Neurodegenerative diseases: a lesion-based approach:

combined grey and white

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

Necrosis grey and white matter; possible causes include

- Infarction / embolic / compromised vascular supply
  - Fibrocartilaginous embolism – large dog breeds, pigs, other species
  - Traumatic feline ischaemic myelopathy (L2 caudally)
  - Feline ischaemic encephalopathy : markedly assymetric predom cerebrum ? Aberrant Cuterebra larval migration
  - Encephalomalacia following intracarotid injection in horses
  - Cerebellar sclerosis - ? compression of rostral cerebellar artery
  - Vertebral fracture
- Intoxications
  - Shiga toxin - Oedema disease
  - Subacute Clostridium perfringens epsilon intoxication (FSE)
  - Enterococcus hirae associated encephalomalacia in chicks
- Disbudding (hot iron) injury
- Intrinsic metabolic
  - Breed associated - Multifocal encephalopathy in Limousin calves
  - Minor WM involvement in Simmental encephalopathy (predominantly grey)
- Acquired metabolic
  - Vitamin E deficiency in chicks and turkey poults : cerebellum (in turkeys lumbar poliomyelomalacia also reported)
  - ?Mulberry heart disease pigs

Clostridium perfringens type D

type	alpha	beta	epsilon	iota
A	++	-	-	-
B	+	++	+	-
C	+	++	-	-
D	+	-	++	-
E	+	-	-	++

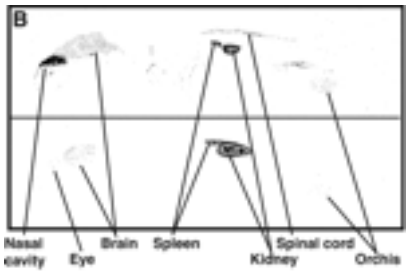
- *Cl perfringens* - up to 15 toxins
- 5 types designated A – E on the basis of production of 4 major exotoxins
- Epsilon v. potent bacterial neurotoxin (BoNTs > tetanotoxin > ε toxin) ; mouse lethal dose 100ng/kg

Clostridium perfringens epsilon toxin

- synthesised and secreted as (inactive) prototoxin
- activation by proteolytic cleavage
  - *Cl perfringens* protease
  - trypsin / chymotrypsin at N- and C-terminal peptides of 14 and 23 residues respectively
- absorbed (compromises intestinal barrier ?)
- forms heptameric pore in MDCK cells and rat synaptosomes (Petit *et al* 2001; Miyata *et al* 2002)

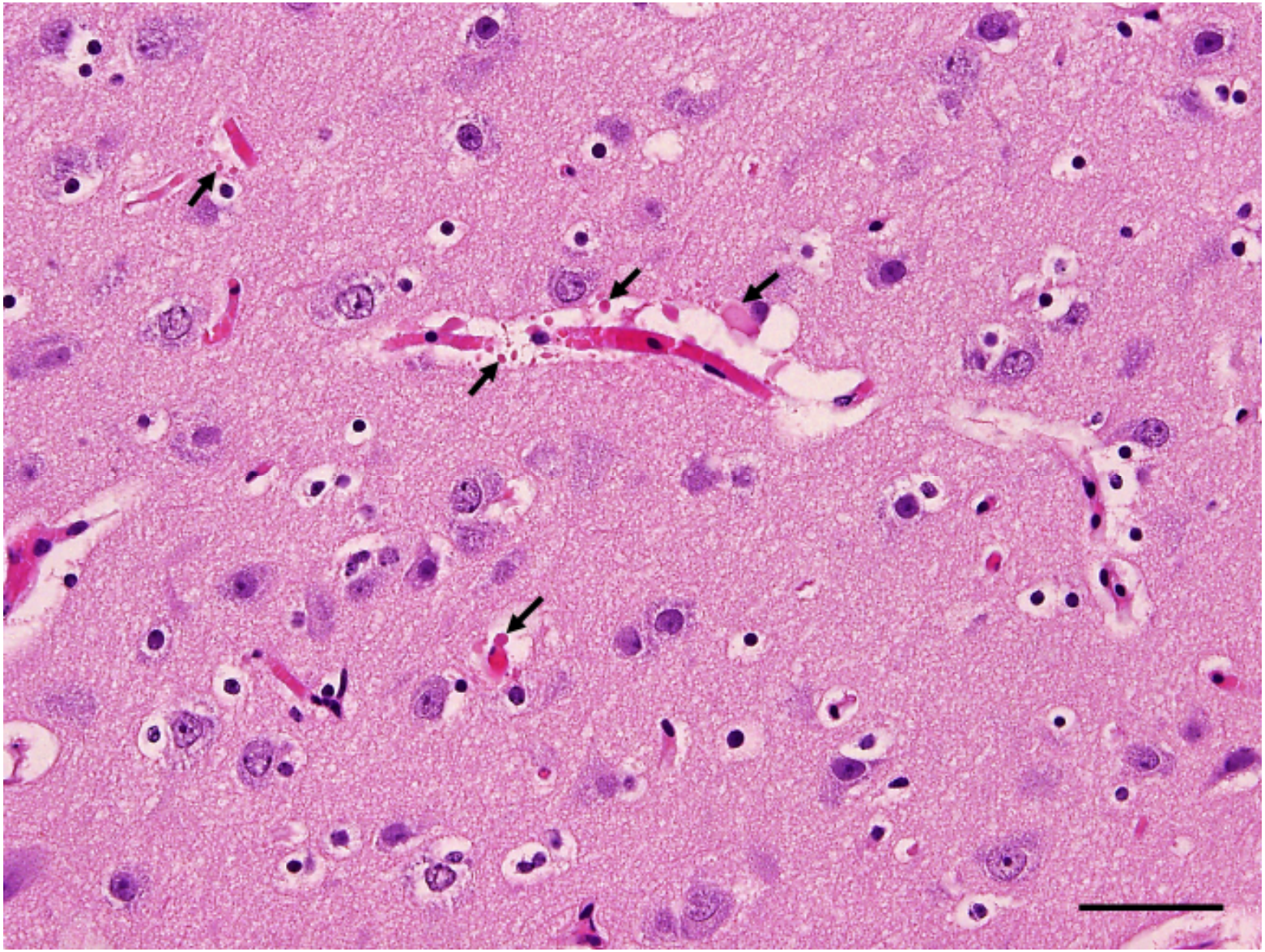
Experimental *Clostridium perfringens* epsilon intoxication

- binding sites
  - predominantly in kidney
    glomeruli, capillaries, collecting ducts
  - brain and spinal cord
  - eye, spleen, nasal turbinate



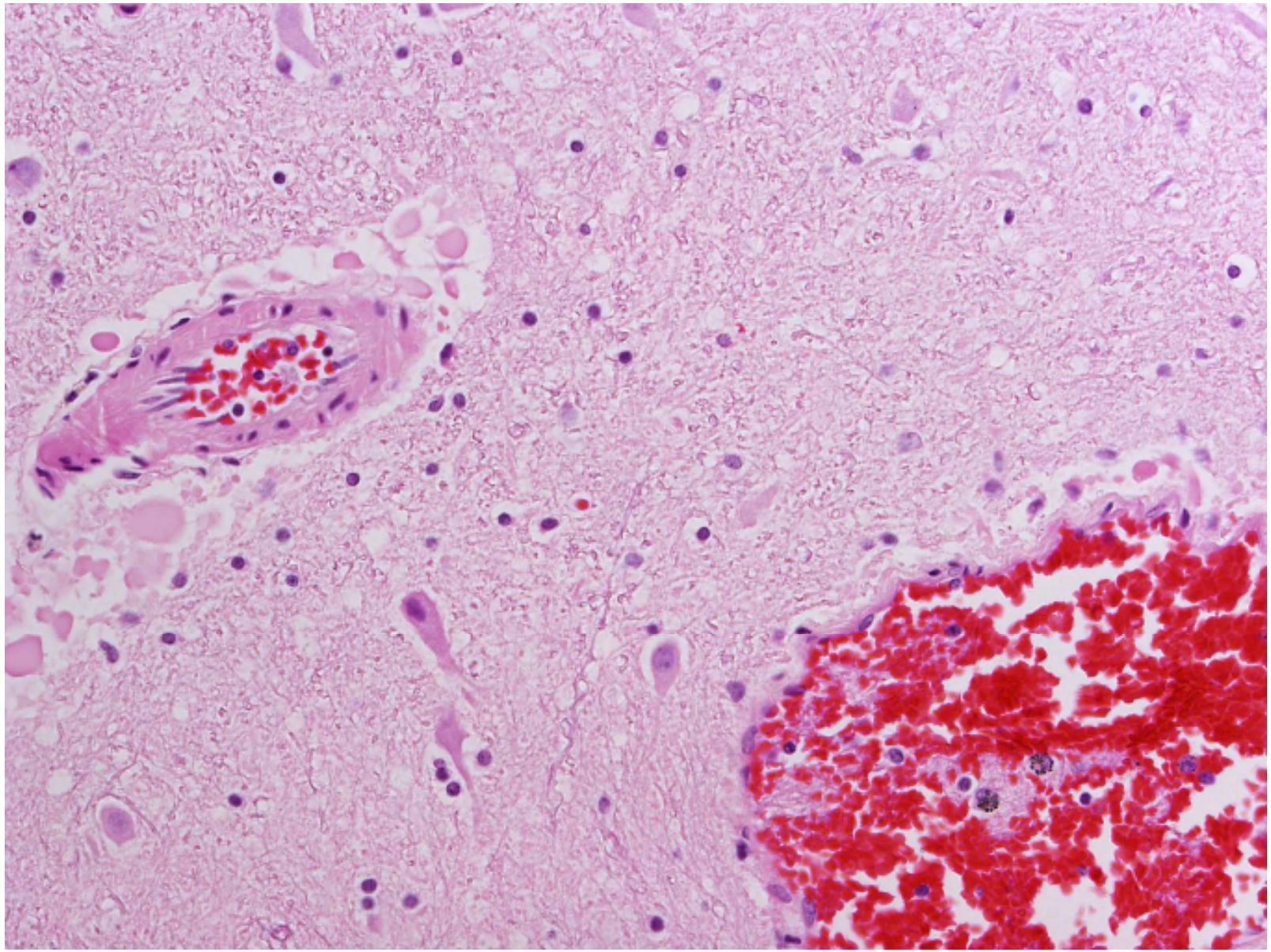
- nephrectomy decreases survival time (exptl murine epsilon intoxication)
- neurotoxicity important pathogenetic mechanism
  - accumulates on luminal surface of vascular endothelium all brain areas; degeneration of endothelial tight junctions
  - crosses blood brain barrier
  - accumulates in neuroparenchyma – occasional binding to glia
- severe perivascular oedema
  - also characteristic of clinical disease in ruminants

(Zhu *et al* 2001; Tamai *et al* 2003; Soler-Jover *et al* 2007)



Early lesion Cl p epsilon intoxication Calf 2 cerebrum; bar= 50 µm

Caution



Artefactual perivascular blebs , porcine

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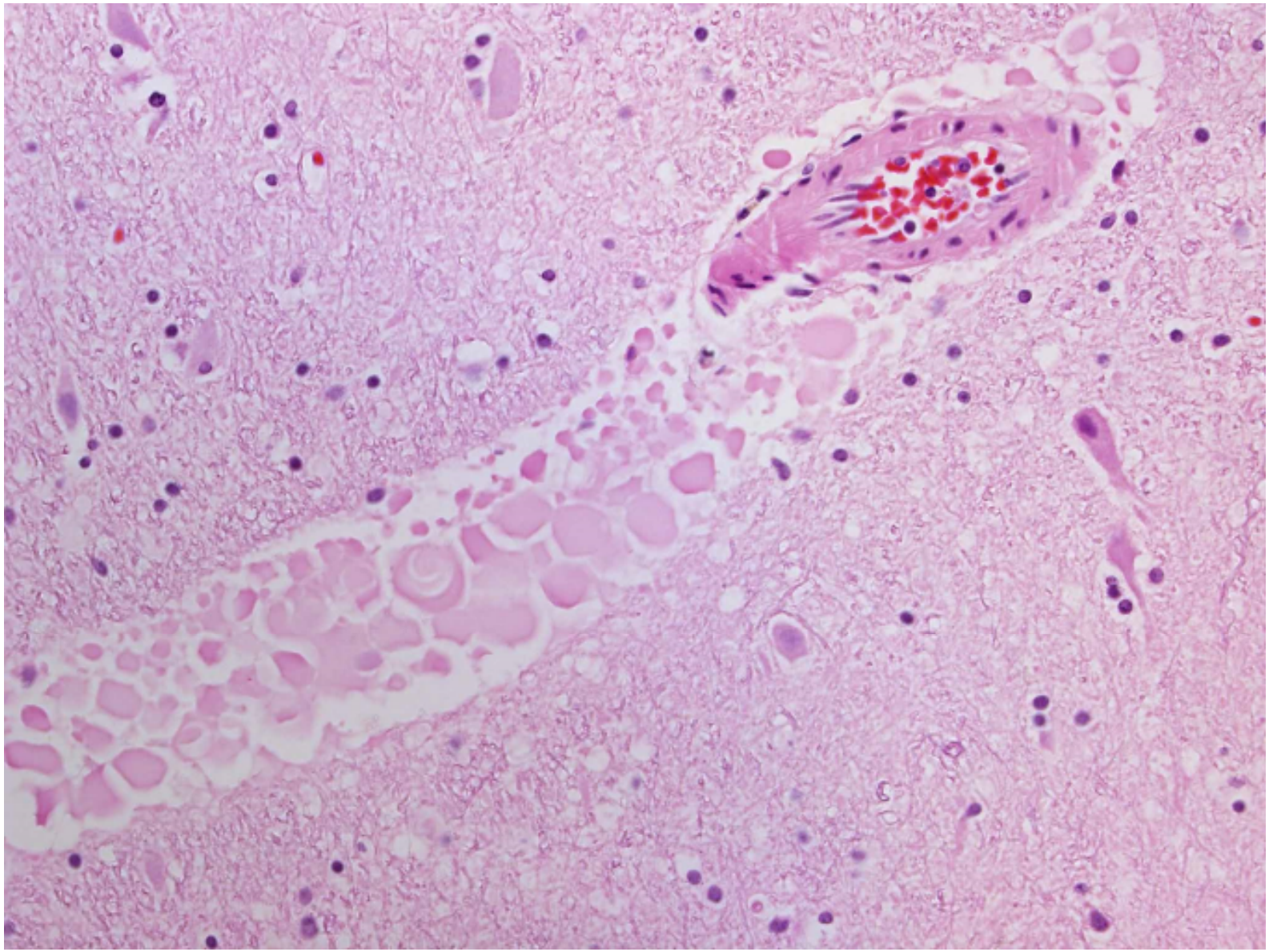

Artefactual perivascular blebs

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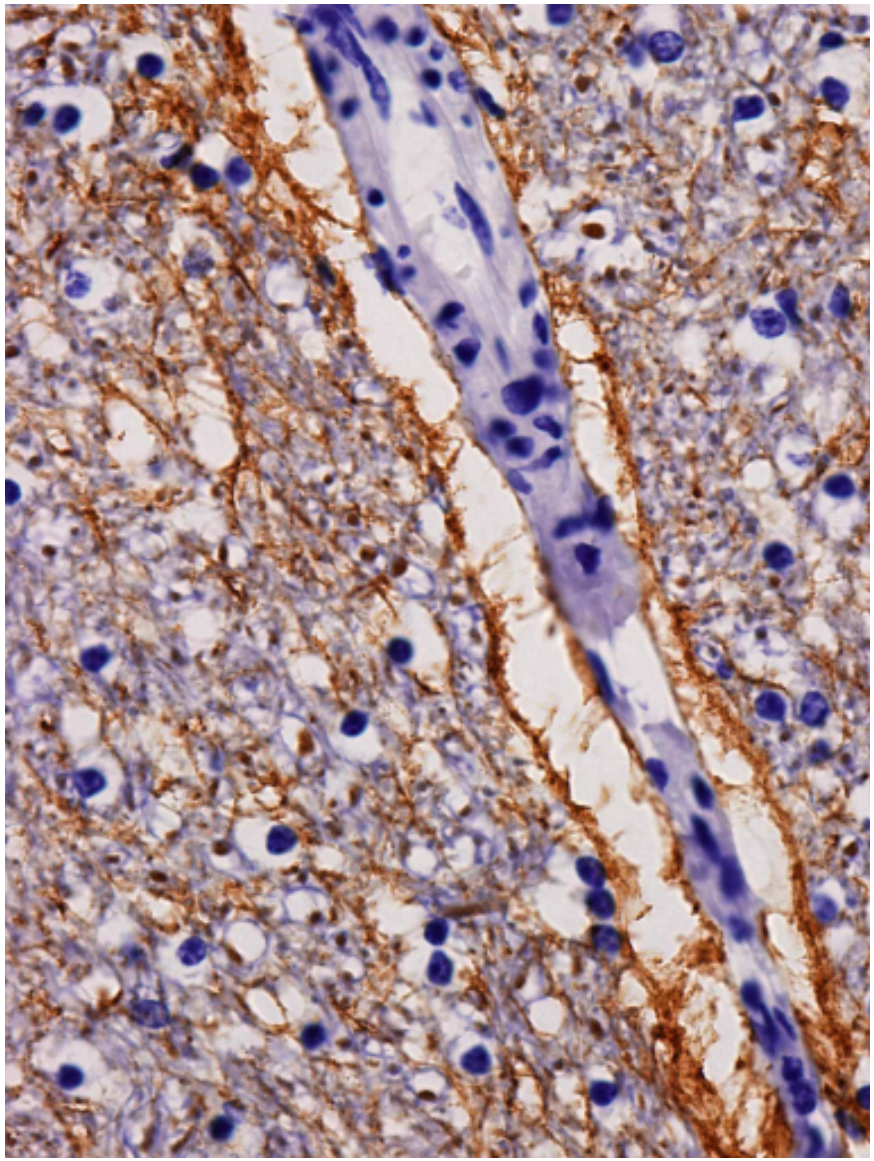

