed characteristics compatable with those reported in multiple cartilagenous exostosis.

Eyes: No retinal abnormalities were observed among the six subjects.

Central Nervous System:

Cerebellum

The most consistent finding in every horse examined was marked reduction in Purkinje cell numbers (Fig. 8). Those cells remaining were degenerate as characterized by first, swelling, then shrinkage and hyperchromasia of the perikaryon (Figs. 9, 10, 11). Proliferation of Bergman glia was noticeable in the absence of Purkinje neurons. Complete loss of cell body was reflected in the presence of empty baskets (Fig. 11). Heterotopic degenerating Purkinje cells and vacuolations were occasionally seen in the granular layer (Figs. 12, 13, 16). Some of the empty spaces among granular cells contained active gitter cells (Fig. 17). Swollen Purkinje cell axons, termed spheroids, could be identified among the granular cells (Fig. 10).

The overall appearance of the granular layer was one of sparsity and irregularity (Figs. 7, 14, 15).

The cerebellar white matter in the vicinity of the deep cerebellar nuclei was mildly vacuolated and some gitter cell activity was apparent (Figs. 18, 19). Gliosis was prominent in some animals. The nuclear cell bodies were not appreciably affected.

Reserve cells were abundant in the meningeal pia matter of every animal studied. Occasionally these cells could be found to follow the pia into folial sulci or the molecular layer and arrange themselves in rosettes (Figs. 24, 25).

Regional comparison of cerebellar lobules found the cranial vermal and hemispheric lobules to be equally deficient in Purkinje neurons. The caudal cerebellar lobe (nodulus and flocculi) had greater numbers of Purkinje perikarya, but displayed degenerative changes in the cell bodies and empty basket formation.

Brain Stem

Sections through the pontine nuclei and caudal olives did not show significant neuronal change. Neurons throughout the brain stem were variably centrally chromatolytic or hyperchromatic (Fig. 22).

Vacuolation within white matter were identified in random regions of the medulla and pons. Swollen axonal spheroids were found in 2 animals (910, 880), (Figs. 20, 21). Sections containing these lesions were at the mid rhomboid fossa and obex, respectively.

Cerebrum

Neuronal changes in the cerebrum were similar to those seen in the brain stem. Some cells were hyperchromatic and shrunken while others were unaffected. Large neuronal cell bodies were normal.

Perhaps the most remarkable changes were the extreme satellitosis shown around smaller neuronal perikarya and moderate gliosis in the surrounding neuropil. These features were seen primarily in the polymorphonuclear cell layer of the cerebral cortex.

Cerebral vasculature was somewhat congested and minor hemorrhages were found intermittently.

Diencephalon and Midbrain

The lesions found in the thalamus were striking. Numerous basophilic parenchymal deposits were evident near the cranial aspect of the interthalamic adhesion, just dorsolateral to the third ventricle (Figs. 26-31). The lesions were frequently related to vascular channels and were consistently grouped in the same location in every animal examined. They ranged from lightly basophilic granules to dark staining

homogeneous ovoid structures which were often vacuolated. The concretions, which stained positively with Von Kossa and Periodic Acid Schiff (PAS) reagents, were surrounded by glial reaction a large percentage of the time. Active astrocytes were abundant in the surrounding neuropil. Neuronal cell bodies in the same area were mildly degenerate, as manifest by loss of cytoplasmic staining properties and swollen nucleoli with chromatin fractionation.

Surrounding diencephalon and mesencephalon exhibited less extensive neuronal degeneration with occasional areas of excessive satellitosis. An overall view of both regions gave the impression of increased glial cellular activity.

Spinal Cord

Neuronal change in the spinal cord was not significant. Lesions were most pronounced in the white matter.

Axonal degeneration and loss, accompanied by phagocytic gemistocyte activity, was found of moderate intensity at all levels of the cord and all funiculi. Swollen axonal spheroids gave way to vacuoles within which gitter cells were frequently found (Figs. 32, 33, 34). One animal showed extensive vacuolation of dorsal spinal nerve tracts and roots in lumbar cord segments (701), (Figs. 26, 27).

Occasional glial nodules were found in both grey and white matter (Fig. 35).

Special Staining Techniques

Luxol fast blue - cresyl echt violet staining procedure did not indicate loss of myelin density, but verified neuronal cell body alterations in the cerebellum. Periodic acid Schiff reagent showed

positive results on midbrain mineral deposits, but was vague in other areas of the nervous system. Some of the degenerating Purkinje perikarya showed a hint of magenta. The trichrome stain for astrocytes did not reveal any significant area of astrocytic infiltration or proliferation.

Viral Isolation Studies on Brain Tissue

Attempts to isolate a virus, specifically Adenovirus or Herpes virus, were met with negative results.

DISCUSSION

Cerebellar disease is manifest clinically as motor incoordination which can be further defined as dysmetria. Dysmetria describes movement in which regulation of rate, range, and force is inadequate. Cerebellar Purkinje cell inhibition of deep cerebellar nuclear neurons indirectly affects upper motor neurons responsible for voluntary locomotion. It is via this mechanism that rate, range, and force of protractive and extensor phases of locomotion are limited. When the inhibitory role of Purkinje cells is disrupted, exaggeration of movement, both flexion and extension, becomes apparent. This form of dysmetria is termed hypermetria.

Interruption of Purkinje cell inhibition may take place as the result of decreased spinocerebellar input to Purkinje neurons or due to Purkinje cellular damage. Interference with transmission from the cerebellum to the cerebrum may result in similar clinical signs. Areas included in this relay system are the brain stem, thalamus, and internal capsule.

Spinocerebellar input to Purkinje cells is in the form of sensory information carried by general proprioceptive fiber tracts. Damage to this system results in sensory ataxia which is defined as lack of the sense of motion or of the position of the body or limbs in space.[12]

The gait abnormalities characteristic of proprioceptive deficit and cerebellar disease overlap to such an extent that it is exceedingly difficult to define system involvement by clinical neurologic examination. Indeed, pathology within the two is often simultaneously encountered. Lesions in either system may be overtly expressed as wide base stance, delayed protraction, hypermetric dysmetria, and tendency to circumduct and excessively adduct the limbs on circling. All of these

features were observed in horses examined in this study and have been cited in previous reports of Arabian cerebellar disease.[2,13,16,26,31] The thoracic limbs were consistently found to be more affected than the pelvic limbs in Arabians seen at Kansas State University (KSU).

Extensor rigidity is a variable finding related to rostral cerebellar lobe dysfunction.[12] It has been reported to give a goose-stepping appearance to the gait when present in the thoracic limbs of horses with cerebellar disease.[16,26] One animal on this project was extremely stiff in the thoracic limbs and somewhat so in the pelvic limbs.

No loss of strength was observed in the Arabians studied. Weakness is typically associated with upper motor neuron damage[24] and not with cerebellar disease.[12]

Trunkal ataxia (sway) was common among horses examined and is attributable to cerebellar disease. Similarly, an intention tremor of the head is very typical. This horizontal and/or vertical tremor is the earliest sign of abnormality reported by owners and the most consistently found clinical manifestation of cerebellar disease along with incoordination. Intention tremor has been described as a form of dysmetria.[12]

Abnormal nystagmus has not been reported in horses with cerebellar lesions. It was not present in those examined for this project.

Another very common finding with cerebellar disease is the lack of a menace reflex. This abnormality has been cited in several species with cerebellar dysfunction and was evident in all but one animal studied. The explanation for lack of a blind response in an otherwise visual animal with normal facial muscle strength is that neuronal tracts

between the visual cortex and facial nucleus course through the cerebullum. Cerebellar lesions presumably interrupt the pathway.[12] I have found the reflex to be absent in normal young foals up to several months of age. It would be a value to further study this phenomenon in normal animals as it relates to age.

Onset of clinical signs of cerebellar disease in Arabians is variable, but is always prior to one year of age. The literature cites cases from birth to nine months with a majority within the two to six month range.[2,13,16,26,31] Arabians in this study ranged in age from one month to several months at the time of onset. For the majority, the two to six month age range applied.

Reports indicate the progression of gait deficit over variable periods of time.[2,13] KSU has maintained two animals for two and a half years (presently aged four and seven years) whom have not appreciably declined. Most of the animals used for this study remained static during the few months they were retained. One horse did seem to become increasingly worse while at the university from six months of age to two years. It is possible that progression of signs over extended periods of time goes unnoticed, however, discrepancy exists in the variable time frame during which horses decline in ambulatory ability. The ability to compensate for cerebellar deficit has been observed in man and animals.[28] As histopathologic lesions do not seem to correlate with the severity of clinical signs, it may be reasonable to relate progression of gait deficit with compensatory ability.

In the normal equine electroencephalogram (EEG), recorded under halothane anesthesia, one sees frequencies which vary from 2 to 30 Hz with 6-10 Hz activity often well represented.[8] Activity within the 6-10

Hz spectrum is usually constant while other frequencies are also observed. The 20-30 Hz spectrum is better represented in the normal equine EEG than it is in the dog.[8] The normal equine EEG should be regularly irregular. There are, however, brief periods of synchrony and abrupt frequency changes (afc). "Sleep spindles" are not prominent in the normal equine EEG taken under halothane anesthesia.

Electroencephalography in the horse is in its infancy, thus the amplitudes and spectra characteristic of specific equine CNS disease are largely undetermined. The findings described in the six animals studied cannot be deemed specific for Arabian cerebellar disease. They do, however, indicate that horses with cerebellar disease consistently show abnormal EEGs. It is interesting that the horse with a menace reflex and the least severe clinical signs also happened to display the least synchrony in his EEG. EEGs on the six animals were read without knowledge of the clinical findings.

The results of laboratory evaluation of cerebrospinal fluid and blood have not been reported for Arabians with cerebellar disease. Complete blood counts and serum chemistries did not reveal abnormal results referable to central nervous system (CNS) dysfunction. Cerebrospinal fluid was normal in color and appearance for all subjects. Elevations in erythrocytes and leukocytes were felt to be due to sample contamination as cytologic interpretation found cellular elements to be within normal limits.

The normal levels of protein in cerebrospinal fluid are relatively low and consist primarily of albumen. Normal for the horse is 20-85 mg/dl. Three animals studied had protein values greater than 200 mg/dl. Elevations in protein content may be due to inflammatory and non-

inflammatory central nervous system disease.[10] The globulin fraction is usually responsible for elevated values but hemoglobin contamination and leakage of serum protein will also increase this parameter.

Pandys were not appreciably elevated in the three subjects with high CSF protein content. Erythrocytes were increased enough (375/ul) in one animal to merit responsibility for protein level, however, this was not the case with the other two horses. Specific gravities of 1.010 were present in the latter which would be compatable with an increase in protein content. Normal specific gravity of equine CSF is 1.004-1.008.[1]

If albumen is the protein fraction which is elevated, the values could be due to vascular leakage due to congestion or vasculitis.[10,12] Presence of moderate vascular congestion was confirmed histopathologically. The increase could also be a result of intrinsic protein release from noninflammatory lesions which result in tissue necrosis.[12] Extensive necrotizing lesions were not observed on pathologic examination, but neuronal cellular degeneration and axonal degeneration were widespread. Further examination of the correlation between degenerative encephalopathies and CSF protein content is warranted.

Creatinine phosphokinase (CPK) has recently become of interest in the evaluation of CSF. It has been found to be elevated in some animals with CNS disease.[33] It does not cross the blood-brain barrier, but is intrinsically released from nervous tissue[30] and is theorized to be an indicator of degenerative processes within the CNS.[32] Of four Arabians in which the enzyme levels were evaluated, one had high normal (8 IU) and two had extremely elevated values (62 IU, 31 IU). Normal CSF CPK in the horse is 0-8 IU.[24] Again, further correlative studies are required for a better understanding of the relevance of CSF CPK activity in CNS disease.

Titres for equine herpes virus and influenza were within normal limits. Viral isolation attempts for adenovirus and fluorescent antibody for equine herpes virus were negative. This would not necessarily rule out a viral etiology, if the lesions seen at necropsy were long term results of earlier infectious insult.

Histopathologic findings in the cerebellums of the Arabians examined were consistent with those described in previous reports.[2,13,16,26,31] The major abnormalities were marked reduction in Purkinje cell numbers and degeneration of those remaining with accompanying granular cell depletion. The Purkinje cellular lesion would indicate a degenerative process. The presence of degenerating cell bodies, empty baskets, spheroids, and glial activity suggest that the lack of Purkinje cell numbers is due to their demise.[18]

Heterotopy of Purkinje cell bodies might initially propose a disturbance in migration which would indicate a developmental lesion, but when paired with near complete absence of normal cells it is more likely another degenerative phenomenon.[3] Purkinje cells have migrated into their permenant locations and anatomically matured long before the external granular cells complete their inward movement to form the internal granular layer. Though there are no figures for the development of the equine cerebellum, those of the bovine may be loosely applied. Purkinje cell maturation is achieved by 100 days of gestation. The external granular layer is at its thickest by 183 days of gestation and continues migration inward up to six months postpartem.[12] Presence of an external granular layer (EGL) two to three cell layers thick is reportedly normal for a five to six month foal.[13] An insult occurring between the time of Purkinje development and completion of the internal

granular layer would conceivably present a picture such as that seen in the Arabian. That is, degeneration of Purkinjes and depletion of granule cells. It is interesting to note that each animal studied had abundant granular cells just beneath the pia matter even as late as two years of age. An alternative explanation for reduction in granular cells is their demise, which may be supported by the glial reaction within that cell layer.

