

Neurodegenerative diseases (a lesion-based approach): white matter

Major lesion groupings

Grey matter

- Neuronal necrosis
 - cerebrocortical, hippocampal, cerebellar
- Neuronal degeneration, spheroid formation
 - Cerebellum, [motor, sensory – with GM / WM], 'multisystem'
- Multi/focal neuroparenchymal necrosis / rarefaction / oedema
- Vacuolation

Grey matter and white matter

- Neuroparenchymal necrosis / rarefaction / oedema
- Neuronal degeneration + axonal degeneration : long fibre tract Wallerian degeneration, spheroid formation
 - motor neurone + tract, sensory neurone + tract, combination
- Vacuolation

White matter

- **Multi/focal neuroparenchymal necrosis / myelinolysis –demyelination / oedema**
- **Secondary demyelination / Wallerian degeneration**
 - **Long fibre tract and other patterns of Wallerian degeneration, spheroid formation – with GM+WM**
- **Hypomyelination**
- **Dysmyelination (lesions of myelin sheath / oligodendroglia)**
- **Vacuolation**

White matter : terminology

- Leucomalacia : necrosis leading to softening of white matter : detectable macroscopically
- Myelinolysis: dissolution of the myelin sheaths of nerve fibers
- Demyelination: destruction, removal, or loss of the myelin sheath of a nerve or nerves
 - Primary (= demyelination) axon intact, at least in early stages
 - Secondary – loss of myelin secondary to axonal degeneration
- Myelinic oedema: splitting of myelin sheath along intraperiod line (widening of extracellular space) observed as vacuolation in routine histological preparations
- Spongiform degeneration: vacuolation of white matter (vacuolar leucoencephalopathy)
- Severe white matter oedema may progress to white matter rarefaction (myelinolysis) and necrosis if extensive or in confined space [? vascular compromise (eg optic canal)]
- Hypomyelination : myelin aplasia / hypoplasia
- Leucodystrophy : disorder of myelin synthesis and maintenance associated with a biochemical abnormality of myelin leading to degeneration, therefore primary demyelination may be a component

Multifocal / focal white matter necrosis

- Parasitic migration eg Parelaphostrongylus spp
 - may involve predominantly / exclusively white matter with minimal inflammatory response
- Shiga toxin - Oedema disease
 - thalamus / midbrain / medulla
- Subacute – chronic *Clostridium perfringens* epsilon intoxication (focal symmetrical encephalomalacia FSE)
 - particularly cerebellar peduncles, also internal capsule and thalamus
- Cyanide intoxication
 - Cat – extensive symmetrical necrosis of cerebral white matter (?chronic repeated exposures)
- Halogenated salicylanide (closantel) intoxication
 - subpial / subependymal / perivascular myelinolysis – may occur in absence of optic nerve necrosis
 - optic nerve necrosis (malacia) ? ischaemia secondary to swelling of intracanalicular segment
- Foetal periventricular leucomalacia (?in utero hypoxia exacerbating pre-existing conditions eg inflammation)
- Experimental exposure to carbon monoxide
 - adult sheep - limited PVN
 - patchy extensive leucomalacia, cerebrum newborn pigs
- Equine leukoencephalomalacia : Fusarium moniliforme toxin-induced white matter injury
 - suggested as cause of leukomalacia in a white tailed deer
- Metronidazole toxicity dogs
 - Brainstem leucomalacia and axonal swellings in vestibulocerebellar pathways
- Leukodystrophy of Dalmatian dogs
 - Focal cavitation of cerebral white matter with axonal loss and macrophages (initially selective myelin loss)

Consider also

- Limousin encephalopathy (mainly white matter lesions but also some grey matter involvement)

Optic nerve / chiasm necrosis

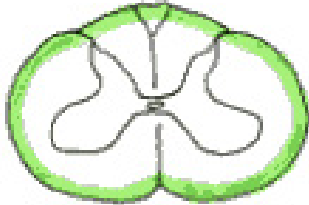
- Halogenated salicylanide (closantel) intoxication
- Helichrysum argyrosphaerum toxicity
- Stypantra spp intoxication

Subpial, circumferential

- Parenteral administration of copper heptonate (neck) leading to accidental injection into spinal canal
- Epidural administration of local anaesthetic containing sodium metabisulphite, prominent subdural fibroplasia

Basic patterns of white matter tract degeneration in spinal cord

C

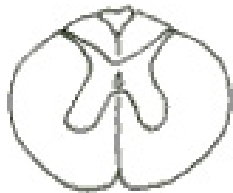


Toxic / iatrogenic

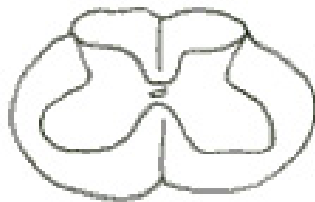
Cervical spinal cord :

Parenteral administration of copper heptonate (neck) – cervical cord; may also occur with other chemicals

T



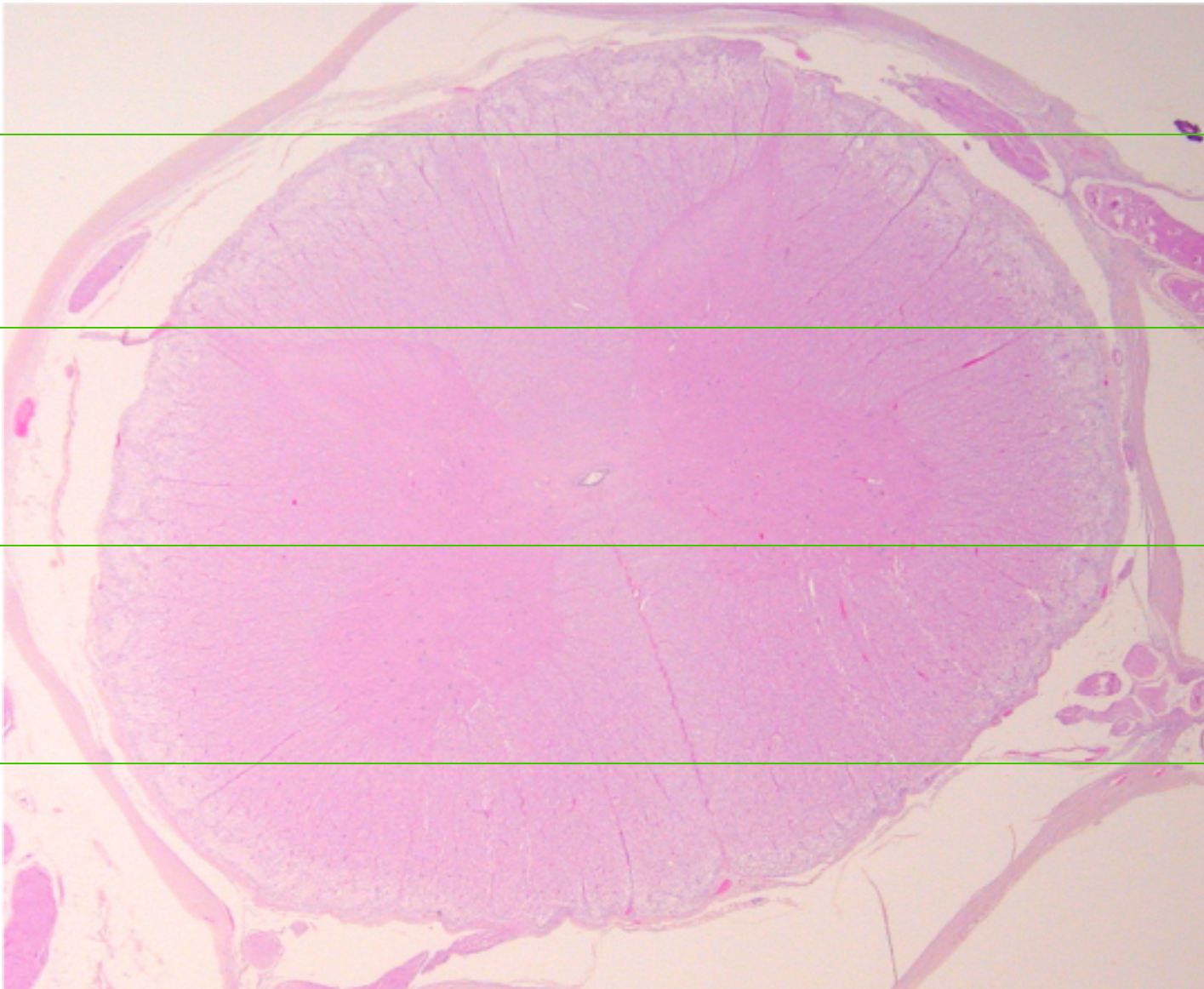
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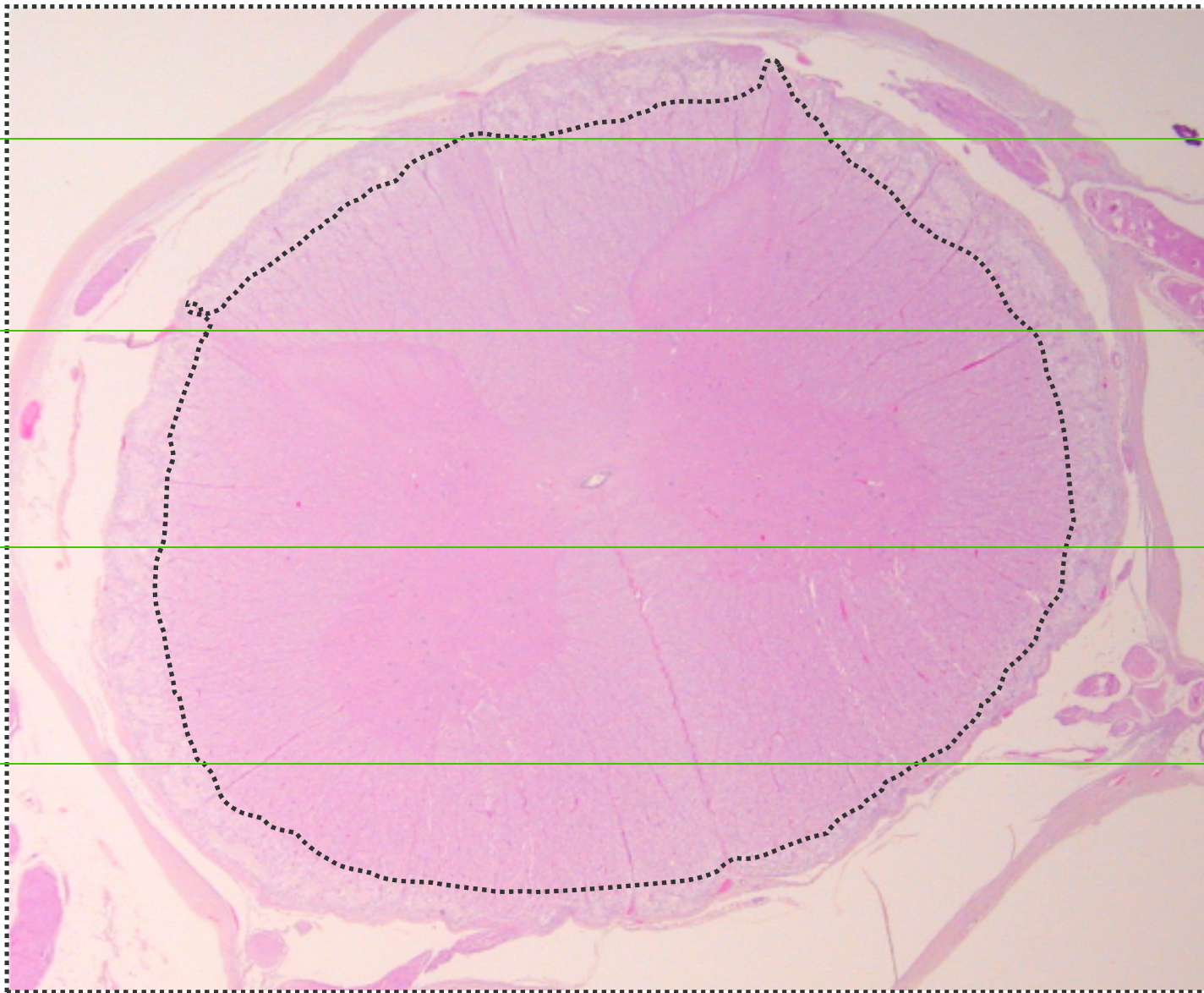
Lumbar spinal cord :

accidental subdural administration of local anaesthetic containing sodium metabisulphite – lumbar cord with subdural fibrosis

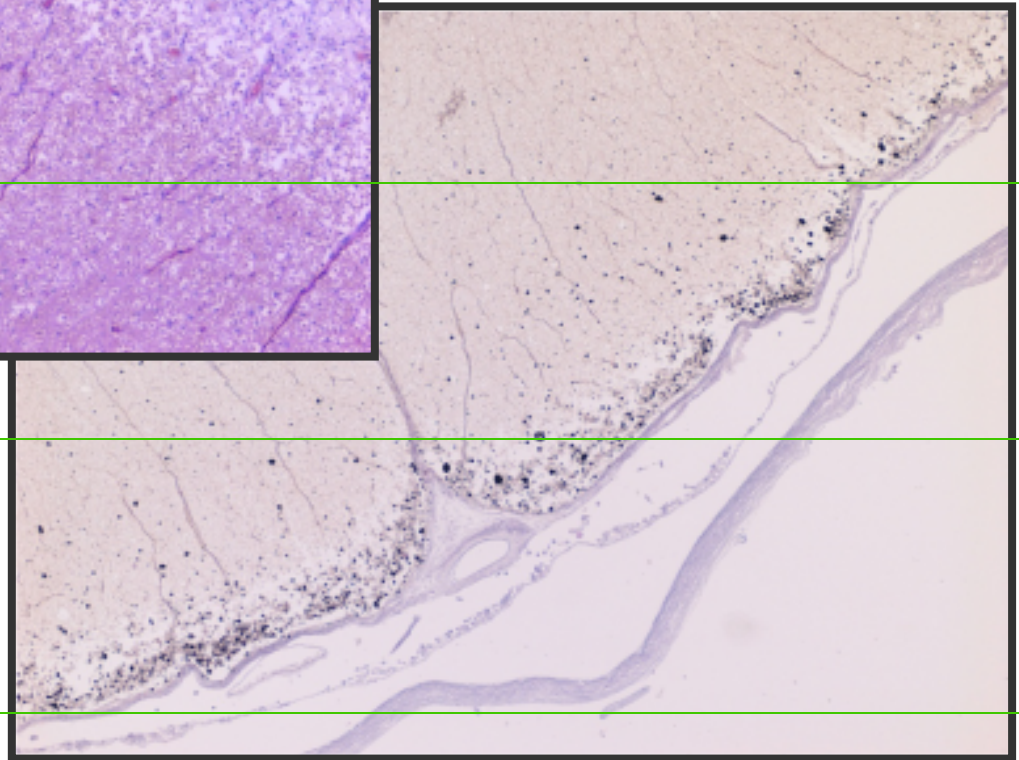
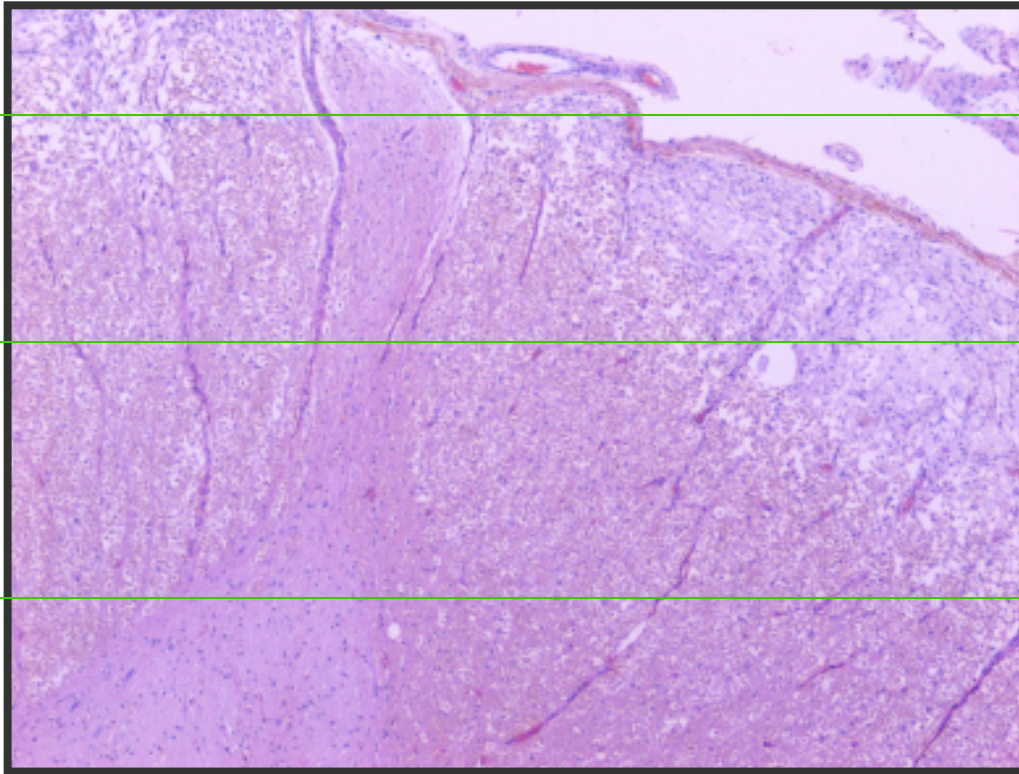




561/97 adult Blackface ewe C7

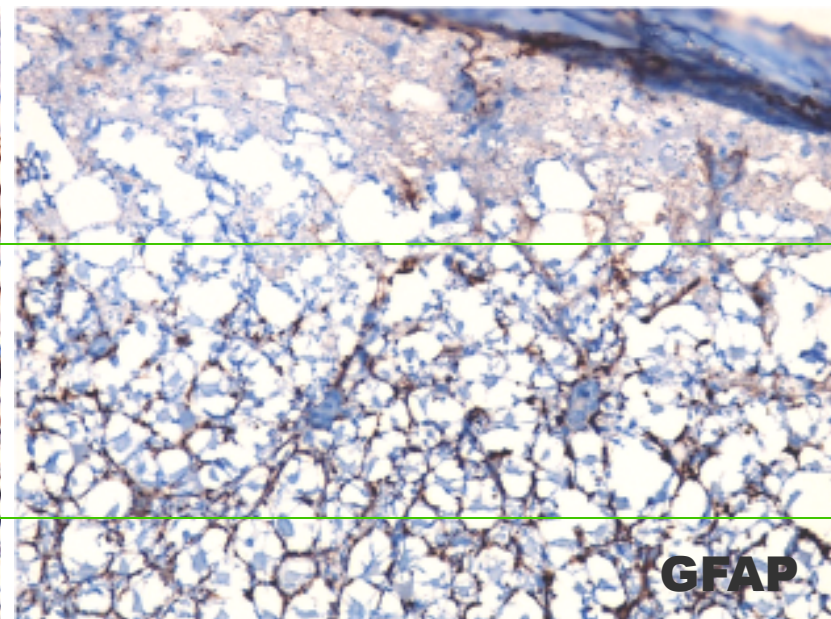
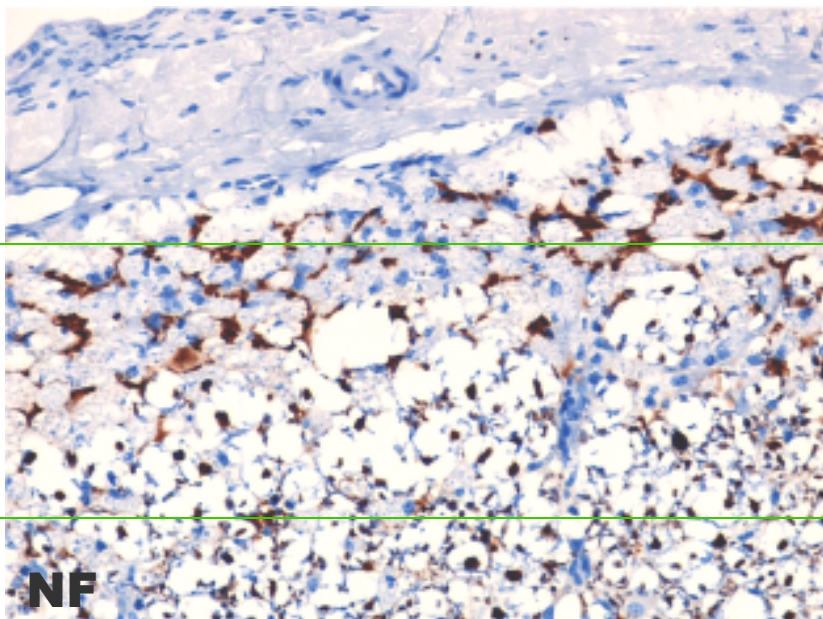
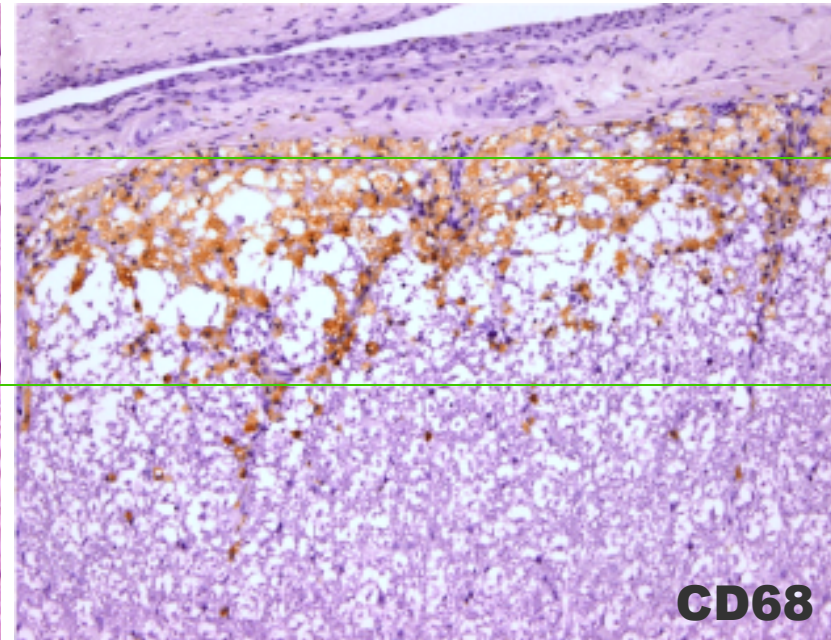
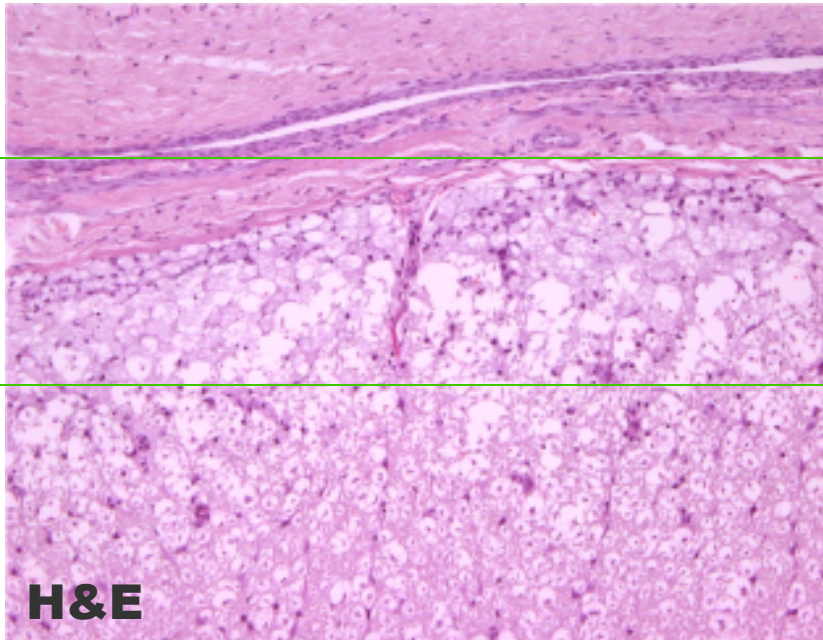