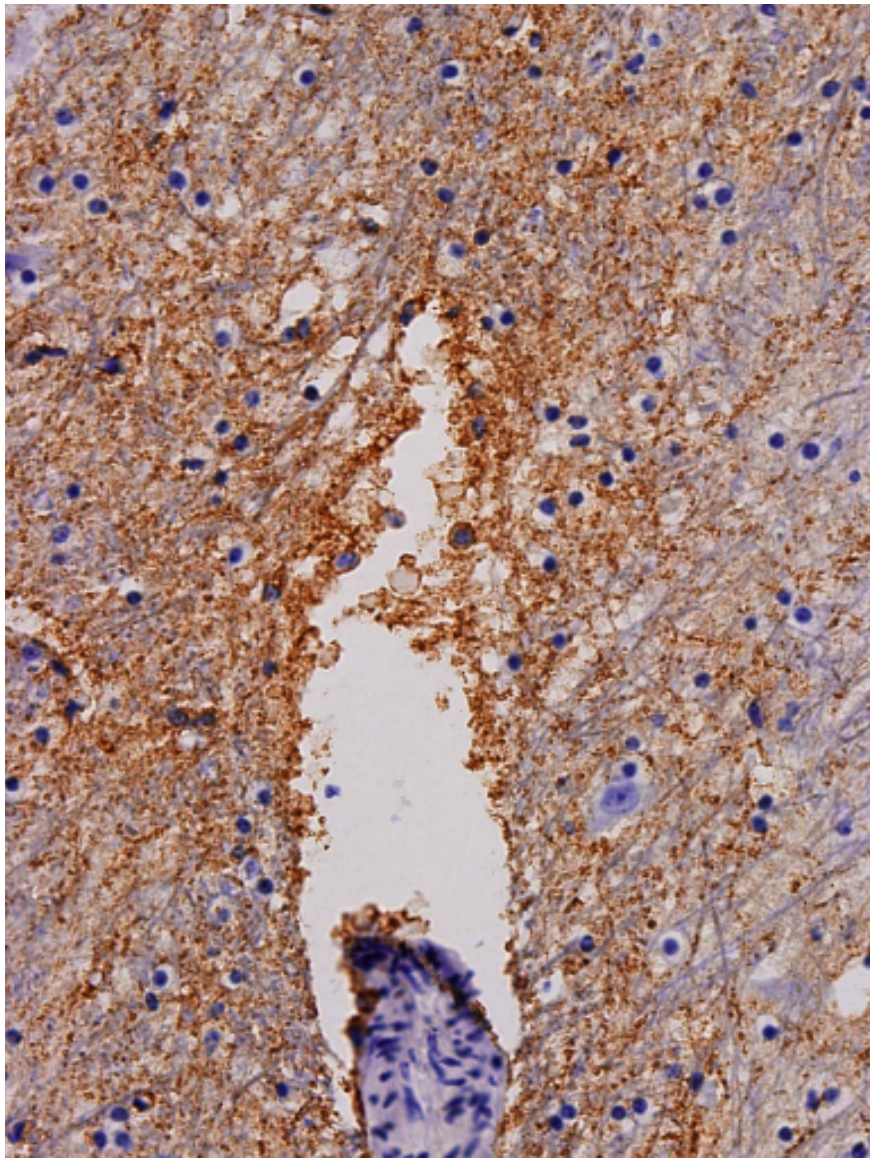

? artefactual perivascular blebs , bovine, AQP4 IHC

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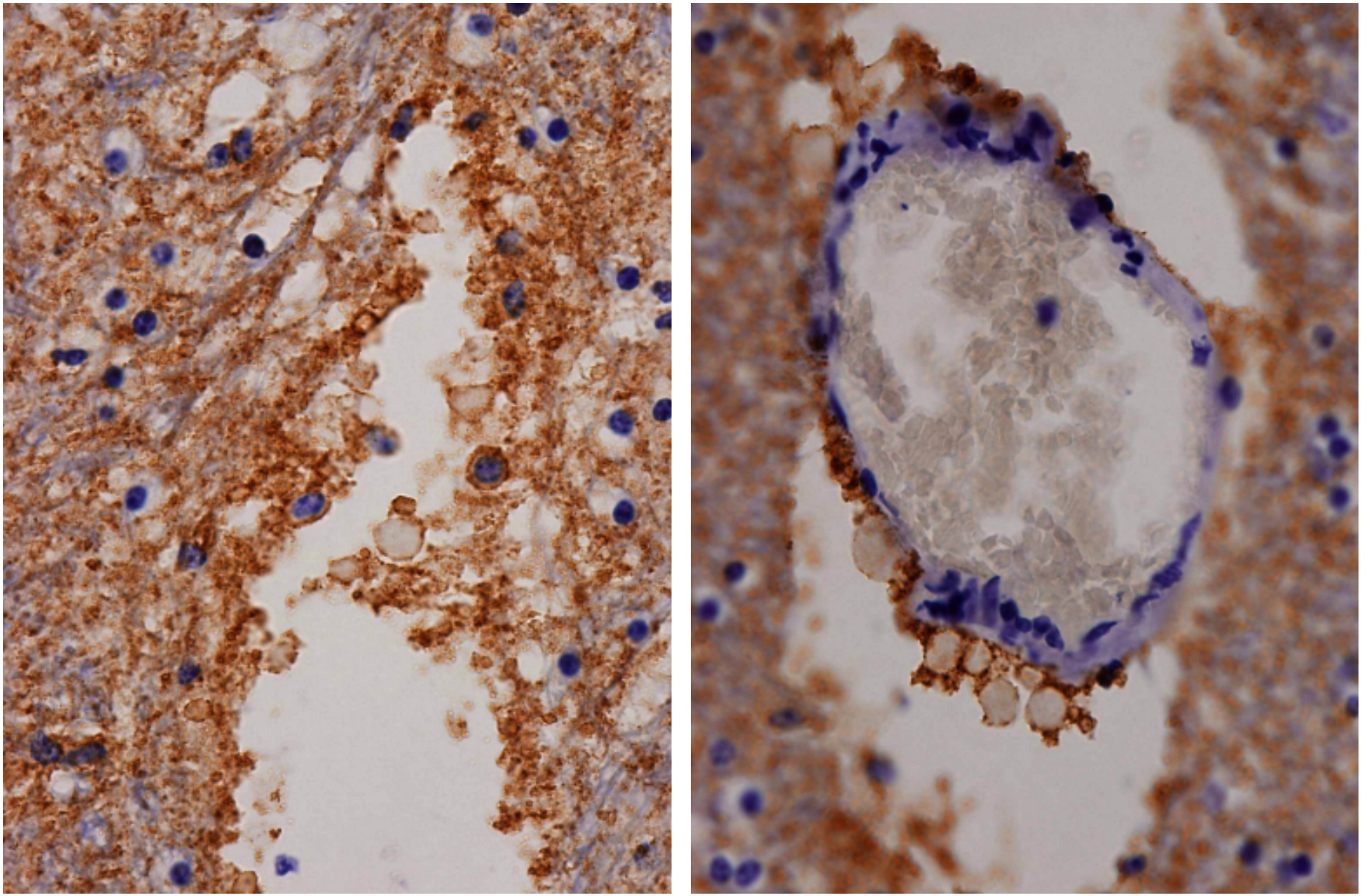
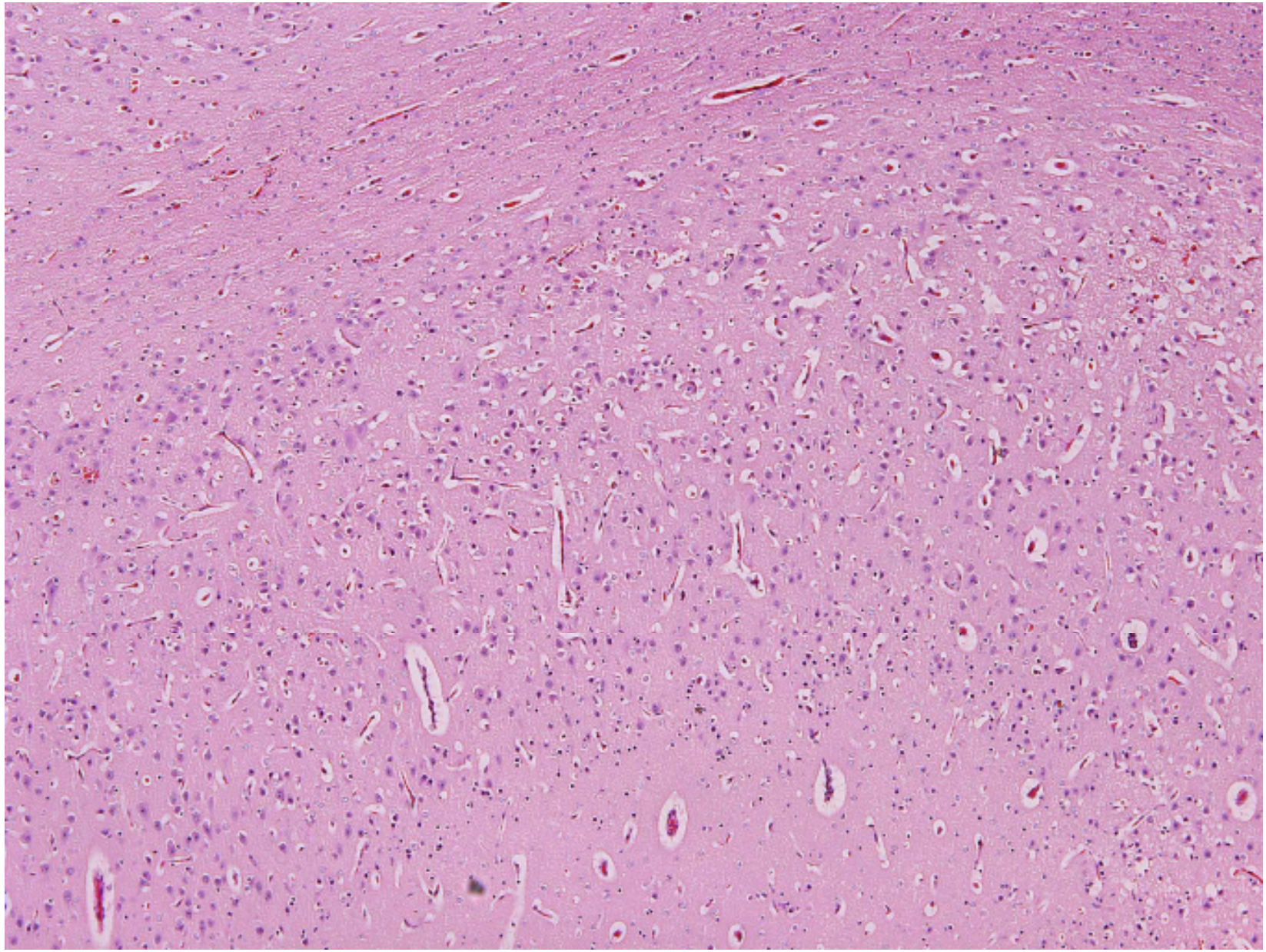
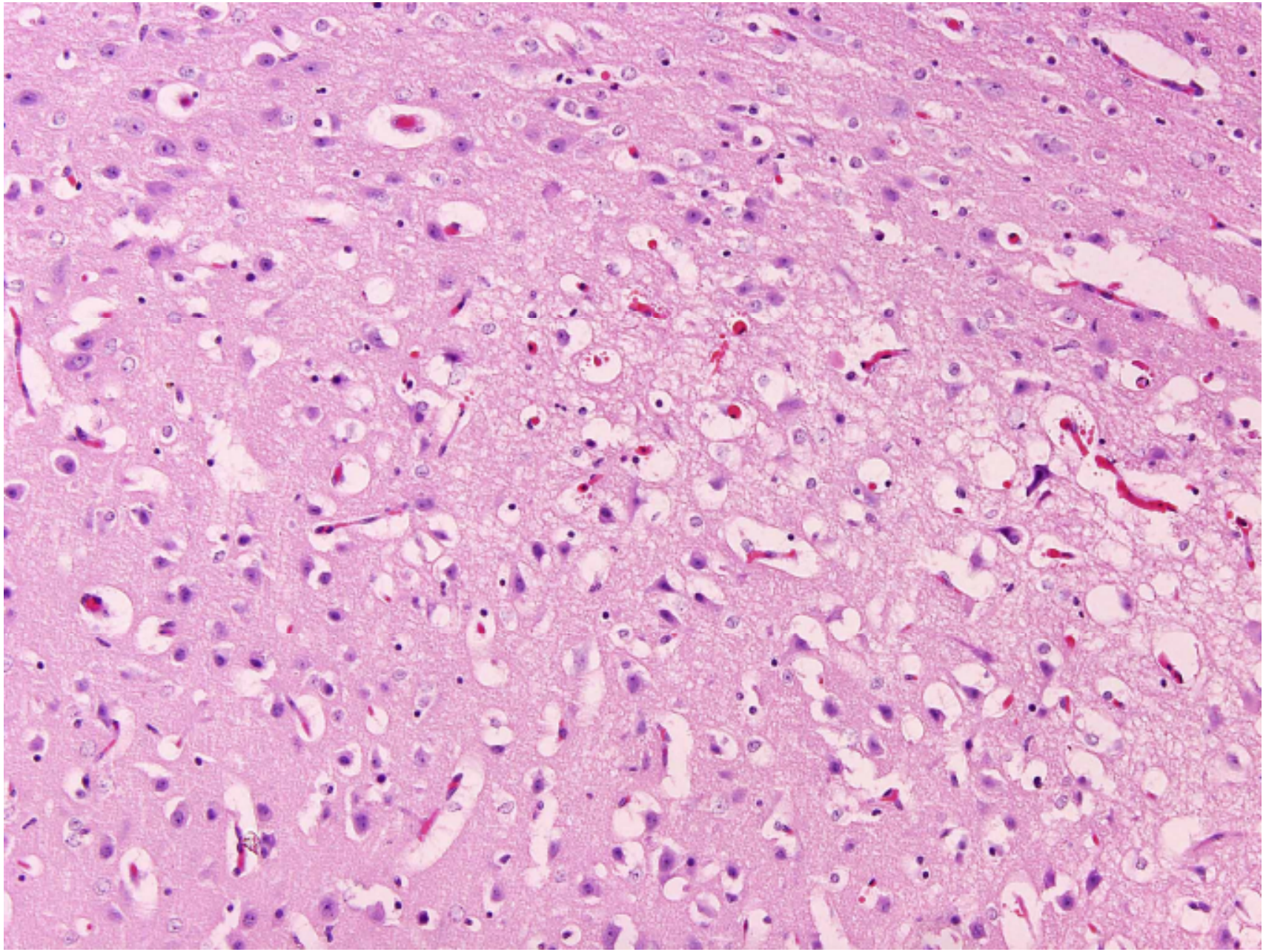