It was not unusual to observe reserve (EGL) cells assuming rosette formation in the sulci of the cerebellar cortex and within the adjacent molecular layer. The cells in this location were not ciliated. Rosettes were also apparent beneath the ependyma of the third ventricle in the diencephalon. In that area the number of cell layers was less than that of the EGL rosettes and cilia lined the internal surface. In both cases the cells radiated from a central lumen.

Subependymal rosette formation has been reported in panleukopenic kittens,[11] lambs experimentally infected with Bluetongue virus,[25] and laboratory animals experimentally infected with myxovirus[20] and reovirus.[23] The structures represent true malformation in man.[25] Rosettes of both ependymal and EGL origin are remniscent of some central nervous neoplastic patterns in humans.[15] This is not to say that the process here is neoplastic, rather it suggests that the cells have reverted, or more likely, remained in a formation which may be typical of an earlier stage of maturation.

Changes in the cerebellar medullae, brain stems, and spinal cords of those animals studied were primarily indicative of widespread axonal degeneration. Axonal swellings, termed spheroids, were found in the brain stems and spinal cords. Vacuolation of white matter was evidence

of axons lost in all three locations. Gliosis was prominently featured in the cerebellums and brain stems and displayed to a milder extent in the cords by gitter cell activity and glial nodular formation.

Axonal lesions in the cords were predominantly in the lateral and ventral funiculi. This would agree with lesions in the same areas reported by Fraser in a Welsh Cobx Arabian.[16] The same report described gemistocytic phagocytosis accompanying the axonal degeneration. A more recent article described spongy vacuolation surrounding the dentate and olivary nuclei, and PAS positive granules within the cell bodies of olivary neurons.[2] Vacuolations of the cerebellar medullae and brain stems observed in the horses in this study were not defined to certain nuclear areas. Neurons containing PAS positive material were seen in the thalamus.

Degenerating perikarya were observed in cerebellar and brain stem nuclei. Specific cellular reactions ranged from central chromatolysis to shrinkage and hyperchromasia. The variable nature of these lesions did not allow their localization to specific nuclear groups, but suggested that they accompanied the widespread axonopathy. Central chromatolysis is often associated with axonal injury and is thougt to be representative of exhaustive efforts to restore axoplasm.[21]

The lesions of utmost interest in this study, aside from those in the cerebellum, were the basophilic parenchymal deposits located in the thalamus. The structures were consistently in the same location in each animal examined, and incited focal microglial response.

Two possible explanations can be made for these depositions. The first is that they are similar to a phenomenon referred to as "micronodular mineralization" which has been associated with a condition in

human infants and chimpanzees known as perinatal telencephalic leukoencephalopathy (PTL).[6,27] The second is that the structures are neurons which have undergone necrosis and subsequent mineralization.

Though the major central nervous lesions in Arabians with cerebellar disease are not those of leukoencephalopathy, the similarity of the micronodules in terms of staining properties, location, and glial reaction is remarkable. These acid glycosaminoglycan deposits are reportedly "a common alteration in the developing striatum which has received little attention in the literature".[27] They have been found in a small percentage of the brains of normal infants, but may be shown more extensively in conjunction with encephalopathy.[27] Such is the case in PTL where the lesions are found predominantly in the basal ganglia and to a lesser extent in the thalamus. The two Arabians from which basal ganglia were examined did not show micronodule formation in that area.

Thalamic deposits in the Arabians stained positively with Von Kossa and PAS techniques. A positive reaction with the same stains is reported for the globular deposits of acid glycosaminoglycans.[6] Mineralized neurons are frequently referred to as "ferruginated" due to the fact that they are depositions of iron and calcium salts.[15] They are commonly found in areas of old infarction.[5,15] These "pseudocalcifications" will stain positively for both calcium and iron.[5,6] The depositions observed in the Arabian in this study were negative for iron with Perl's Prussian Blue. In light of the fact that Von Kossa technique does not stain specifically for the calcium ion (it stains the anionic portion of the compound), Carr's chloranilic acid technique was employed in sections containing the lesions. Chloranilic acid is an organic acid

which forms salts with various cations including calcium.[29] The specimens on which this technique was employed were negative for calcium.

The deposits observed in Arabian thalami were often in the proximity of a blood vessel which, in at least one instance, was quite dilated. Reports indicate that vascular channels may be found associated with micronodules.[27]

Focal microglial response to the structures in the thalamus is another aspect of the Arabian brain lesion which is compatable with "micronodular mineralization", although this feature would be expected with neuronal mineralization as well. Finally, astrocytic infiltration in areas of intense nodule formation was common to both the thalami of Arabians studied and those areas of primary affliction described in chimpanzees with PTL.

While in the opinions of some the thalamic depositions appeared to be mineralized neurons, and indeed, surrounding neuronal perikarya lacked vitality, the possibility that the structures may be "micronodular mineralizations" has been substantiated through the special staining procedures which this study employed.

It is tempting to endeavor to relate the cerebellar and thalamic lesions seen in these six cases of Arabian cerebellar disease. Any attempt to do so is contingent upon definitive identification of the thalamic deposits, and even then, it is difficult task. Two types of relationships can be postulated based on the assumption that the thalamic nuclear neurons are mineralized. First, the two lesions may be within a common pathway, between cerebellum and thalamus, along which transynaptic degeneration could occur. Secondly, the two areas may be related by a common vulnerability to the same etiologic insult. If the

"micronodular mineralization" proposal is to be adhered to, the latter relationship may still be feasible. On the other hand, the significance of micronodules has not been well established, and the finding may be entirely incidental.

The thalamus functions as a relay center for sensory information in route to the cerebrum. It also integrates motor activity via afferent input from the cerebellum and basal ganglia.[19] From this standpoint, it is an ideal place to localize the overlap of proprioceptive and motor deficit witnessed clinically in patients with cerebellar disease.

The thalamic lesion observed in the Arabians was well localized to an area of the dorsomedial thalamus on a cross section through the tuber cinereum. As specific as this may seem, it is exceedingly difficult to pinpoint a specific thalamic nucleus as the affected site.

The ventrocaudal thalamic nuclei receive proprioceptive fiber tracts from the spinothalamic system,[19] while fibers, arising primarily from the cerebellar dentate nucleus, course through the rostral cerebellar peduncle in route to the ventrorostrolateral thalmic nuclei.[12] A small percentage of the dentatothalamic fibers also terminate in the intralaminar nuclei of the thalamus, these being the central medial and paraventricular nuclei.[28]

Assuming that the thalamic deposits are mineralized neurons and involve the ventral or midline thalamic nuclei, a transynaptic chain degeneration may be proposed. Presumably this process would be one of retrograde nature, the thalamus being affected prior to the cerebellum.

Unfortunately, the ventral thalamic nuclei do not correspond to the apparent location of the lesion. From a regional standpoint, the medial dorsal nucleus of the thalamus seems to correlate well. This nucleus is

the largest of nine medial nuclei and includes the better part of an area between the midline nuclei and internal medullary lamina.[19] The medial nuclear group is reported to take part in a diffuse cortical projection system, "receiving axons only from other diencephalic and telencephalic structures".[12] Conflicting evidence suggests that a few cerebellar fibers "end diffusely in the poorly differentiated medial zone of the thalamus" of all vertebrates.[28] A follow-up statement poses the uncertainty with thich this area in lower vertebrates may be related to the internal medullary lamina or ventrolateral nuclei in mammals. This seems to suggest that any cerebellar connections in the medial thalamic area are of a more primitive nature. Another source questions the functional significance of the medial thalamic nuclei.[19]

The "common vulnerability" hypothesis is an interesting one, regardless of the nature of the thalamic globules. A common denominator underlying both postulated identities for those structures and the characteristic Purkinje cell lesion in the cerebellum in hypoxic cellular injury.

Hypoxia has been considered to play a role in PTL either directly by electrolyte or metabolite alteration or indirectly as a consequence of its effect on the heart resulting in inadequate brain perfusion.[17] The fact that micronodular mineralization accompanies this disease implicates its presence as a possible result of hypoxia.[6] However, its significance as a useful index of perinatal hypoxia has been questioned.[27]

The association of ferruginated neurons with areas of infarction and hemorrhage has, on two occasions, lead human pathologist consultants to remark on the similarity of the Arabian thalamic lesions with those

observed in human infants who have suffered a perinatal asphyxic episode.[4,22] It should be pointed out that difficulty during parturition has been denied by owners of the animals in this study and has not been associated with cerebellar diseased Arabian foals in past reports. This does not, however, preclude the possibility of such an association.

Vulnerability of Purkinje neurons to metabolic injury such as hypoglycemia, hypoxia, or hyperthermia has been well established.[3,9,5] Basket and granular cells follow in their susceptability to hypoxia, whereas Golgi neurons are most resistant.[5] In the animals studied granular cell loss allowed visualization of Golgi neurons which would not normally be so prominent. The degenerating Purkinje perikarya observable in Arabian cerebellums were uniformly eosinophilic and shrunken, often into triangular forms. Such an appearance is referred to as "homogenizing cell change" and is suggestive of ischemic or hypoglycemic insult.[21,5,22]

The term hypoxia has been used somewhat loosely here to indicate lowered cellular oxygen supply. Technically, this could be the result of decreased brain perfusion (ischemia/oligaemia) or decreased alveolar uptake (anoxia/hypoxia). It has been determined that the end result of systemic hypoxia on CNS tissue is ischemia.[5] Therefore, oligaemia or ischemia more accurately describe the lack of adequate cellular oxygen supply.

The CNS lesions in Arabian horses are mild in comparison to those routinely encountered with ischemic brain damage. For this reason the nature of the injurious episode would have to be fairly subtle. Generalized cerebral and cerebellar cortical damage accompanied by severe thalamic alterations can be seen in hypotensive incidences of

slow onset and long duration.[5] It seems equally as reasonable that short transient episodes of oligaemia to brain tissue could result in mild cellular change for which the ability to compensate is related to the number of episodes.

The presence of micronodular mineralization in prematurely aborted and stillborn infants in indication of in utero damage.[6] Furthermore, the possibility of placental abnormality was suggested as an inciting agent for PTL babies showing signs the first few days of life.[17] On the basis of the lesional similarities between the Arabian with cerebellar disease and the PTL affected infant, and under the hypothesized "common vulnerability" relationship between regions of the brain affected, the possibility of prenatal hypoxic brain damage in Arabian foals should be considered.

In utero viral infection resulting in cerebellar disease has been established in nearly every domestic specie with the exception of the horse and dog. Viral isolation and titre assessments on affected foals have not revealed evidence of such an insult. The presence of rosette formation in affected Arabians is the only finding which might substantiate viral influence. Those species in which cerebellar disease is a result of in utero viral infection generally manifest more dramatic lesion than those seen in Arabians. In hog cholera and BVD induced cerebellar hypoplasia the viruses effect on the vascular system is thought to induce certain CNS lesions.[14,7] Regarding cerebellar disease in the Arabian, it may be pertinent to consider the effect of a non-neurotropic infectious agent in the fetal blood supply. Histopathic evidence, other than rosette formation, is indicative of degenerative process in Arabians, whereas in virally induced cerebellar disease, the abnormality is of a hypoplastic nature.

Heredity has long been assumed to play a role in the etiology of Arabian cerebellar disease. The extensive inbreeding of these animals allows relation between a large percentage of both affected and unaffected individuals. In one breeding trial done at KSU the mating of two affected mares to a "carrier" stallion (one, a father x daughter mating) resulted in two normal colts. The predominance of cerebellar disease in the Arabian breed cannot be ignored. This fact alone implicates a genetic component in the etiologic scheme. However, the presence of a second factor is a distinct possibility. Sponseller postulated hereditary predisposition to a filterable agent in conclusion of his study of Arabian cerebellar disease.[31] Without disregarding the potential role of an infectious agent, hereditary predisposal to placental abnormalities or vascular anomalies is proposed.

SUMMARY

Cerebellar disease in six Arabian horses was clinically manifest as intentional head tremor, ataxia, dysmetria, trunkal sway, base-wide stance, and often, lack of a menace response. Signs were shown as early as a few days of age and as late as "several months" of age with the majority of foals displaying abnormalities from two to six months. The progression of signs and severity of gait disturbance were also variable.

Cerebellums showed no overt signs of change. Histologically the cerebellums were largely devoid of Purkinje cells and those remaining were degenerating. The granular layer was sparsely populated with granule cells, but contained glial activity, as did the empty Purkinje cell layer. Cerebellar lesions were generally indicative of a degenerative process. Subpial and subependymal rosette formation were the only indications of a possible hypoplastic phenomenon. White matter vacuolation and spheroid formation were representative of axonal loss throughout the brain stems and spinal cords examined. Glial response was apparent in these areas as well.

Basophilic parenchymal deposits were identified in well localized groups within the thalamus. Each lesion incited substantial focal glial reaction. The structures stained positively with Von Kossa and periodic acid Schiff (PAS) reagents, but negatively with Perl's prussian blue (PPB) and Carr's chloranilic acid test for calcium. Based on staining reaction, the deposits were postulated to be similar to acid glycosaminoglycan globules such as those described in human infants and chimpanzees with perinatal telencephalic leukencephalopathy (PTL).