561/97 adult Blackface ewe C7



561/97 adult Blackface ewe
subpial myelopathy
associated with copper injection
C7: H&E; Marchi

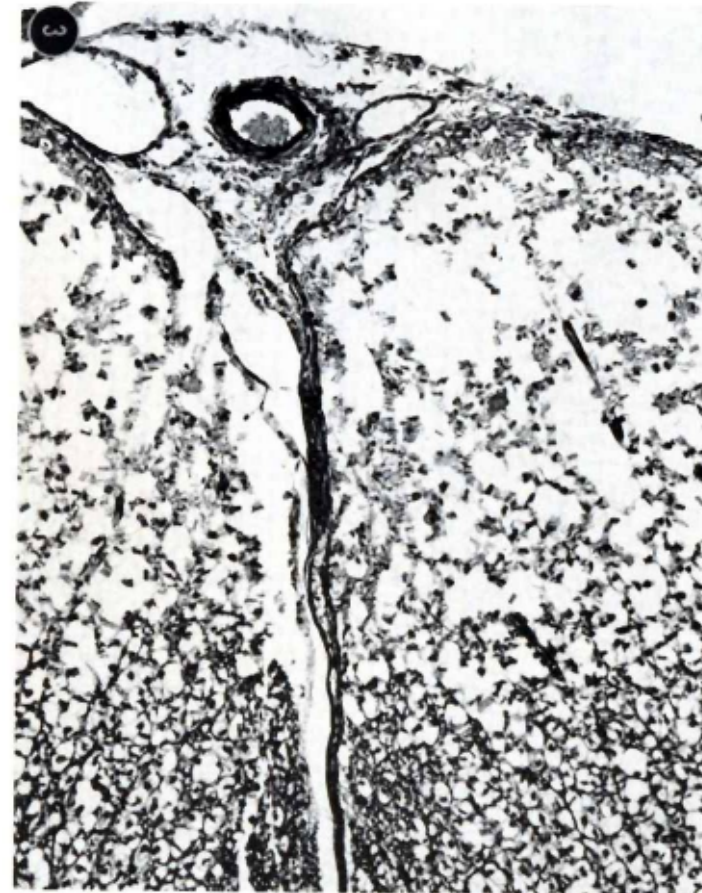
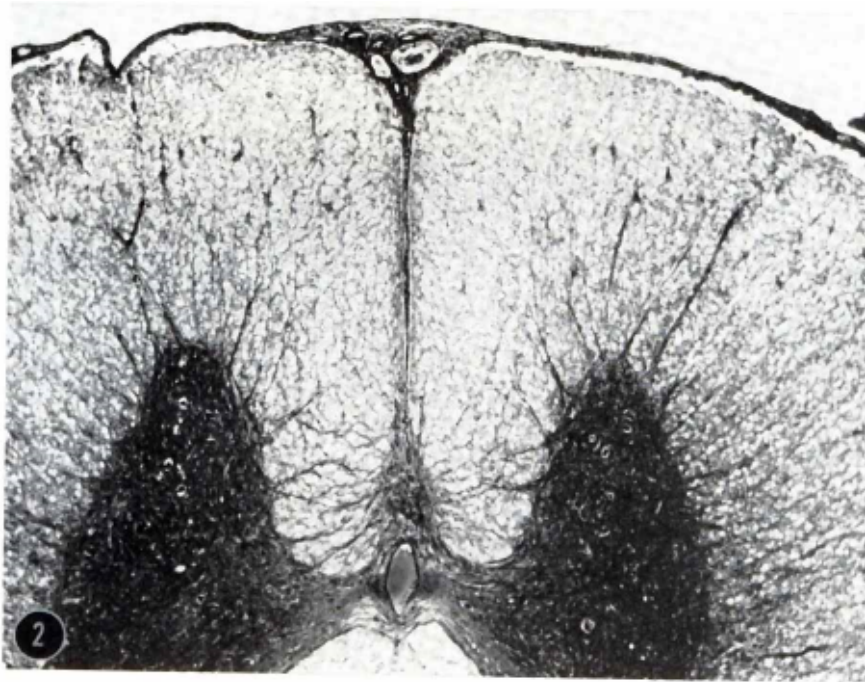
Subpial myelopathy, cervical spinal cord



Details of ovine subpiel cervical myelopathy cases

Case ref.	Breed / age	No affected / management group	Onset clinical signs (calendar month)	Medication copper preparation (manufacturer)
475, 476/94	Welsh mountain / adult ewes	2/350	January	Details NK
580, 581/96	Swaledale / adult ewes	NK	February	Cu heptonate Pfizer
561, 562/97*	Scottish blackface / adult ewes	3 / several hundred	March	Cu heptonate Young's
451, 452/98	Dalesbred / adult ewes	NK	February	Cu heptonate Young's
567/98*	Scottish blackface / adult ewes	2 / several hundred	February	Cu heptonate C Vet
1530/00	Swaledale / adult ewes	NK	February	Cu heptonate Young's
226, 227/01	Swaledale / adult ewes	4 / 300	January	Details NK
456, 457/02	Mule X / adult ewes	4 / 180	February	Cu heptonate Swaycop
E433/04	Swaledale / adult ewes	3-4 / 300	February	Cu heptonate Swaycop
E482/04	Swaledale / adult ewes	5 / 120	February	Cu heptonate Novartis
27S217	Suffolk X mule / adult ewes	3/365	January	Cu heptonate Novartis
E96/06	X bred / 9 months	4 / 20	January	Cu heptonate Novartis

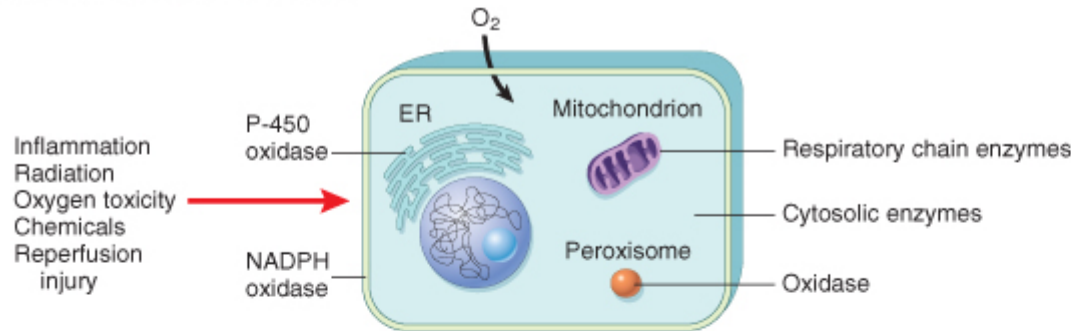
* same flock, cases in consecutive years



Morphologic alterations produced by copper in neural tissues

Vogel FS & Evans JW (1961) J Exp Med 113 997-1004

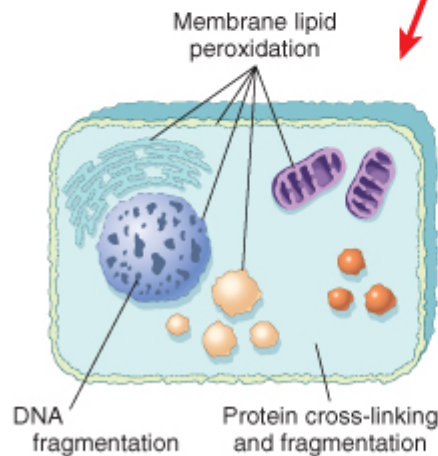
A. FREE RADICAL GENERATION



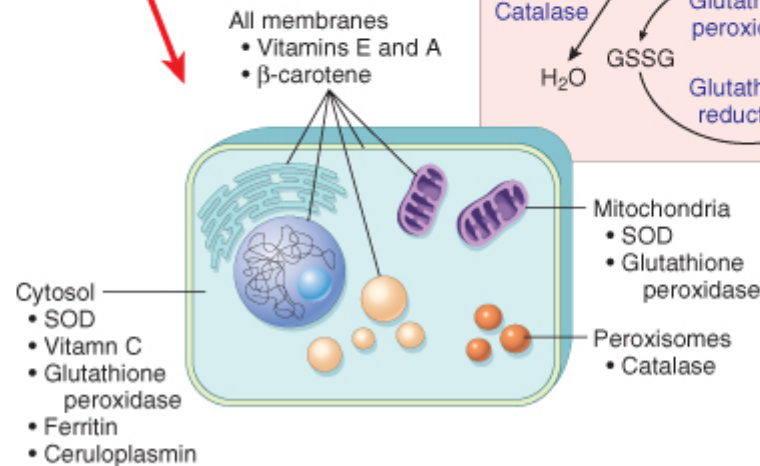
Pathologic basis
of disease
Kumar *et al*
7th edn

Reactive oxygen
species:
 $O_2^{\cdot -}$, H_2O_2 , OH^{\cdot}

Reactive oxygen
species:
 $O_2^{\cdot -}$, H_2O_2 , OH^{\cdot}

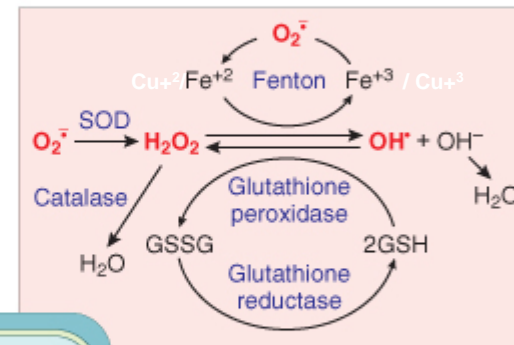


B. CELL INJURY BY FREE RADICALS



C. NEUTRALIZATION OF FREE RADICALS – NO CELL INJURY

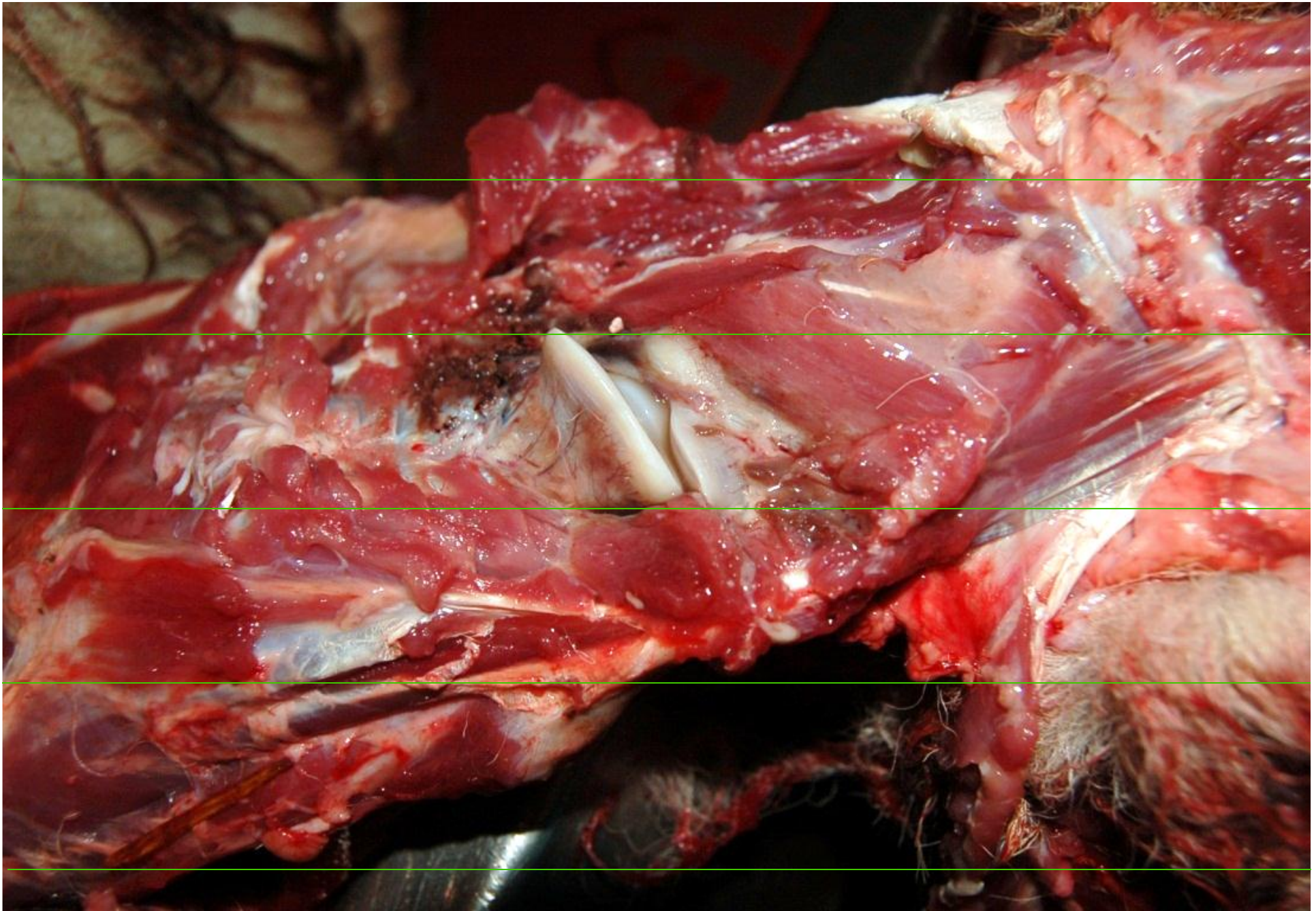
© Elsevier 2005



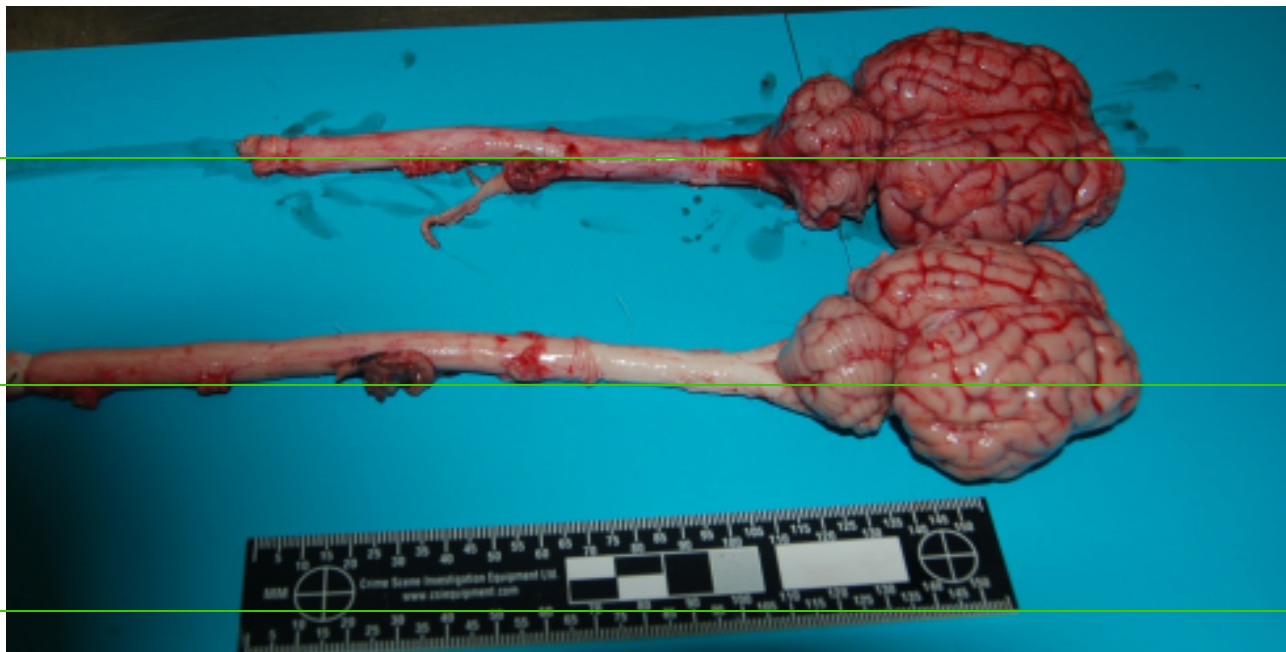
Fenton reaction: $H_2O_2 + Cu/Fe^{2+} \Rightarrow Cu/Fe^{3+} + OH + OH^-$; OH is potent cause of lipid peroxidation of membranes \Rightarrow autocatalytic propagation of membrane damage

Copper analysis

Sheep	S/cord copper (fixed C2) umol/kg DM
E482/04 Subpial myelopathy Parenteral copper administered 5 days earlier	310
E483/04 Clostridial epsilon intoxication Adult ewe submitted for PME on same day as E482/04 to same RL: identical sampling, duration of fixation, and tissue selection for copper analysis Parenteral copper administered 2-3 weeks earlier	56







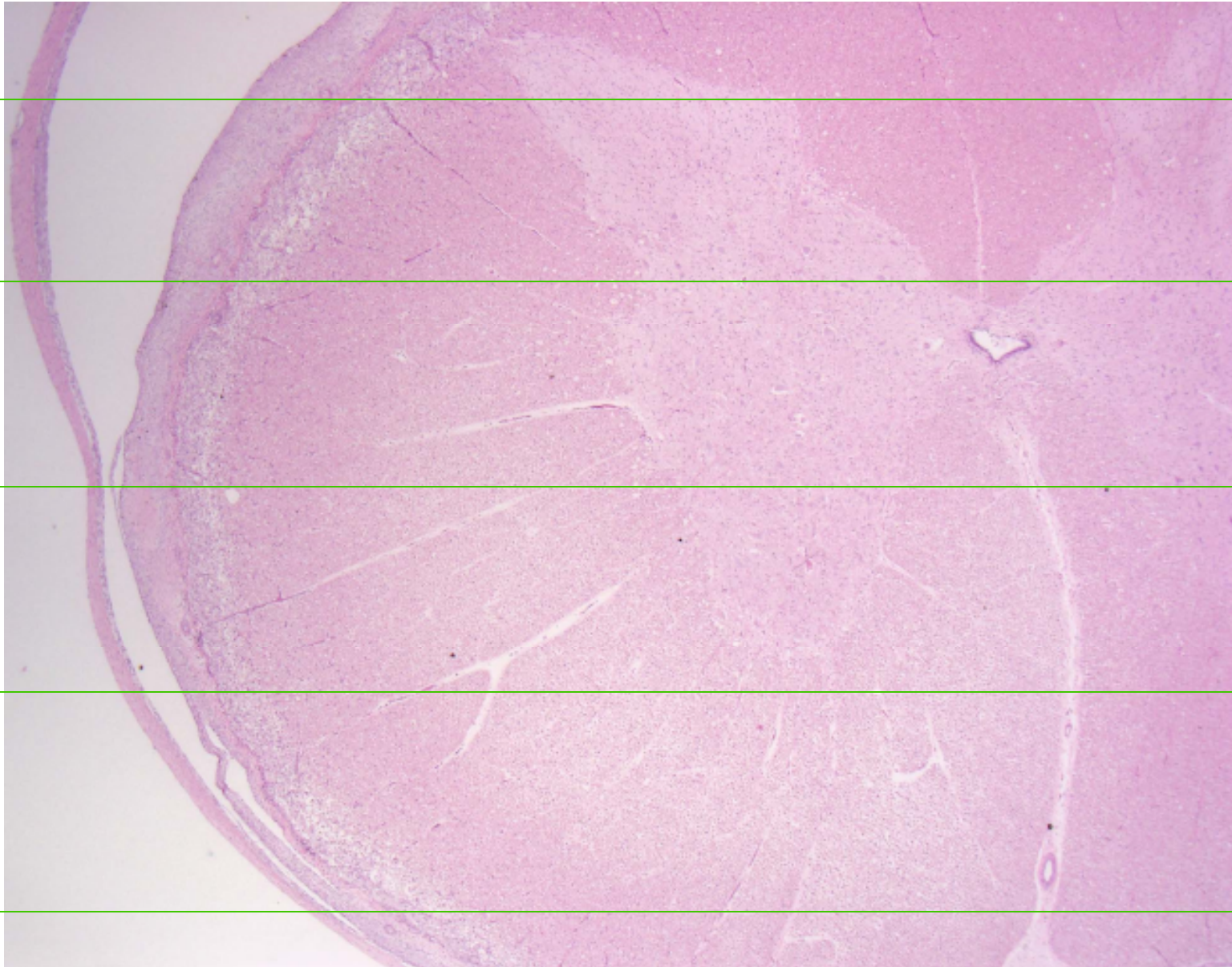
- 26 S448

Subpial lumbar myelopathy following epidural anaesthesia

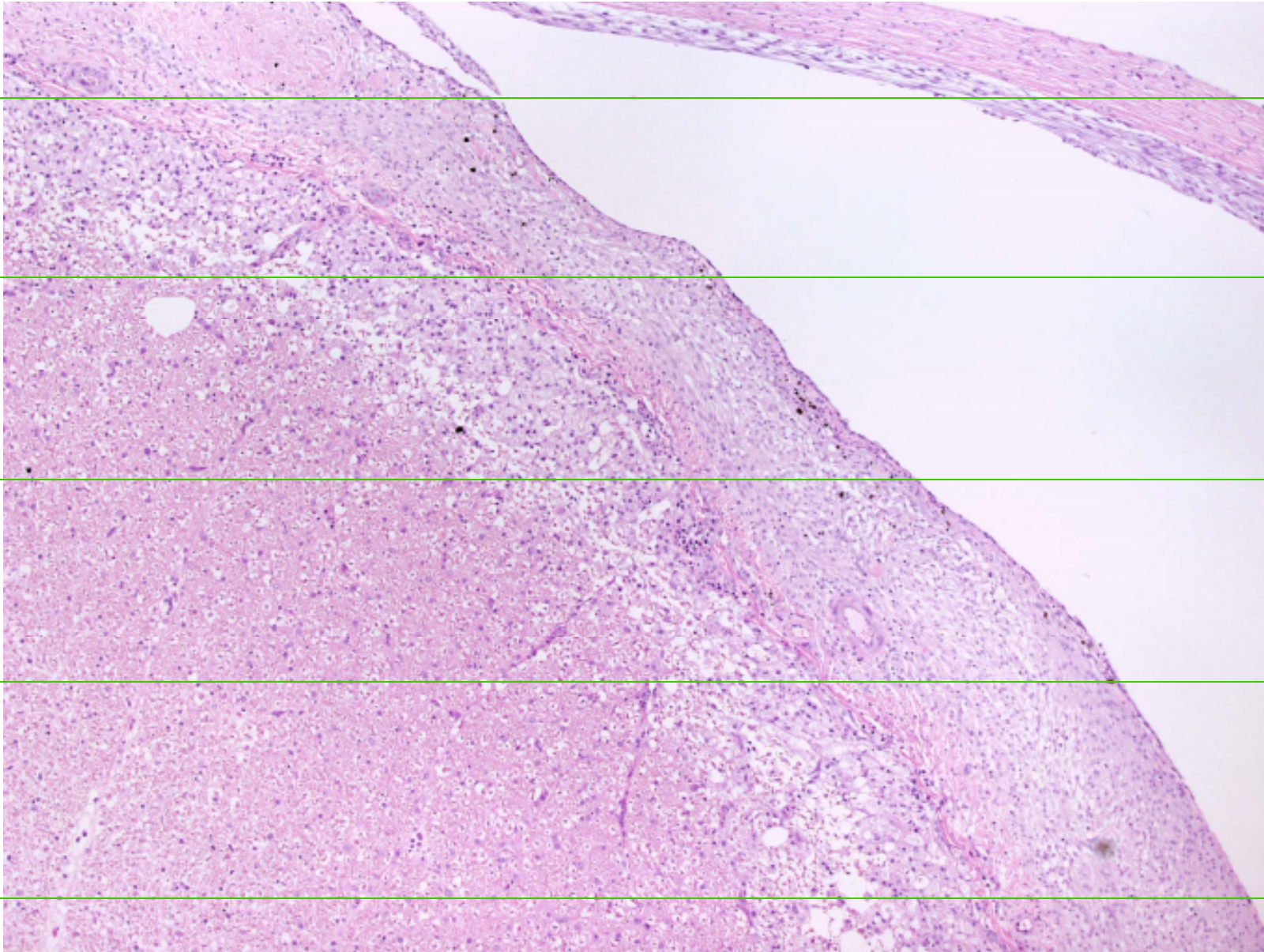
- Epidural anaesthesia for vasectomy
- 5% w/v solution Procaine hydrochloride containing sodium metabisulphite 0.1% w/v as antioxidant (Willcain™)
- Hindlimb paralysis following surgery
- Non progressive
- Due to lack of clinical improvement, ram killed humanely approx. 1 week after epidural
- PME