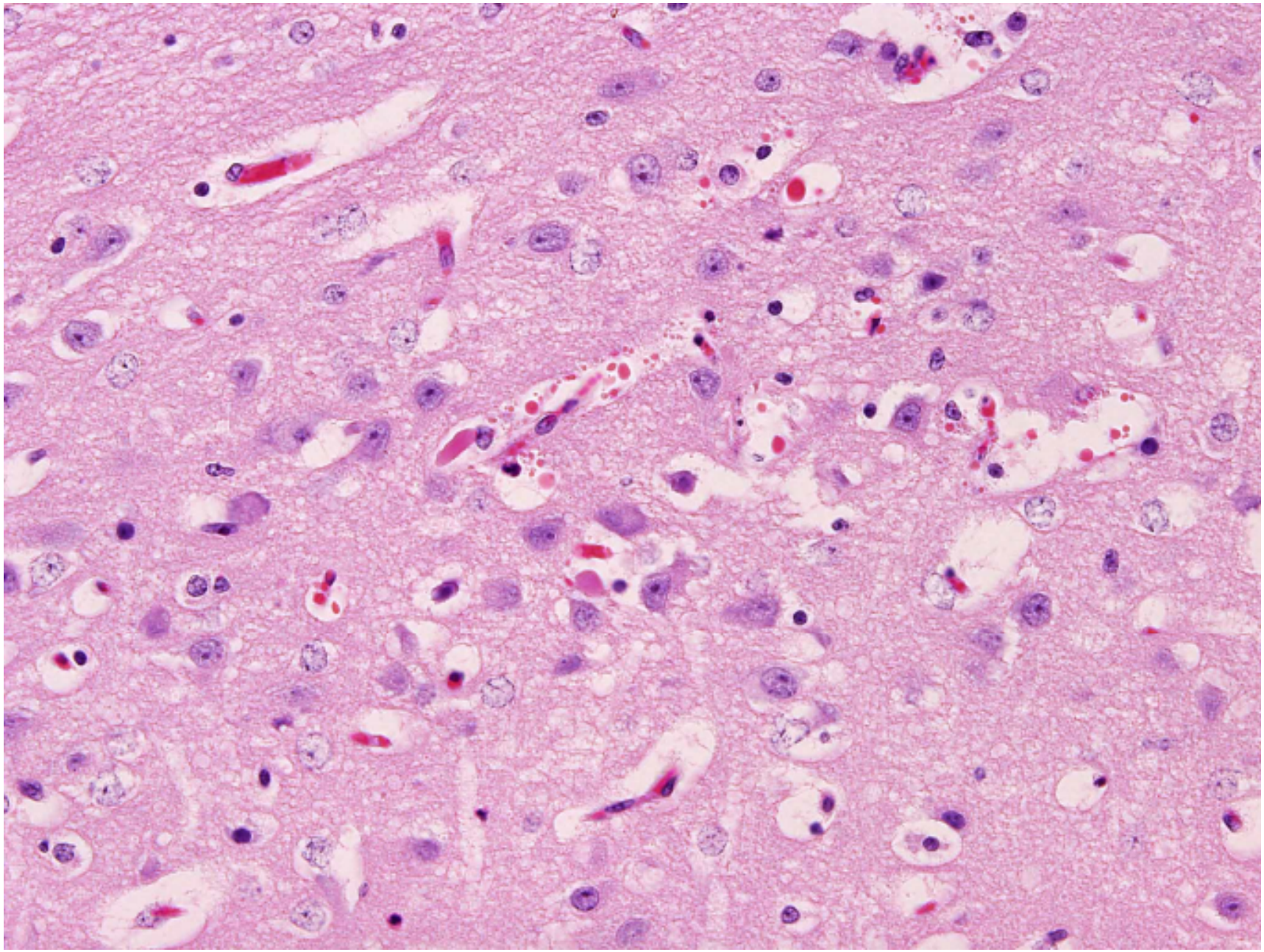
? Artefactual perivascular blebs , bovine, AQP4 IHC



Clostridium perfringens epsilon intoxication



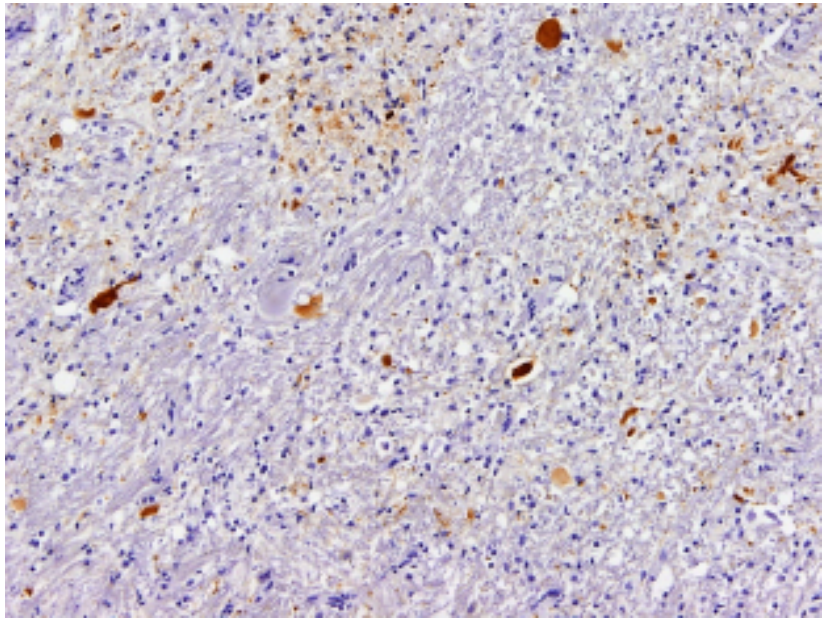
Clostridium perfringens epsilon intoxication

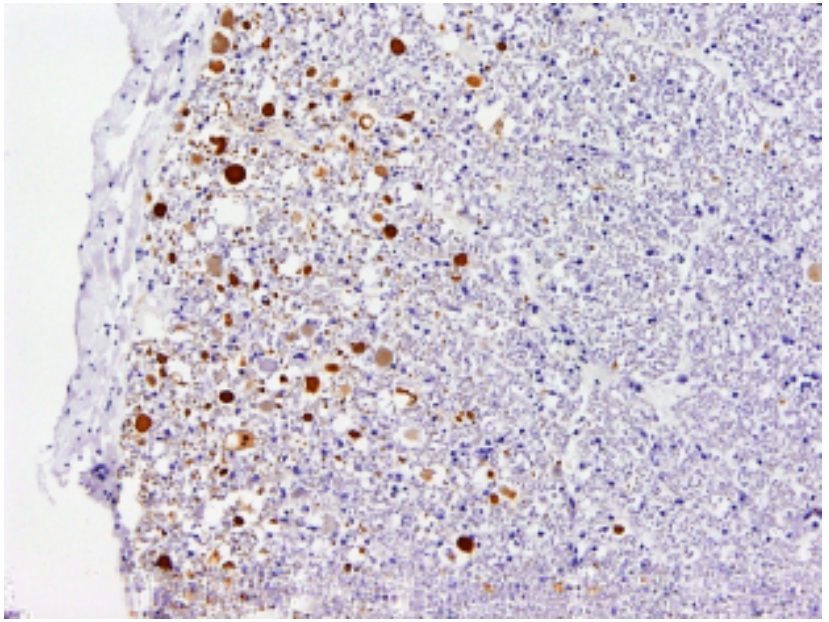


Clostridium perfringens epsilon intoxication

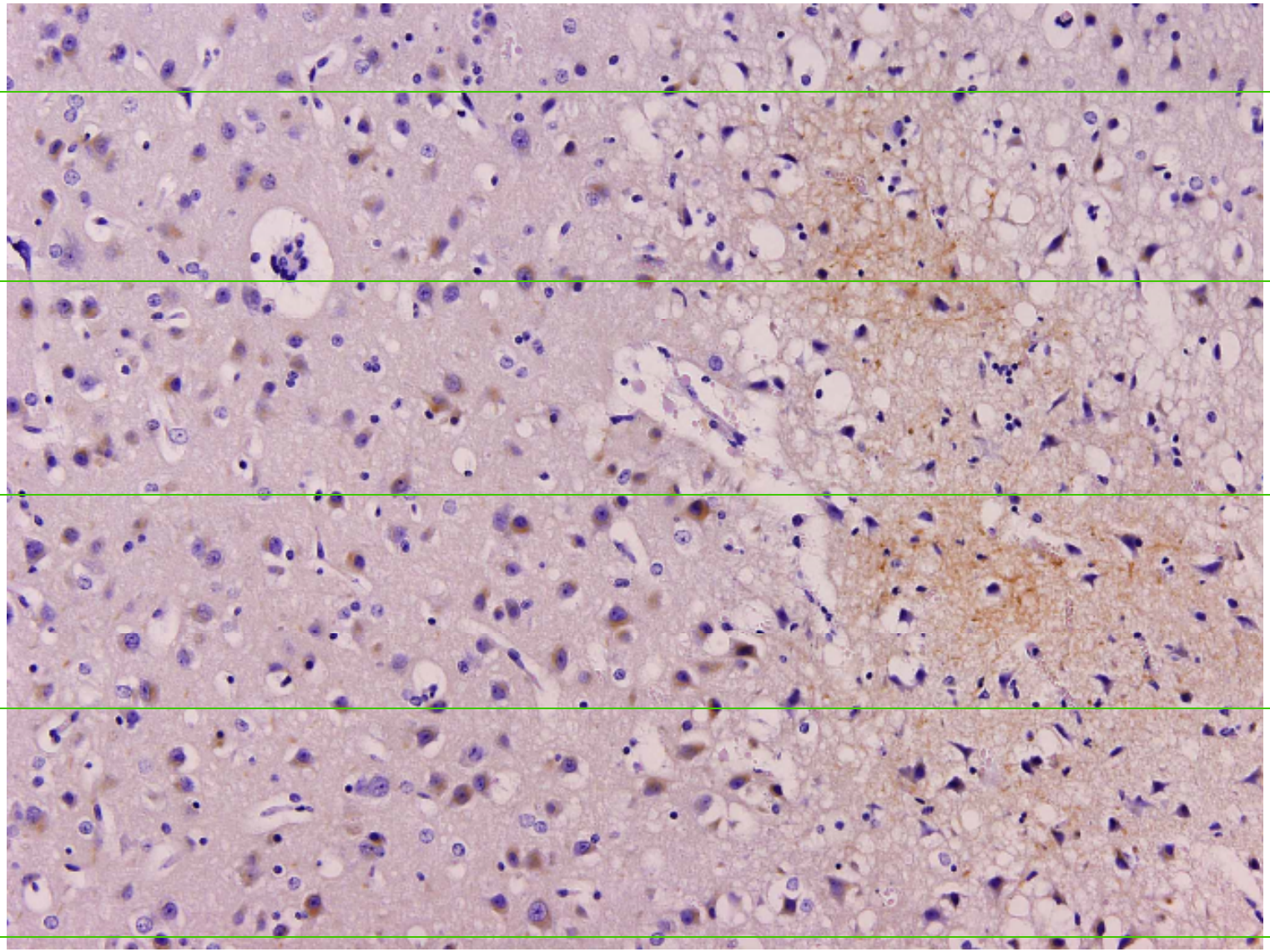
Amyloid precursor protein

- Precursor of amyloid-β (Alzheimer's disease)
- Cell adhesion (development)
- Fast axonal transport
- Synaptic transmission and plasticity
- Neuroprotective
- Increased expression detected @ 1 hr > injury in head impact model of early axonal injury in sheep (Lewis et al 1996)

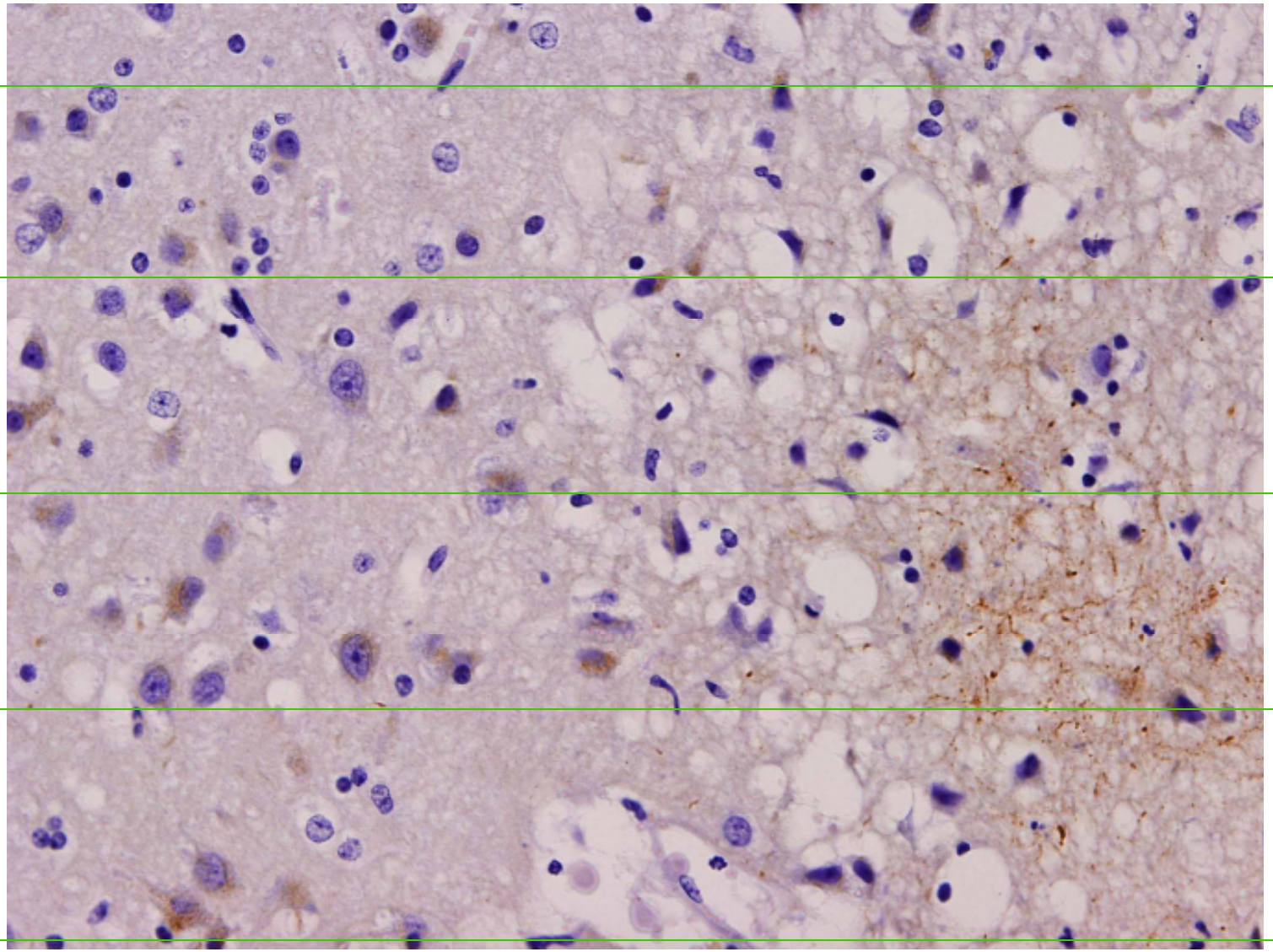




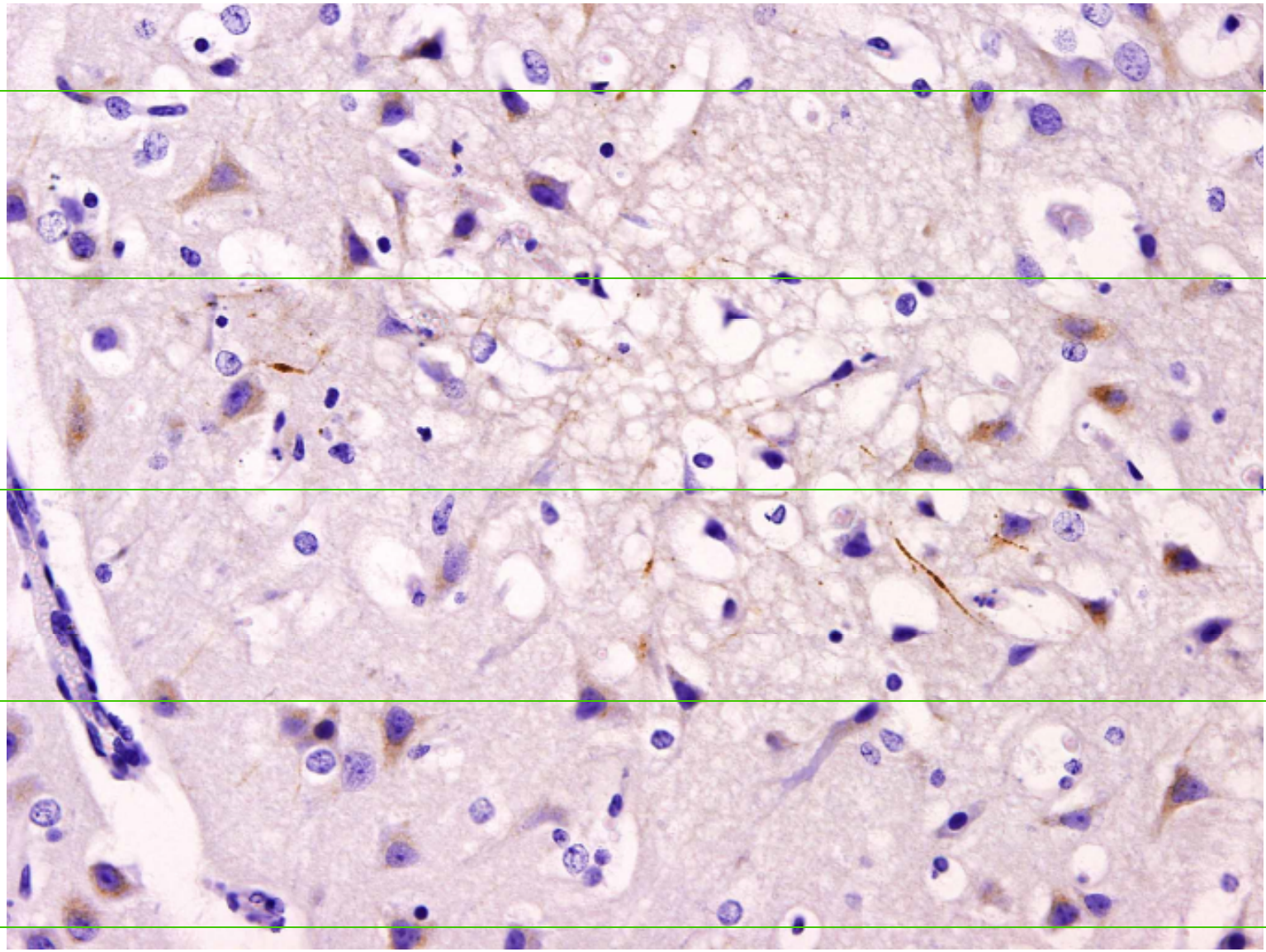
spinal cord C1 - ovine occipital condylar dysplasia