Theorized relationships between the cerebellar and thalamic lesions were that of a common pathway degeneration or that of common vulnerability. Hypoxia was suggested as the common insult. The possibility of an inherited predisposition to a second etiologic factor, such as vascular anomaly or placental abnormality, was proposed.

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TABLES

TABLE 1: Summary of historical data collected on Arabian foals

ARABIAN CEREBELLAR DISEASE

HISTORICAL SUMMARY

	1307	910	508	880	987	701
Sex:	Male	Male	Female	Female	Male	Female
Birth Date:	July'82	Spring'82	May'83	May'83	June'82	May'83
Onset Age:	1 mo.	3 mo.	2 mo.	several mos.	less than 1 year	a few days
First Sign:	stagger	head tremor	head tremor	head tremor	head tremor	head tremor
Medicine Adm During Pregnancy:	1*	1,2*	3*	0*	3*	0*
Necropsy Age:	11 mo.	2 yr.	1 yr.	1 yr.	2 yr.	1 yr.

*
1--paste wormer
2--Leptospirosis vaccination
3--Encephalitis/Tetanus
0--unknown

TABLE 2: Summary of clinical neurologic signs observed in Arabian foals with cerebellar disease

ARABIAN CEREBELLAR DISEASE
SUMMARY OF NEUROLOGIC EVALUATION

	1307	910	508	880	987	701
Head Tremor						
Vertical:	+	+	+	++	+	+
Horizontal:	+	+	+	++	+	+
Gait						
Weakness:	0	0	0	0	0	0
Ataxia:						
a) Fore:	++++	+++	++	++	+	++
b) Hind:	+++	++	+	+	+	+
Oysmetria:						
a) Fore:	++++	+++	++	+	+	++
b) Hind:	+++	++	+	+	+	+
Spasticity:						
a) Fore:	++++	0	0	0	0	0
b) Hind:	++	0	0	0	0	0
Knuckling:	0	0	0	(+)	0	(+)
Basewide:	(+)	(+)	0	(+)	0	(+)
Circumduction at Circle:	(+)	(+)	0	(+)	0	(+)
Oelayed Protraction:	(+)	(+)	0	(+)	0	(+)
Backing:	NO	R	NO	R	NO	R
Trunkal Ataxia:	(+)	(+)	(+)	0	0	(+)
Menace:	0	0	0	0	(+)	0
Nystagmus:	0	0	0	0	0	0

0=None Observed +=Mild +++=Marked NO=Not Oone
(+)=Positive Observation ++=Moderate ++++=Severe R=Reluctant

TABLE 3: Summary of electroencephalographic findings in Arabians with cerebellar disease

ARABIAN CEREBELLAR DISEASE

ELECTROENCEPHALOGRAPHY

	1307	910	508	880	987	701
*Excessive Synchrony (2-4Hz)	+	+	+	+	+	+
*Excessive Synchrony (6-7Hz)	+	+	+	++	+	++
*Excessive Synchrony (9-10Hz)	++	++	++	+	++	++
**Overall Synchrony	2	6	3	5	1	4

*+=Synchrony at that frequency present
++=Predominant frequency present

**1 represents the least overall synchrony and 6 the most overall synchrony

TABLE 4: Summary of cerebrospinal fluid analyses of Arabian foals with cerebellar disease

ARABIAN CEREBELLAR DISEASE

CEREBROSPINAL FLUIO EVALUATION

	1307	910	508	880	987	701	Normal
COLOR[1]:	0	0	+	+	0	0	0
APPEARANCE[2]:	0	0	0	+	0	0	0
WBC(No./ul):	2	2	10	7	0	2	0-6
RBC(No./ul):	0	7	49	375	40	7	0
SPECIFIC GRAVITY:	1.008	1.008	1.010	1.008	1.005	1.010	1.004-1.008
PANOYS[3]:	+	+	0	+	0	0	0/+
GLUCOSE(mg/dl):	61	63	67	51	63	71	40-80
CPK(IU):	NO	6.6	NO	62	8	31	0-8
PROTEIN(mg/dl):	42	55	204	207	32	268	20-85
TITRES[4]:	NO	(-)	(-)	(-)	(-)	(-)	(-)

1. 0=Colorless
   +=Xanthochromic (EOTA)

2. 0=Clear
   +=Slightly Cloudy

3. 0=Clear
   +=Trace

4. (-)=Negative
   Equine Influenza less than 1:10
   Rhinopneumonitis less than 1:2

NO=Not Oone

TABLE 5: Hematology results from Arabian foals with cerebellar disease

ARABIAN CEREBELLAR DISEASE

HEMATOLOGY

	1307	910	50B	880	987	701	Normal
WBC(No./ul):	11,100	6,600	8,100	12,400	5,440	4,700	6,000-12,500
RBC($x10^6$)	10.6	7.9	7.3	12.69	8.5	8.7	7-13
PCV(%):	37.2	29.1	25.8	43.1	34.5	35	32-52
Hb(gm/dl):	13.4	11.2	9.5	15.8	12.1	13.2	11-18
MCV(fl):	35	37	36	34	41	41	34-58
MCHC(g/dl):	36	38	36.7	36.7	35.2	37	31-37
Seg(No./ul):	5,880	4,020	5,340	7,190	2,700	890	2,700-6,700
Bands(No./ul):	-	-	-	120	-	-	less than 100
Lymphs(No./ul):	4,550	2,440	2,750	4,170	2,530	3,660	2,000-5,500
Monos(No./ul):	330	60	-	370	100	140	less than 1,000
Eos(No./ul):	330	60	-	120	50	-	less than 1,000

TABLE 6: Blood chemistry profiles of Arabian foals with cerebellar disease

ARABIAN CEREBELLAR DISEASE

BIOCHEMICAL PROFILE

	1307	910	508	880	987	701	Normal
TP(gm%):	6.9	5.8	6.0	6.4	5.7	5.5	6.1-8.4
FIB(mg.dl):	300	200	300	300	200	200	100-500
ALB(gm%):	3.6	3.1	3.3	3.6	3.5	3.4	2.7-4.2
BUN(mg/dl):	19	18	16	20	11	13	8-24
Cr(mg/dl):	1.0	1.5	2.2	1.3	1.6	1.6	1.2-1.9
GLU(mg/dl):	130	81	112	203	121	141	70-110
SAP(IU/l):	362	163	367	369	147	265	60-320
CPK(IU):	732	-	-	-	296	-	less than 50
P(mg/dl):	5.7	4.8	7	7.4	6.3	6.8	2-3.9
Ca(mg/dl):	11.8	10.8	10.4	10.9	11.0	10.5	10.5-12.9
Cl(mg/dl):	96	103	106	106	99	97	98-106
K(mg/dl):	4.5	4.9	4.0	4.5	5.1	4.2	2.7-4.4
Na(mg/dl):	132	144	145	142	139	141	130-150

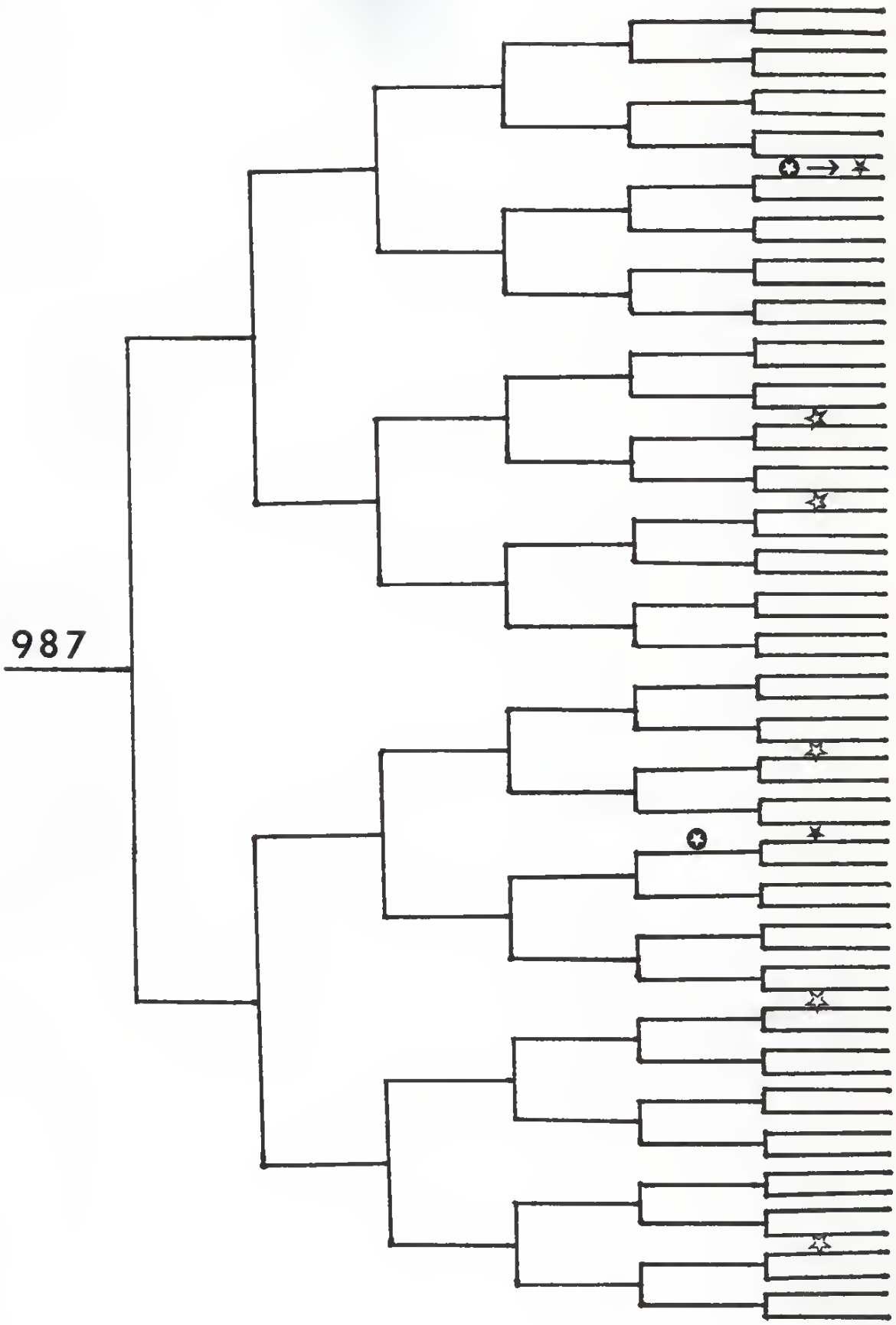
FIGURES

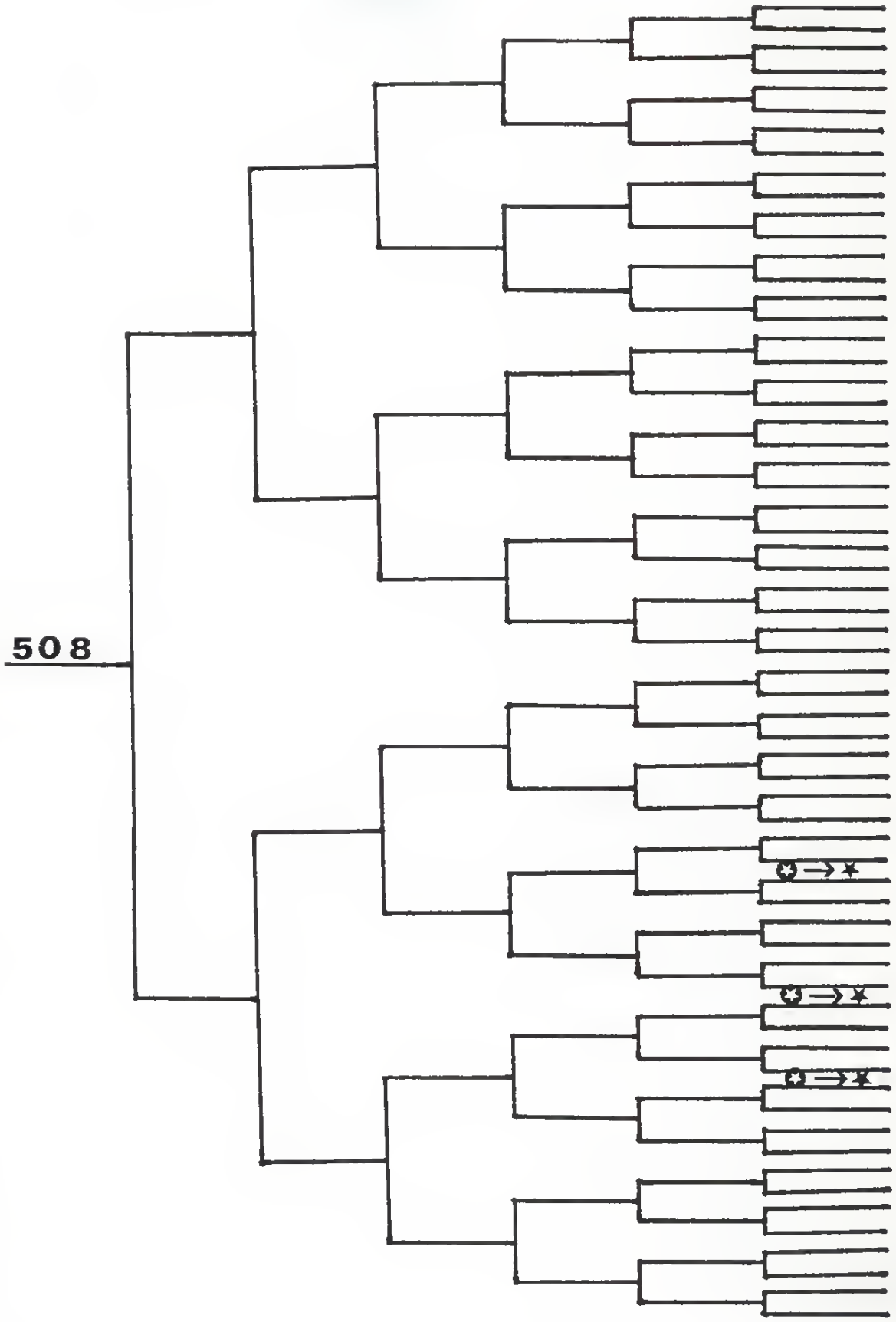
Figs. 1-5--Pedigree charts of five of the Arabians in this study indicating common ancestry.