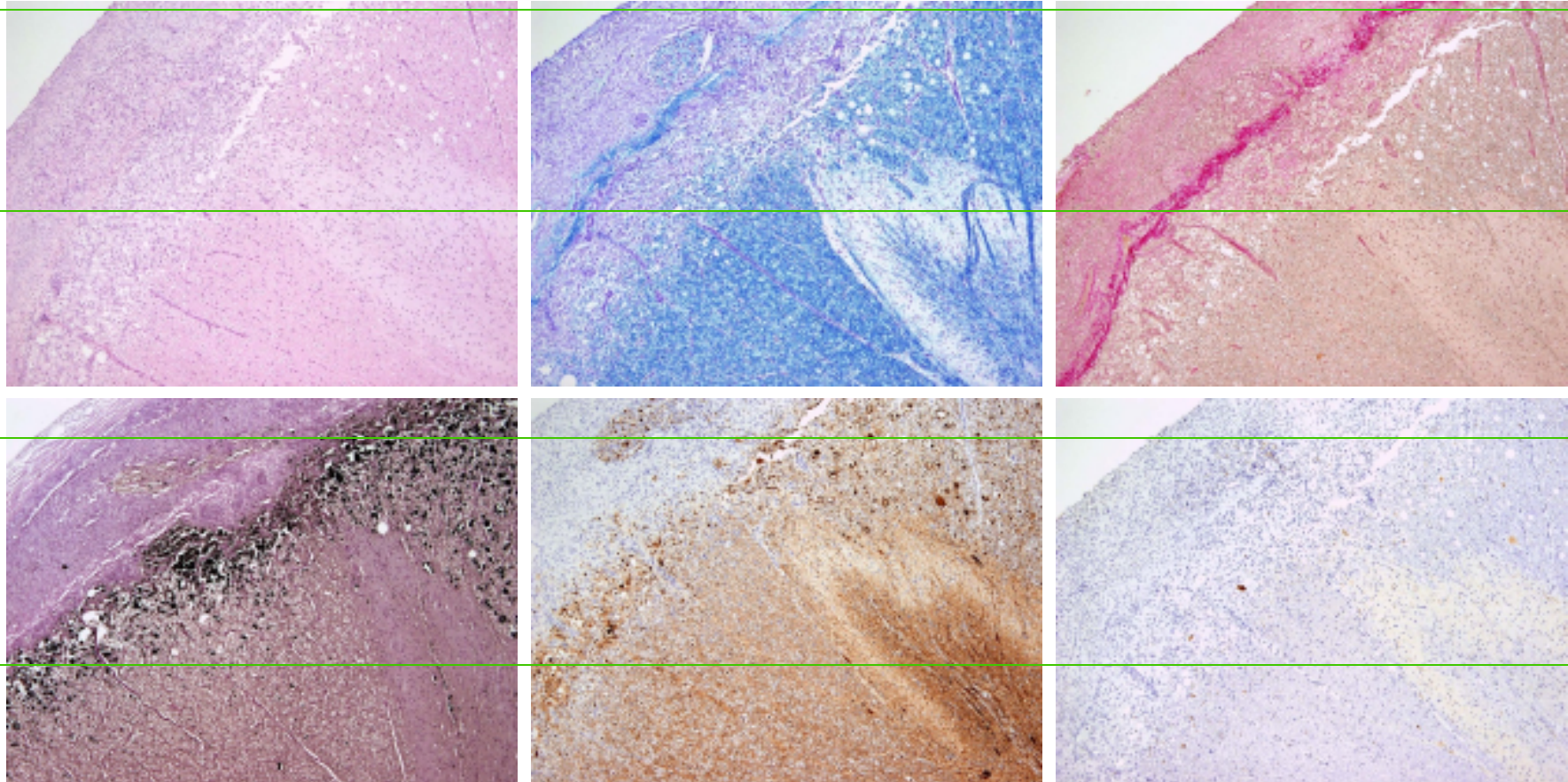
Subpial lumbar myelopathy following epidural anaesthesia



Subpial lumbar myelopathy following epidural anaesthesia

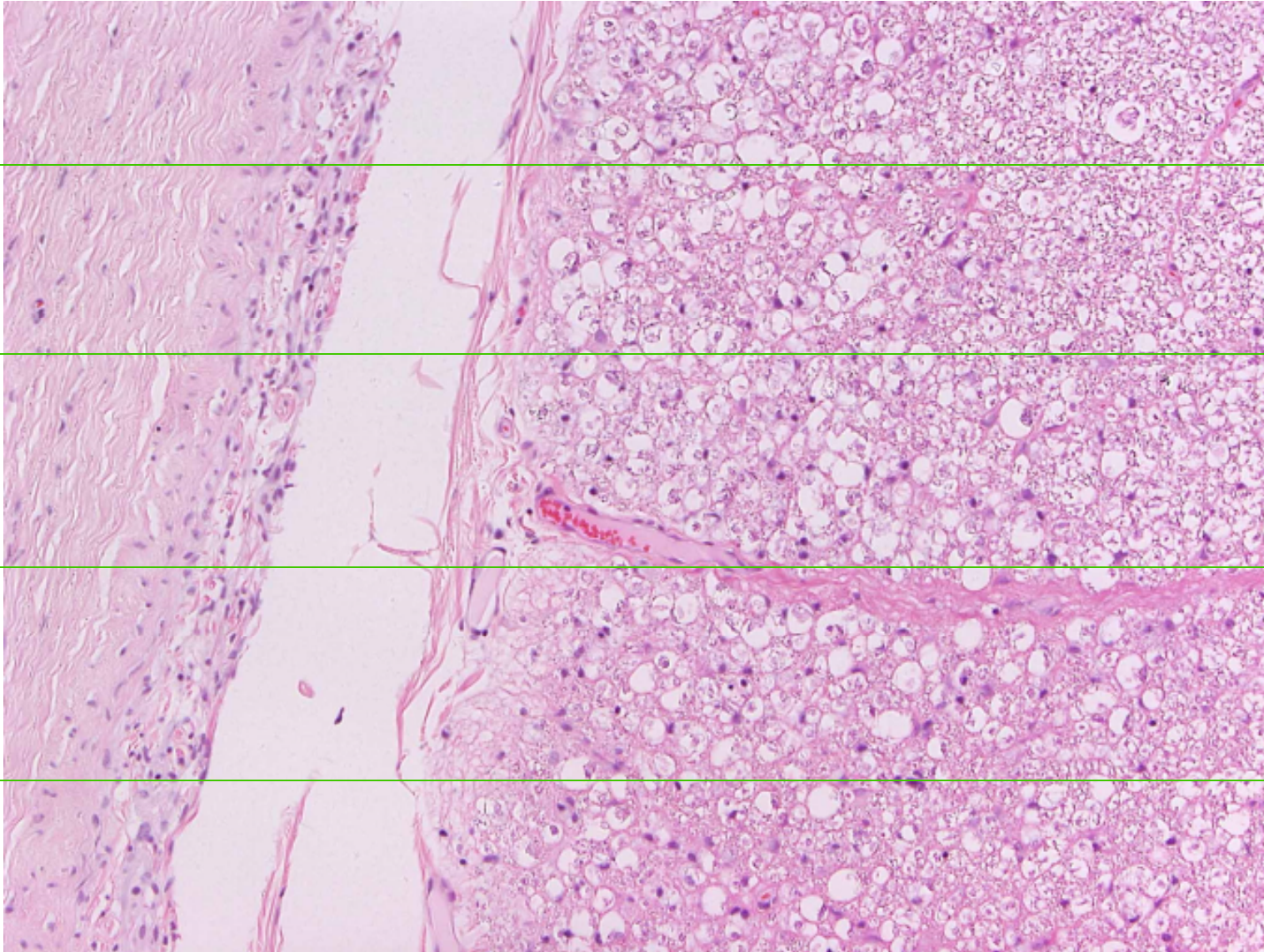


Subpial lumbar myelopathy following epidural anaesthesia

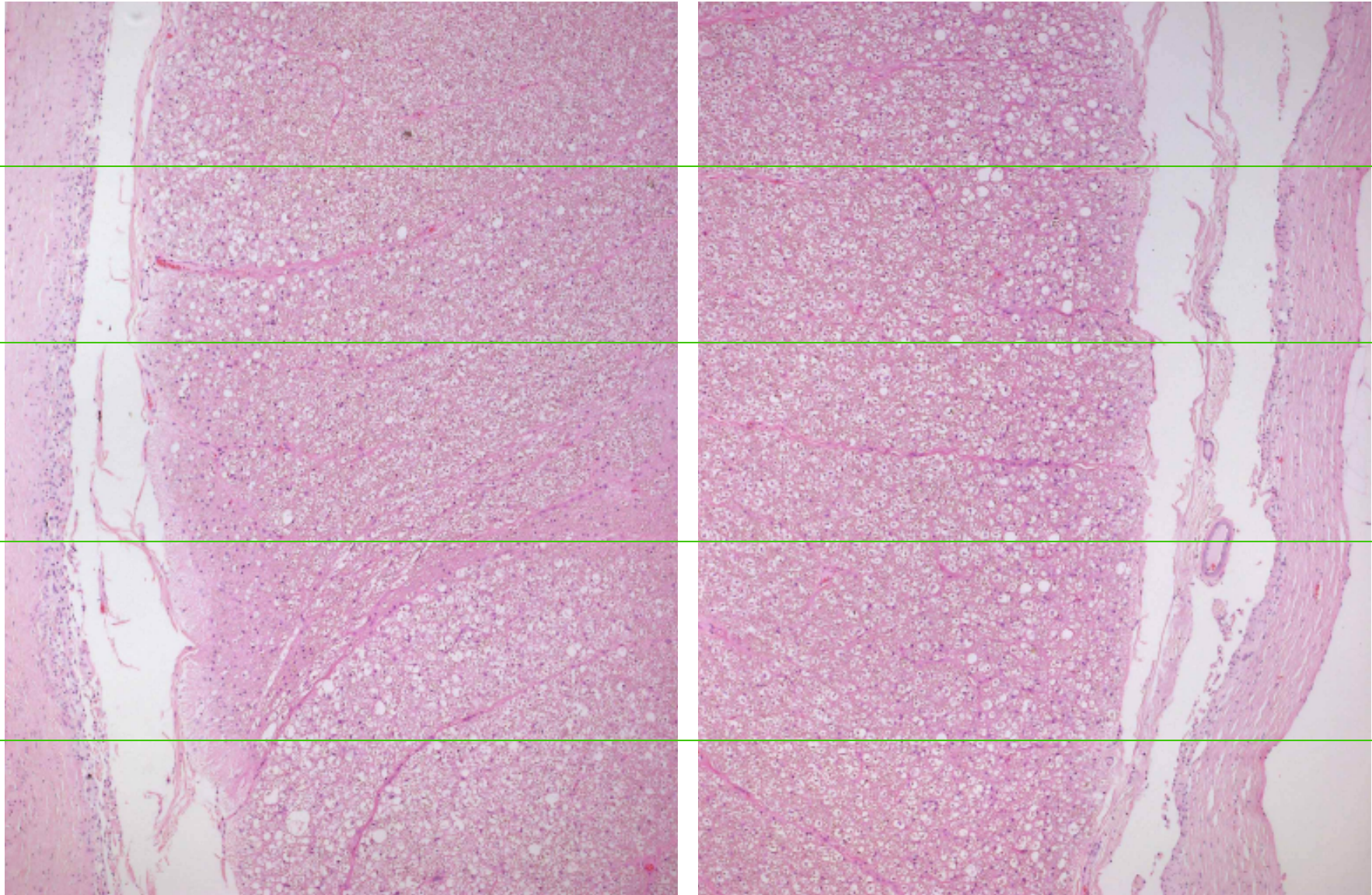


Subpial lumbar myelopathy following epidural anaesthesia

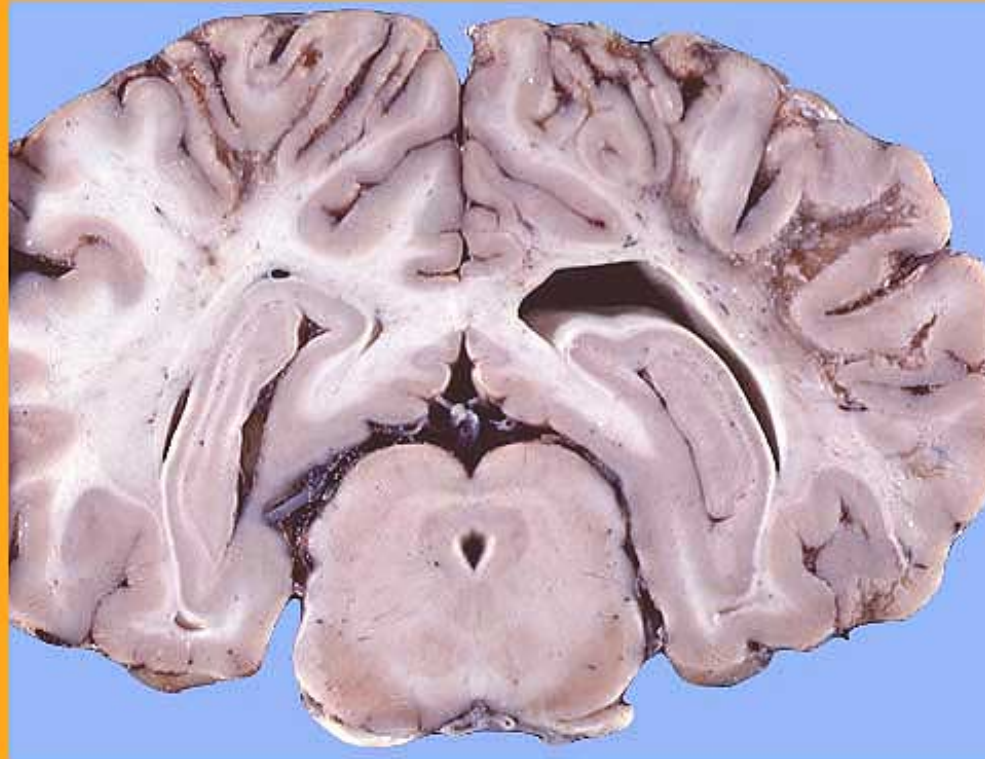
- 5% w/v solution Procaine hydrochloride (Willcain™) data sheet
- not for epidural injection
contains sodium metabisulphite 0.1% w/v as antioxidant
- Only one local anaesthetic is licensed for epidural use in animals - it does not contain sodium metabisulphite
- Long term spinal cord damage following subdural injection of chloroprocaine in man thought to be due to the sodium metabisulphite stabilising agent -controversial; (at low pH bisulphite $\rightarrow \text{SO}_2 \rightarrow \text{H}_2\text{SO}_3$?)
- Sodium metabisulphite is no longer included in human epidural anaesthesia preparations



Recumbancy following nitroxylin administration, ewe; onset within hours, static clinically for 12 weeks

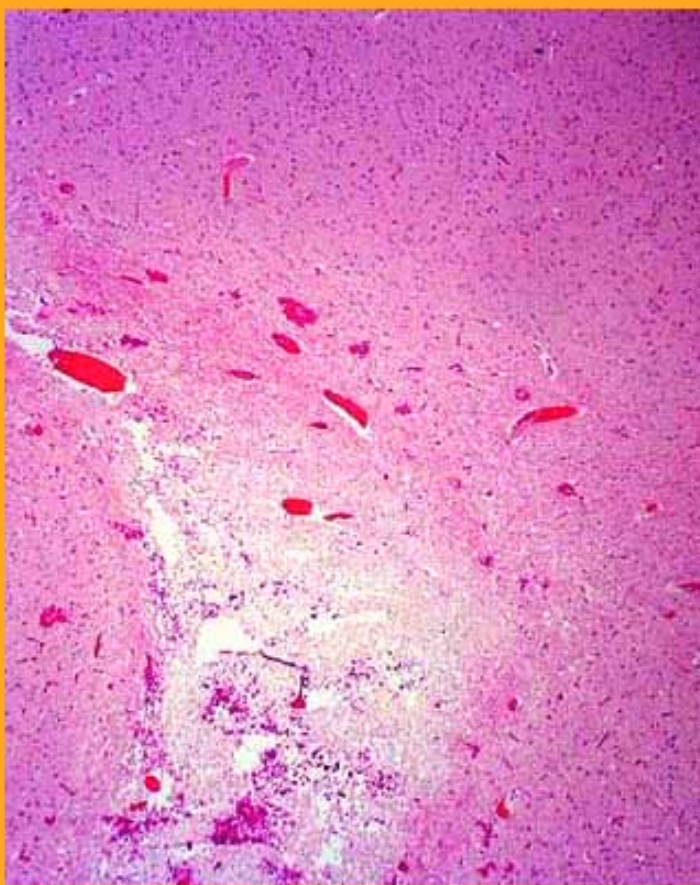


Recumbancy following nitroxynil administration
subcutaneous injection in neck, ewe;
onset within hours, static clinically for 12 weeks



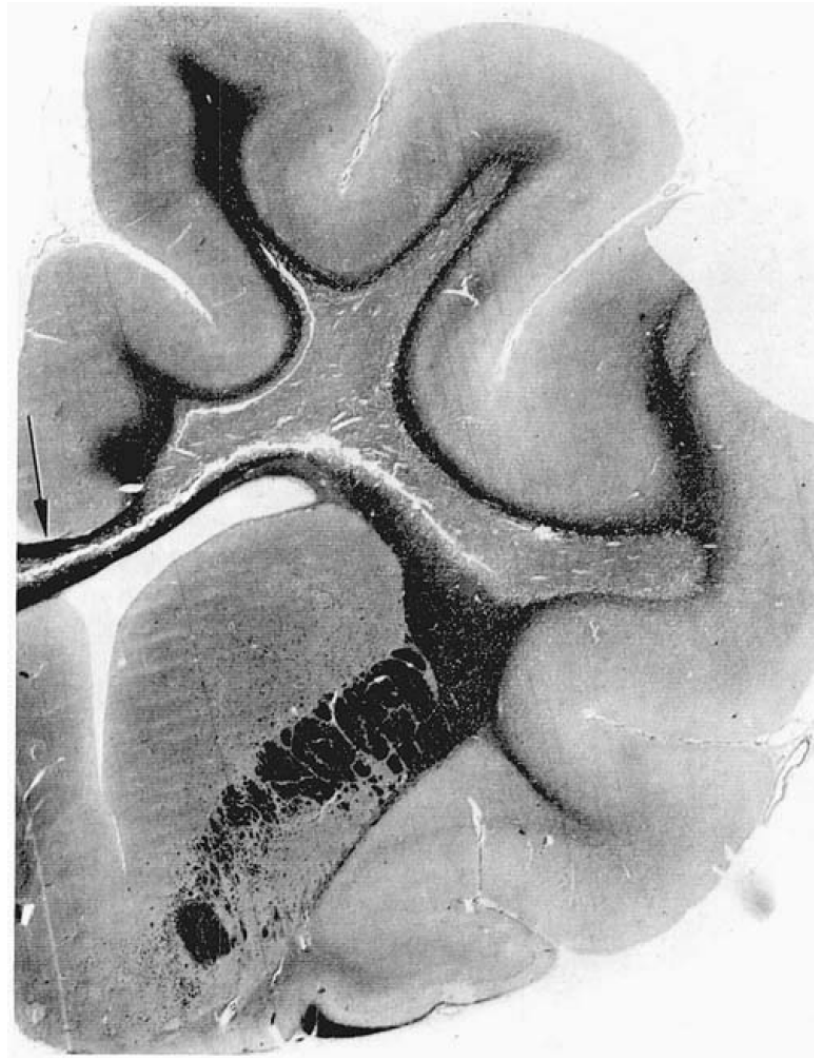
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Equine Leukoencephalomalacia - Cross section of the fixed brain at the level of the rostral colliculus, with advanced cavitation of the subcortical cerebral white matter



© 2001 College of Veterinary Medicine, Cornell University

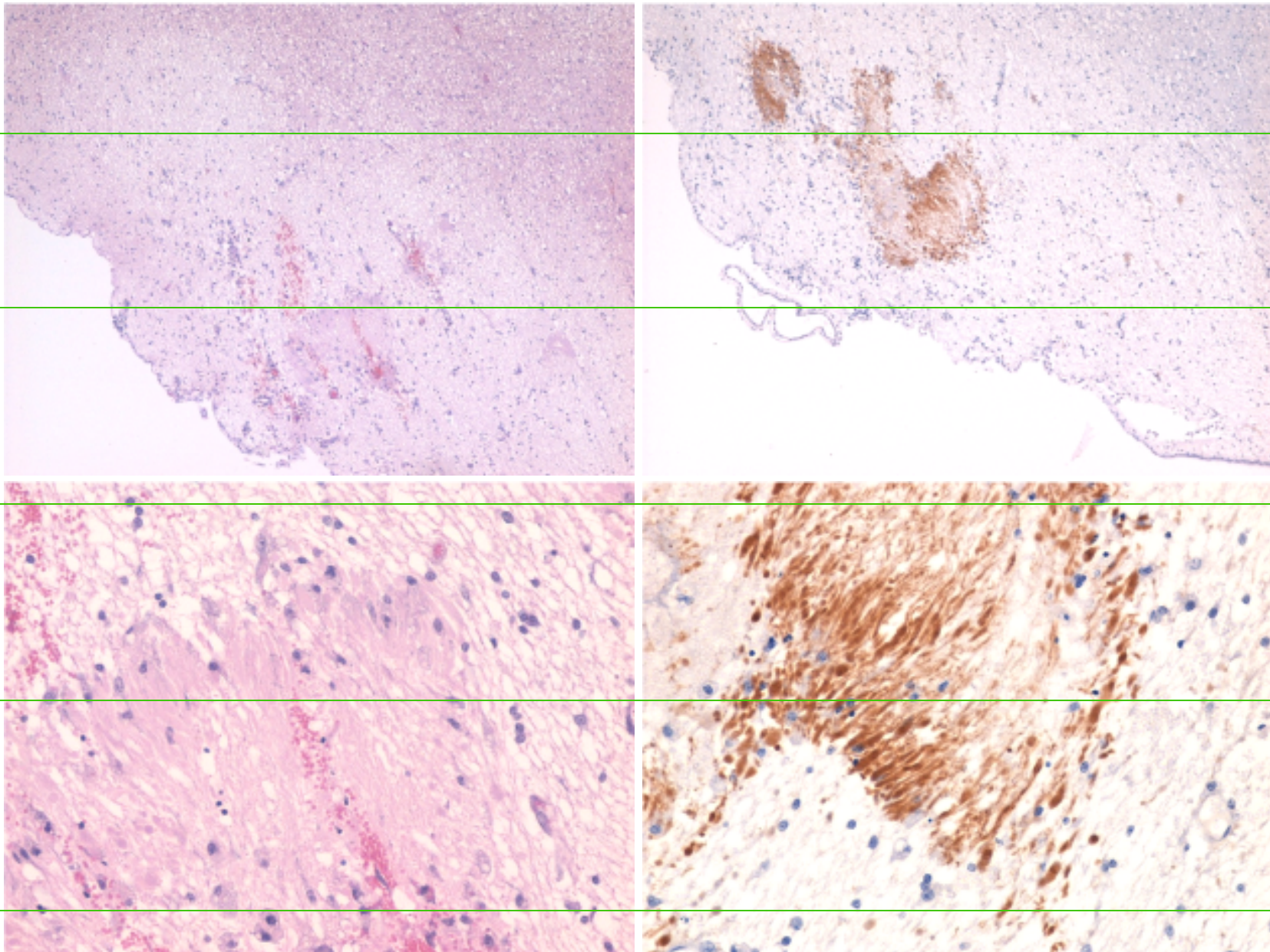
Equine Leukoencephalomalacia - Acute congestion, edema and necrotizing change in the subcortical white matter seen at low magnification