Clostridium perfringens epsilon intoxication; APP IHC



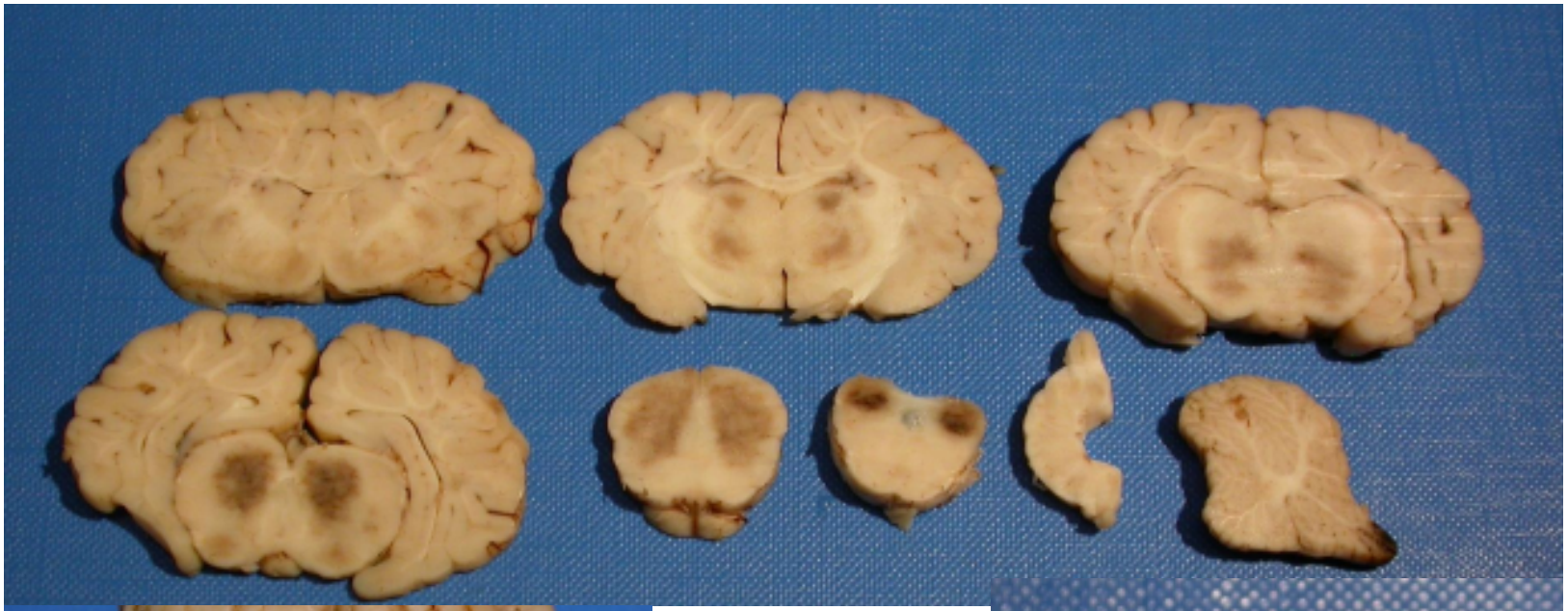
Clostridium perfringens epsilon intoxication; APP IHC

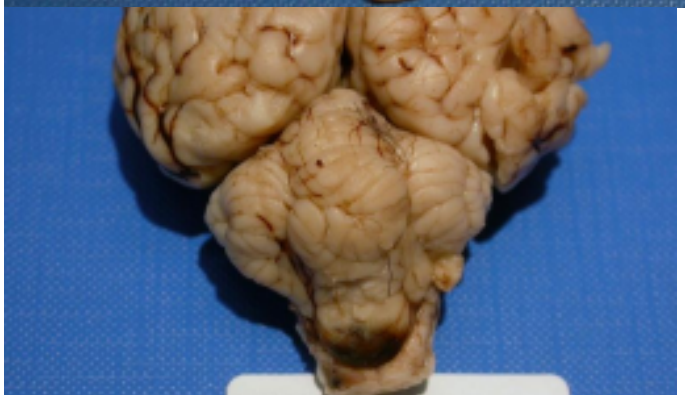


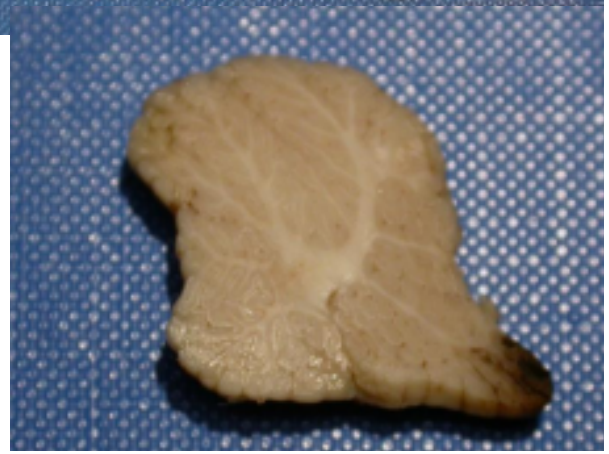
Clostridium perfringens epsilon intoxication; APP IHC

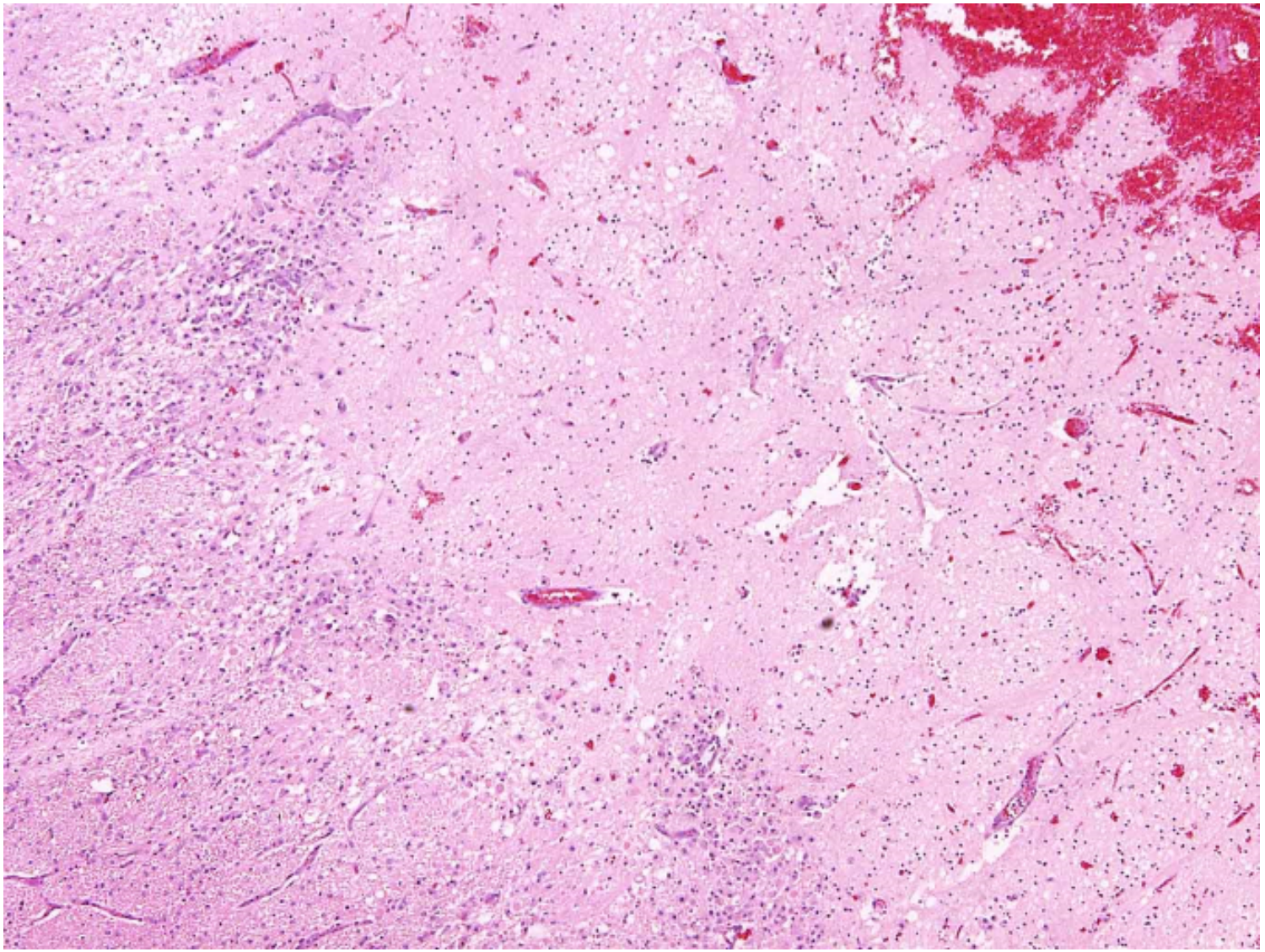
Type D enterotoxaemia in sheep

- 3rd most common cause of death in feedlot lambs despite availability of effective vaccine (Salmon *et al* 1988)