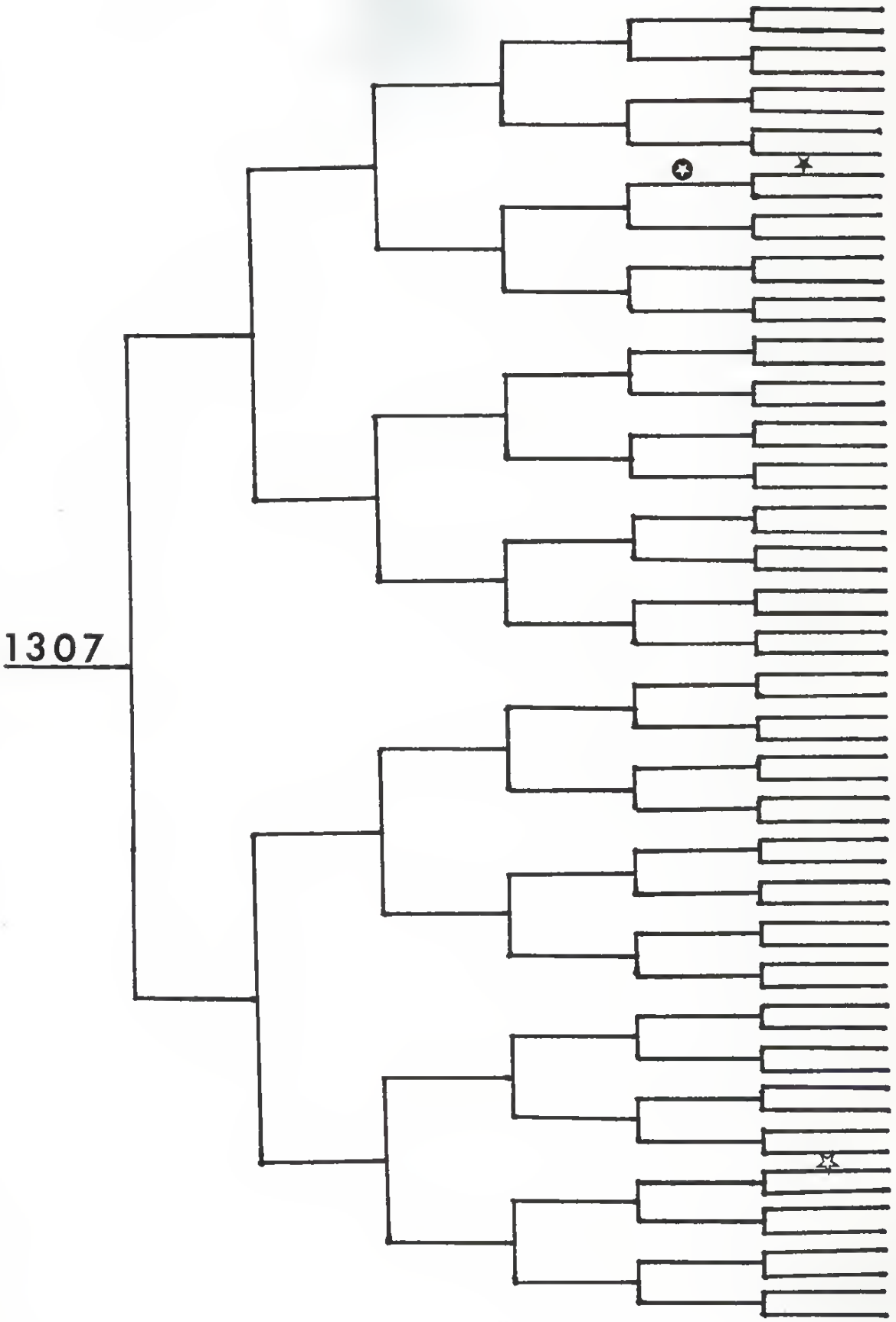
☆ -Indicates the one common stallion among all five animals.

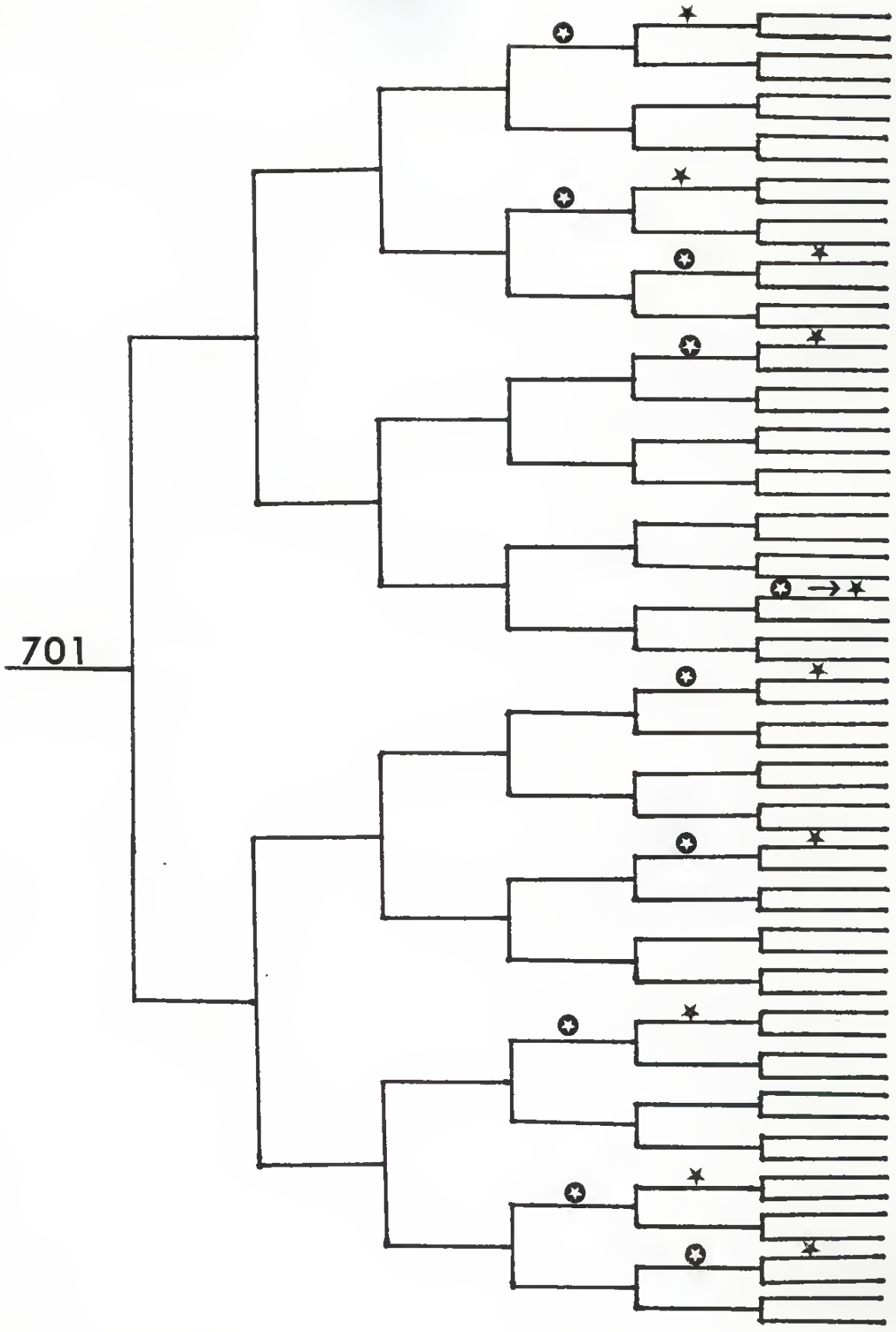
★ -Designates a father-daughter mating of the same stallion.

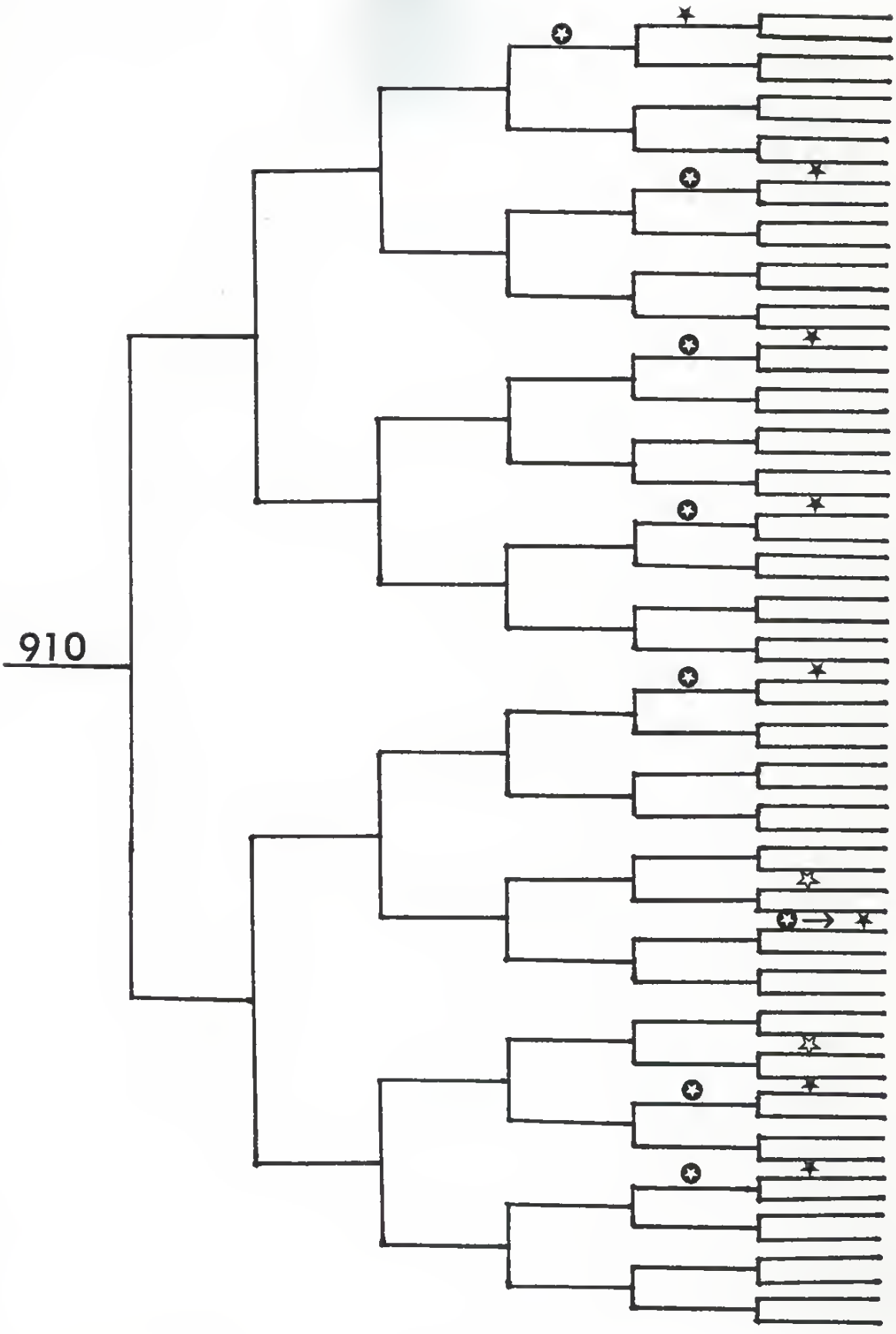
✪ -Respresents the son of that father-daughter mating.


987


508


1307


701


910

6	7
8	9

Fig. 6,7--Typical wide based placement of the thoracic limbs. Nos. 1307 & 701.