Leukoencephalopathy in a Cat Due to Accidental Cyanide Poisoning

LFB cerebrum

Path. vet. **3** 190-195 (1966)



Halogenated salicylanilide (closantel) toxicity (ovine)

Periventricular leucomalacia

Generation of PVL by repeated umbilical cord occlusion in near-term fetal sheep and its possible pathogenetic mechanism

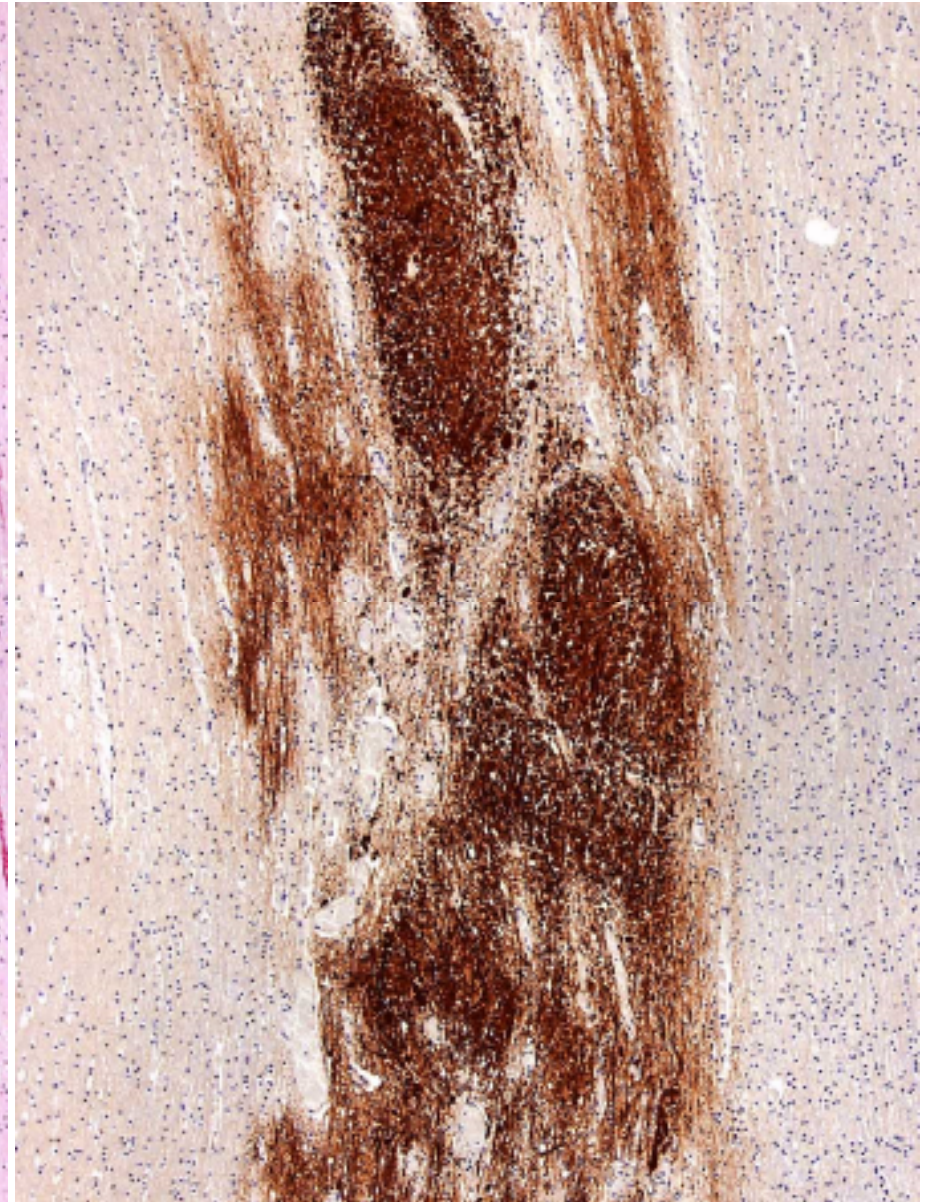
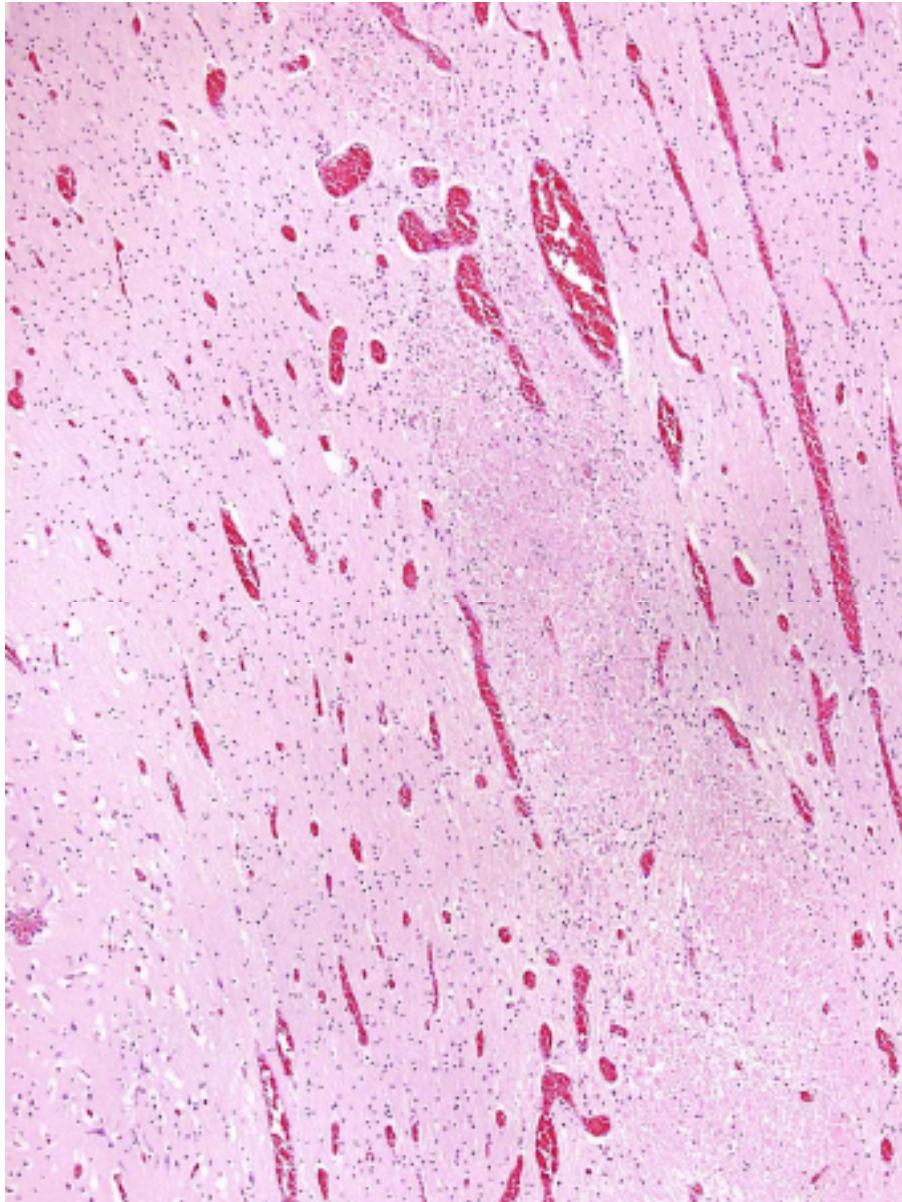
Marumo et al, Biology of the neonate, 2001 79: 39-45

5/14 - PVL : higher BP and higher plasma lipid peroxide levels prior to cord occlusion

4/14 – lesions cortical, subcortical WM and thalamus: systemic hypotension during cord occlusion



12 S119 – pre-term lamb from ewe with markedly elevated [BHB]



■ PVN bovine foetus H&E, βAPP IHC

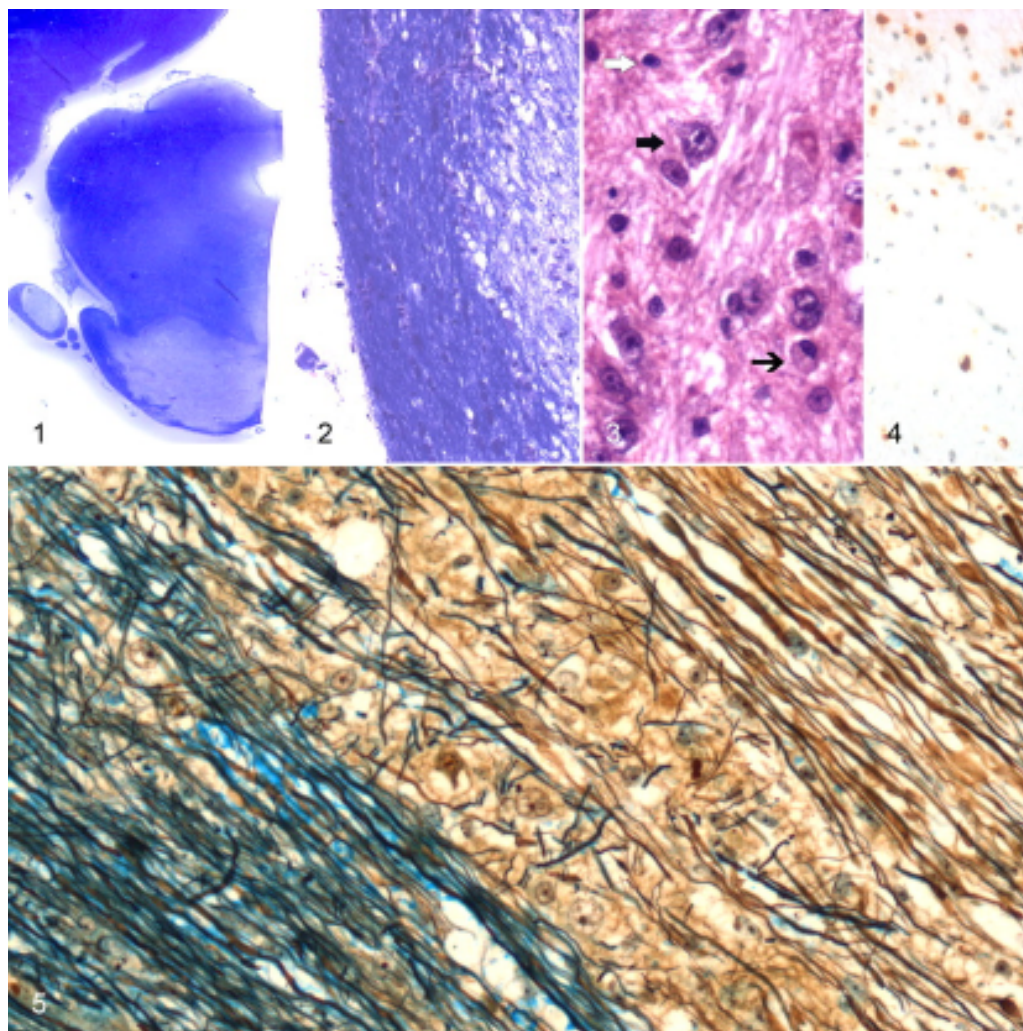
Myelinolysis / demyelination

Myelinolysis: dissolution of the myelin sheaths of nerve fibers.

Demyelination: destruction, removal, or loss of the myelin sheath of a nerve or nerves.

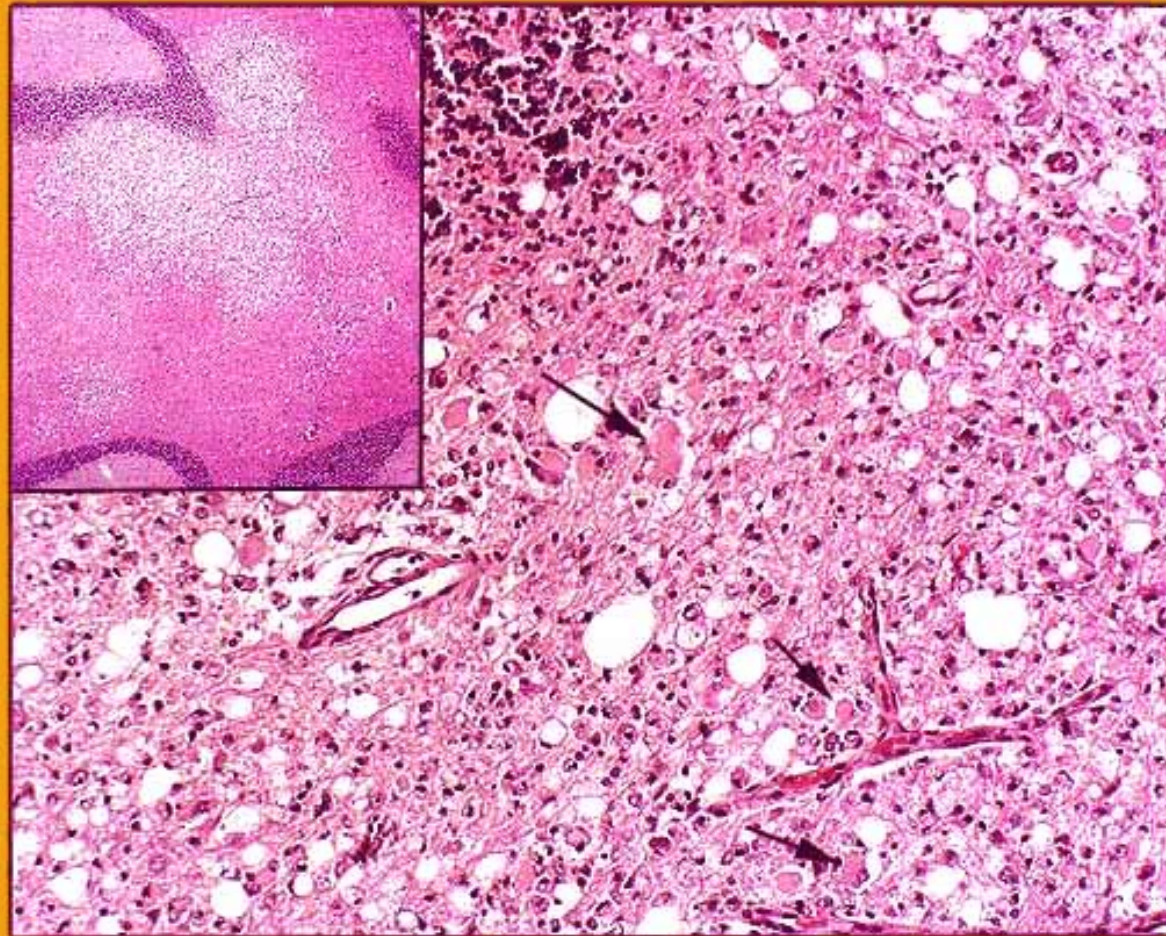
- Halogenated salicylanide (closantel) intoxication
 - subpial / subependymal / perivascular myelinolysis – may occur in absence of optic nerve necrosis
- Pontine myelinolysis
 - Recently reported in a cat (Poncelet et al)
 - Human cases associated with rapid correction of hyponatraemia
- Chronic oedema of white matter can lead to slow myelin destruction
- Perivascular demyelination
 - Cerebral and dural venous thrombosis in rhesus monkeys – patchy areas of perivenular demyelination centrum semiovale and internal capsule
- Leucoencephalomyelopathy of Romney lambs – 2-3mths
 - Widespread severe vacuolation and myelin loss especially cerebellar peduncle, central white matter, dorsolateral SCTs also caudal brainstem and dorsomedial and ventrolateral funiculi of spinal cord
- Leucoencephalomyelopathy of Rottweiler dogs
 - Demyelination midcervical spinal cord, dorsolateral funiculus
- Afghan hound myelopathy
 - Severe reduction in myelin all funiculi midthoracic segments, tapering cranially and caudally, loosening and vacuolation of white matter progressing to depletion
- Miniature Poodle dog
 - Extensive myelin loss spinal cord > midbrain > smaller foci elsewhere in brainstem and in corpus callosum
- Leucodystrophy of Dalmatian dogs
 - Centrum semiovale, internal capsule, optic nerves, spinal cord: early lesion loss of myelin progressing to cavitation
- Rosenthal fibre encephalopathy – juvenile variant in Labrador, Scottish terrier, Miniature poodle and Bernese Mountain dog (and 4 year Swiss Alpine sheep)
 - Astrocytic changes accompanied by myelin vacuolation and loss beginning in predilection sites for astrocyte changes
- Canine distemper virus infection of the CNS (white matter disease) Early phase (21 – 24 days pi)
 - Predilection for sites close to CSF : spinal cord funiculi, hippocampal fornix, optic tract, rostral medullary velum, cerebellar peduncles; lesions initially purely degenerative with mixture of primary demyelination and concurrent axonal and myelin injury with early astrogliosis; with survival, a non-suppurative response develops

Figure 1. Brain; cat.



Poncelet L et al. Vet Pathol 2010;48:751-753

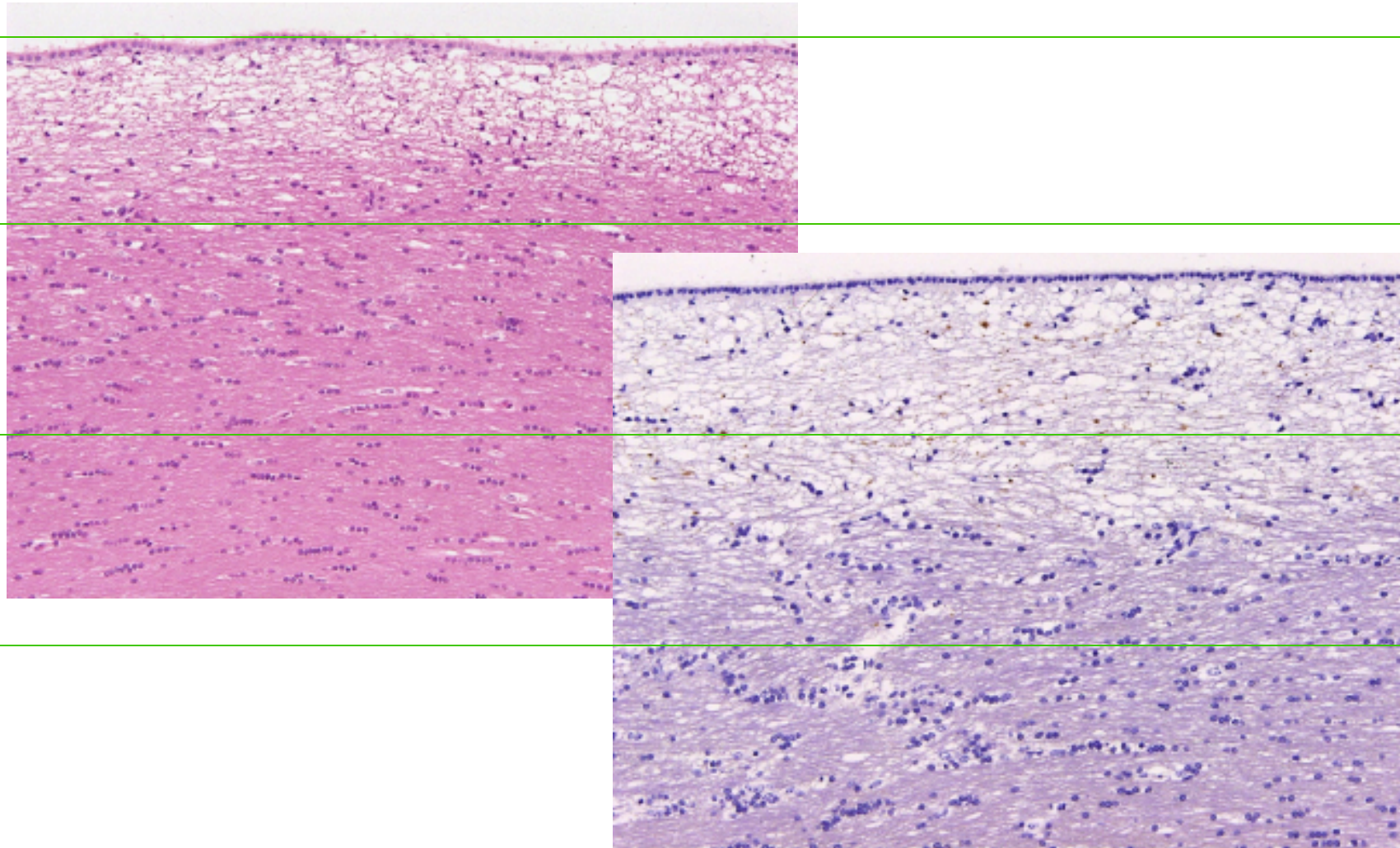




© 2001 College of Veterinary Medicine Cornell University

Canine Distemper - Demyelination and degeneration in the cerebellar white matter. Notice the absence of perivascular cuffing, indicating that this is an early lesion. At the higher magnification gemistocytes are numerous (arrows) along with macrophages, and capillary endothelium is prominent.