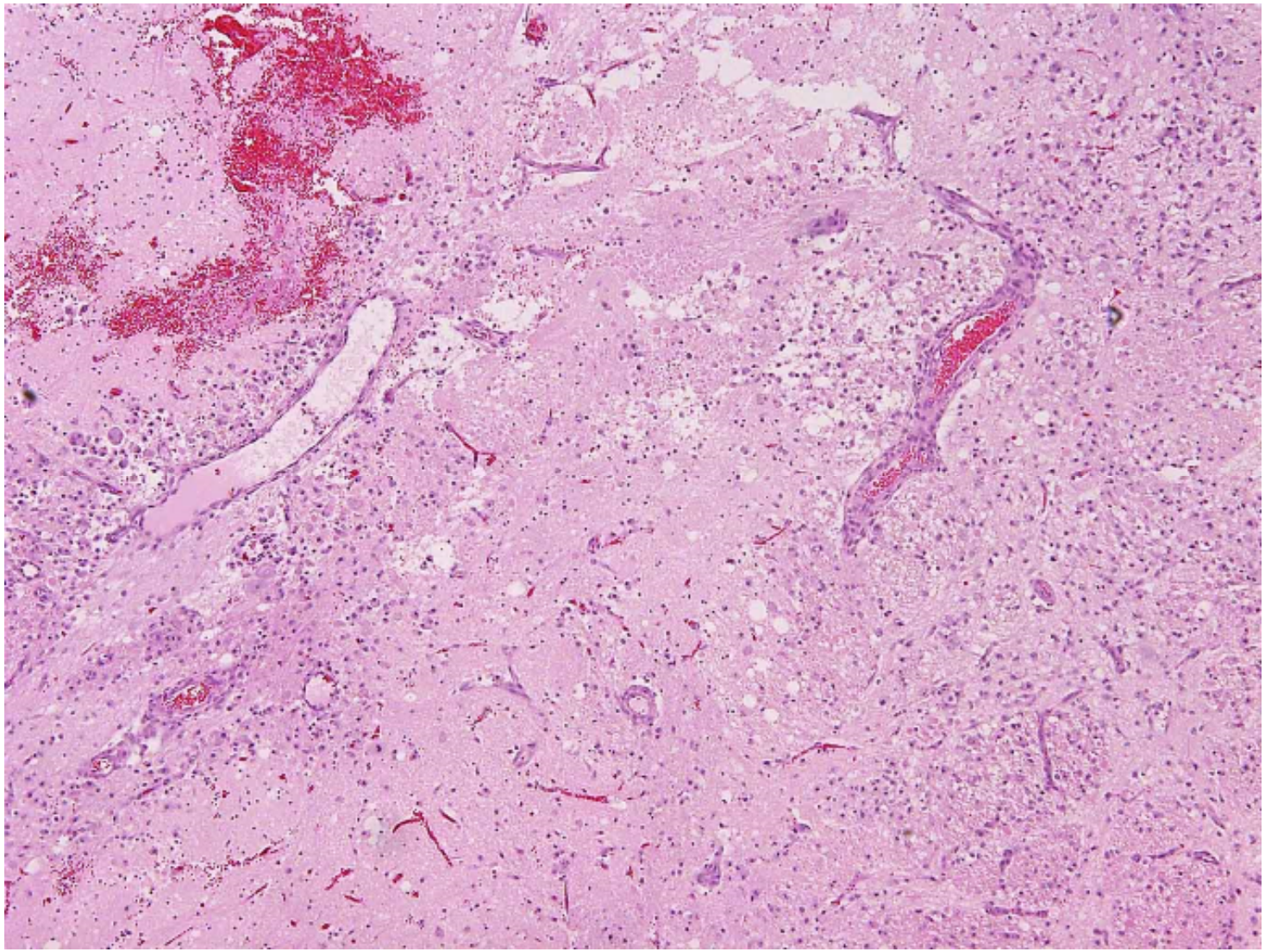




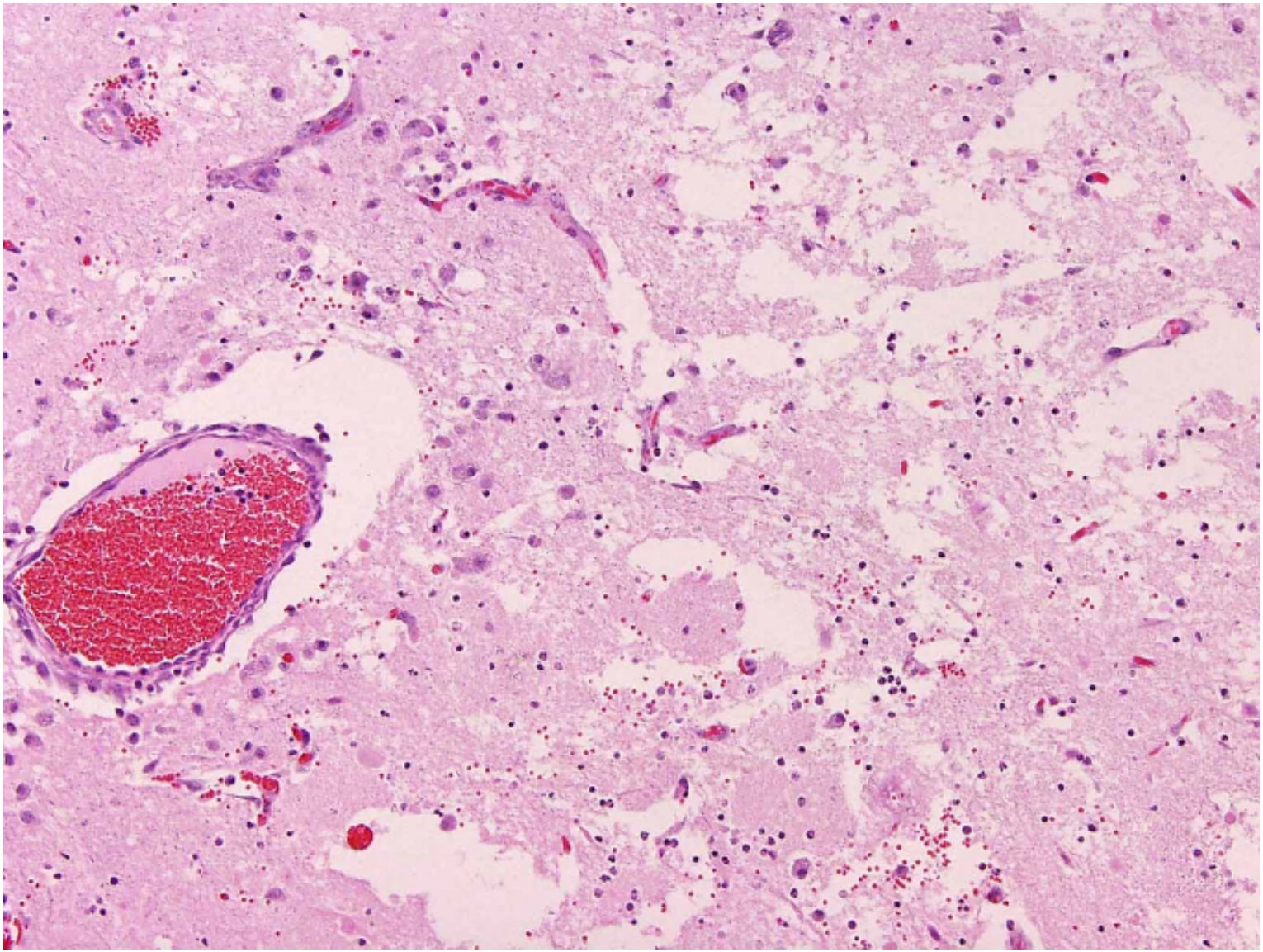




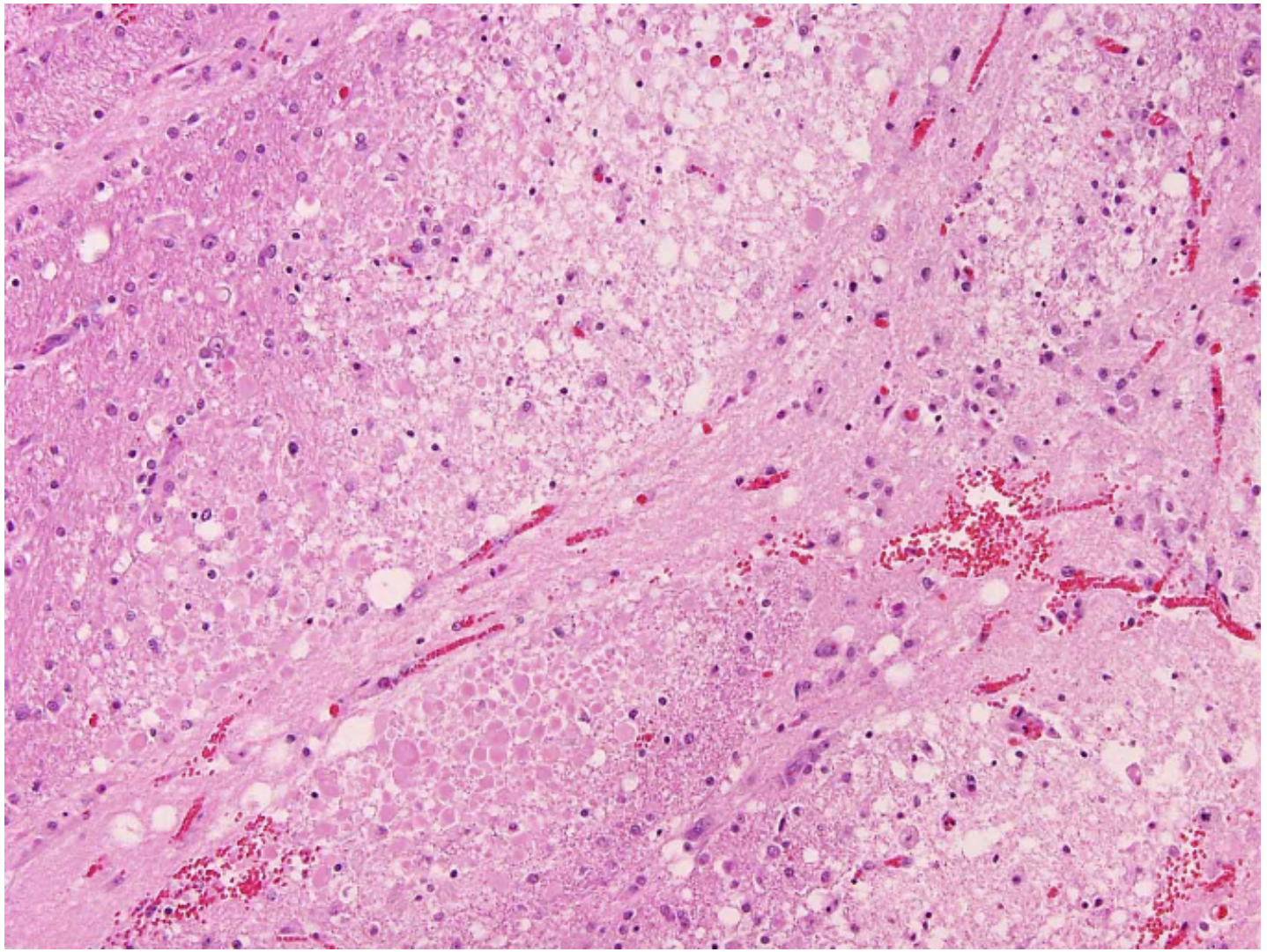
Cl perfringens epsilon intoxication, lamb, striatum



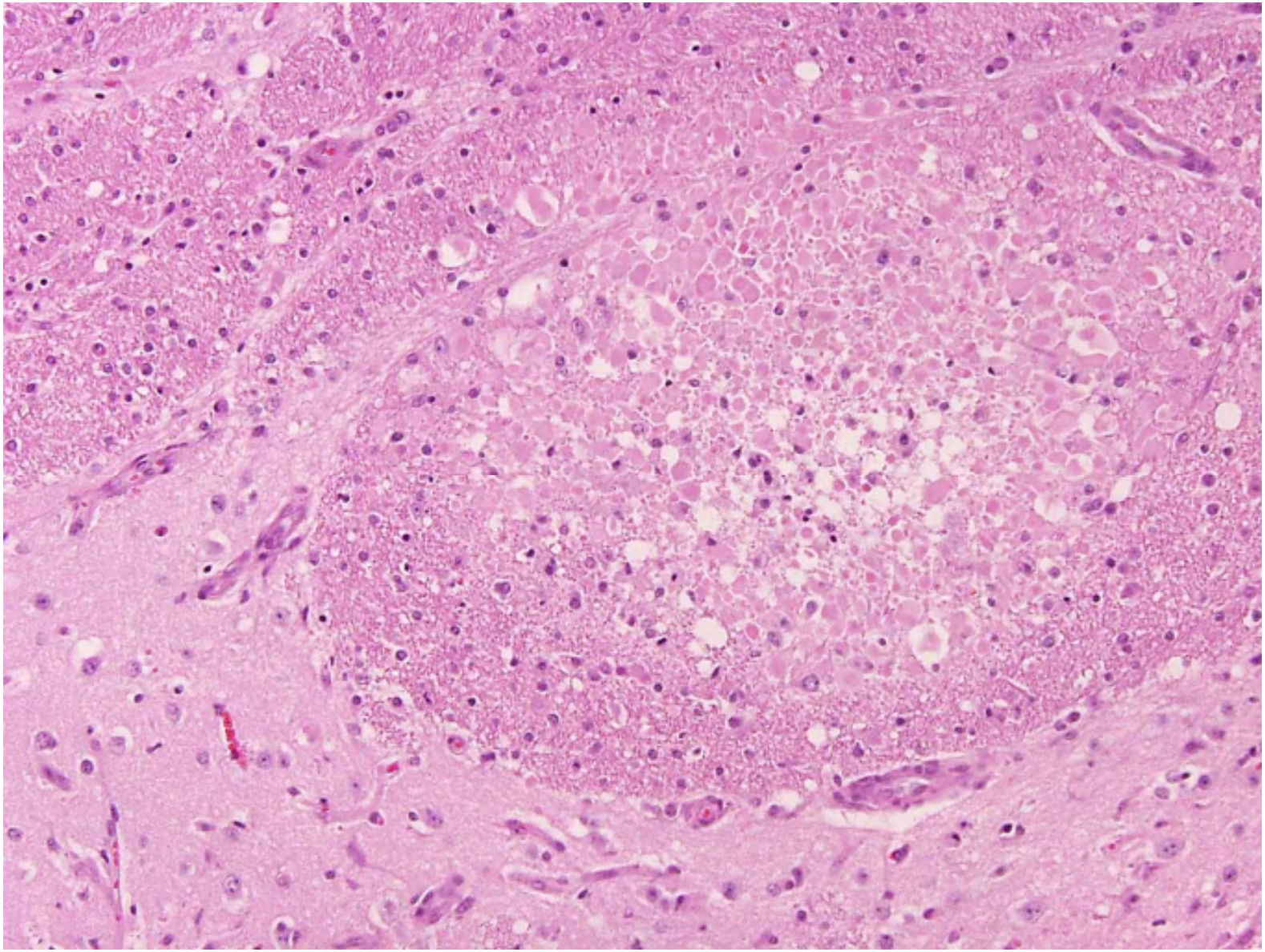
Cl perfringens epsilon intoxication, lamb, striatum



Cl perfringens epsilon intoxication, lamb, striatum



Cl perfringens epsilon intoxication, lamb, striatum



Cl perfringens epsilon intoxication, lamb, striatum

Clostridium perfringens type D enterotoxaemia : cattle : textbooks

- important disease of calves
  - most common between 1- 3 months
  - sudden deaths in feedlot cattle ? not due to Cl p type D – controlled trial found no protective effect of vaccination
  - rare in adults
- same risk factors as lambs - confined to calves that are overfed
- high milk intake or change to high starch diet – increased substrate / disruption of enteric microbial balance
- macroscopic lesions in calves dying of enterotoxaemia may resemble those in lambs
  - splenic swelling more common
  - rapid autolysis of kidney not prominent ; sometimes subcapsular renal blood clot

Clostridium perfringens type D enterotoxaemia: cattle : refereed publications (1)

Natural disease

- Seven presumptive cases recorded in cattle on basis of histopathological findings (no testing for epsilon toxin)
  - 6 weeks (Munday *et al*, 1976)
  - 4 weeks, 5 months, 18 months (Buxton *et al*, 1981)
  - 3 months, 2 adult dairy cows (Fairley, 2005)
- no macroscopic abnormalities recorded
- Fairley 2005 – detailed histopath - perivascular hyaline protein droplets present
- no risk factors identified

Clostridium perfringens type D enterotoxaemia: cattle : refereed publications (2)

Experimental epsilon intoxication

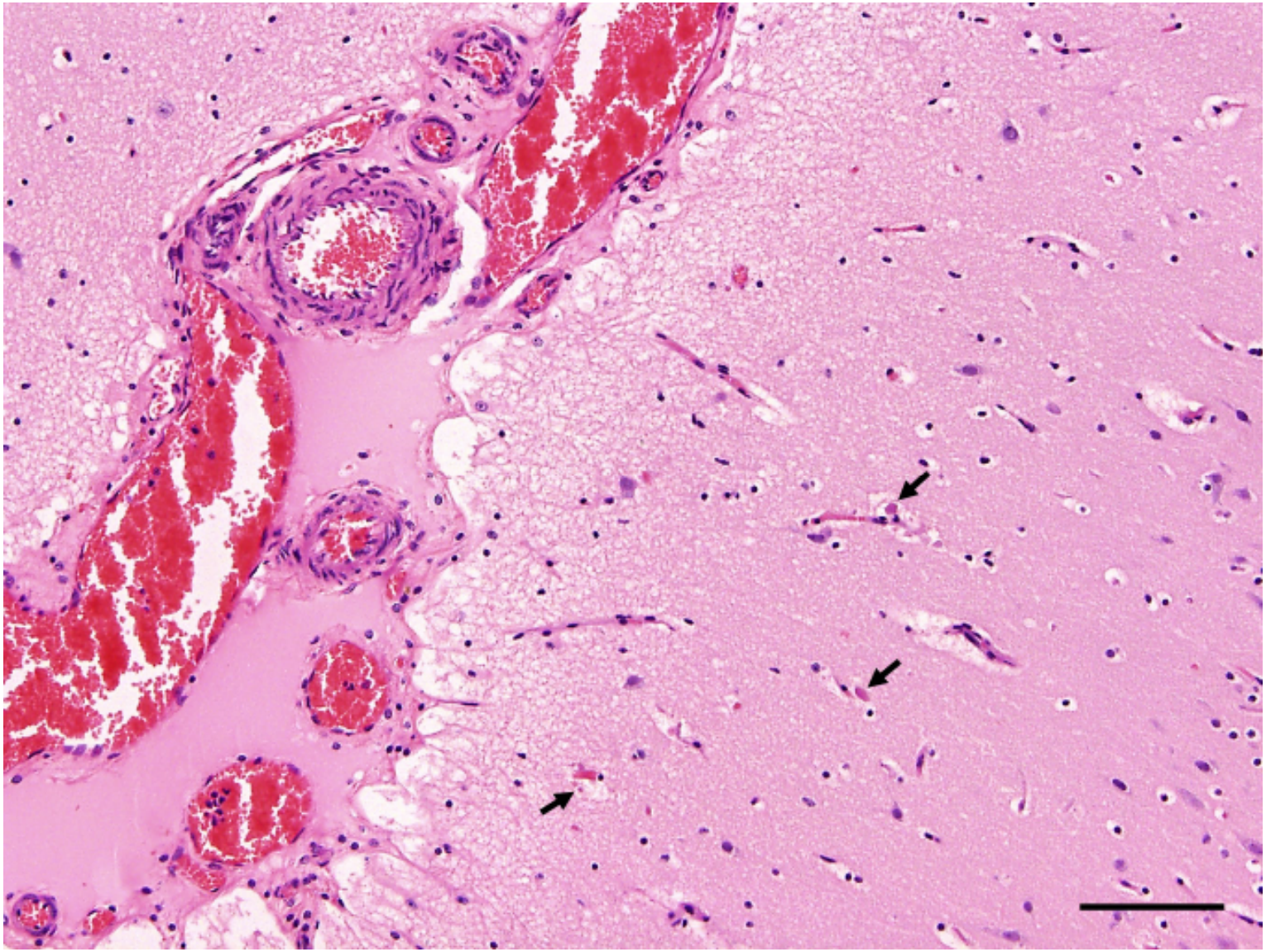
- 3 x 6-month-old calves
- jugular infusion of epsilon toxin (120 mouse LD50/kg Bwt)
- hyperaesthesia, dyspnoea, intermittent tonic clonic convulsions all 3 calves, onset between 2 and 60 minutes after end of administration
- killed when lost consciousness, between 70 and 110 minutes after onset of clinical signs
- PME – severe pulmonary oedema with copious persistent foam and distension of interlobular septa
- histology - perivascular proteinaceous oedema

Cerebral vasculopathy in neonatal calves (1)

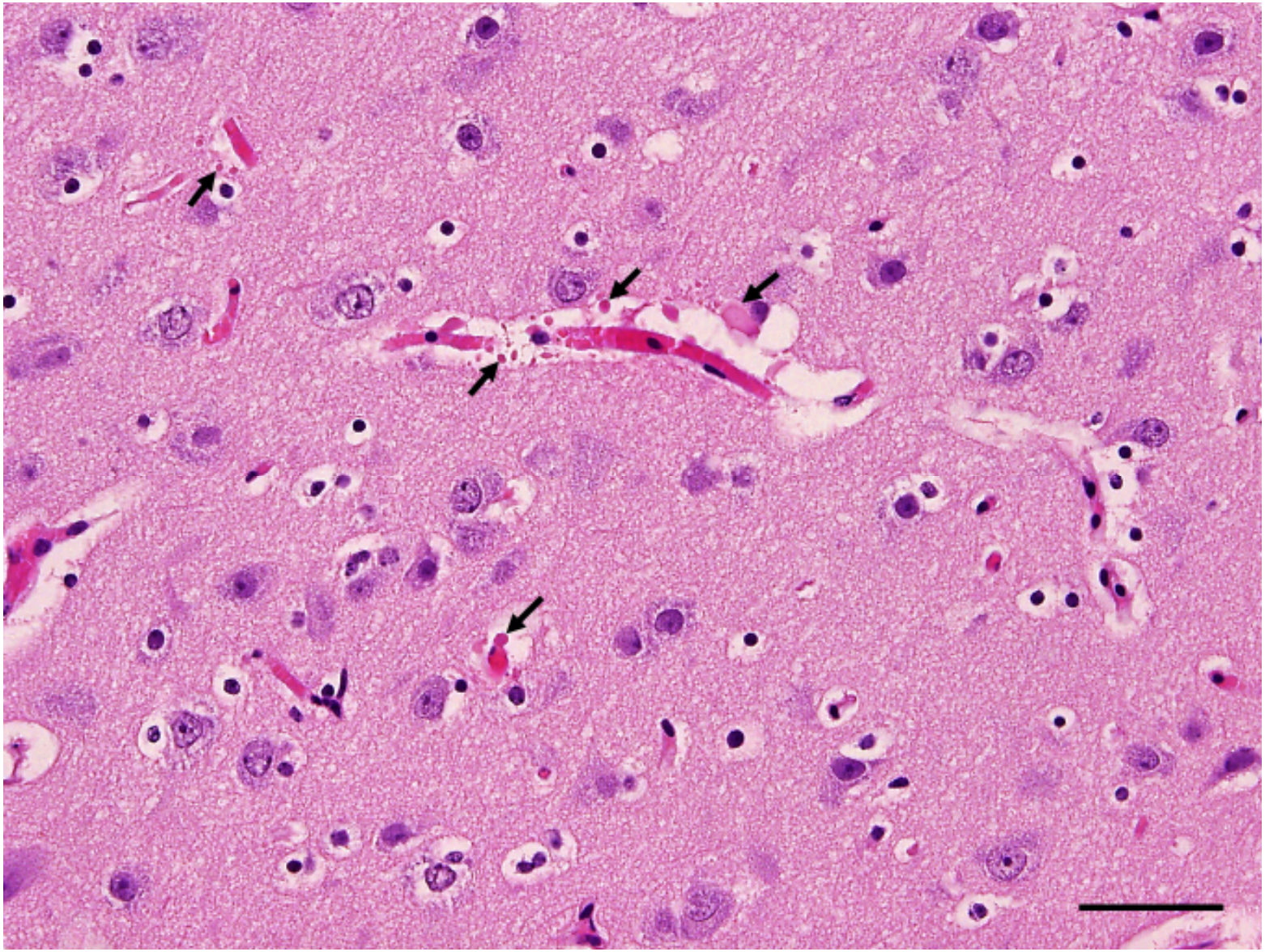
- Mixed 25 cow beef suckler and hill sheep farm in Cumbria
- Cows housed in traditional stone buildings in winter
- Case 1 – 5th calving born B&A early morning
- Discovered 'flat out' later same day and died at 21.30
- PME – pulmonary oedema
- Lab tests
  - Pb neg
  - NSO
  - Histo – cerebral vasculopathy with perivascular hyaline protein droplet formation; extensive exfoliation of collecting duct epithelium; pulmonary oedema

Cerebral vasculopathy in neonatal calves (2)