Fig. 8--Resting base-wide stance in the pelvic limbs. No. 701

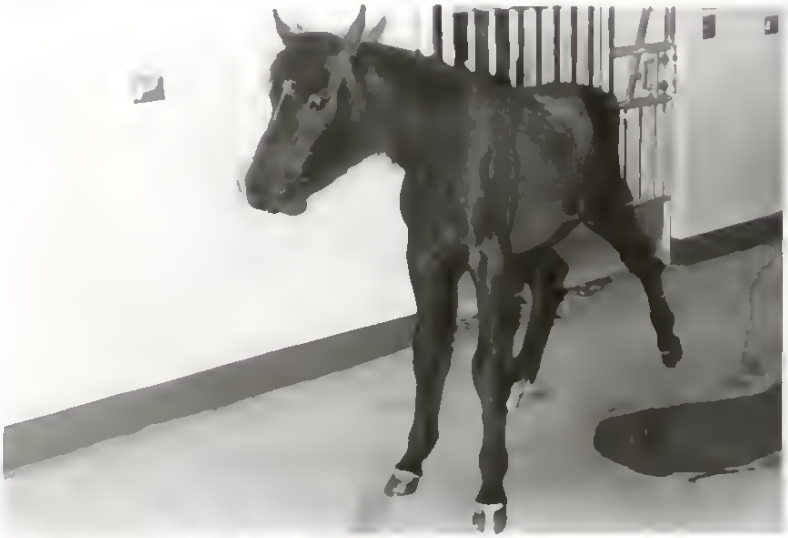
Fig. 9--Narrow based stance in the thoracic limbs with base-wide placement of the pelvic limbs. Note the elevation of the head typical of resistance. No. 701.

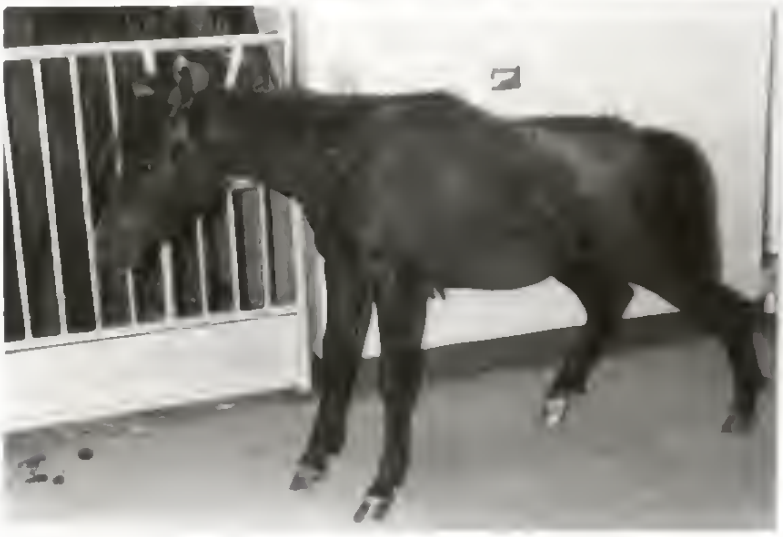
10

11

12

Figs. 10-12--Motor drive sequence of a severely affected Arabian foal exhibiting extensor rigidity in both thoracic and pelvic limbs. No. 1307.





13	14
15	16
17	18

Fig. 13--Cerebellar folium devoid of Purkinje cell bodies. Note the irregularity of the granular layer (gr). No. 701. H & E.

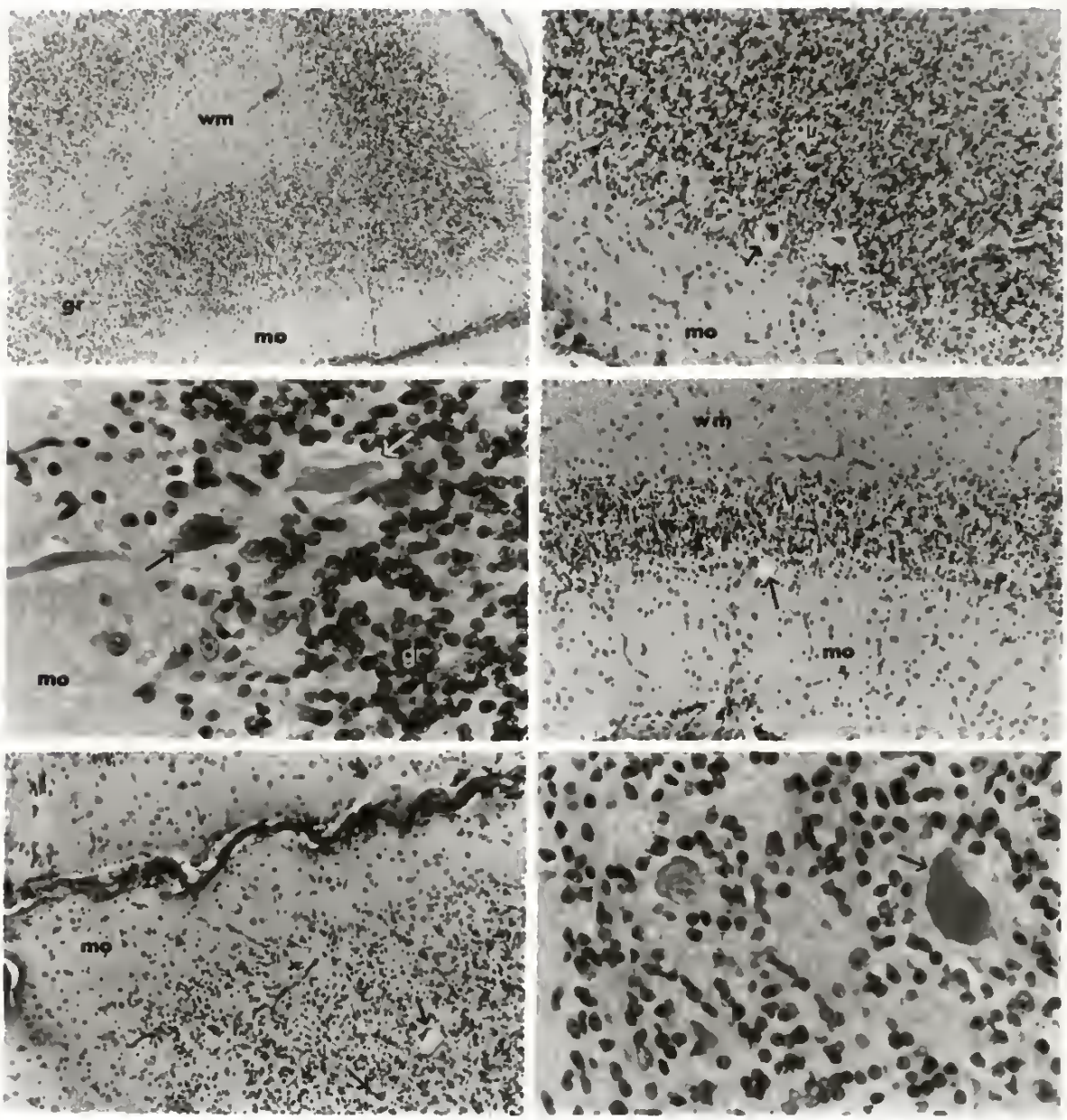
Fig. 14--Degenerating Purkinje cell bodies (arrows). No. 508. H & E.

Fig. 15--Degenerating Purkinje cell (black arrow) and axonal torpedo (white arrow). No. 701. H & E.

Fig. 16--Empty basket remaining where a Purkinje cell body has been lost. No. 701. H & E.

Fig. 17--Two heterotopic, degenerating Purkinje cell bodies among the granular cells. No. 701. H & E.

Fig. 18--Degenerating Purkinje cell body within the granular cell layer (arrow) accompanied by a centrally chromatolytic Golgi neuron. No. 701. H & E.


wm
gr
mo
mo
mo
wm
mo
mo

19	20
21	22
23	24

Fig. 19--Cerebellar folium displaying granular layer irregularity and depletion. Note the lack of Purkinje cells. No. 701. H & E.

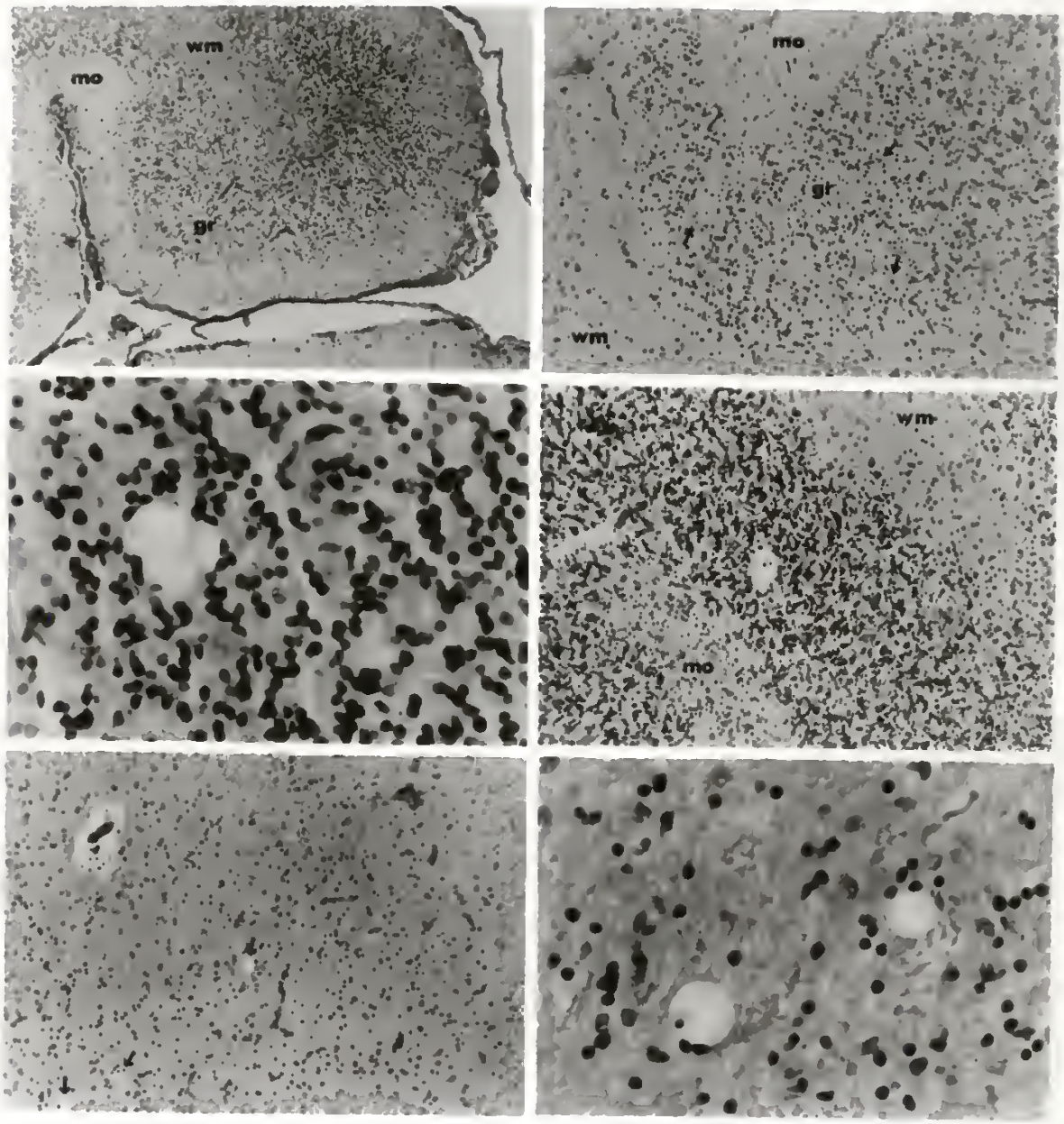
Fig. 20--Depletion of granular cells allows visualization of numerous Golgi neurons (arrows). No. 1307. H & E.

Fig. 21--Vacuolation within the granular layer indicative of Purkinje cellular demise. No. 1307. H & E.

Fig. 22--Gitter cell actively phagocytizing debris within a vacuole among the granule cells. No. 880. H & E.

Fig. 23--Cerebellar white matter vacuolation signifying axonal loss. No. 1307. H & E.