Amyloid precursor protein APP IHC



White matter rarefaction ovine oxyclozanide toxicity



White matter vacuolation

Acquired toxic / metabolic

- Hepatic encephalopathy (+ renal etc encephalopathy)
- Hexachlorophene toxicity (calves)
- Halogenated salicylanide (closantel) intoxication
- Helichrysum argyrosphaerum toxicity
- Stypandra spp intoxication
- Furazolidone intoxication
 - focal vacuolation and small haemorrhages in cerebral and cerebellar white matter
- Eggplant (Solanum melongena) pregnant cows and newborn calves
 - diffuse in cerebellar and cerebral
- Bromethalin-based rodenticides – dogs and other species
 - diffuse white matter spongiosis with myelin splitting and vacuolation

Breed-related disorders including

- Maple syrup urine disease (branched chain ketoacid decarboxylase deficiency) – polled Hereford cattle and polled Shorthorn calves - extensive in cerebral, cerebellar, optic
- Polled Dorset lambs – profound status spongiosis especially brainstem and spinal cord
- Syndromes of vacuolation / rarefaction in brainstem and especially cerebellar central white matter in Jersey (Saunders 1952), Shorthorn and Hereford (Hulland 1957) and AngusXShorthorn (Young 1961) calves
- Several breeds of dog in which myelin pallor is also a feature :

Spinal WM vacuolation in fibre tract distribution

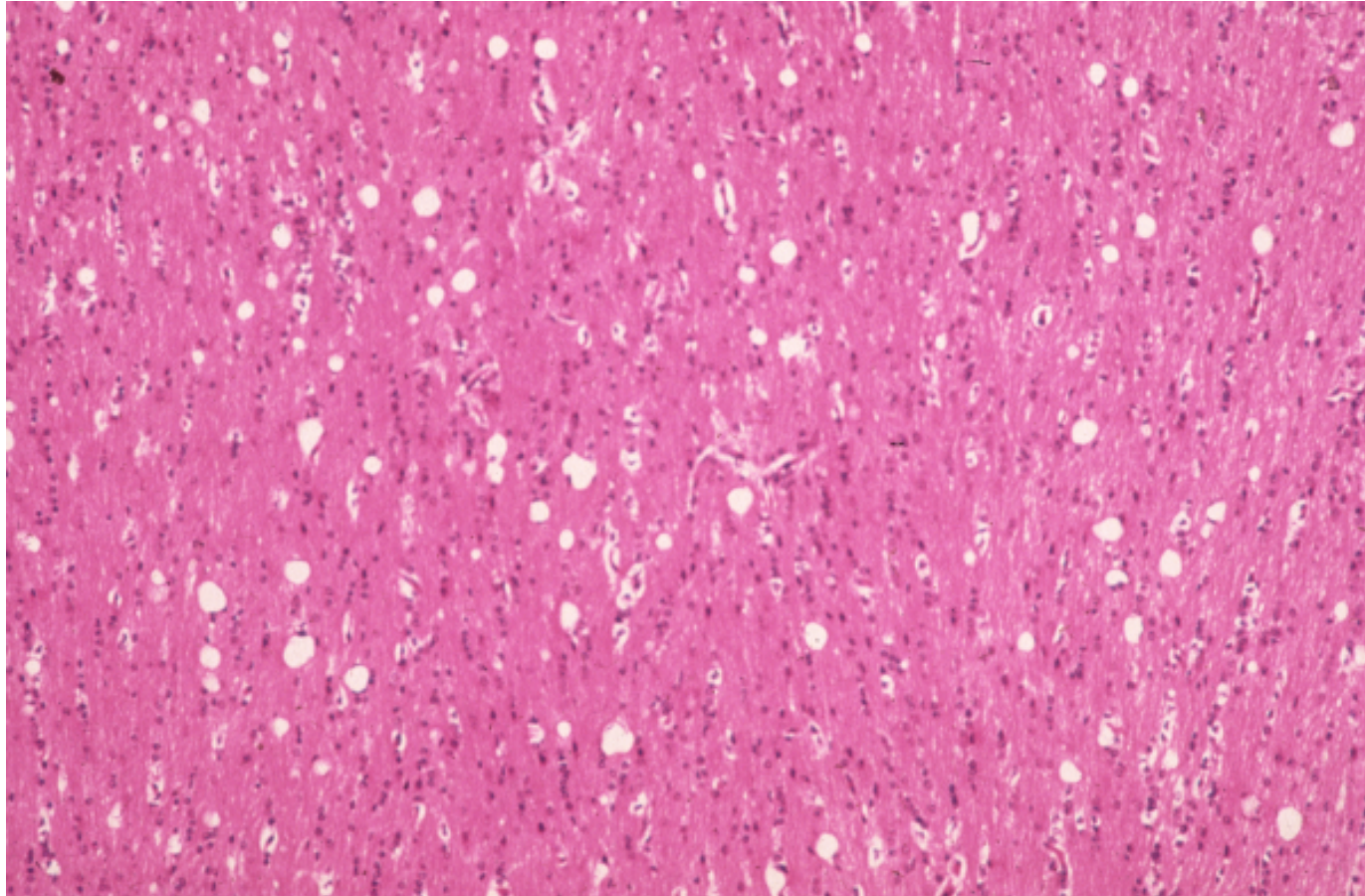
- Texel lamb
 - Marked white matter vacuolation dorsal funiculus and dorsolateral part of lateral funiculus; no WD or neuronal chromatolysis detected
- Congenital spinal myelopathy of Simmental calves
 - Widespread vacuolation all funiculi spinal cord, lesser involvement of brainstem, rare WD (Hindmarsh 1995)
 - Similar lesion in Holstein Friesian (Hindmarsh 1995)

Caution:

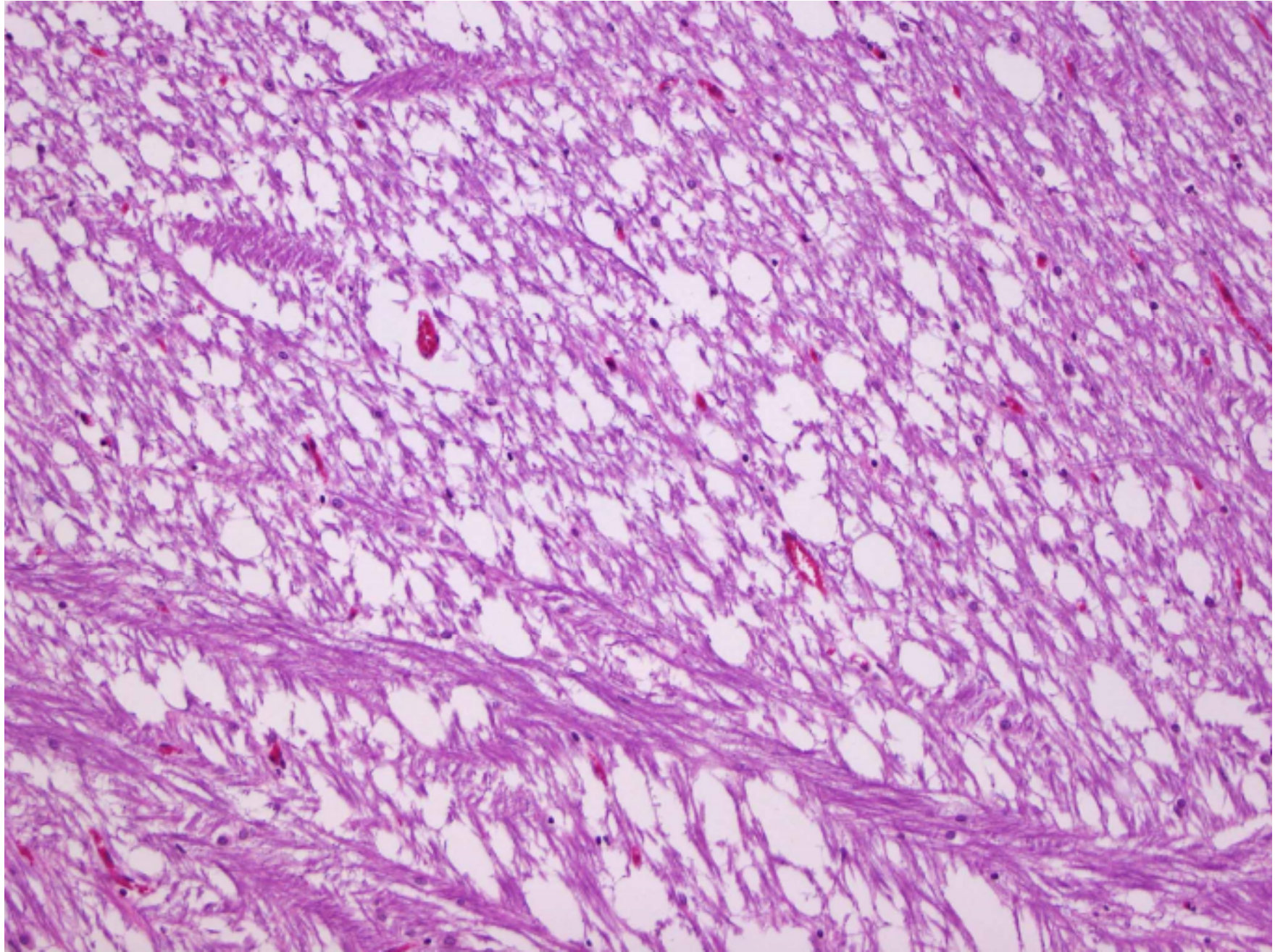
Background / artefact particularly in heavily myelinated tracts

Processing artefact

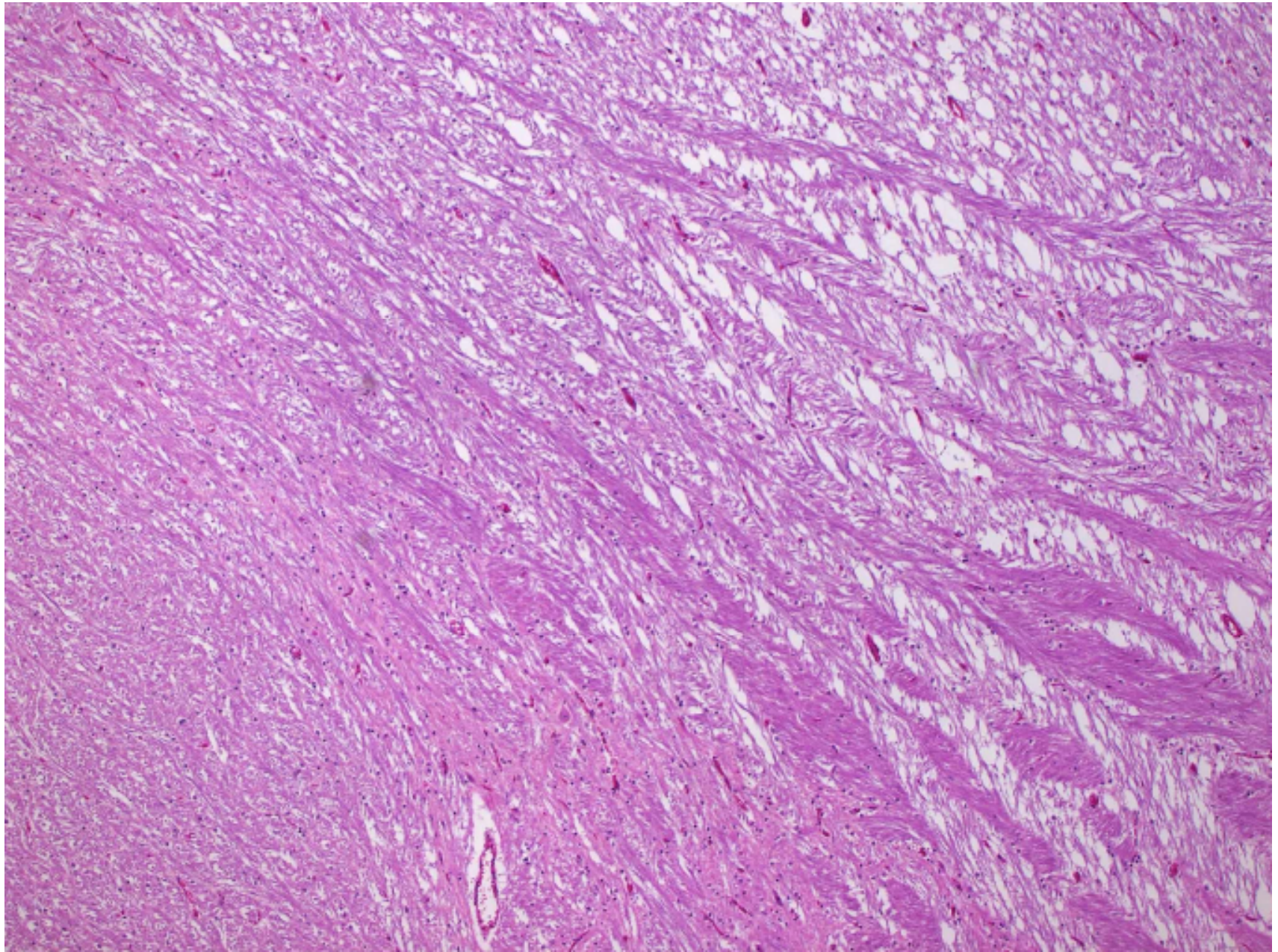
Post mortem change



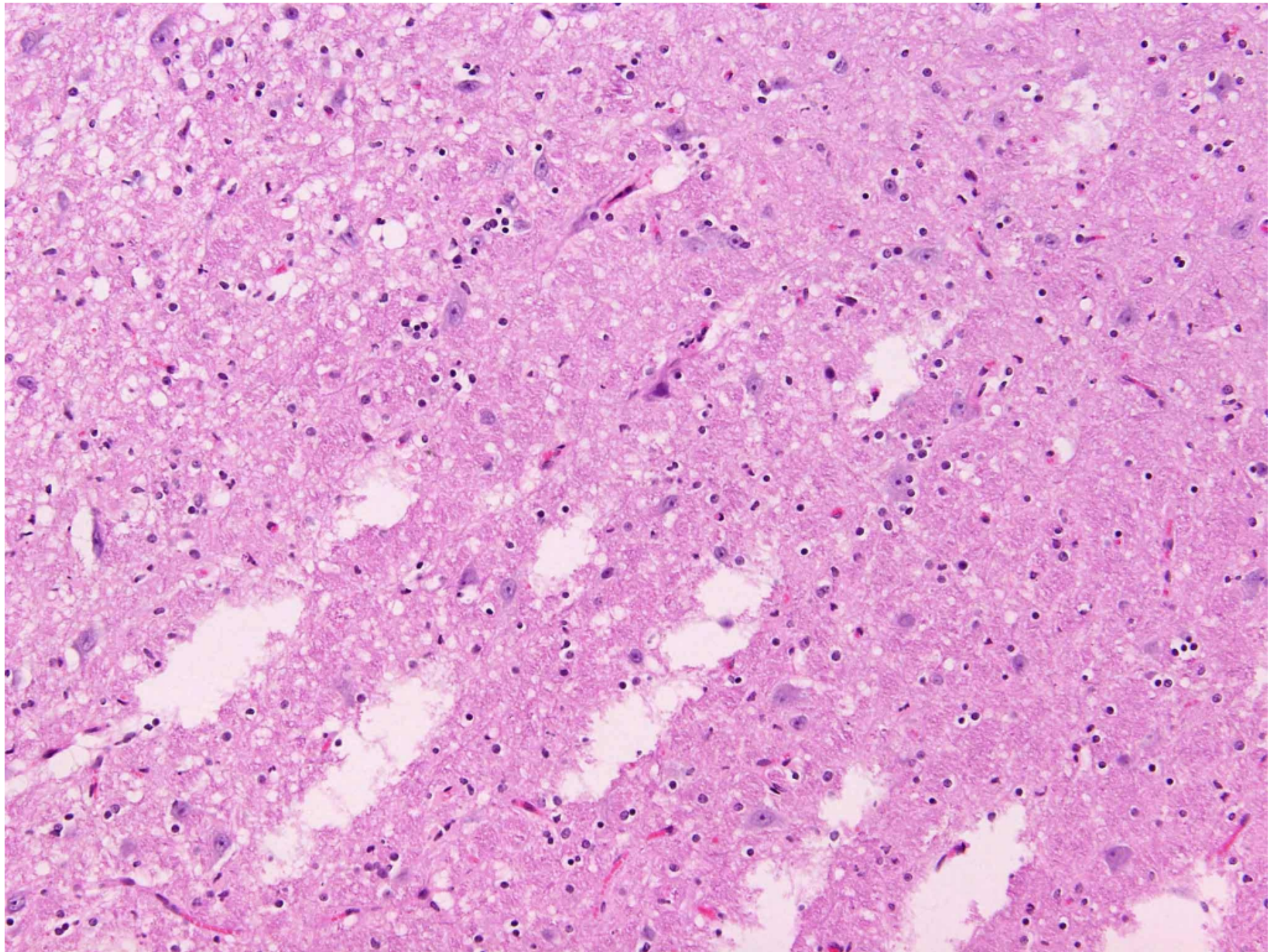
Processing artefact (48 hours in 70% alcohol)
Corpus callosum, juvenile bovine brain (PG2/88)