- Case 2 – 6th calving born 7 days after case 1
- Similar history to calf 1 - uneventful birth, lively and sucked soon afterwards
- Following day became dull, deteriorated rapidly with terminal neurological signs
- PME – slight lung congestion
- Lab tests
  - Cl perfringens alpha and epsilon toxins but not beta toxin detected by ELISA in LI content
  - NSO
  - Histo – cerebral vasculopathy ; pulmonary oedema



Calf 2 cerebrum; bar = 100 μm

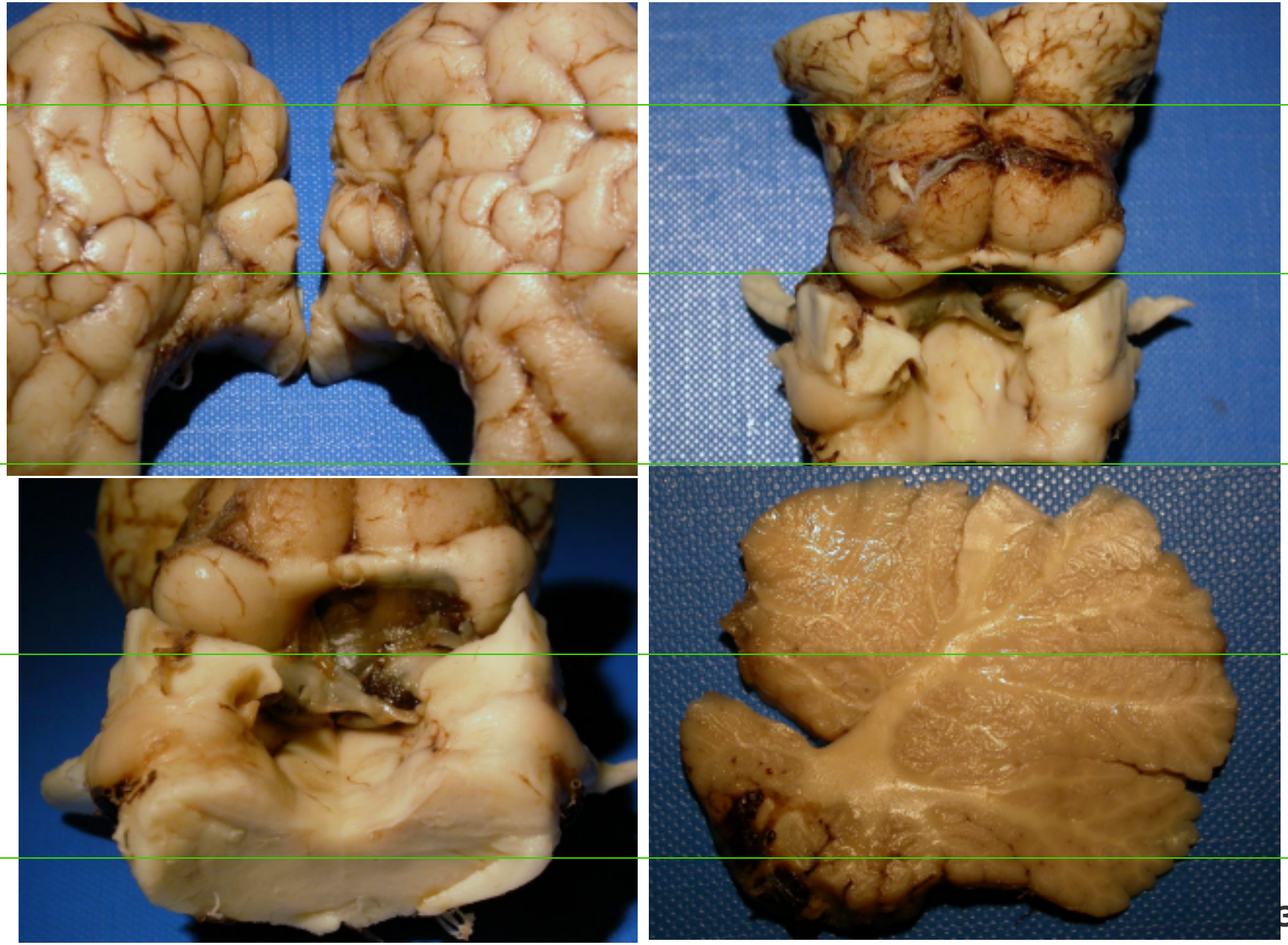


Calf 2 cerebrum; bar= 50 µm

Cerebral vasculopathy in neonatal calves (3)

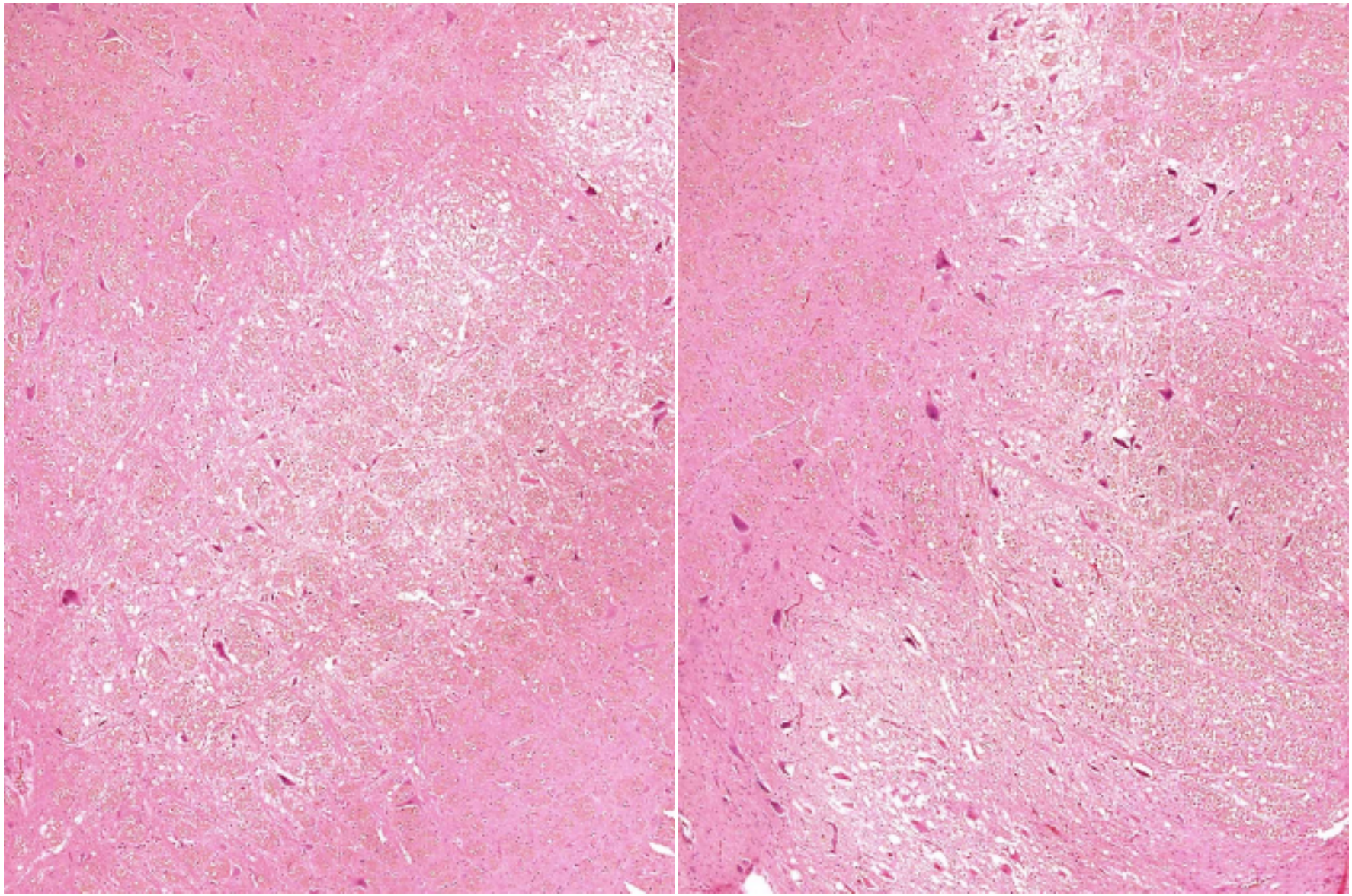
- Host risk factors appear unremarkable
- Potential environmental factor
  - Prior to cattle being housed in shed, was used to house lambs on intensive finishing diet
  - Only occasion this done on farm
  - Lambs vaccinated and no disease reported in that group
  - ? High enviromental contamination
- Cl perfringens routinely colonises GI tract of calves and lambs within 24 hours of birth (Smith & Crabb, 1961; Smith 1965)