Fig. 24--Phagocytic activity within a white matter vacuole in the cerebellum. No. 1307. H & E.


wm
mo
gr
mo
gr
wm
wm
mo

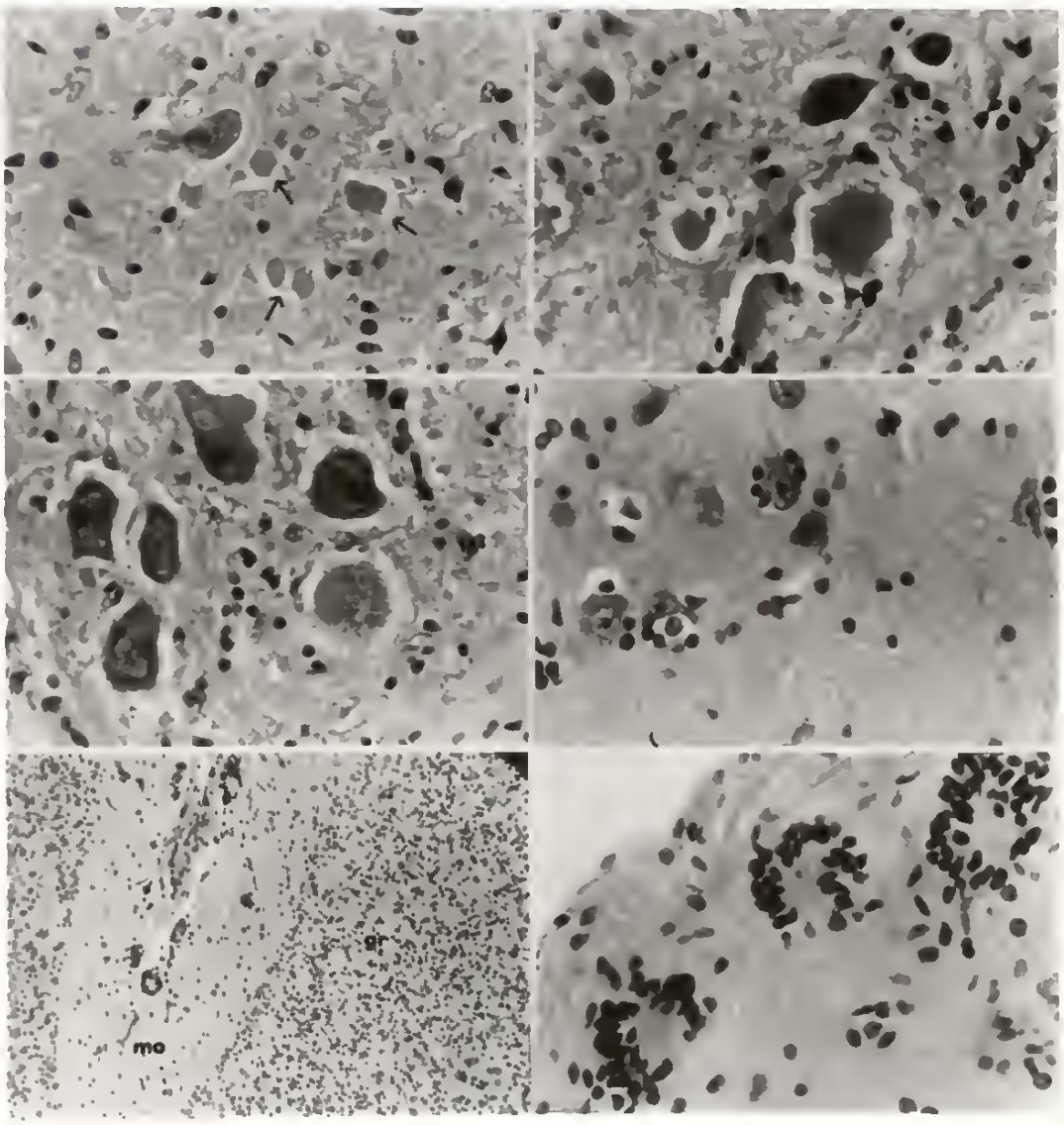
25	26
27	28
29	30

Figs. 25,26--Spheroids (swollen axons) in the brain stems of two animals studied. Nos. 910, 880. H & E.

Fig. 27--Central chromatolysis in neuronal cell bodies in the brain stem. No. 1307. H & E.

Fig. 28--Satellitosis involving small neurons of the cerebral cortex. No. 910. H & E.

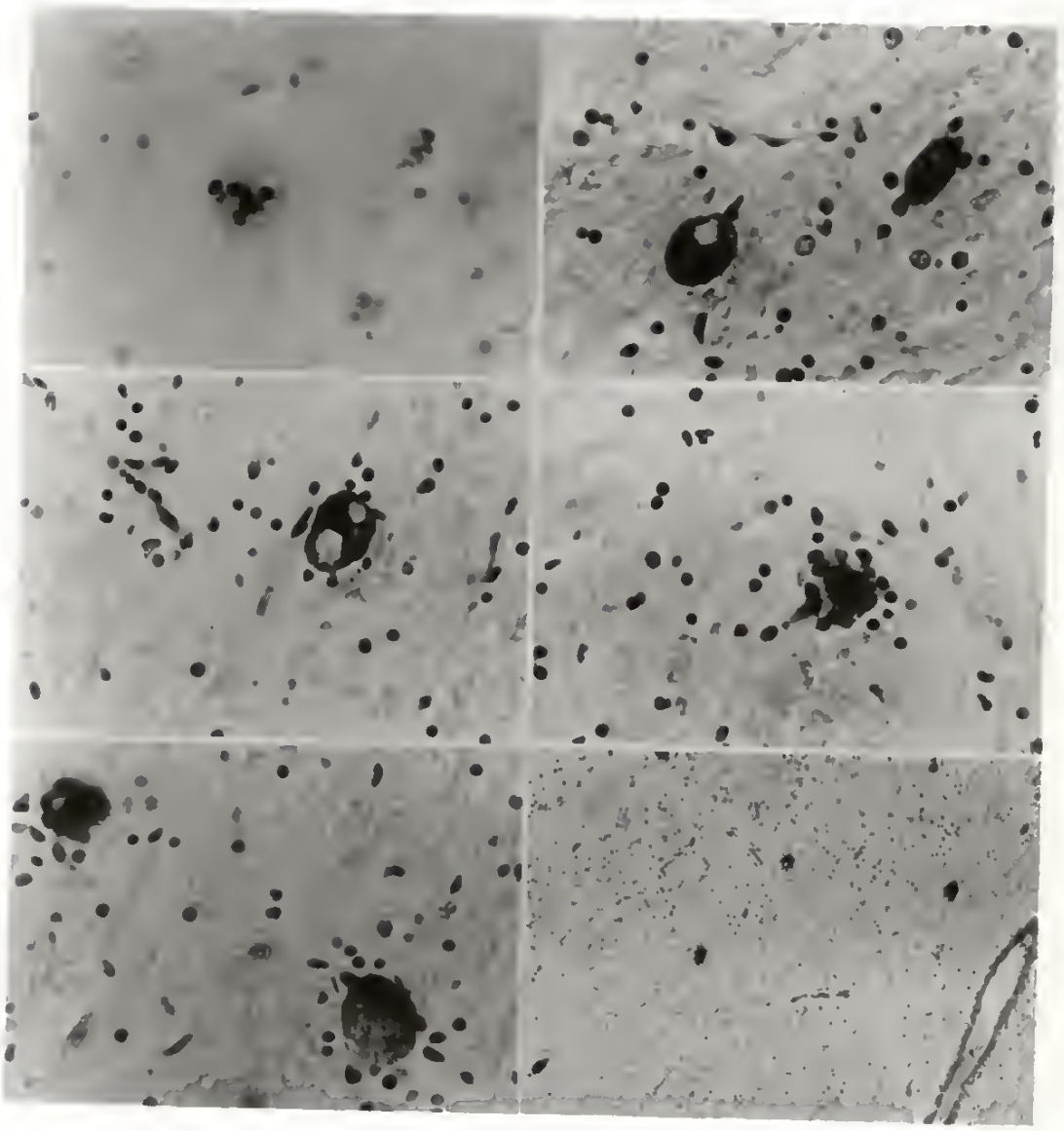
Figs. 29,30--Cells of the external granular layer in rosette formation both extramolecular (29) and intramolecular (30). No. 1307. H & E.


gr
mo

31	32
33	34
35	36

Fig. 31--Thalamic basophilic parenchymal deposit.
Von Kossa.

Figs. 32-36--Thalamic basophilic parenchymal deposits.
H & E.



37	38
39	40
41	42

Fig. 37--Vacuolations within the white matter of the thoracic spinal cord indicative of axonal loss. No. 910. H & E.

Fig. 38--Microphagocytic activity within a vacuole in the white matter of the lumbar spinal cord. No. 701. H & E.

Fig. 39--Axonal spheroid located in the dorsal grey horn of the lumbar spinal cord. No. 880. H & E.

Fig. 40--Glial nodule in the ventral grey horn of the thoracic spinal cord. No. 910. H & E.

Figs. 41,42--Vacuolated dorsal nerve tract and root as they exit the lumbar spinal cord. No. 701. H & E.

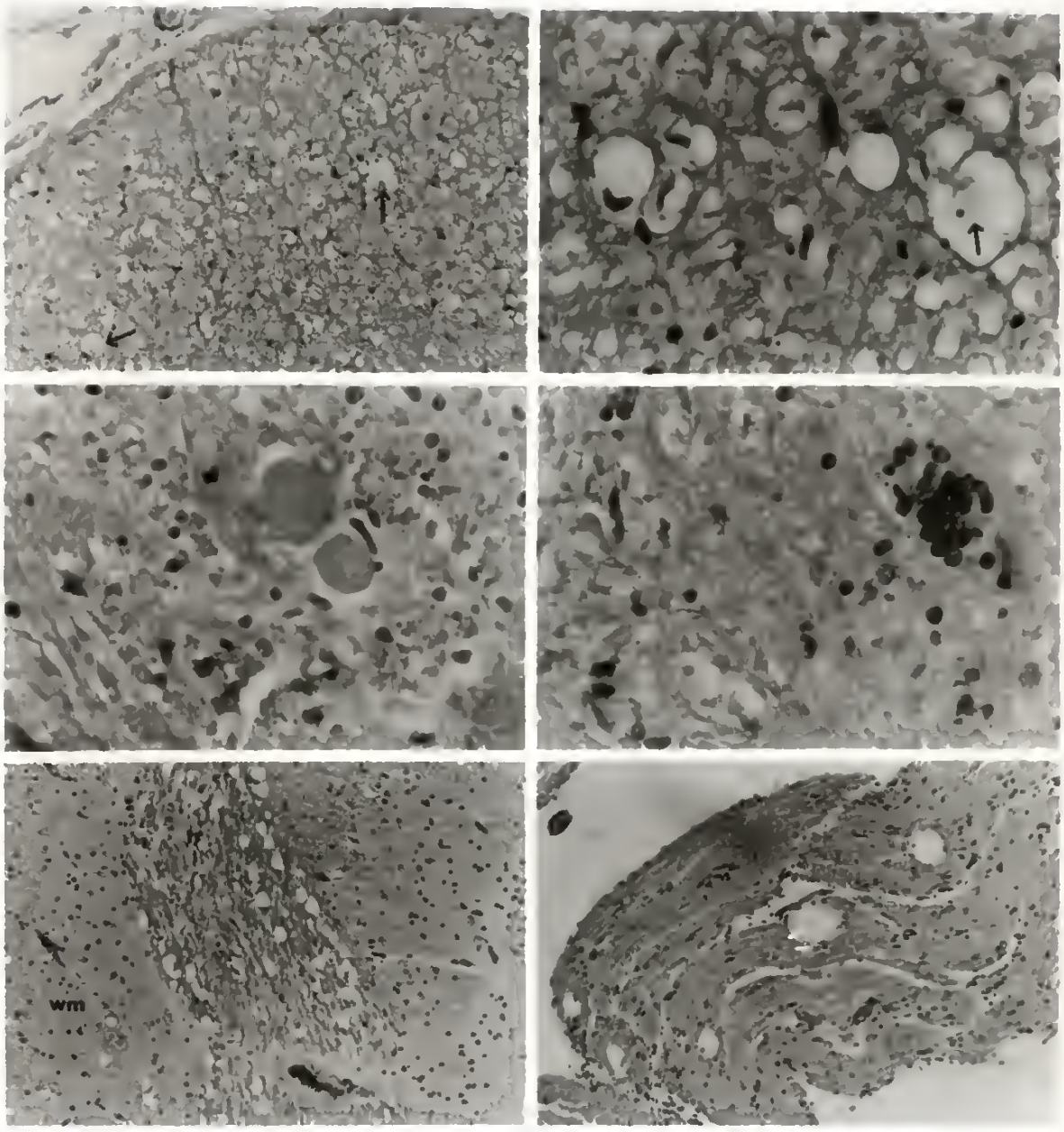

wm

Fig. 43--Normal horse. Montage III, 3 uv/mm,
30 mm/sec paper speed.
Normal EEG showing an abrupt frequency change.