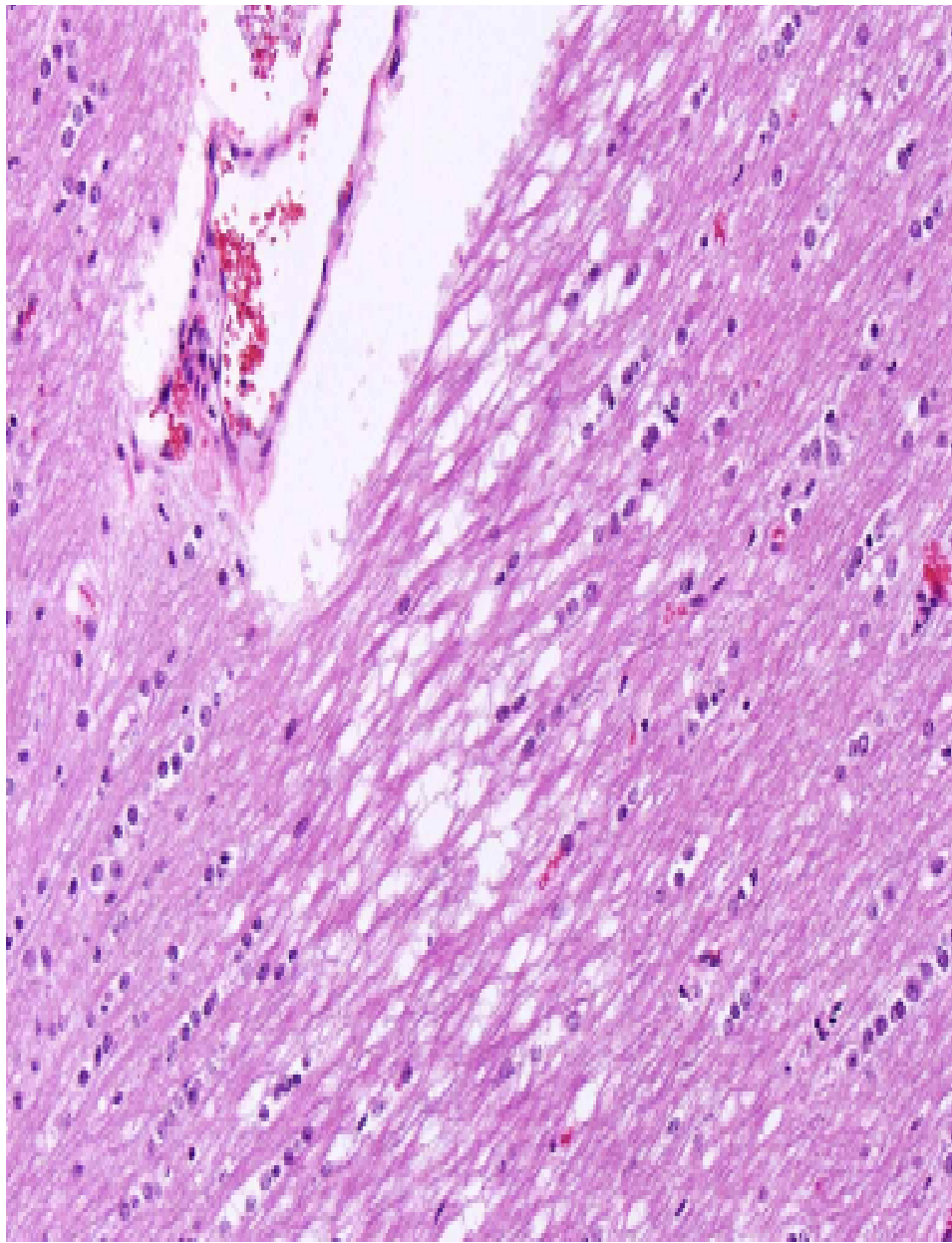


Incomplete fixation

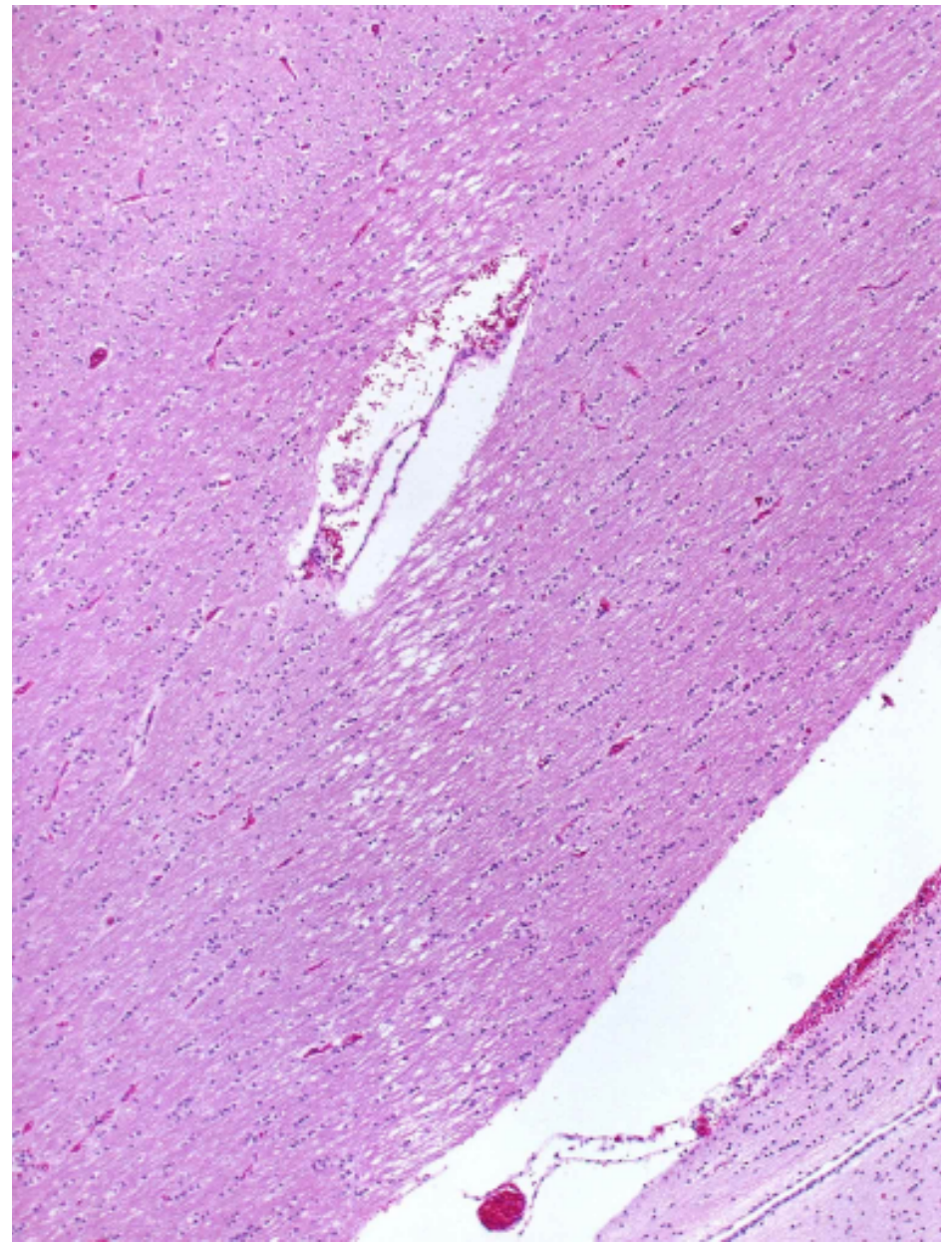


Incomplete fixation

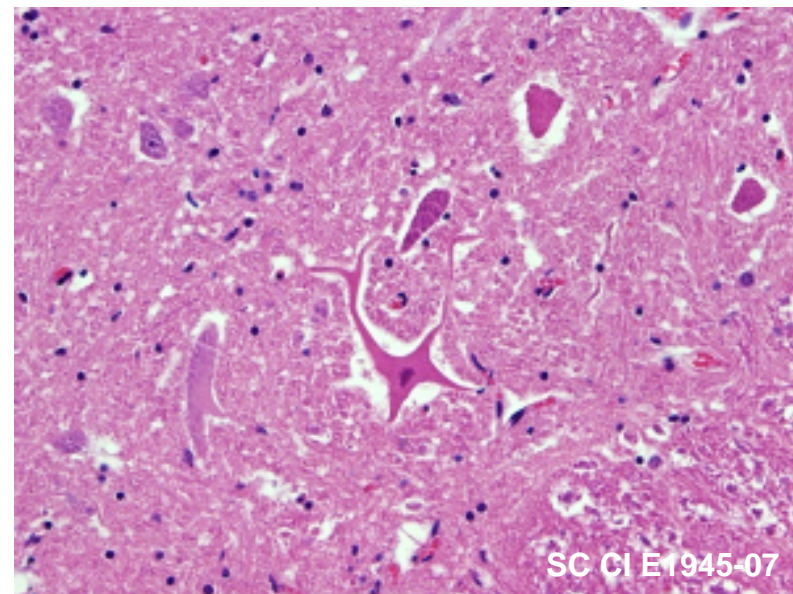
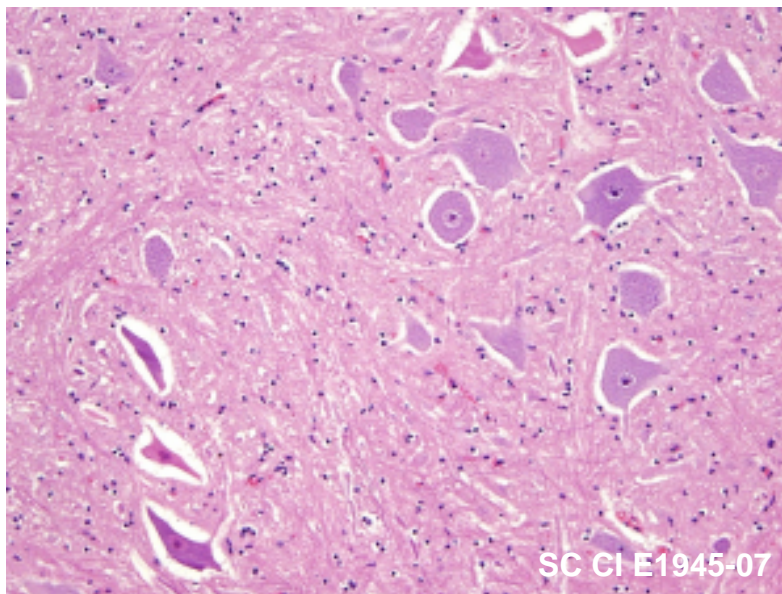
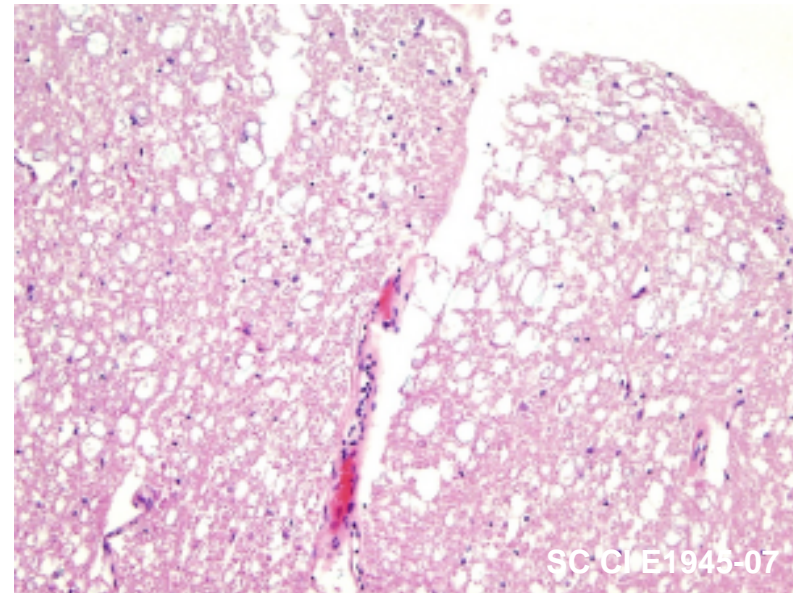
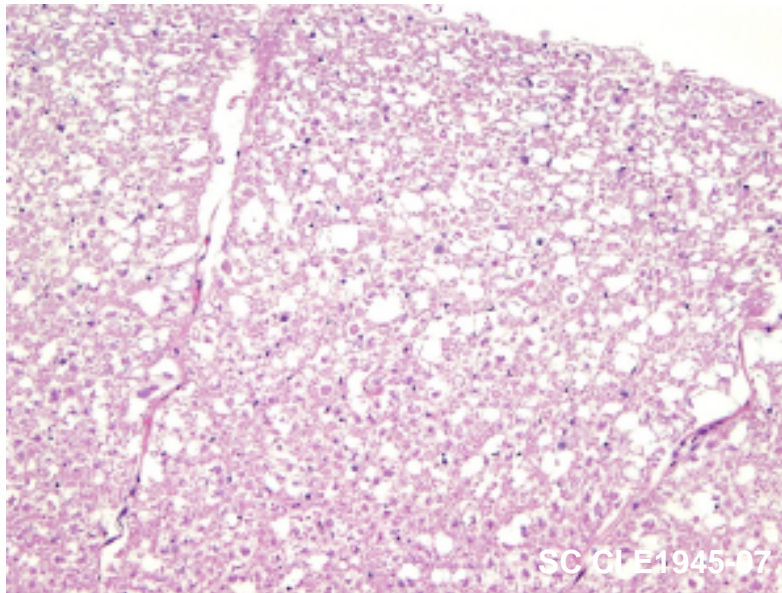


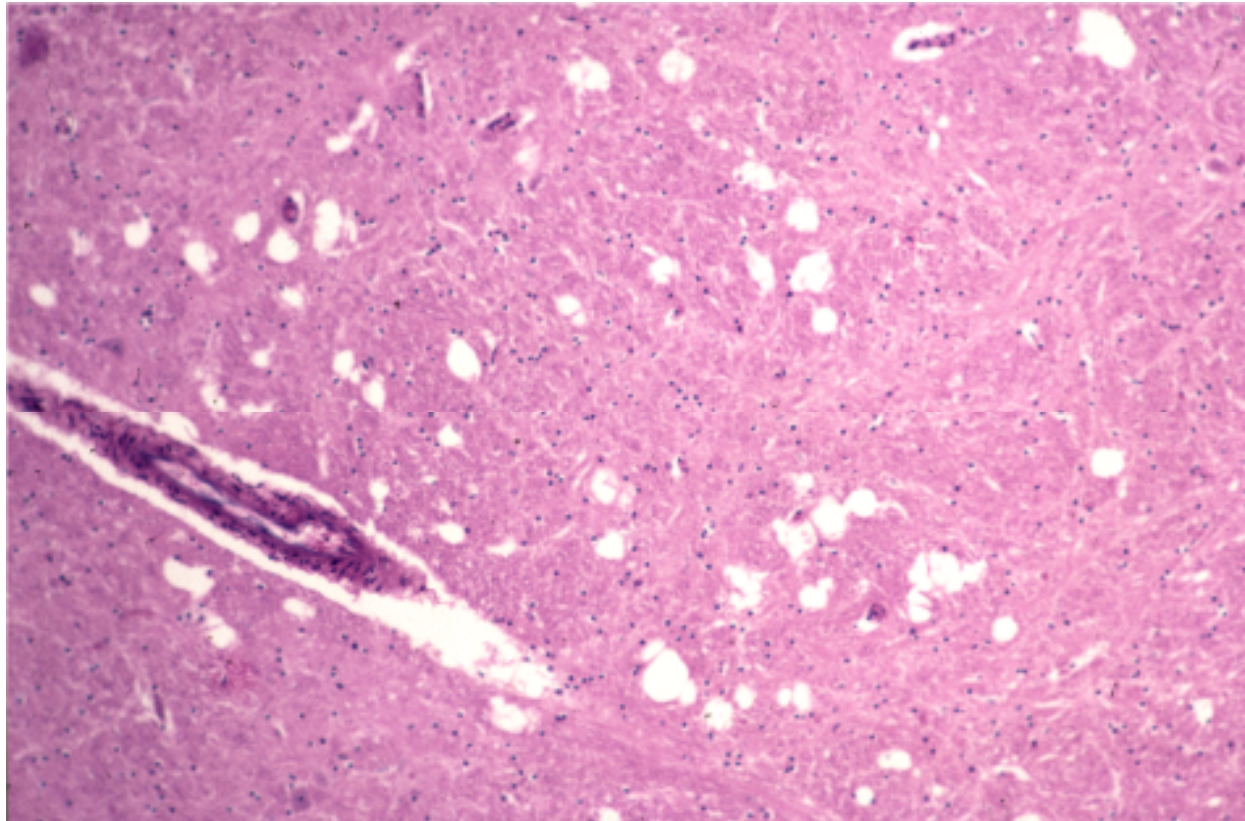


Artefact

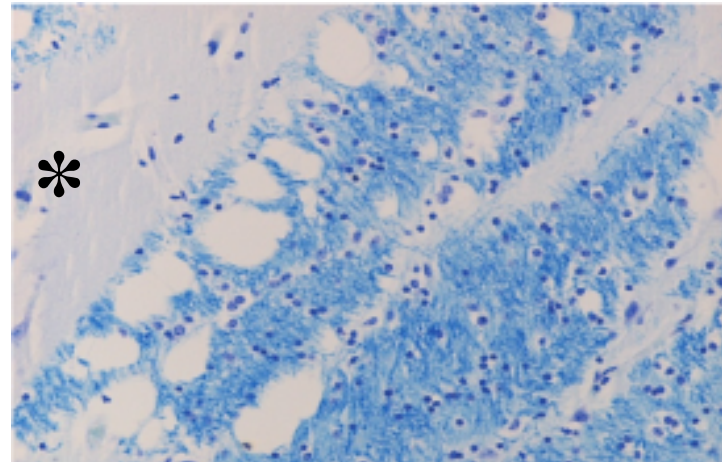
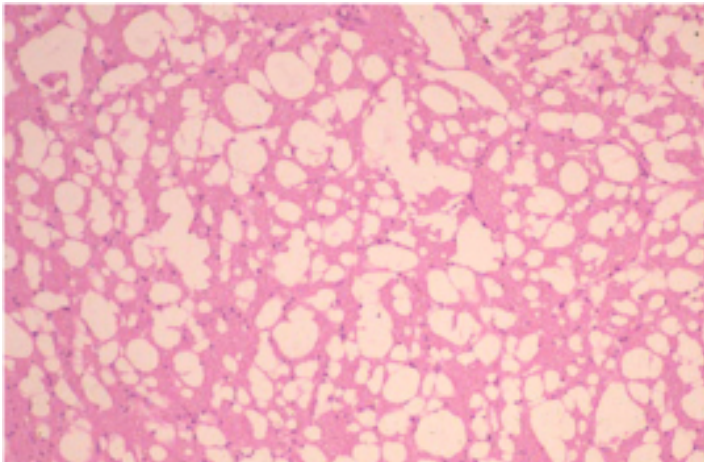
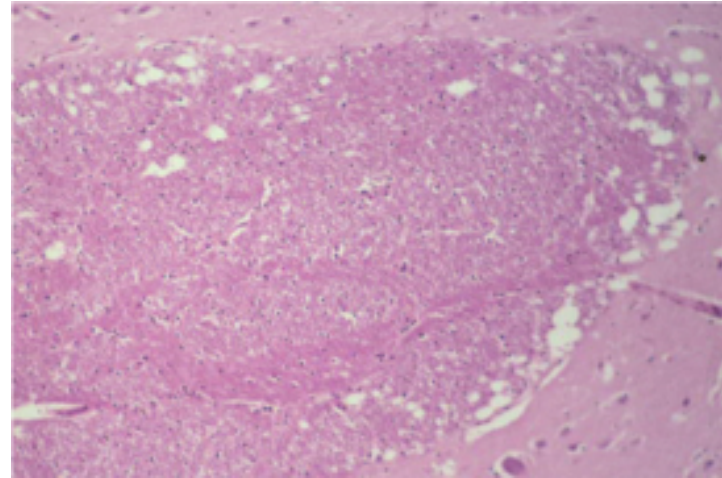
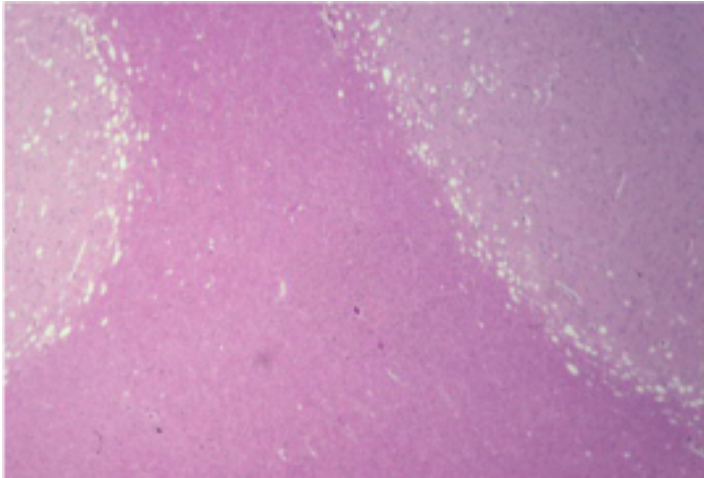


Post-mortem change - Beware !



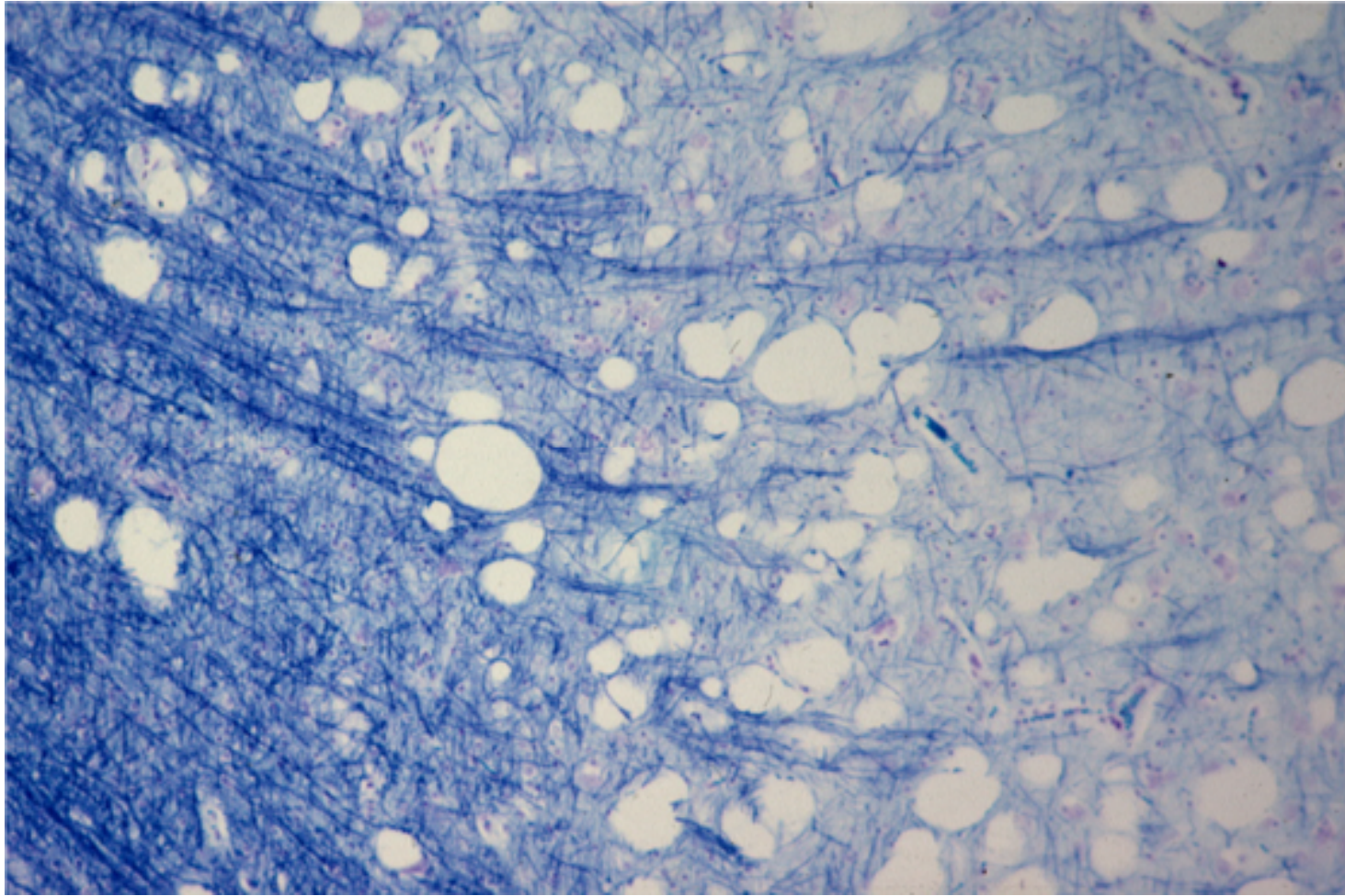


Incidental vacuolation of substantia nigra, midbrain, adult bovine

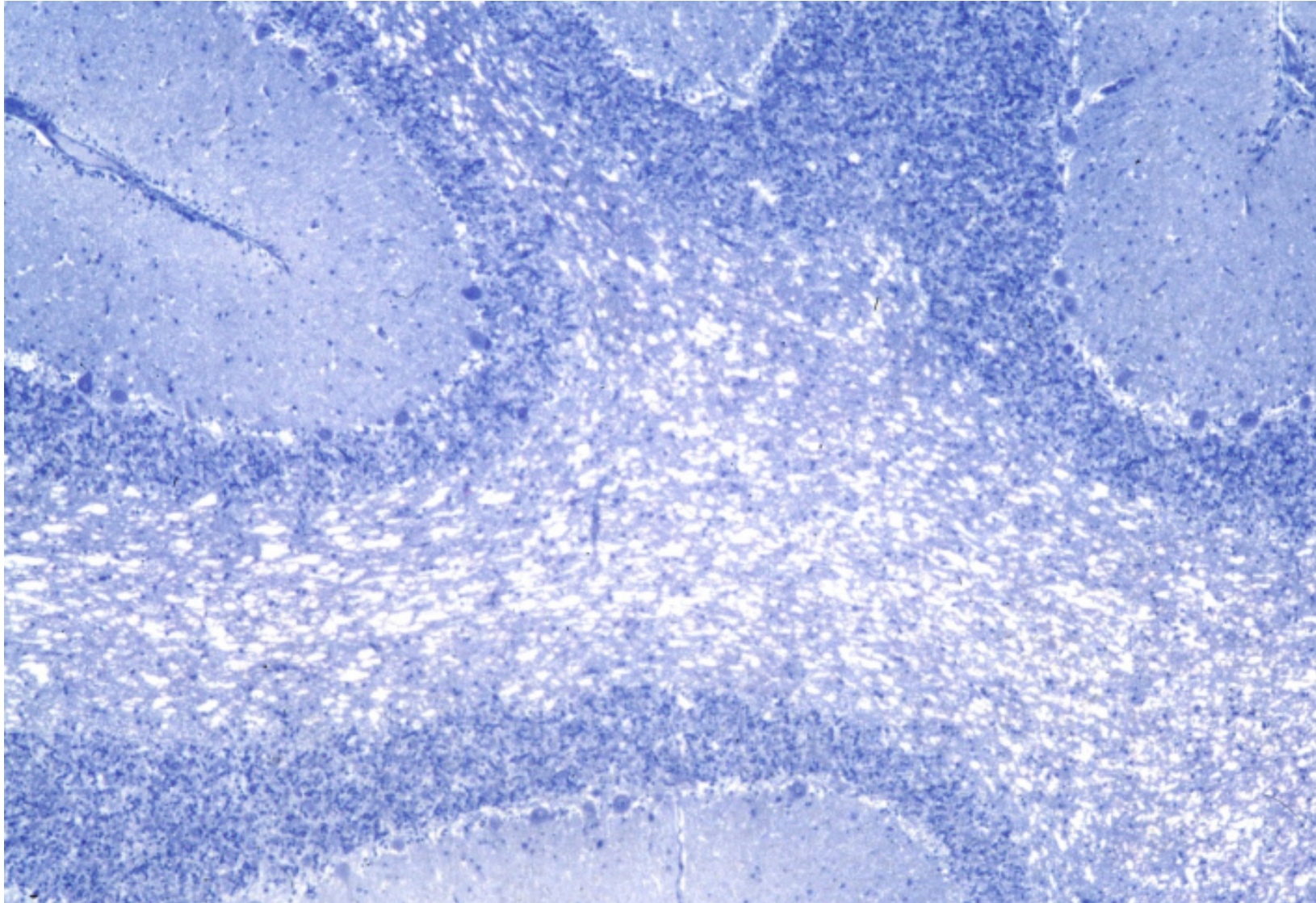


Hepatic encephalopathy : interface cerebral cortex and striatum / basal nuclei; more extensive in brainstem

* 6 months old Blond d'Aquitaine male calf (E714/05)



Hepatic encephalopathy
Luxol fast blue / cresyl violet

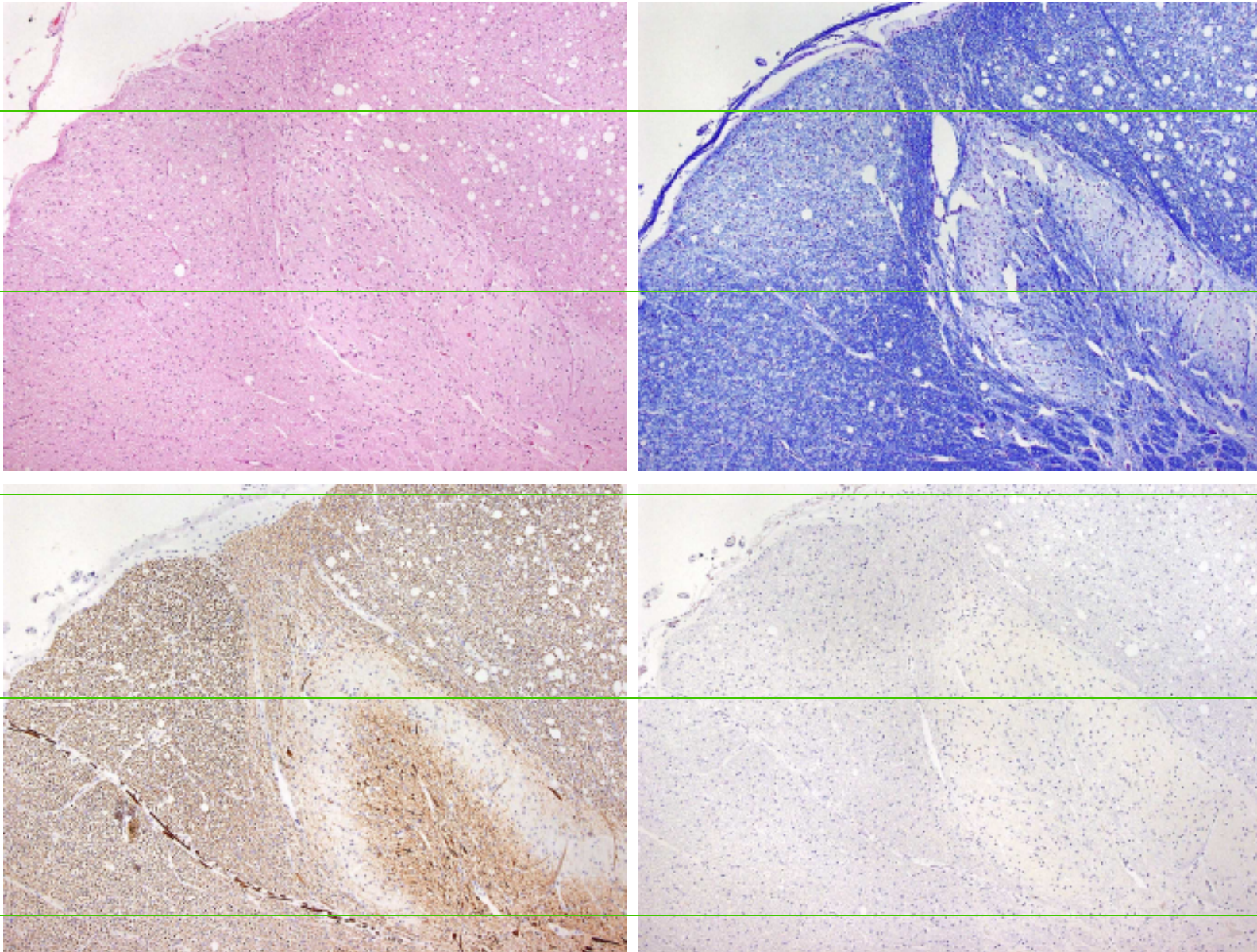


Hereford calf: aminoacidopathy (branched chain ketoacid
decarboxylase deficiency: maple syrup urine disease
Luxol fast blue / cresyl violet