Presumptive Cl perfringens epsilon intoxication, adult bovine

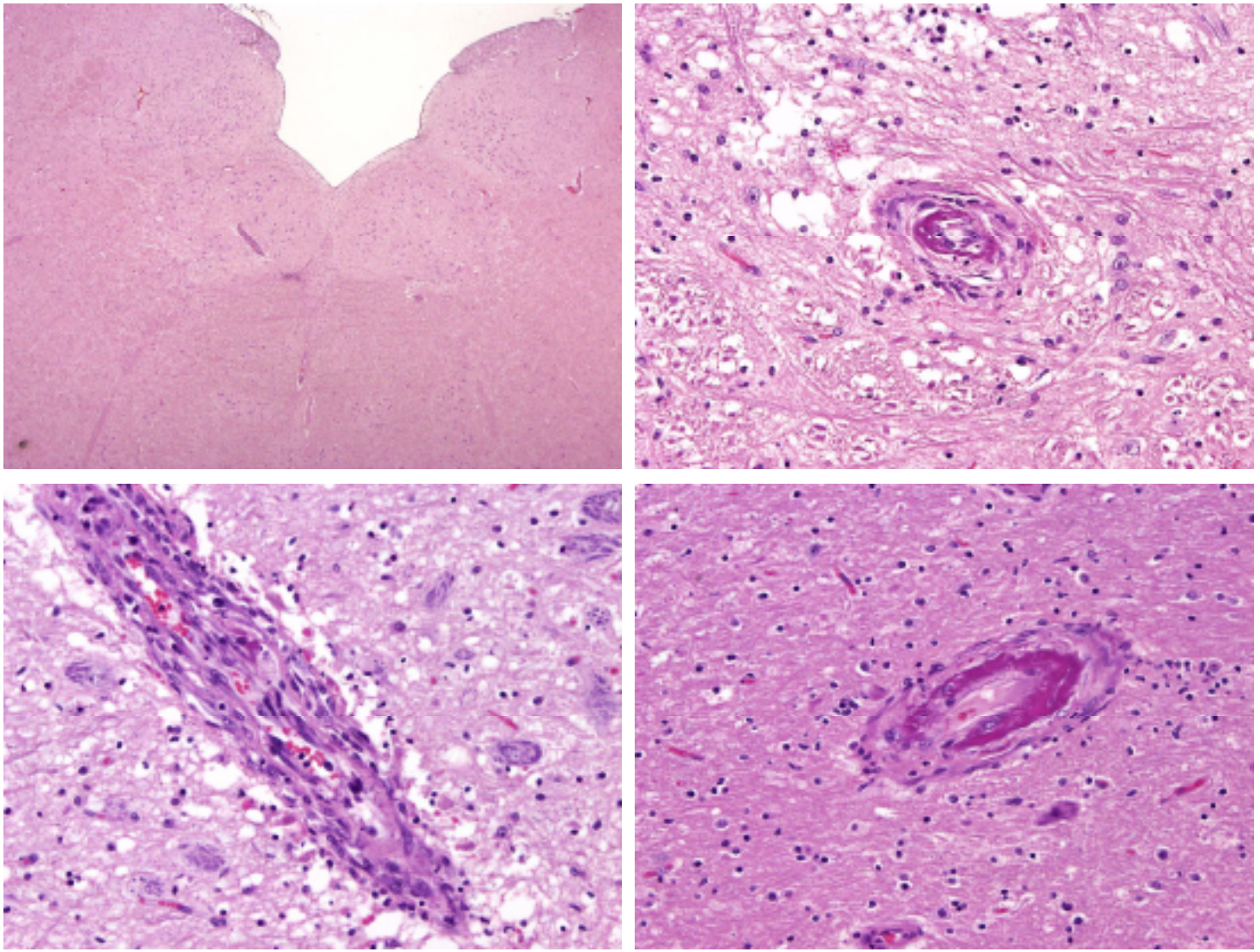


Presumptive Cl perfringens epsilon intoxication, adult bovine

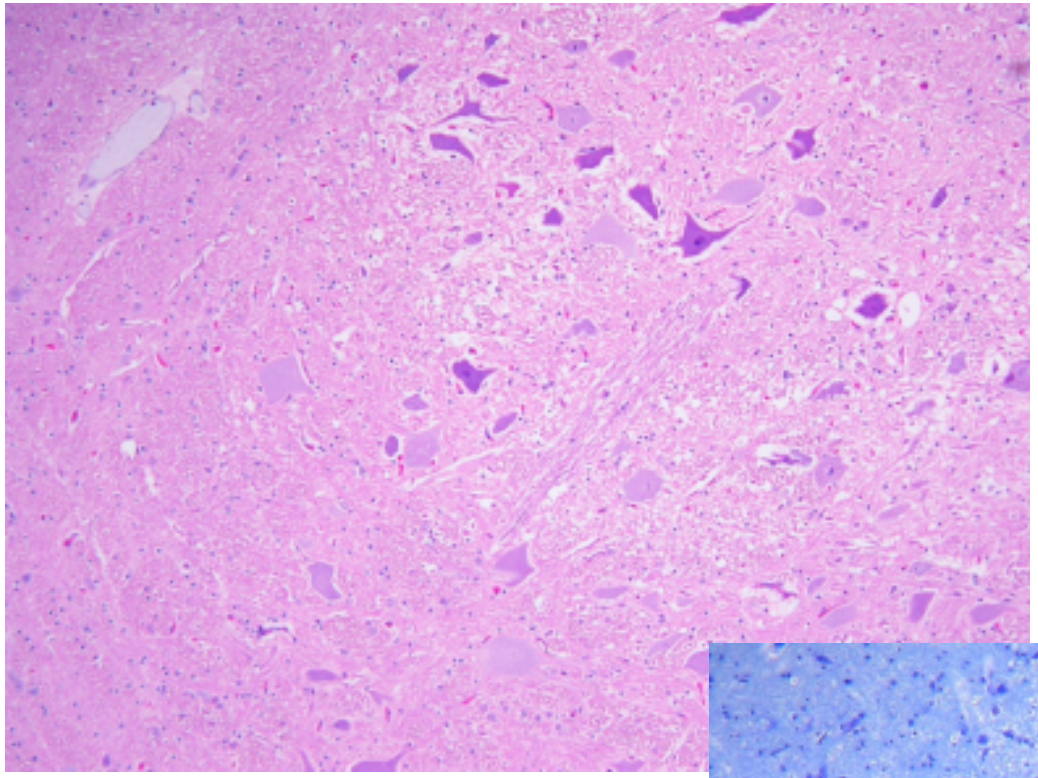
Oedema disease

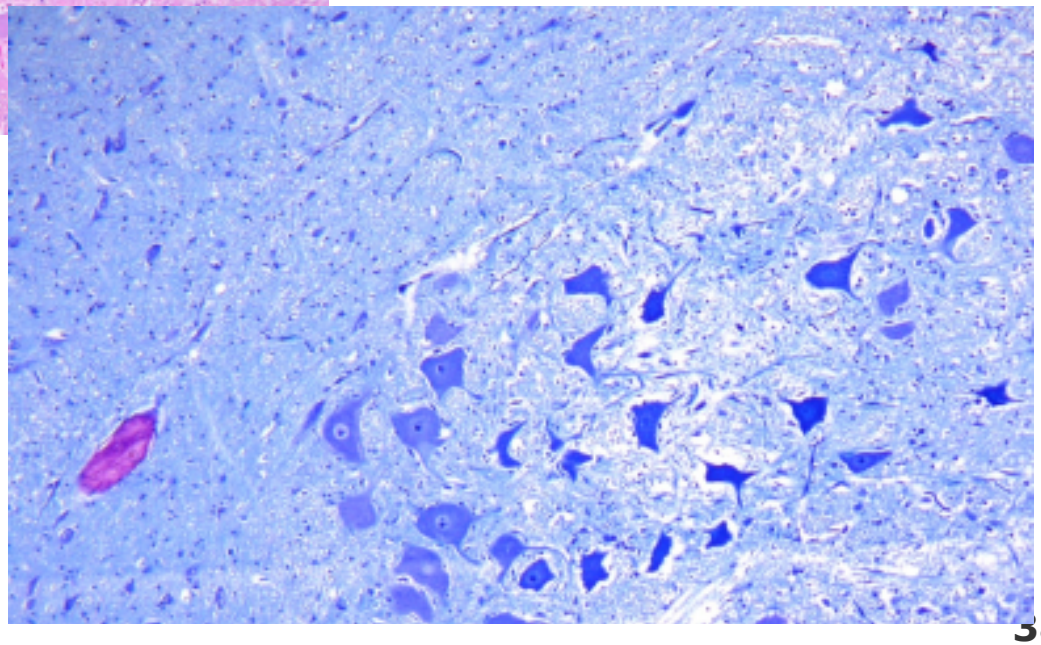


- Oedema disease

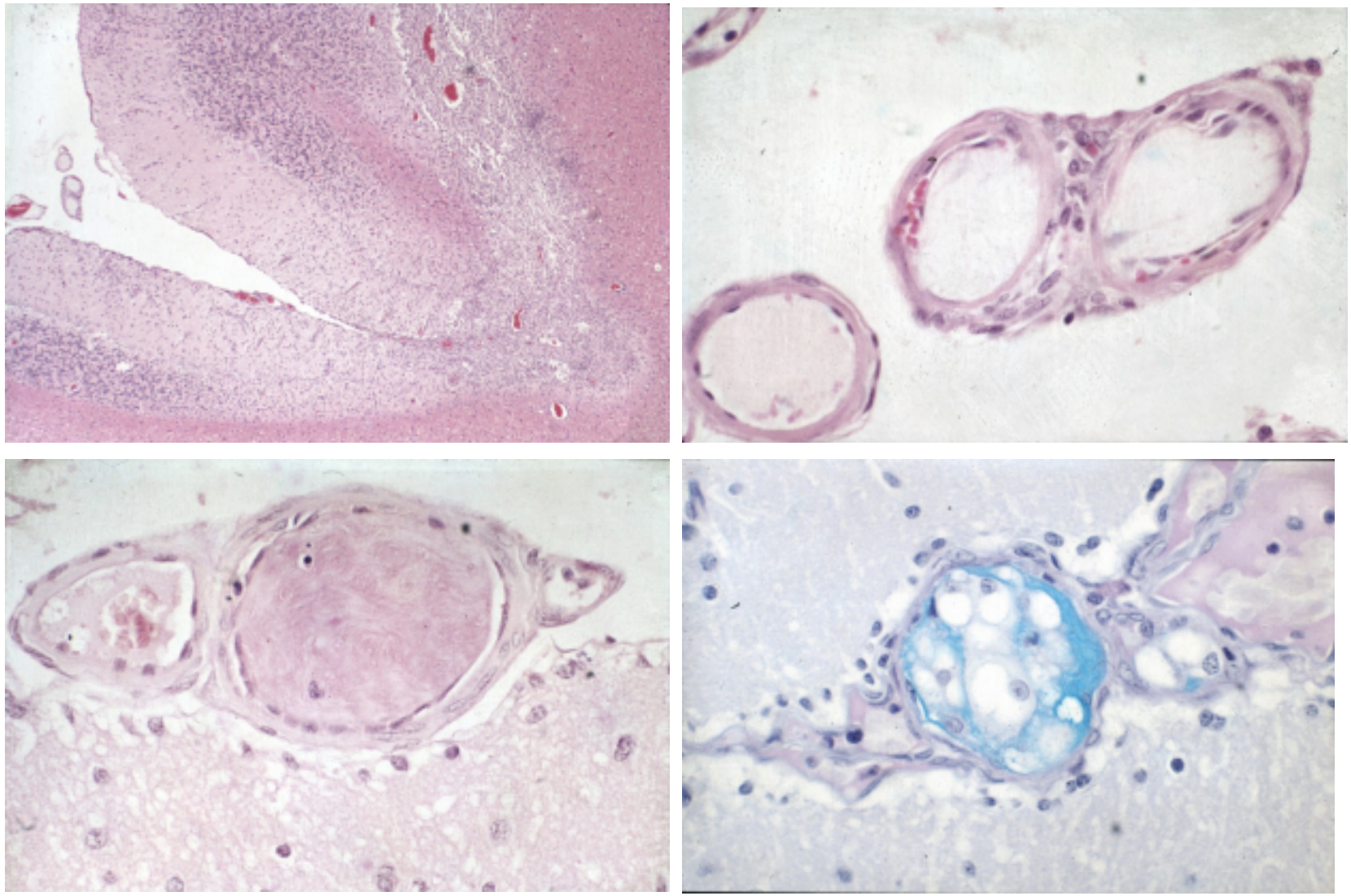


Oedema disease

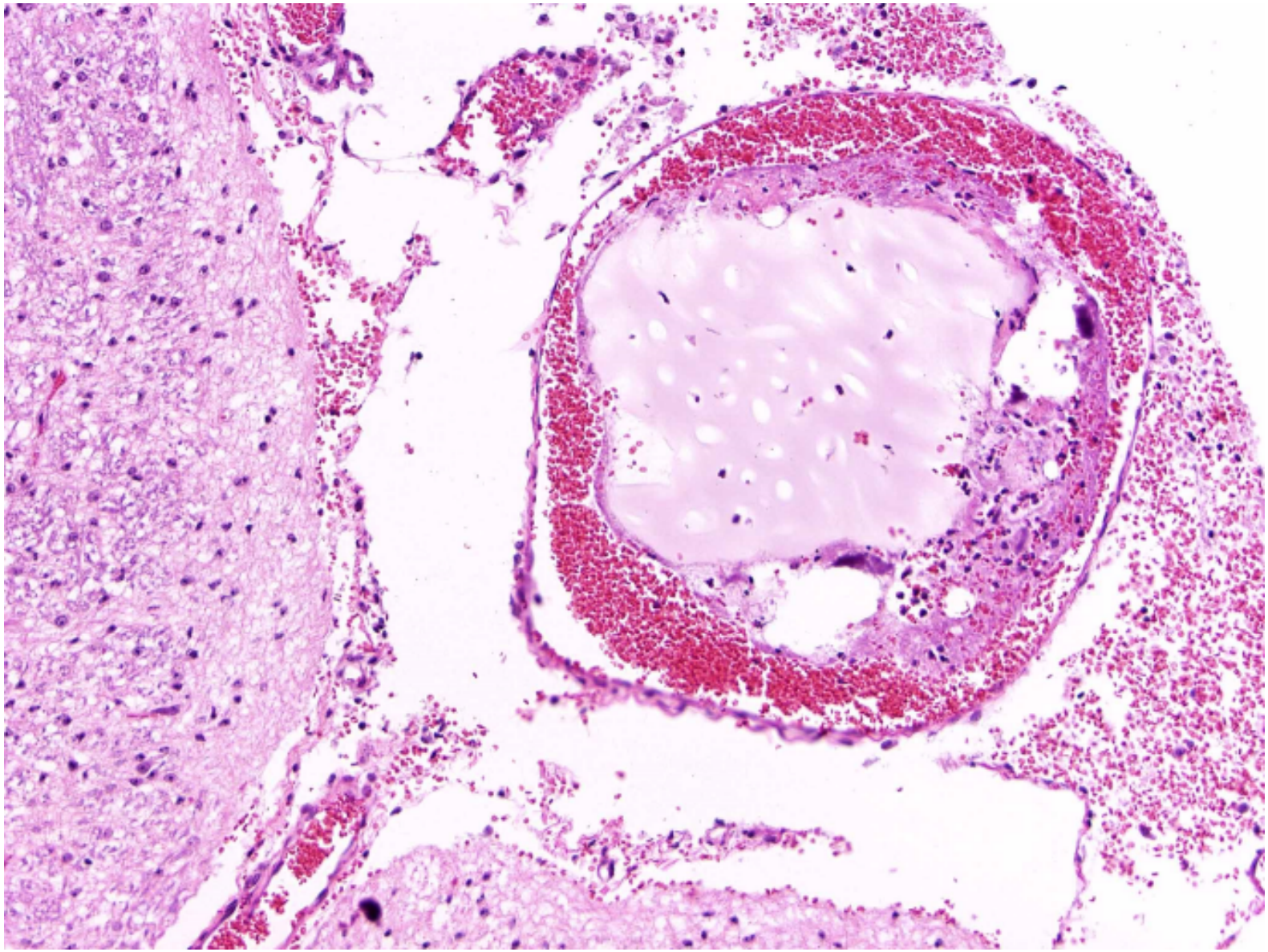




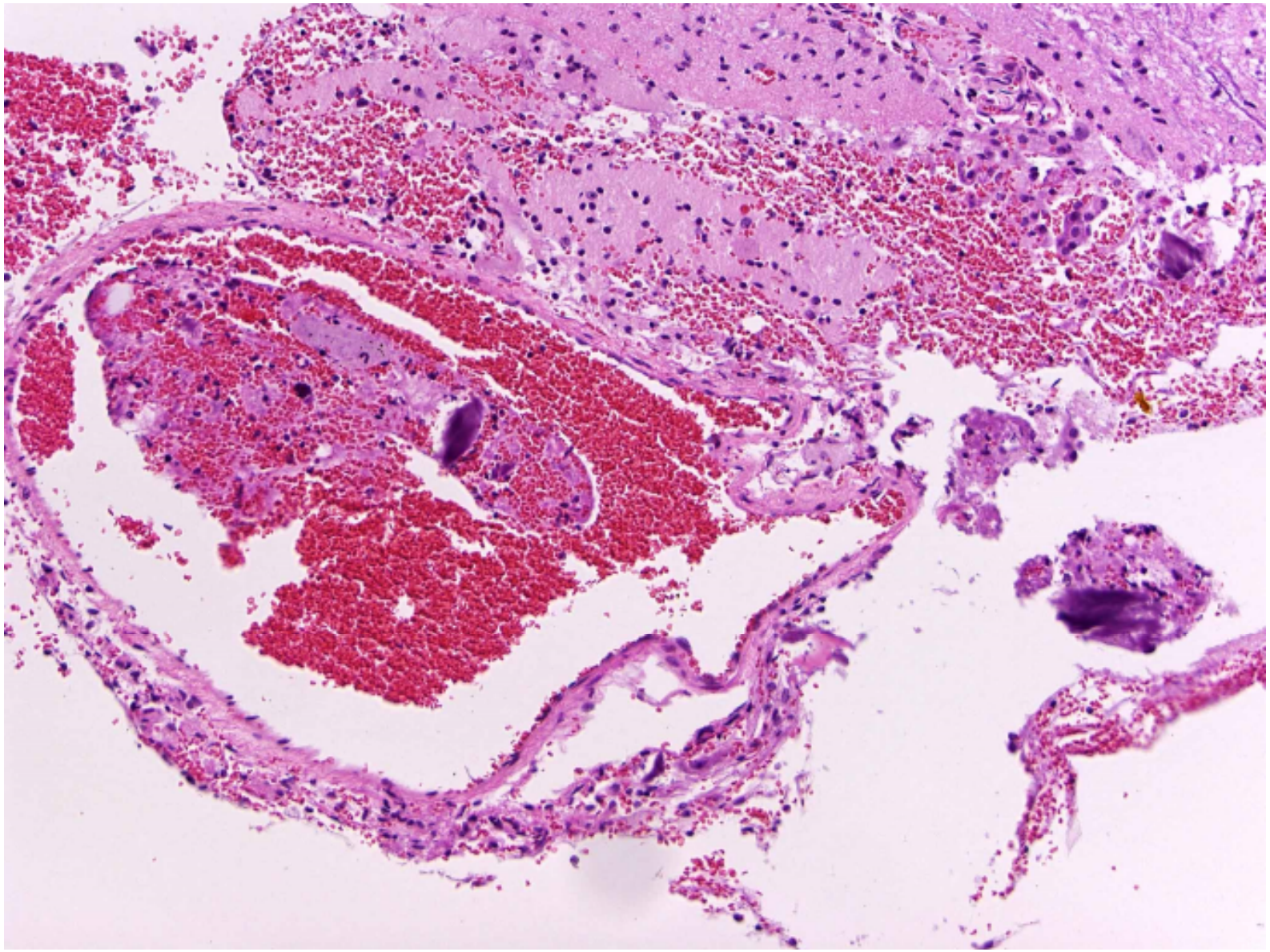
Acute grey matter infarct
Fibrocartilaginous embolism , porcine



Grey / white matter infarction, fibrocartilaginous embolism, porcine cerebellum



Caution

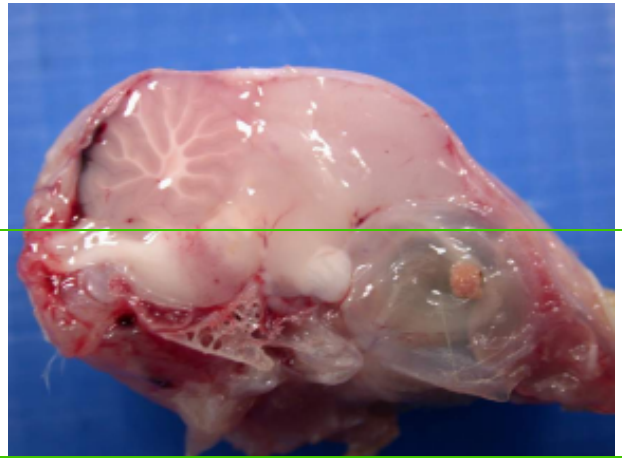


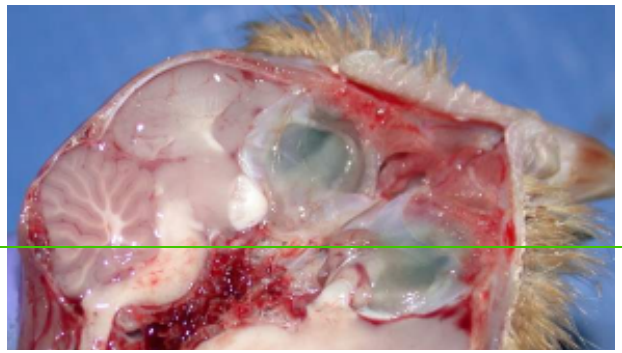
Caution

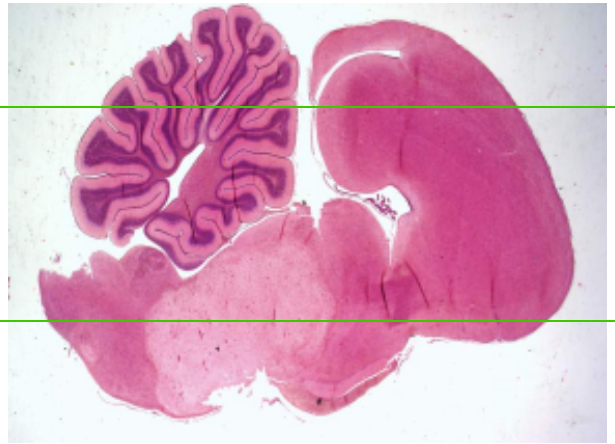
Enterococcus associated encephalomalacia

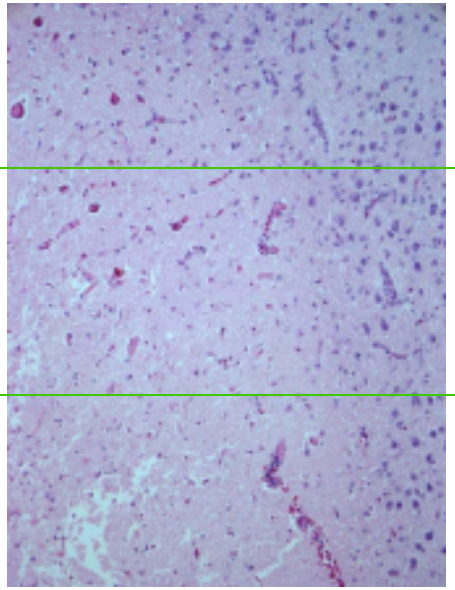
- Broiler / layer chicks
- Days 3 – 8
- Seldom > 1%
- Focal symmetrical encephalomalacia
- Cerebellum spared

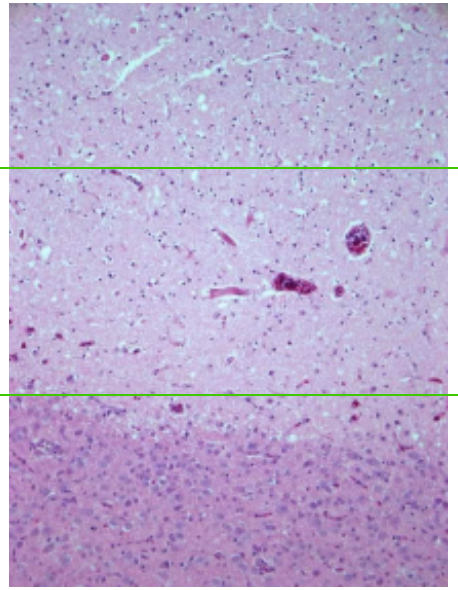
- Enteroccus hirae isolated from viscera, brain?