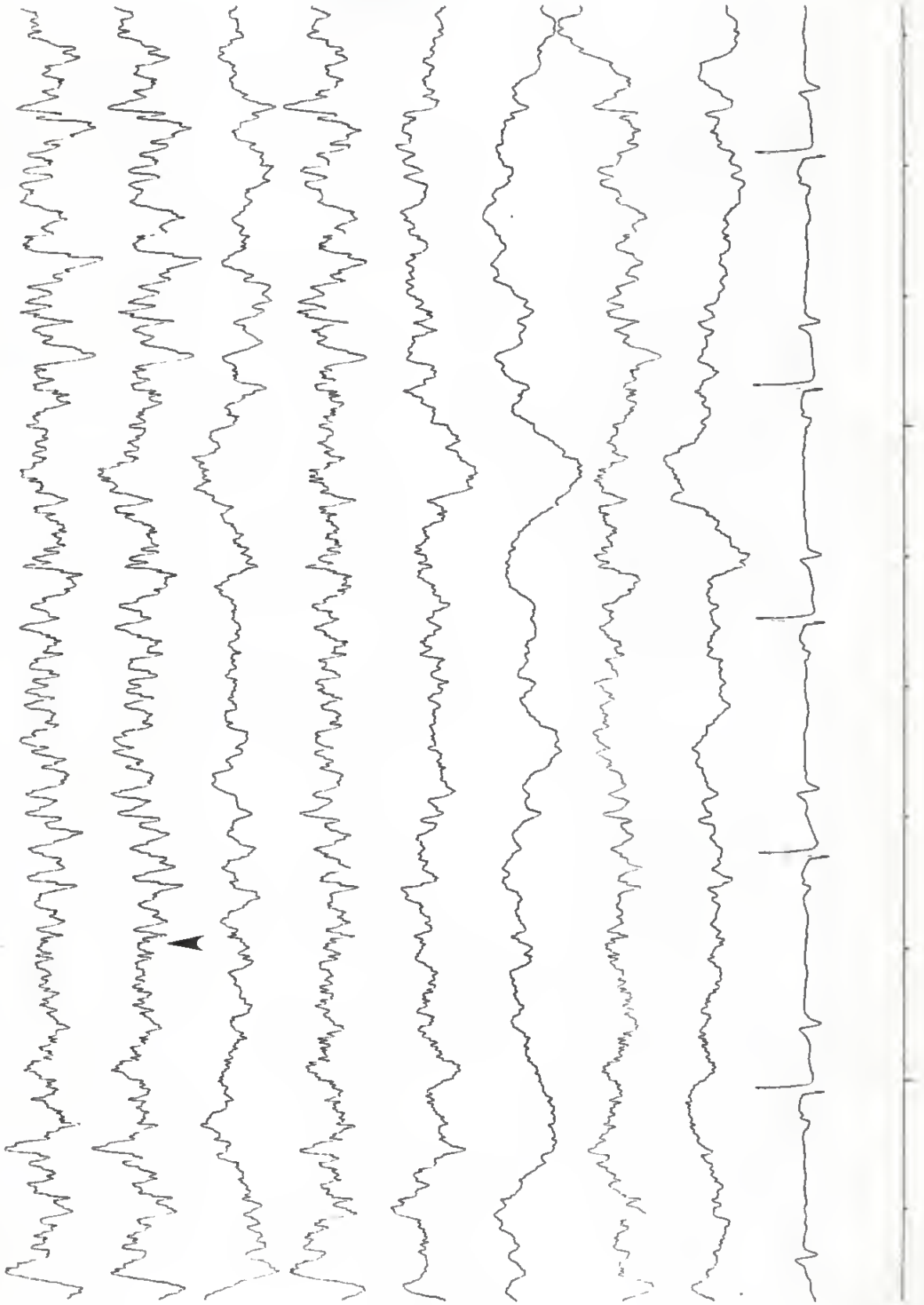


Fig. 44--Horse 880. Montage IV, 5uv/mm, 30mm/sec paper speed. Arrows indicate asymmetrical 6-7 Hz activity. AFC indicates abrupt frequency change.

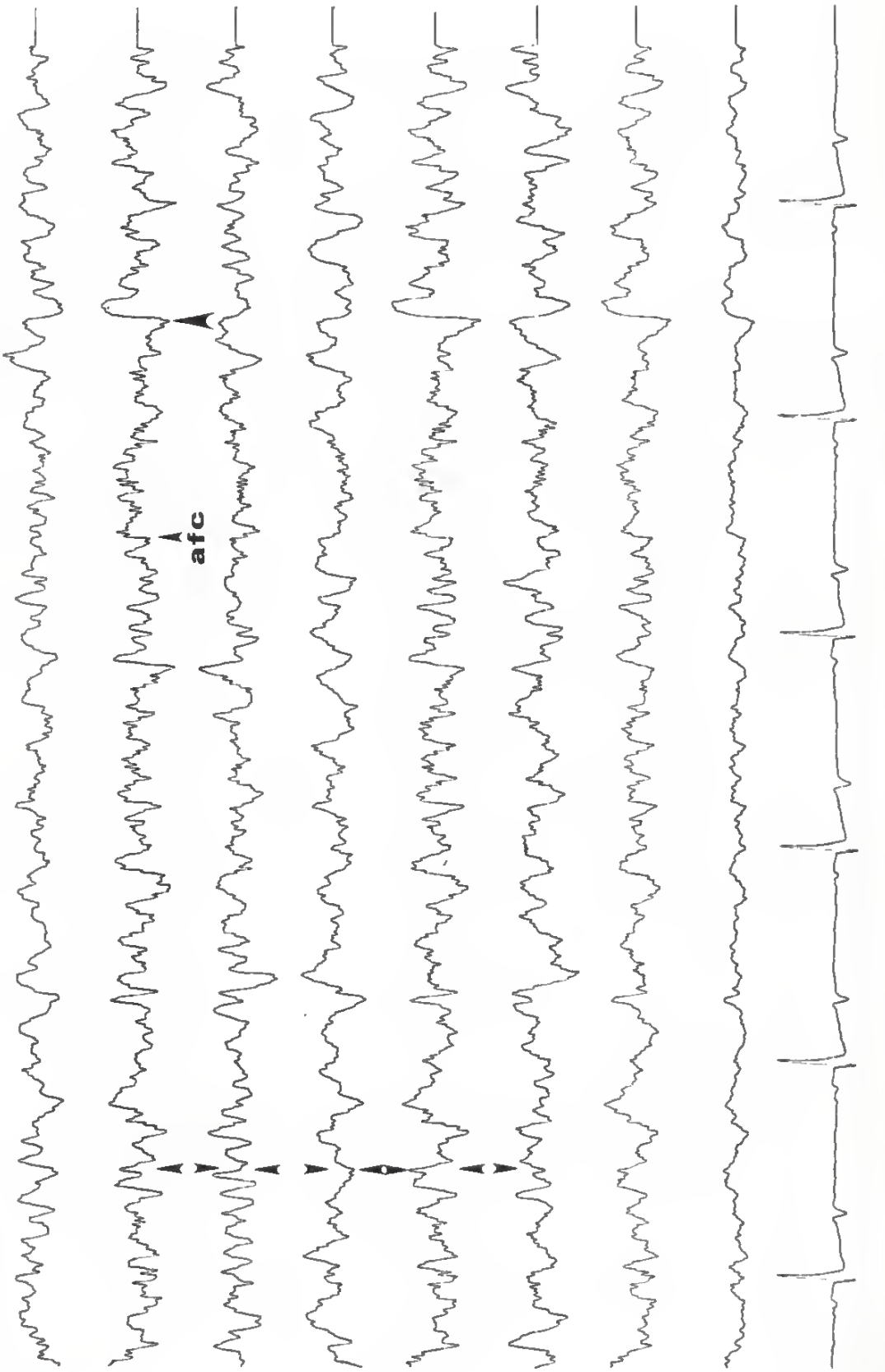

afc

Fig. 45--Horse 1307. Montage II, 3uv/mm, 30mm/sec paper speed. Arrows indicate areas of abrupt frequency changes. Notice also symmetrical 9-10 Hz activity.

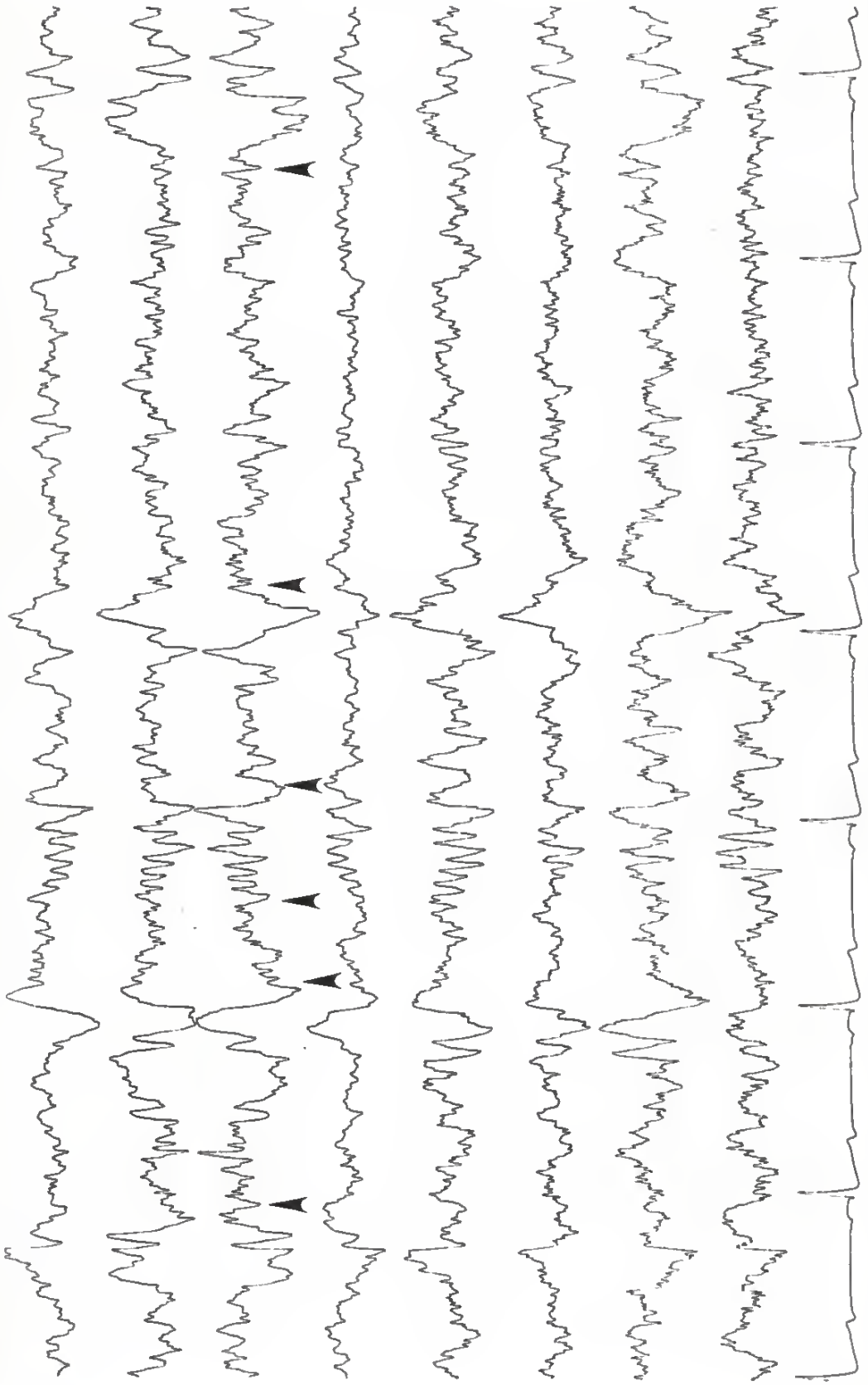
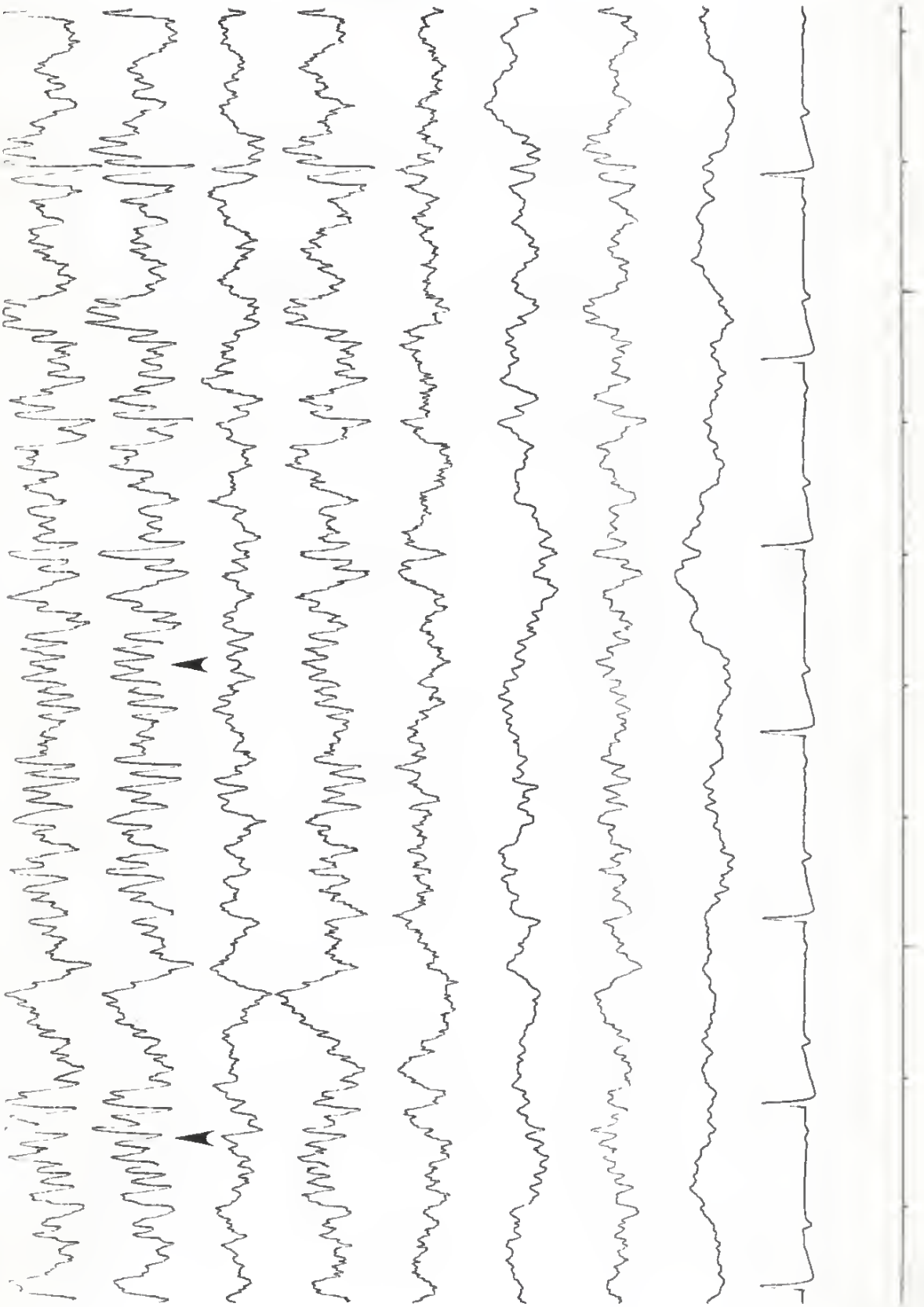


Fig. 46--Horse 910. Montage III, 3uv/mm, 30mm/sec paper speed. Arrows indicate 9-10 Hz activity which in this montage is most obvious in the transfrontal and transtemporal leads.