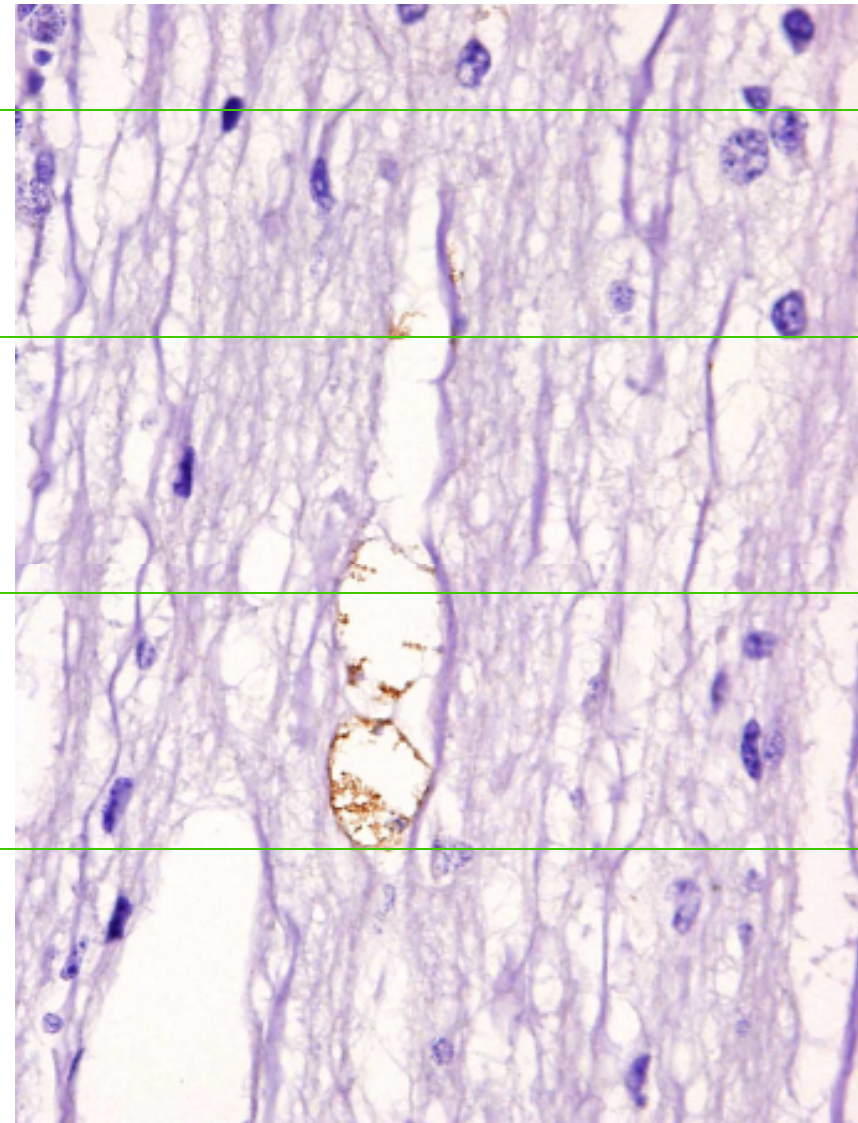
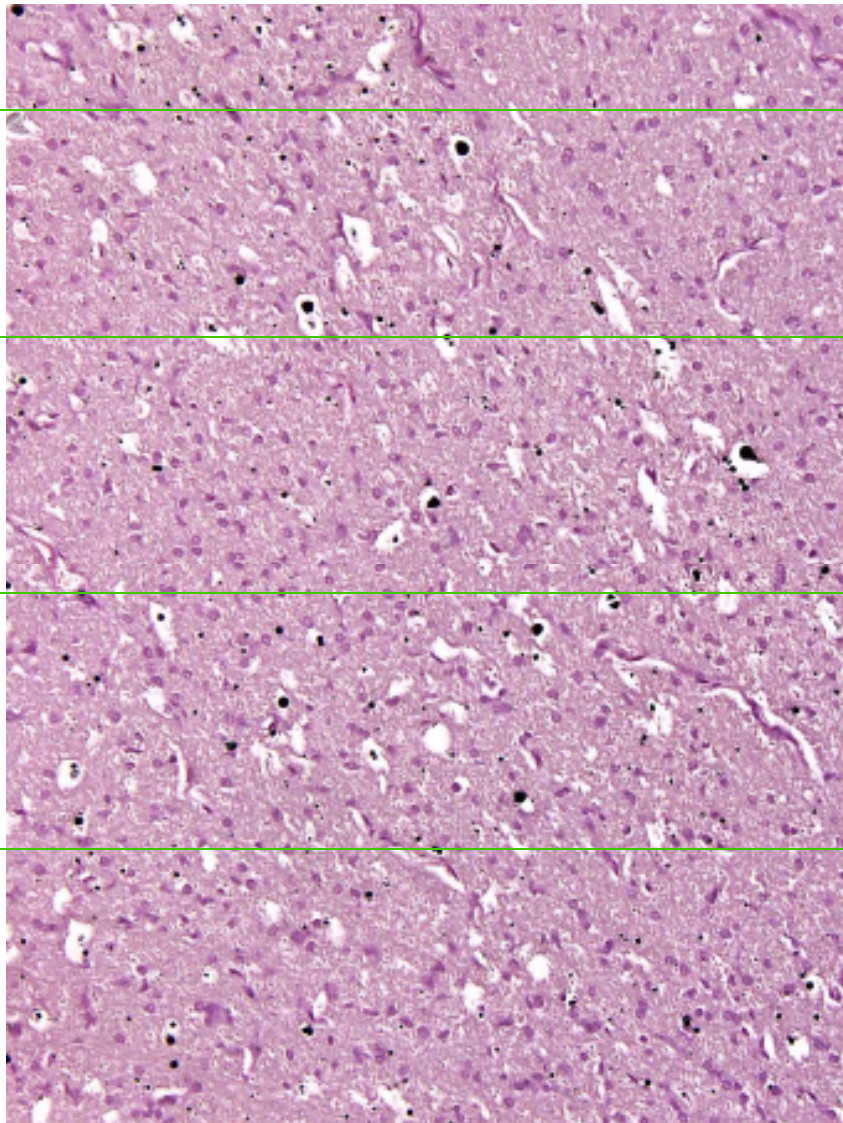
Spinal white matter vacuolation in fibre tract pattern:

- Texel lamb

- ☐ Marked white matter vacuolation dorsal funiculus and dorsolateral part of lateral funiculus
- ☐ No WTD or neuronal chromatolysis detected



4 m.o. Texel lamb; C1 H&E, LFB, NF and βAPP



E792-07 4 m.o. Texel lamb; C1 Marchi and CD68

Hypomyelination

- Deficiency of stainable myelin; usually diffuse

In utero viral infection

- Porcine congenital tremor (PCT) A2
- Persistent pestivirus infection (BDV, BVDV, CSFV-PCT A1)
- Also recorded following *in utero* Japanese encephalitis virus infection in piglets

Intrinsic

- β Mannosidosis in Saller's cattle and AngloNubian goats
- Breed-associated disorders associated with primary hypomyelination in
 - Landrace (PCT A3) and Saddleback (PCT A4) piglets,
 - Hereford cattle (with marked oedema of grey and white matter)
 - ? syndromes of vacuolation / rarefaction / hypomyelination in brainstem and especially cerebellar central white matter in Jersey (Saunders 1952), Shorthorn and Hereford (Hulland 1957) and AngusXShorthorn (Young 1961) calves
 - Toy Fox and Rat terriers (with hyperplastic goitre), Springer spaniel, Samoyed, Chow, Weimaraner, Bernese Mountain, Dalmatian breeds of dog
 - Siamese cats

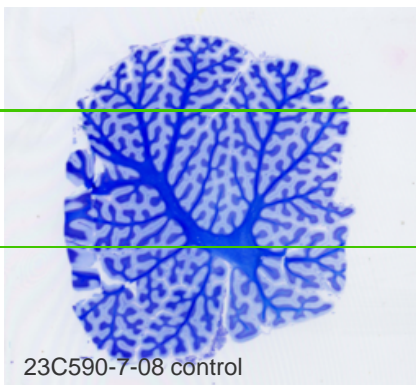
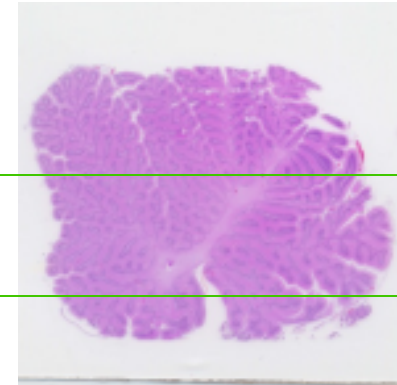
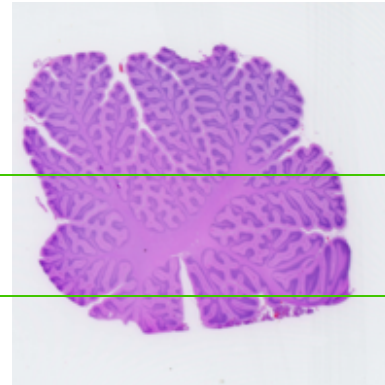
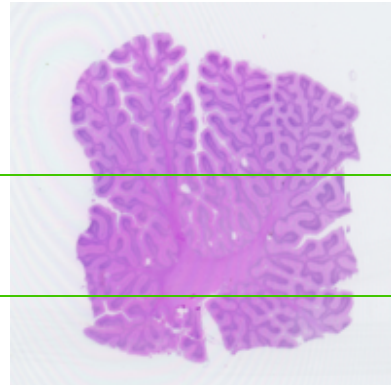
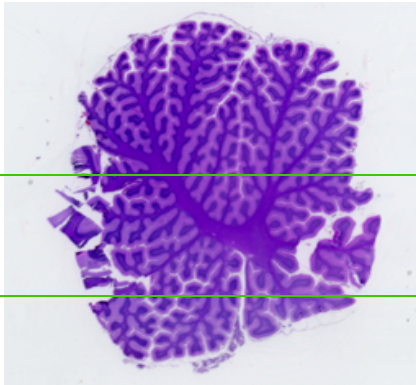
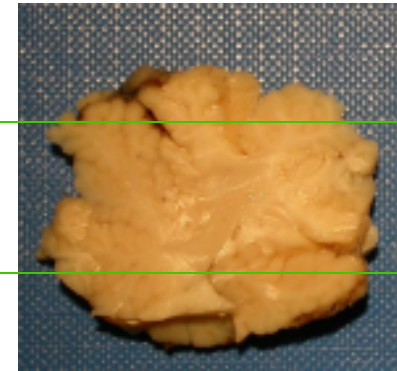
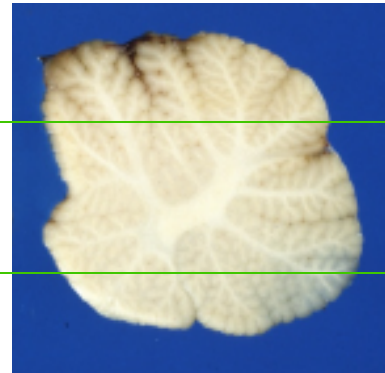
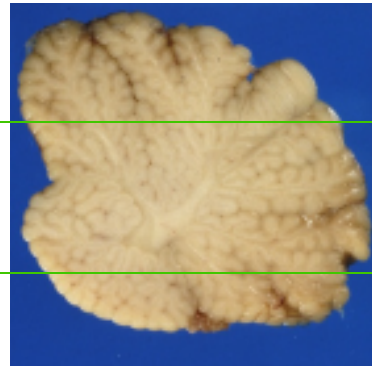
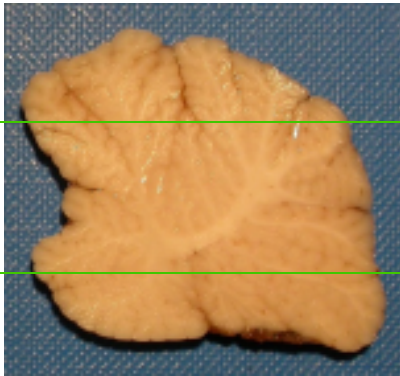
Toxic

- *In utero* exposure to trichlorfon (OP) – PCT A5

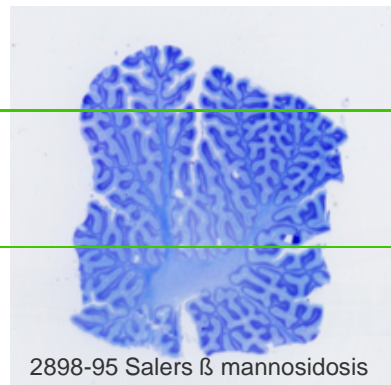
Unknown

- Congenital adductor weakness (splay leg) in piglets
 - deficient myelination of lumbar descending (UMN) tracts at birth
- ? Hypothyroidism

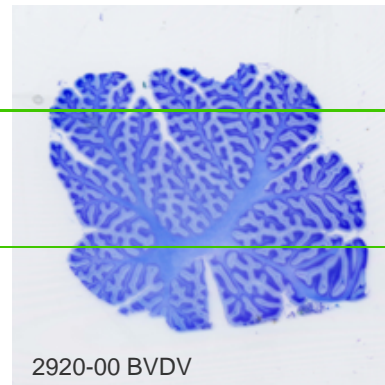
Bovine CNS hypomyelinating diseases



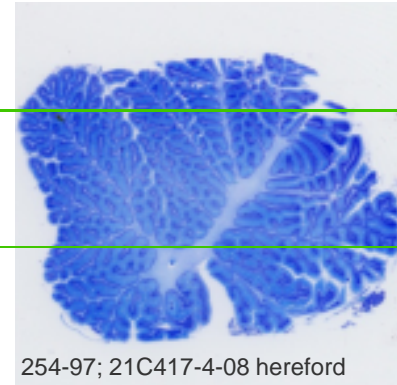
23C590-7-08 control



2898-95 Salers β mannosidosis

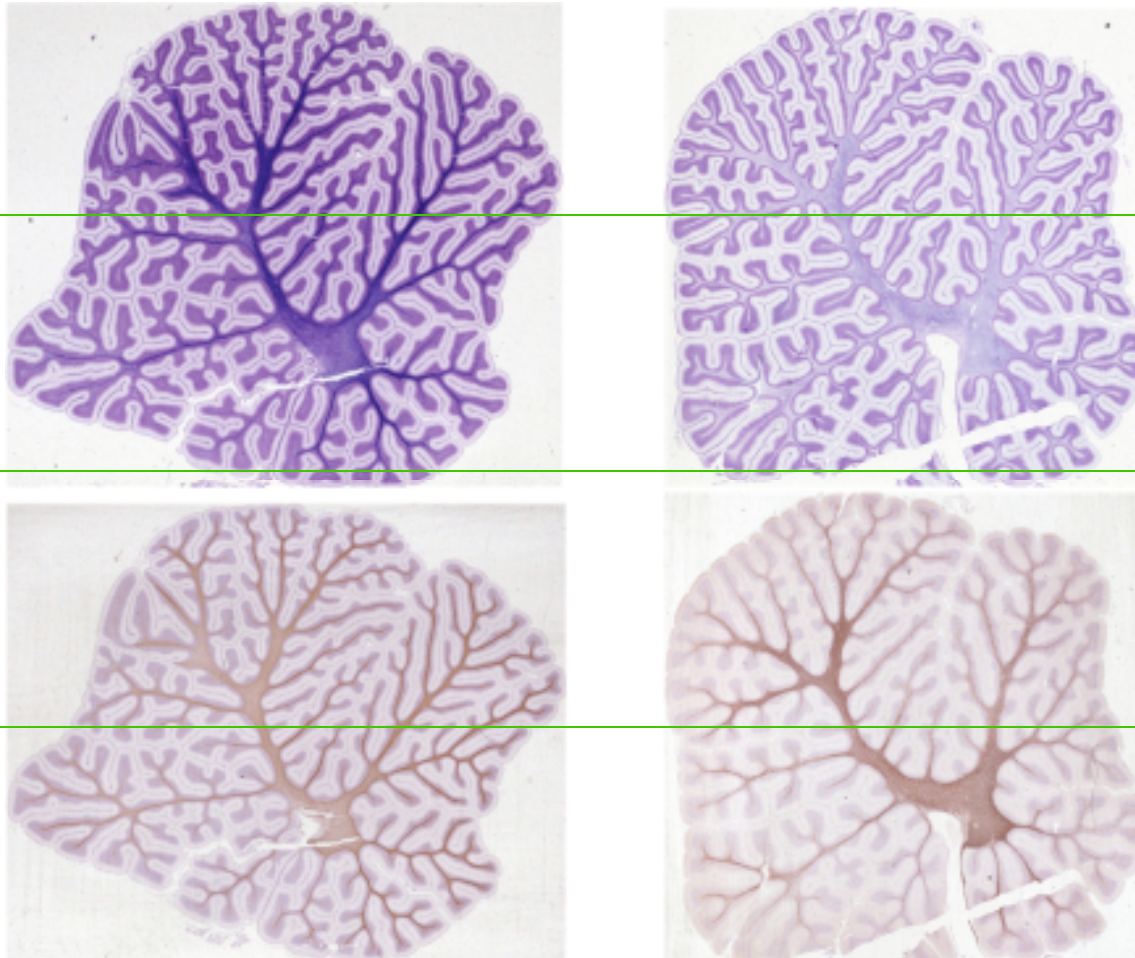


2920-00 BVDV

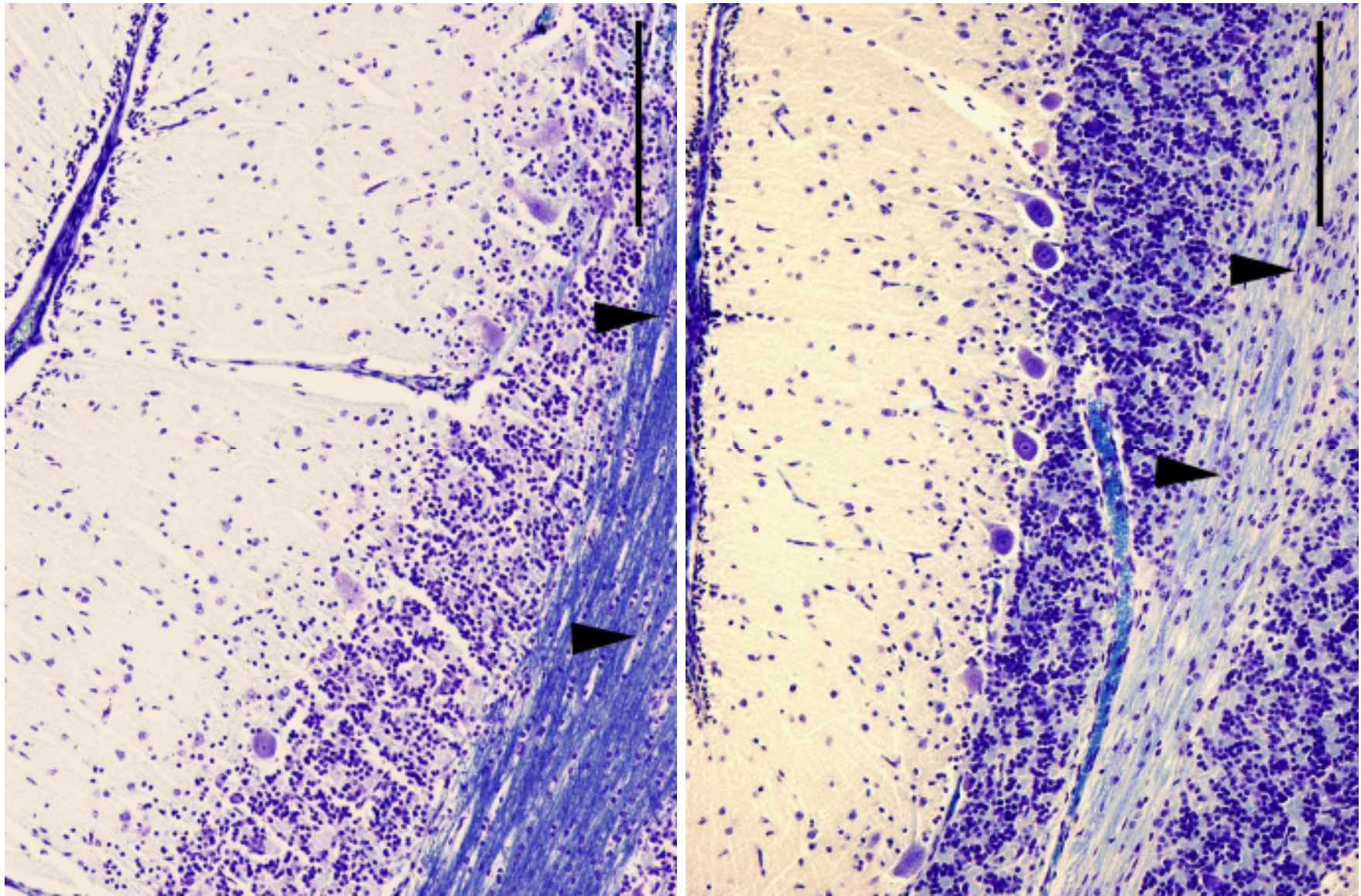


254-97; 21C417-4-08 hereford

Hypomyelination : Border disease



- Persistent pestivirus infection (BDV)



■ Neonatal calf cerebellum, LFB, unaffected and BVDV PI

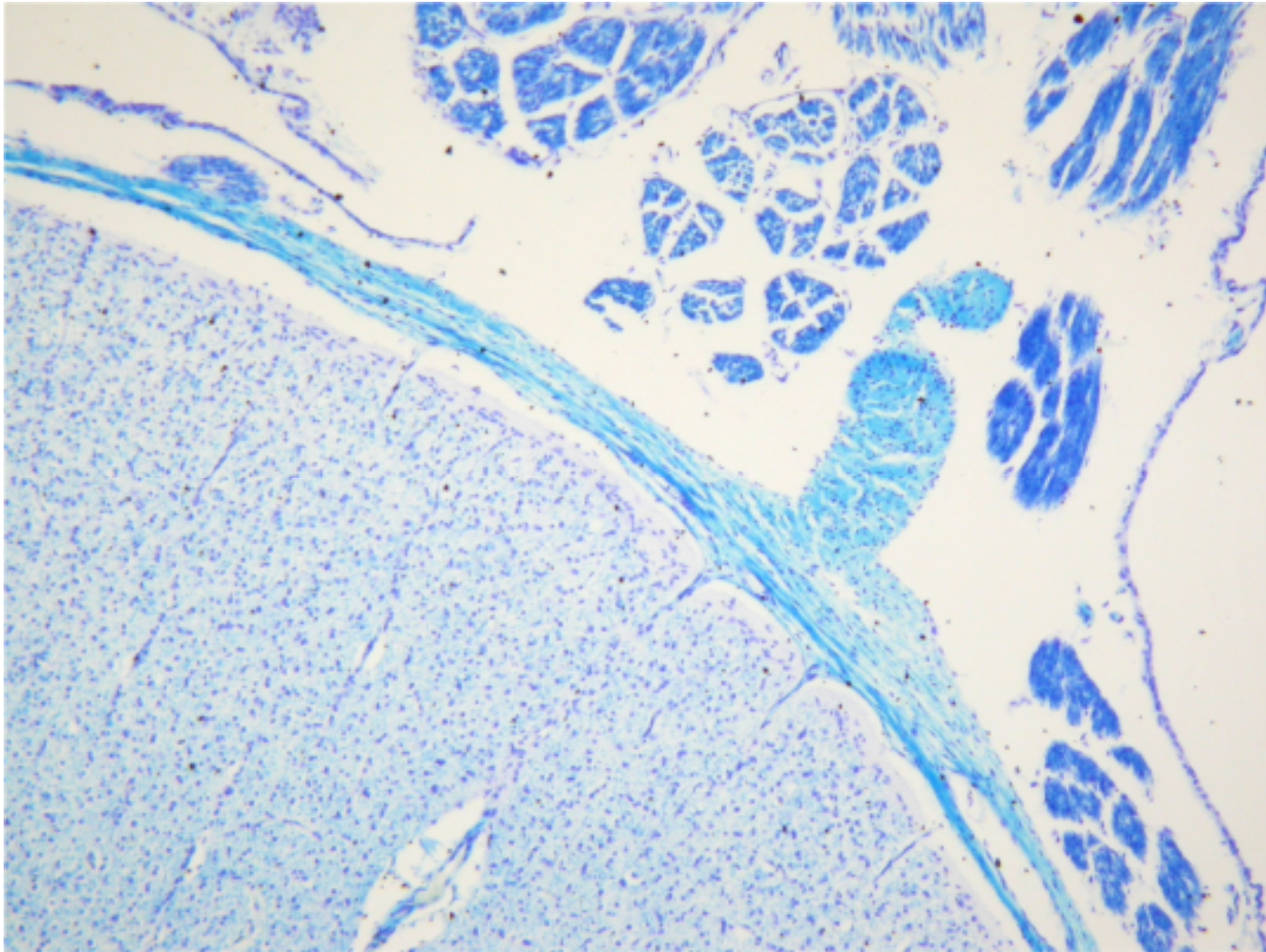
TABLE 4.4. Congenital tremor of pigs—diagnostic taxonomy