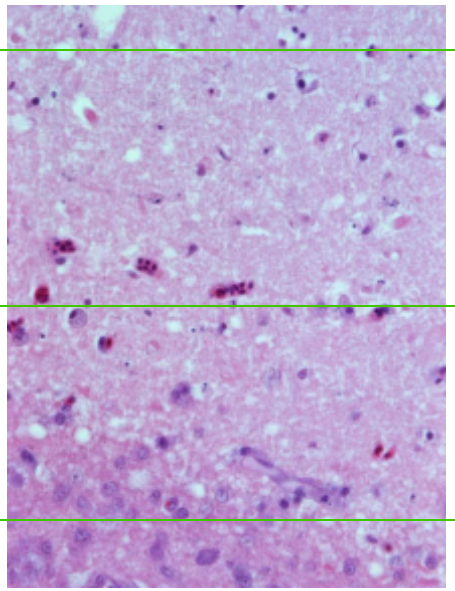


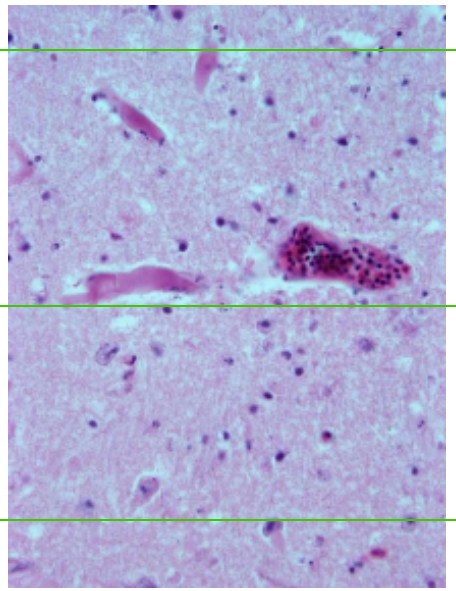








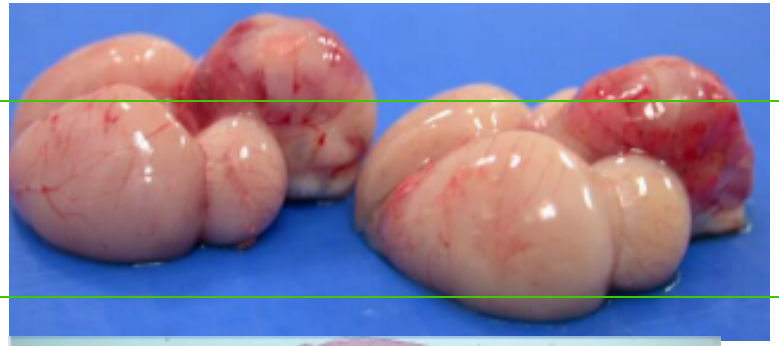


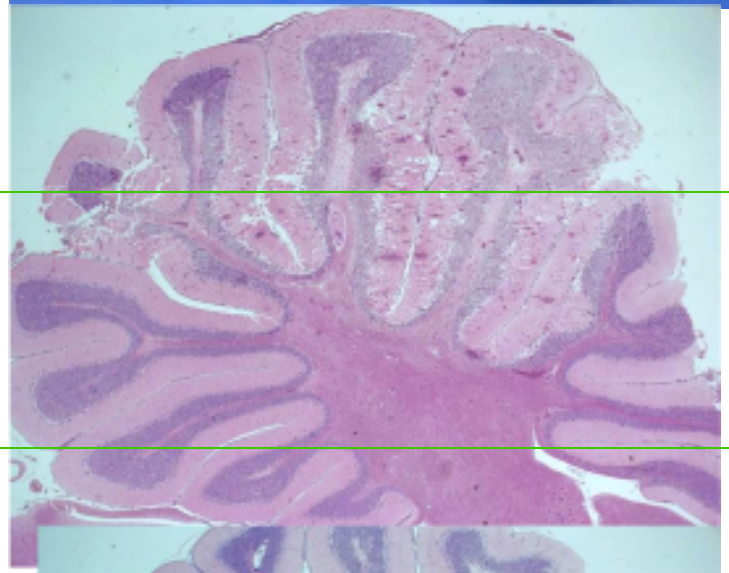


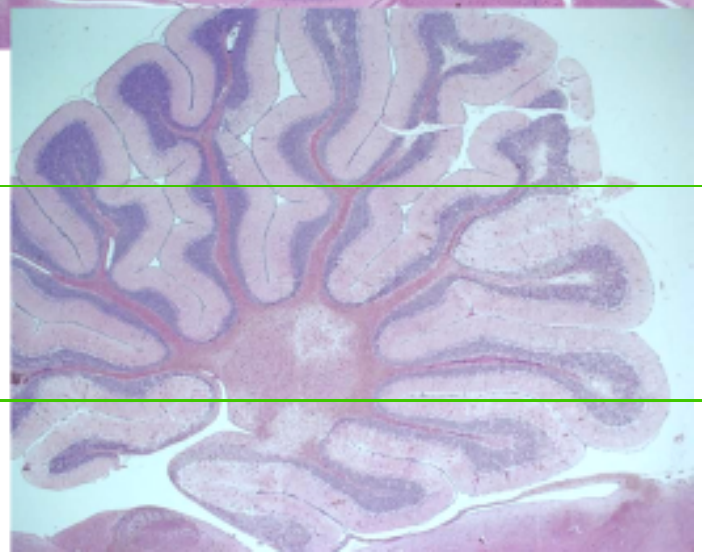
Images courtesy A Wood

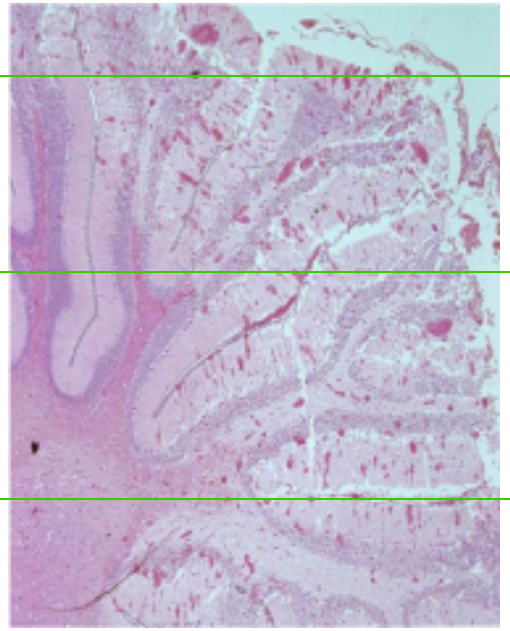
Nutritional encephalomalacia (vitamin E deficiency)

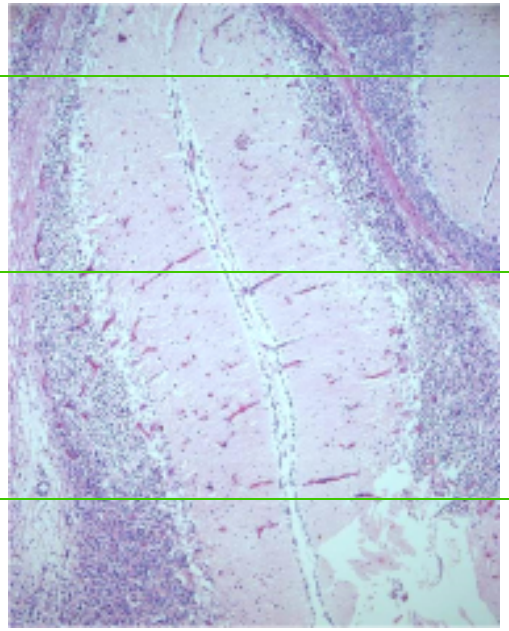
- Chickens, turkeys (ducks, gamebirds?)
- ~ 15 – 30 days (up to 50 days)
- Old or improperly stored foodstuff, rancid fat
- Confined without alternative food source
- Peroxidative injury – thrombosis, haemorrhage and ischaemic necrosis

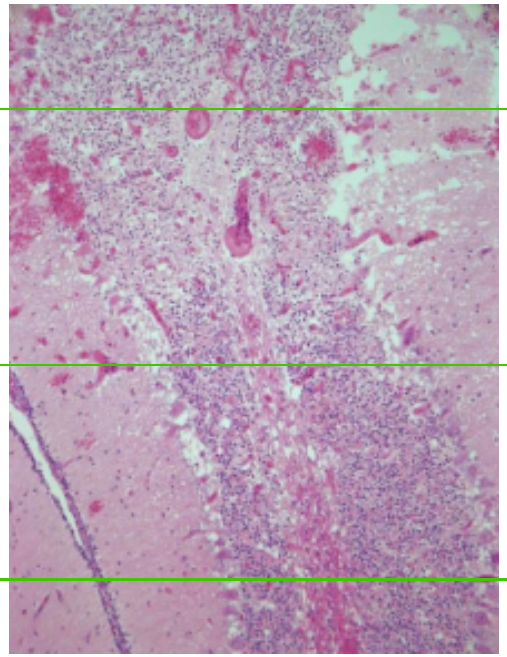


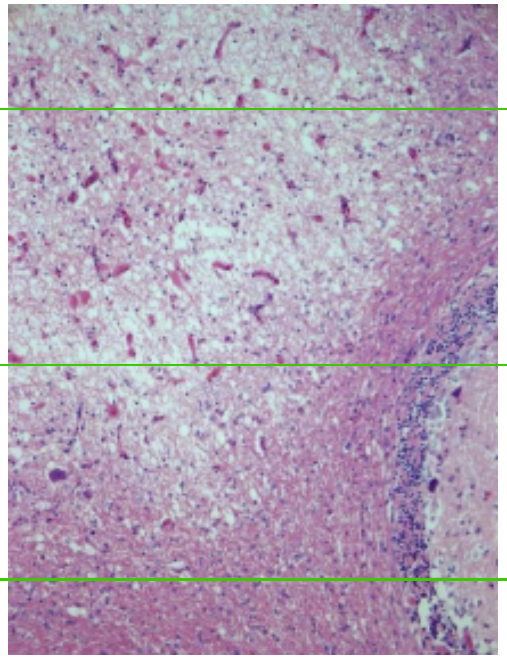










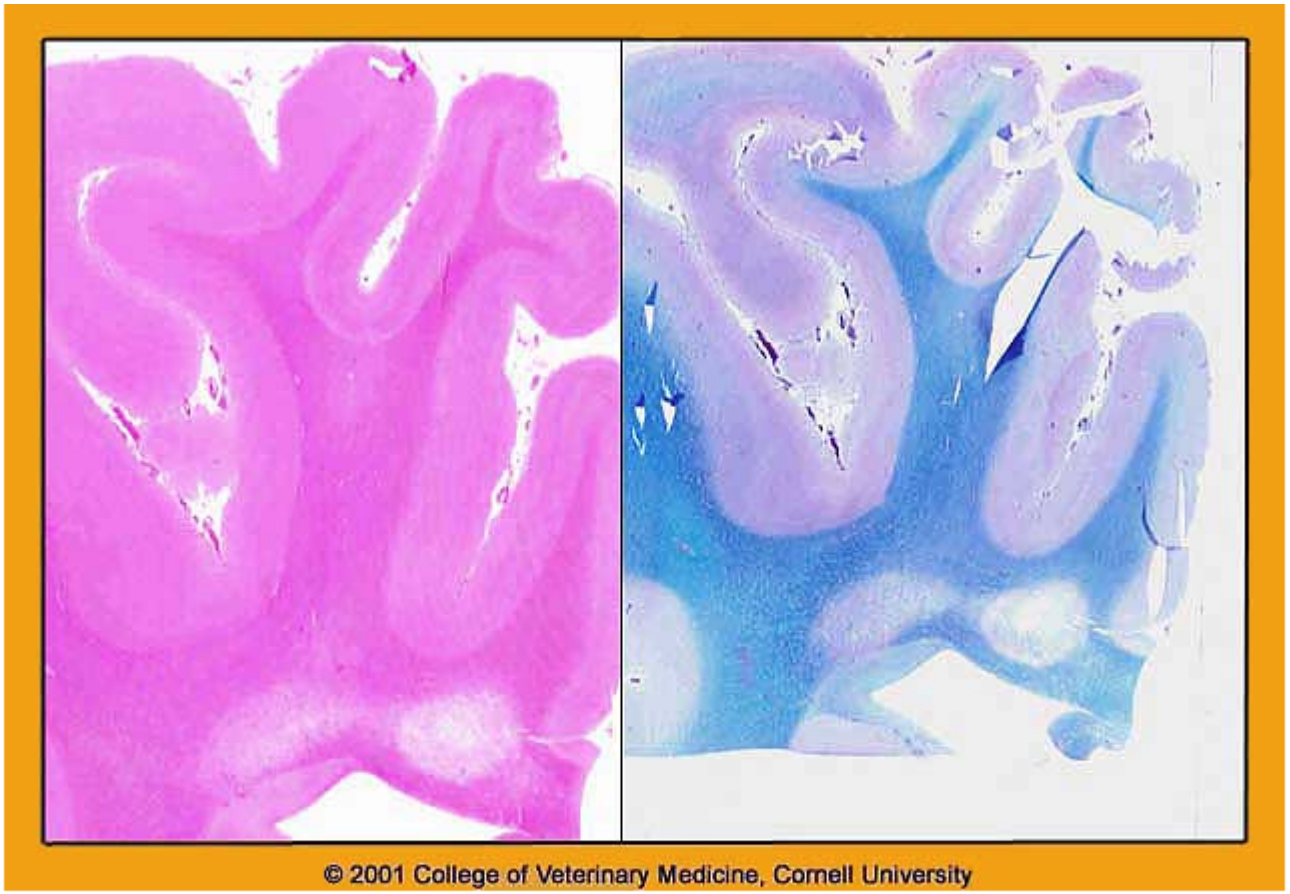


Images courtesy A Wood

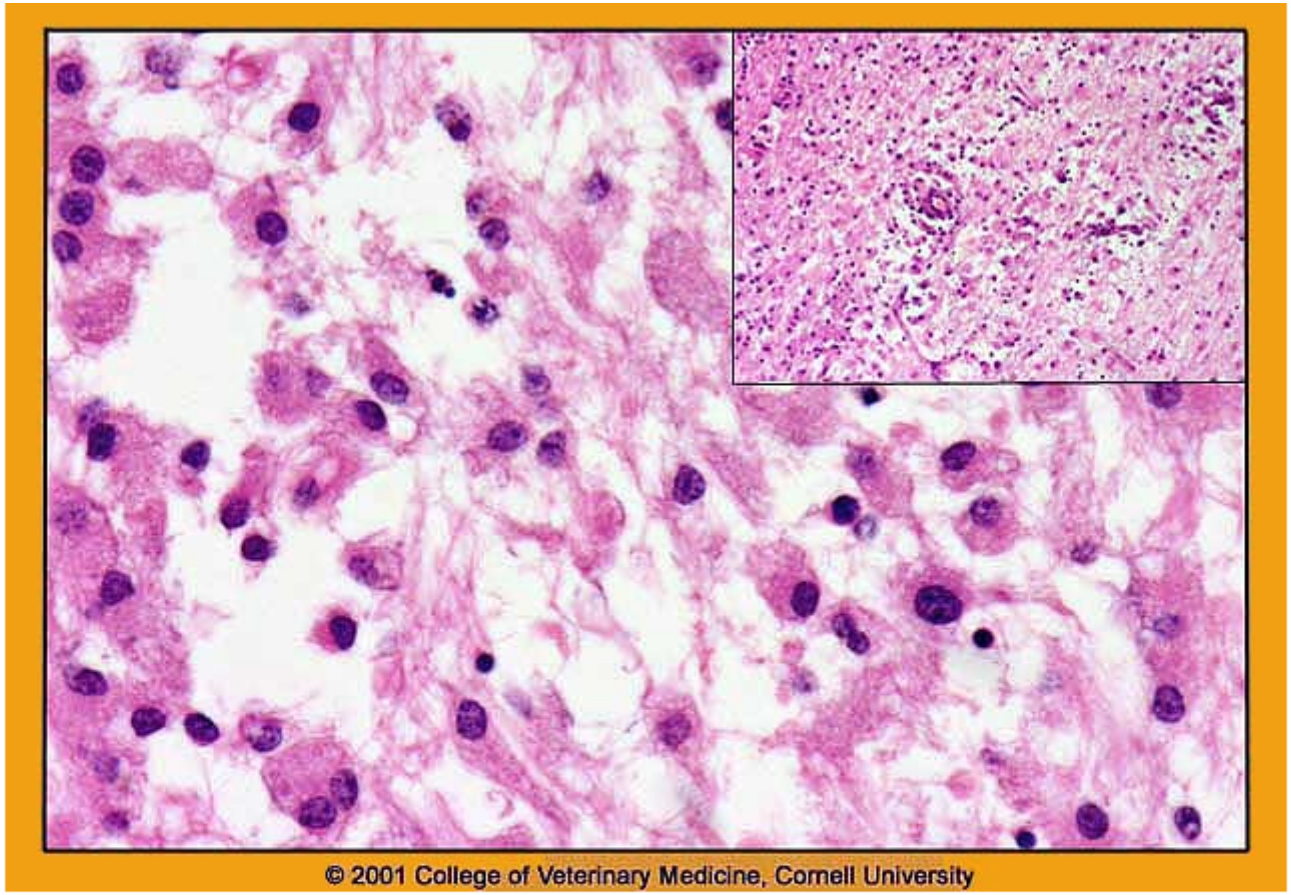
Necrosis grey and white matter; possible causes include

Intrinsic metabolic

- Breed associated - Multifocal encephalopathy in Limousin calves
  - Cerebrocortical white matter, optic chiasm, rostral thalamus, lateral geniculate bodies, zona incerta, substantia nigra, white matter of cerebellar peduncles and lateral corpora quadrigemina



Multifocal Encephalopathy of the Limousin Calf - Cerebrum. Discreet focal areas of myelin and tissue loss are clearly evident in the corona radiata. (Right panel luxol fast blue stain). See also the following four figures



Multifocal Encephalopathy of the Limousin Calf - Higher magnification detail from the previous figure at the margin of the lesion. Myelinophages and reactive astrocytes dominate the reaction in this active lesion. There has been much tissue disruption but numerous axons still survive (see following figures).