APPENDIX

Fig. 1--Questionnaire used in the study of cerebellar disease in Arabian horses

CEREBELLAR OISEASE IN ARABIANS--QUESTIONNAIRE

Animal name or description:

1. Date of birth: _____ 2. Age at onset of signs: _____
3. Any abnormalities during or immediately after birth? _____
   If so, describe: _____
4. Was mother sick while pregnant? _____. If so, describe the type of illness: _____
5. Was mother given any drugs during pregnancy? (worming medications, injections, etc.) _____. List medications and injections given: _____
6. What was mother fed during pregnancy and how were she and the foal housed? _____
7. What were the first abnormalities witnessed in the foal and did they get worse over time? _____
   _____
8. Were other horses on the farm sick at any time during the mares pregnancy or before the foal started showing signs? _____
9. Any other relatives with the same problem? Please list maternal:
   _____
   _____
   paternal: _____
   _____

Fig. 2--Standard format used in clinical neurologic evaluation of Arabian horses with cerebellar disease

NEUROLOGIC EXAMINATION

I. Mental Status:

II. Head Posture: Tremor - horizontal - vertical Tilt

III. Cranial Nerves:

I. _____ VII. _____

II. _____ VIII. _____

III. _____ IX. _____

IV. _____ X. _____

V. _____ XI. _____

VI. _____ XII. _____

Menace + / -

IV. Neck: a) Pain on palpation (Pressure on midline) + / -

Location _____

b) Flexion/Extension _____

V. Gait

	RF	RR	LF	LR
weakness				
ataxia				
spasticity				
dysmetria				

Notes:

VI. Backline Pressure:

VII. Lateral Resistance:

VIII. Reflexes:

Fig. 3--Schematic representation of electrode placement for EEGs

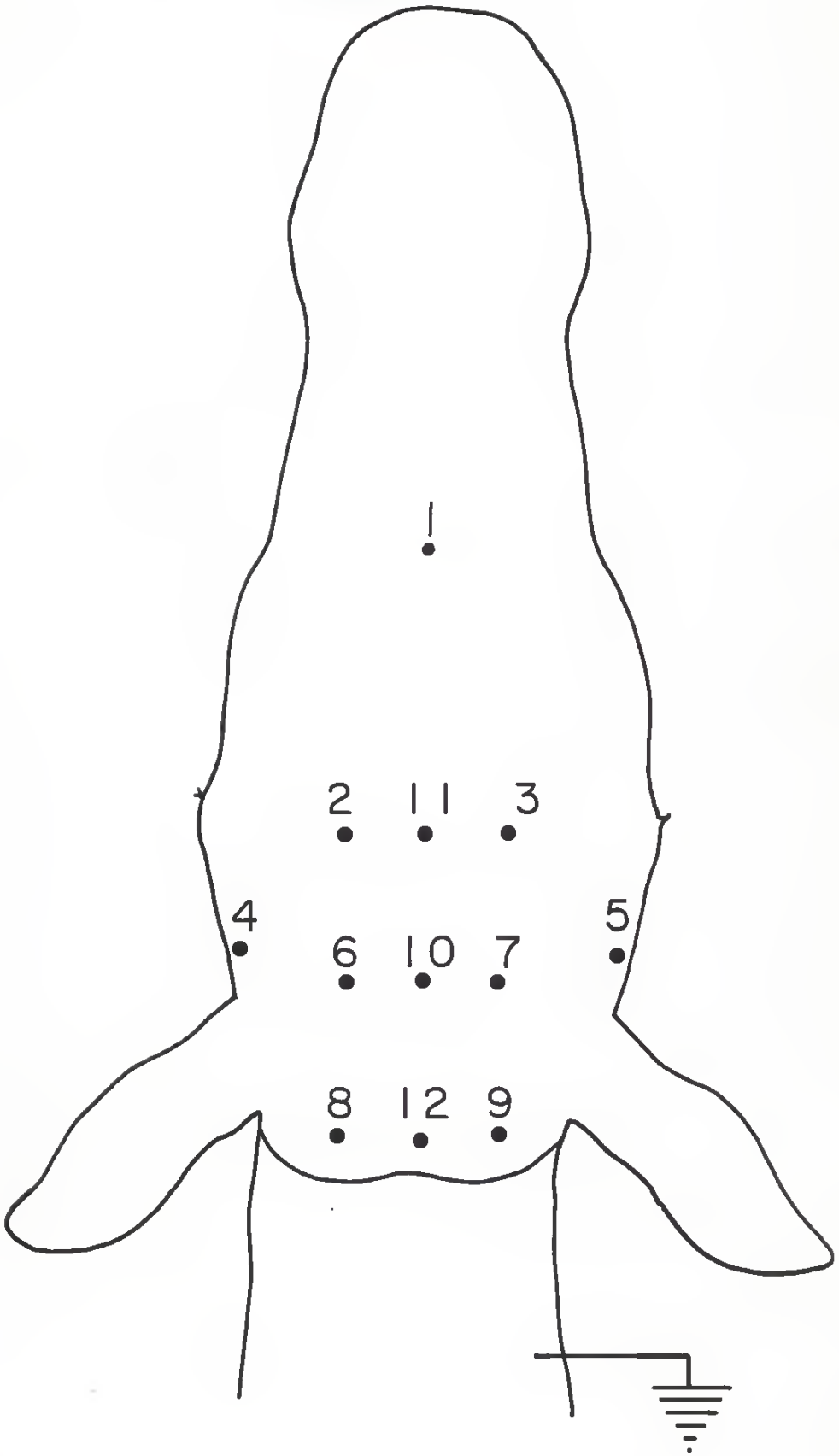

1
2
11
3
4
5
6
10
7
8
12
9

Table 1--Montages and channels used in electroencephalographic recordings

Montage

Channel		1 A	2 B	3 C	4 D	5 E	6 F
1	G1	2	2	2	11	2	2
	G2	1	6	3	2	10	4
2	G1	3	6	4	2	3	4
	G2	1	8	5	3	10	6
3	G1	4	8	10	3	4	6
	G2	1	4	6	11	10	8
4	G1	5	4	6	10	5	8
	G2	1	2	7	4	10	9
5	G1	6	3	7	4	6	9
	G2	1	7	-10	5	10	7
6	G1	7	7	12	5	7	7
	G2	1	9	8	10	10	5
7	G1	8	9	8	6	8	5
	G2	1	5	9	7	10	3
8	G1	9	5	9	8	9	3
	G2	1	3	12	9	10	2
9	G1	36	36	36	36	36	36
	G2	37	37	37	37	37	37

CEREBELLAR DISEASE IN THE ARABIAN HORSE

by

Margaret Turner Beatty
B.S., Emporia State University, 1978
D.V.M., Kansas State University, 1984

AN ABSTRACT OF A THESIS

submitted in partial fullfillment of
the requirements for the degree

MASTER OF SCIENCE

Department of Pathology
College of Veterinary Medicine
KANSAS STATE UNIVERSITY
Manhattan, Kansas

1984

Cerebellar disease in the equine is found predominently among the Arabian breed. This has led to the assumption that hereditary factors play an etiologic role in the disease process.

Six young Arabian horses exhibiting signs of cerebellar disease were obtained from various regions of the country and evaluated clinically and histopathologically. The signs shown on neurologic examination and the lesions seen microscopically were compared among the six animals in an attempt to further the present knowledge concerning the nature and etiology of cerebellar disease in the Arabian.

Historical accounts described the animals as having been normal for a period prior to onset of signs. Head tremor was the initial evidence of abnormality presenting within a range of one to several months of age. This was followed by incoordination characterized by ataxia and hypermetric dysmetria. Proprioceptive deficit was manifest as tendency to circumduct and excessively adduct the limbs on circling, trunkal sway, and wide based stance. Gait deficit was more pronounced in the forelimbs than the rear, and was bilaterally symmetrical. One animal exhibited extensor rigidity and goose-stepping action in the thoracic limbs. No weakness in the limbs was apparent. Abnormal nystagmus was not observed, but five out of six animals had no reaction to menace testing.

The signs were progressive to a point at which they reached a plateau or failed to decline rapidly enough that they could be described as progressive. Individual ability to compensate for cerebellar deficit may explain this phenomenon.

Cerebrospinal fluid (CSF) examination revealed increased protein in three animals. This was thought to be related to red blood cell contamination in one horse and cellular degeneration or serum protein leakage secondary to congestion in the other two. Creatinine phosphokinase (CPK) levels in CSF were elevated in three animals. It is theorized that increased CPK activity is a reflection of degenerating processes in the CNS. Attempts to identify the presence of a virus in CSF were unsuccessful.

Pathologic studies found no gross lesions related to CNS disturbance. Histopathologic examination revealed marked cerebellar and thalamic abnormalities and widespread axonal degeneration.

Sub-pial or subependymal rosette formation was found in two of the six animals. This feature has been reported in virally induced CNS disease. It may be evidence of an earlier stage of cellular development.

The axonal lesions were typified by vacuolation and gitter cell activity. Occasional spheroid formation was observed. Neuronal cell body changes in the brain stem and cerebellar nuclei were interpreted to be related to axonal injury, but could not be localized to specific nuclear groups.

Purkinje cells of the cerebellar cortex were markedly reduced in numbers and degenerate in appearance. Granular cells were also depleted. Glial activity was present among both cell layers. Degenerating cell bodies, axonal spheroids, empty baskets, and glial reaction were suggestive of a degenerative phenomenon as opposed to developmental failure.

Well localized basophilic deposits surrounded by microglial reaction were found in the thalamus of each animal studied. The globules exhibited the same staining properties as "micronodular mineralization", a lesion observed in the basal ganglia and thalami of human infants and chimpanzees with perinatal telencephalic leukoencephalopathy (PTL). Their presence amidst degenerating neuronal cell bodies suggested an alternative identity as mineralized neurons. However, this could not be substantiated with special staining techniques.

Two theories were proposed relating thalamic and cerebellar lesions. The first was that of a common pathway along which transsynaptic retrograde degeneration could take place. The thalamic depositions would have to be neuronal elements for this proposal to apply. The second relationship was that of a common vulnerability to injury. The insult was hypothesized to be prenatal or perinatal hypoxia in this case.

Ischemic cellular injury is thought to be an etiologic factor in PTL, and thus, in micronodule formation. However, these lesions have been observed in a small percentage of normal infant brains. Hypoxic brain damage is often manifest as hemorrhage or areas of local infarction. The presence of mineralized neurons is associated with both these lesions. Thus, they would conform to the hypoxic insult theory, were the globules determined to be neurons. Purkinje neurons are notoriously vulnerable to ischemia. Their generalized loss and the degenerative appearance of those remaining was typical of such an injurious phenomenon.

The preponderance of equine cerebellar disease occurring in Arabians cannot be ignored. A genetic influence is most certainly part of the etiologic explanation, but pedigree analysis will not sufficiently substantiate this theory. Although each of the six horses studied were related in the seventh or eighth generation removed, so are they related to normal animals by the same common ancestor. Breeding trials will best allow the hereditary hypothesis to confirm itself.

The presence of a second factor, predisposed by heredity, has been postulated. This seems to be a very good possibility, given the variable nature of the occurrence of cerebellar disease.

In utero viral infection is a possibility that has not been solidified despite titre assessment and isolation attempts. It is postulated that perinatal hypoxic episode may be the suspected second factor. An hereditary and/or viral influence on the integrity of the placenta or fetal vascular system which would result in abnormal oxygen delivery to the fetal brain may be the cause of ischemic cell loss in the developing nervous system. Difficulty at parturition would be another period during which hypoxic brain damage could occur. Yet, only in one case did owners report birthing problems.

This study has made some progress toward determination of a reasonable etiologic explanation for Arabian cerebellar disease through the further identification of CNS lesions. At the same time it has raised questions and pointed out alternative hypotheses concerning the disease process. Further investigation can only enhance our limited knowledge of CNS disease entities.