Cause	Type*					
	AI	AII	AIII	AIV	AV	B
	Virus, hog cholera	Virus, unknown	Genetic, S-L recessive	Genetic, autosomal recessive	Chemical, trichlor- fon	Unknown
<i>Field observations</i>						
Proportion of litters affected	High	High	Low	Low	High	Variable
Proportion of pigs affected within litter (approx.)	≥ 40%	≥ 80%	25%	25%	≥ 90%	Variable
Mortality among affected pigs	Medium-high	Low	High	High	High	Variable
Sex of affected pigs	Both	Both	Male	Both	Both	Any
Breed of dam (pure or crossbred)	Any	Any	Landrace	Saddleback	Any	Any
Recurrence in successive litters of same parents	No	No	Yes	Yes	Yes	?
Duration of outbreak	≤ 4 mo	≤ 4 mo	Indefinite	Indefinite	≤ 1 mo	?
<i>Laboratory observations</i>						
<i>Macroscopic</i>						?
Cerebellum:whole brain ratio (≤ 8% = abnormal)	↓	~	~	~	↓	↓ ~
Spinal cord size (weight)	↓	~	↓	↓	↓	
<i>Microscopic (CNS)</i>						?
Myelin deficiency	+	+	+	+	+	
Myelin aplasia (partial)	—	—	+	—	—	
Oligodendrocytes swollen	+	+	—	—	—	
Oligodendrocytes reduced in num- ber	~	~	+	~	~	
<i>Neurochemistry (spinal cord)</i>						?
Total DNA	↓	~	↓	↓	↓	
Whole lipid/g	↓	↓	↓	↓	↓	↓ ~
Cerebrosides/g	↓	↓	↓	↓	↓	↓ ~
Lipid hexose:phosphorus ratio	↓	↓	↓	↓	~	↓ ~
Cholesterol esters characteristic of demyelination	+	+	—	+	—	— —
<i>Serology</i>						?
Maternal antibodies to hog cholera	+	—	—	—	—	— — —

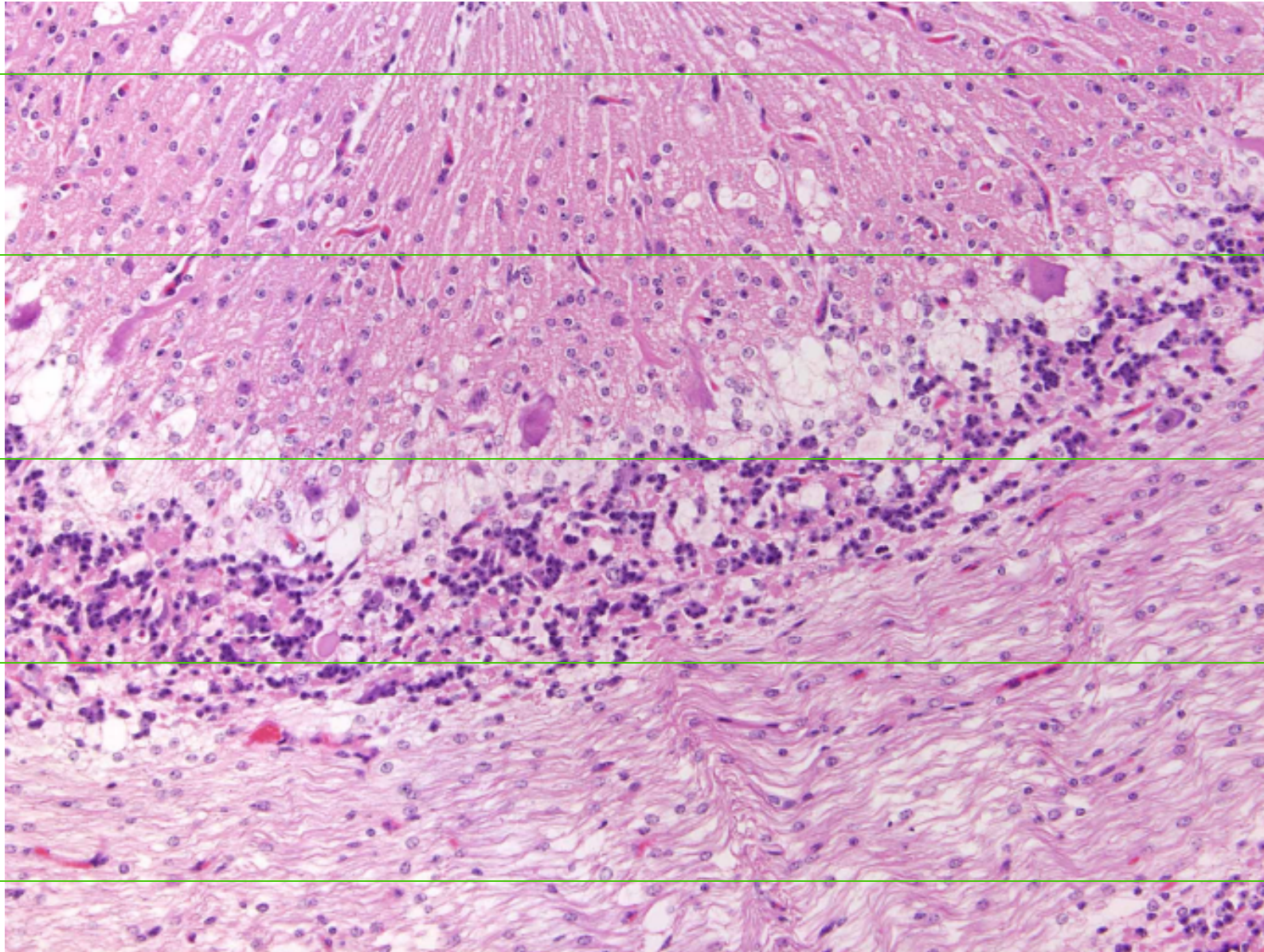
Note: + = present; — = absent; ↓ = not significantly changed; ↓ = decreased.

*Type A = a form of congenital tremor with defined pathological characters and known etiology; Type B = a form of congenital tremor as yet inadequately characterized and/or of unknown etiology.

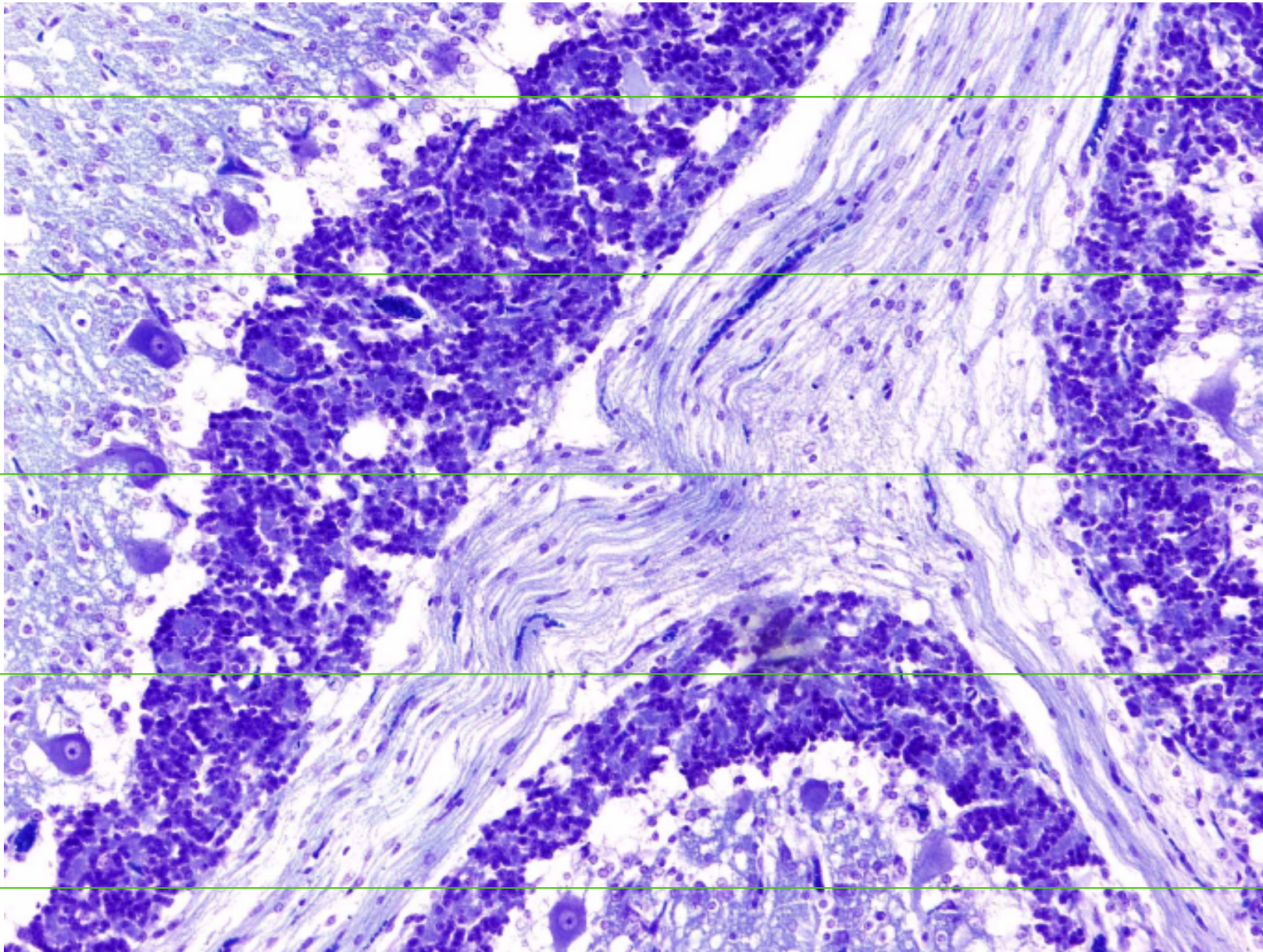
PCT A2



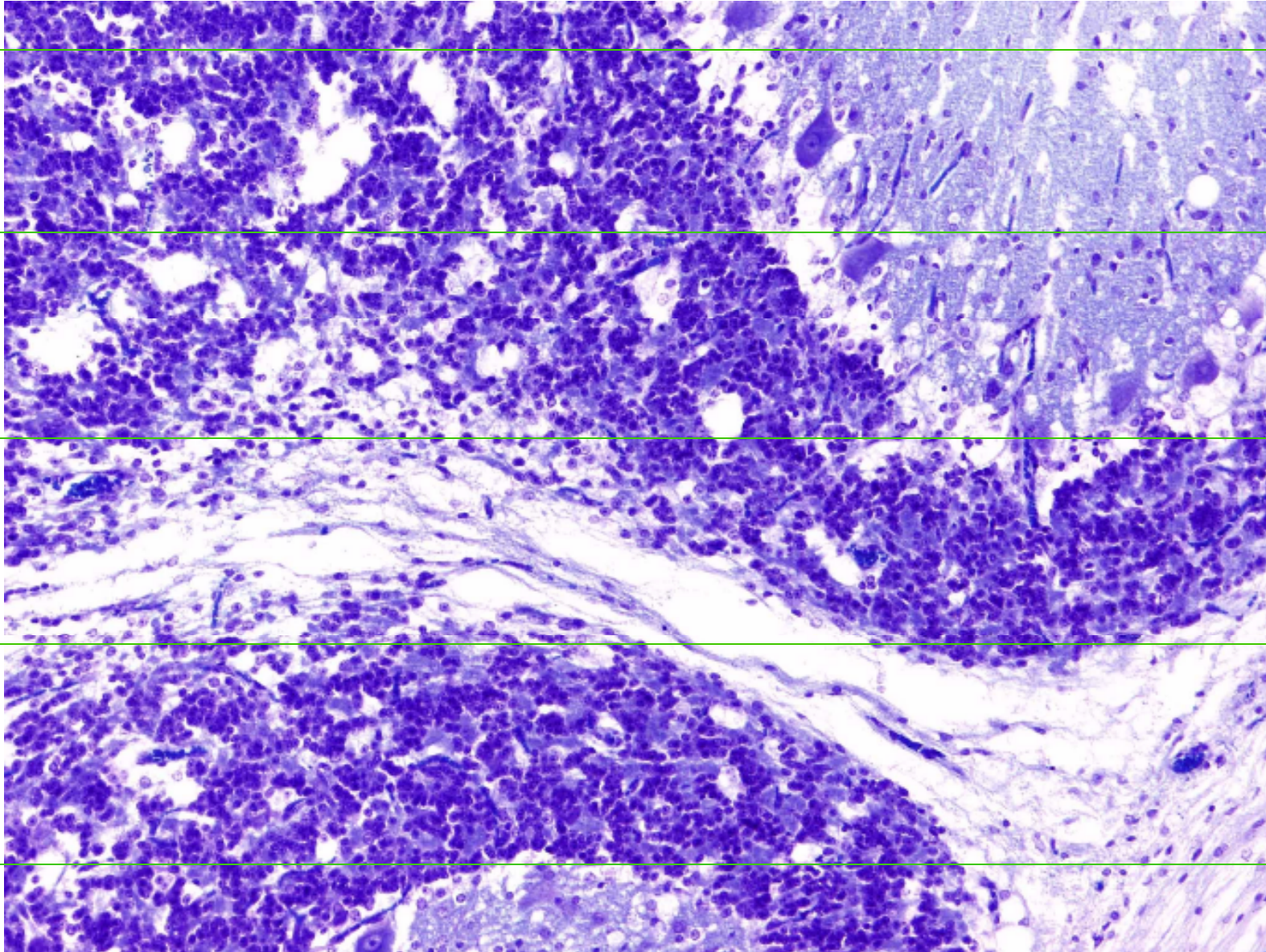
Hereford neuraxial oedema with hypomyelination



Hereford neuraxial oedema with hypomyelination



Hereford neuraxial oedema with hypomyelination

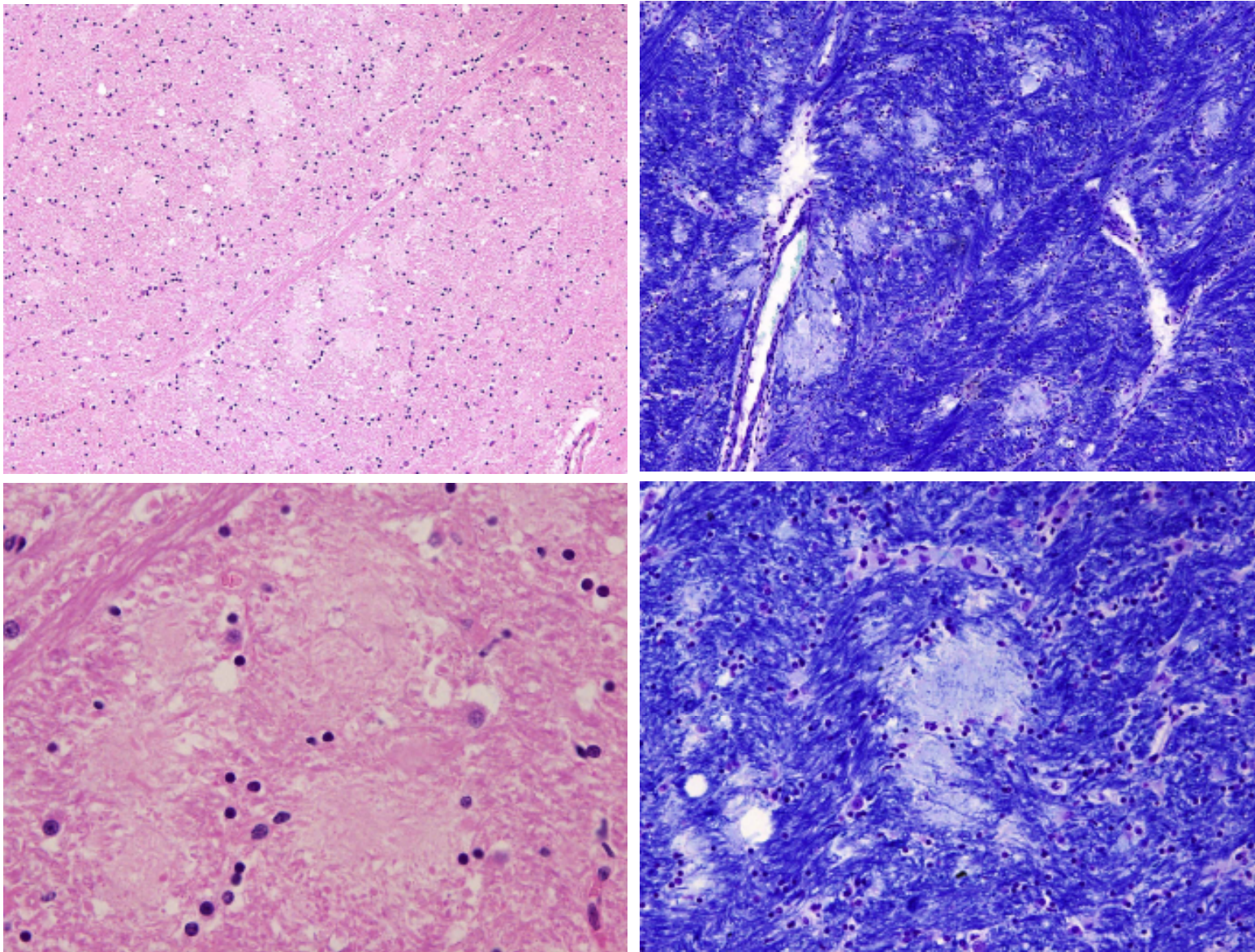


White matter: more degenerative disorders...

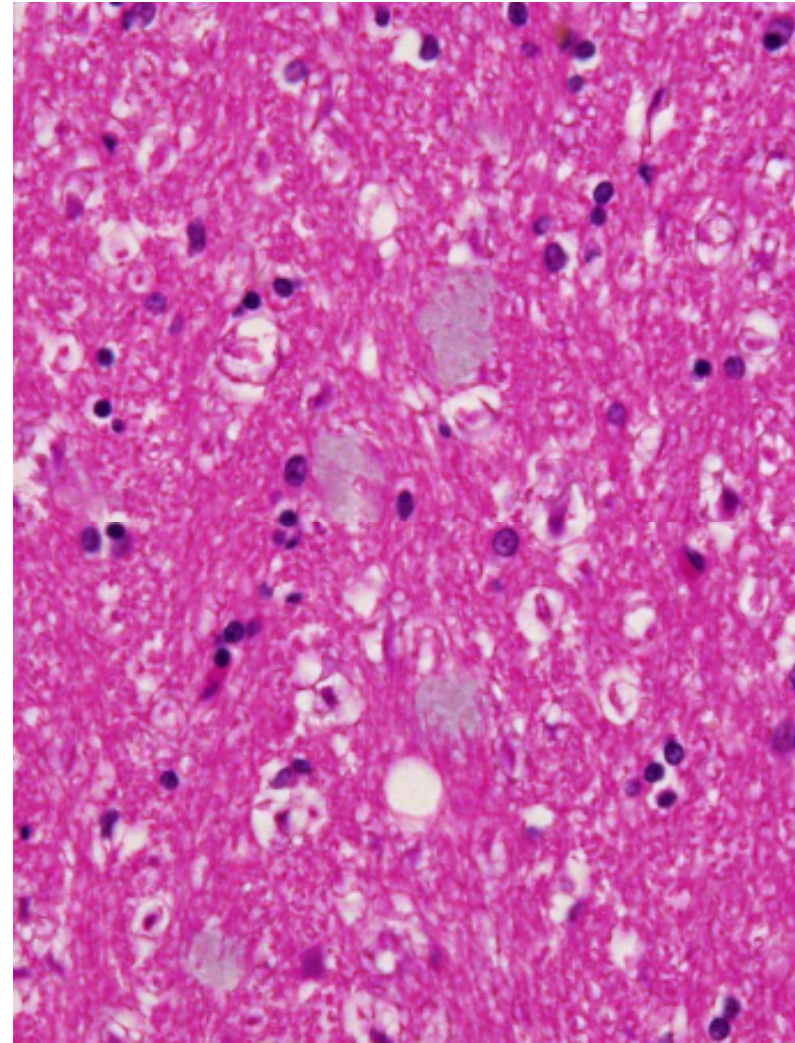
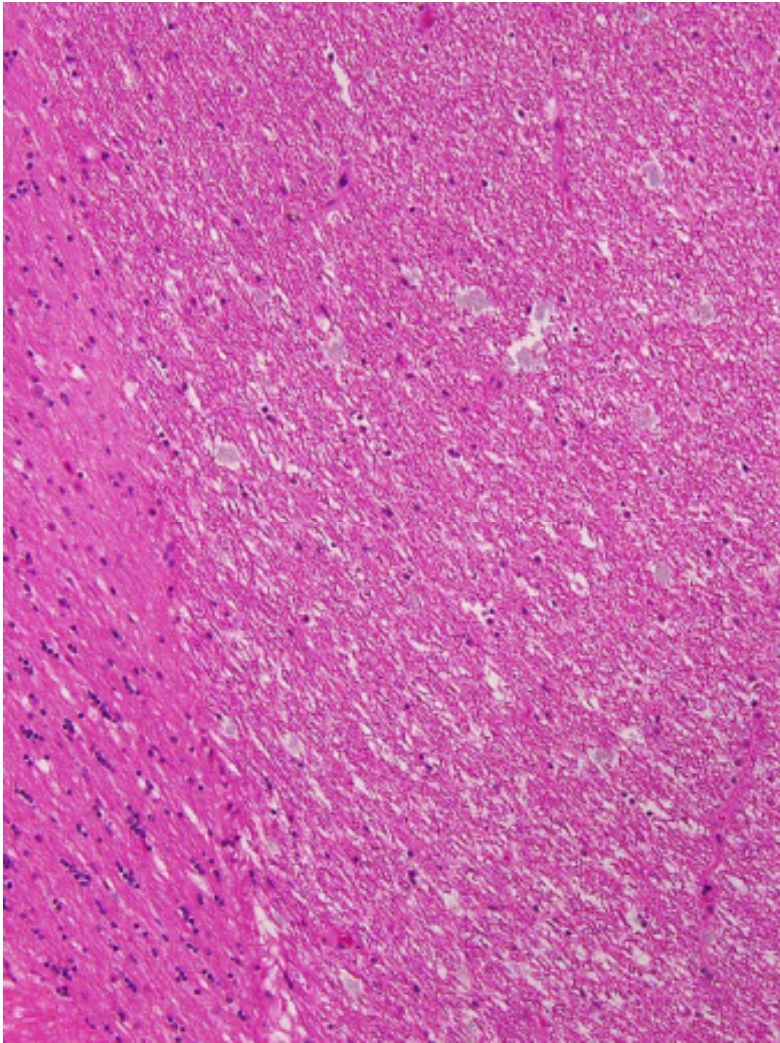
- Oligodendroglial dysplasia
 - Ataxia of Charolais cattle
 - Bull mastiff
- Congenital leucoencephalopathy (dancing calf syndrome)
 - Associated with maternal consumption of tagasaste (*Chamaecytisus palmensis*); throughout neuraxial white matter and optic nerve, most severe in brainstem and spinal cord. Plaques up to 100µm [consisting of proliferations of presumptive oligodendroglial processes (EM)]; accompanied by gliosis, oligodendroglial vacuolation and pycnosis, macrophages

Caution:

- Mucicyte / Mucocyte / Buscaino bodies
- Lysosomal enzyme deficiency
 - Globoid cell leucodystrophy associated with galactocerebrosidase deficiency – polled dorset sheep



Charolais ataxia (oligodendroglial dysplasia)



Mucicyte artefact