



Surgical Neuropathology of Epilepsy

A presentation for the Eighth Annual International Neurosurgery Conference

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Disclosures, etc

- I have no financial relationships to disclose, except that many of the illustrations in this presentation come from my collection and were used in my textbook, *Modern Surgical Neuropathology* (Cambridge University Press, 2009). I derive small royalties from sales of the book. The images are copyright (Douglas C Miller, 2009) and I have given permission for their use here. I would appreciate that the copyright be respected.

Beginnings of Neurosurgical Treatment of Epilepsy

- Neurosurgical excision of brain tissue thought to be the site of epileptic seizure genesis has a substantial history
- The earliest modern approaches to this means of treating seizures came from the pioneering work of Wilder Penfield and his colleagues at the Montreal Neurological Institute, although a few cases had been reported involving successful treatment of seizures by surgery earlier, going all the way back to Victor Horsley in 1886 in England. Others in Germany (Kraus and collaborators) and in the USA (Cushing, of course), were also early pioneers, but it was Penfield and his team at MNI who first organized a thorough team approach utilizing electrophysiological testing as well as thorough neurological examinations to guide neurosurgical resections, particularly for temporal lobe epilepsy. In part this was simply because the scientific advances in electroencephalography permitted these more advanced approaches. Penfield also began some of the first systematic studies of surgically removed epileptogenic lesions, and was one of the last of the great neurosurgeon/neuropathologists; he in fact authored a major text of CNS pathology

Neuropathology and Epilepsy

- Clearly there are many causes of epilepsy: genetic disorders, developmental disorders (some genetic, others sporadic), neoplasms, trauma, infections, ischemia, etc. Neurosurgical treatment is almost exclusively useful for FOCAL seizures, arising from distinct anatomic sites (“epileptogenic foci”). While autopsy neuropathology catalogued a great many lesions associated with epilepsy in the life of patients undergoing autopsy, the surgical neuropathology of epileptogenic lesions did not develop until more modern neurosurgical procedures demanded that neuropathologists deal with specimens arising from such surgery. Thus the identification and characterization of the types of lesions which lead to focal epilepsy has only been a function of working surgical neuropathologists for about 20-30 years, and is still largely restricted to those large centers where there is an adequate volume of such specimens to keep an interested neuropathologist “in practice”. This presentation will deal with the surgical neuropathology of specimens resulting from epilepsy surgery. It will therefore not touch on types of primary generalized epilepsy without a seizure focus, whether from genetic abnormalities of ion channels or other metabolic defects.

Case Selection Biases

- Not all types of epilepsy are treatable by neurosurgery
 - Primary generalized seizures
 - Bilateral seizure origins (some, not all)
 - Genetic/Metabolic Seizure Disorders (eg Lafora Disease)
- Not all epilepsy surgery procedures produce tissue amenable to neuropathological analysis
 - Subpial transections
 - CUSA aspiration

Consequences of Selection Bias

- The described pathology is mostly that of chronic intractable partial complex seizures, with or without secondary generalization
- There is a preponderance of temporal lobe lesions

Other Selection Biases

- Case mix by age and seizure type or syndrome seem to vary by institution:
 - The NYU Epilepsy Center (at least when the author was there) operates on few infants or young children, but Yale University Medical Center, for example, has published extensive descriptions of “cortical dysplasia” in infants and younger children
 - NYU has become a center for patients with Tuberous Sclerosis Complex, so they see a disproportionate number of such cases compared to other institutions
 - The MU Epilepsy Center, while a designated “Level 4” Center, is still young and is still building its patient population and range of services. Relatively few pediatric patients have been seen here except for those with epilepsy and tumors.

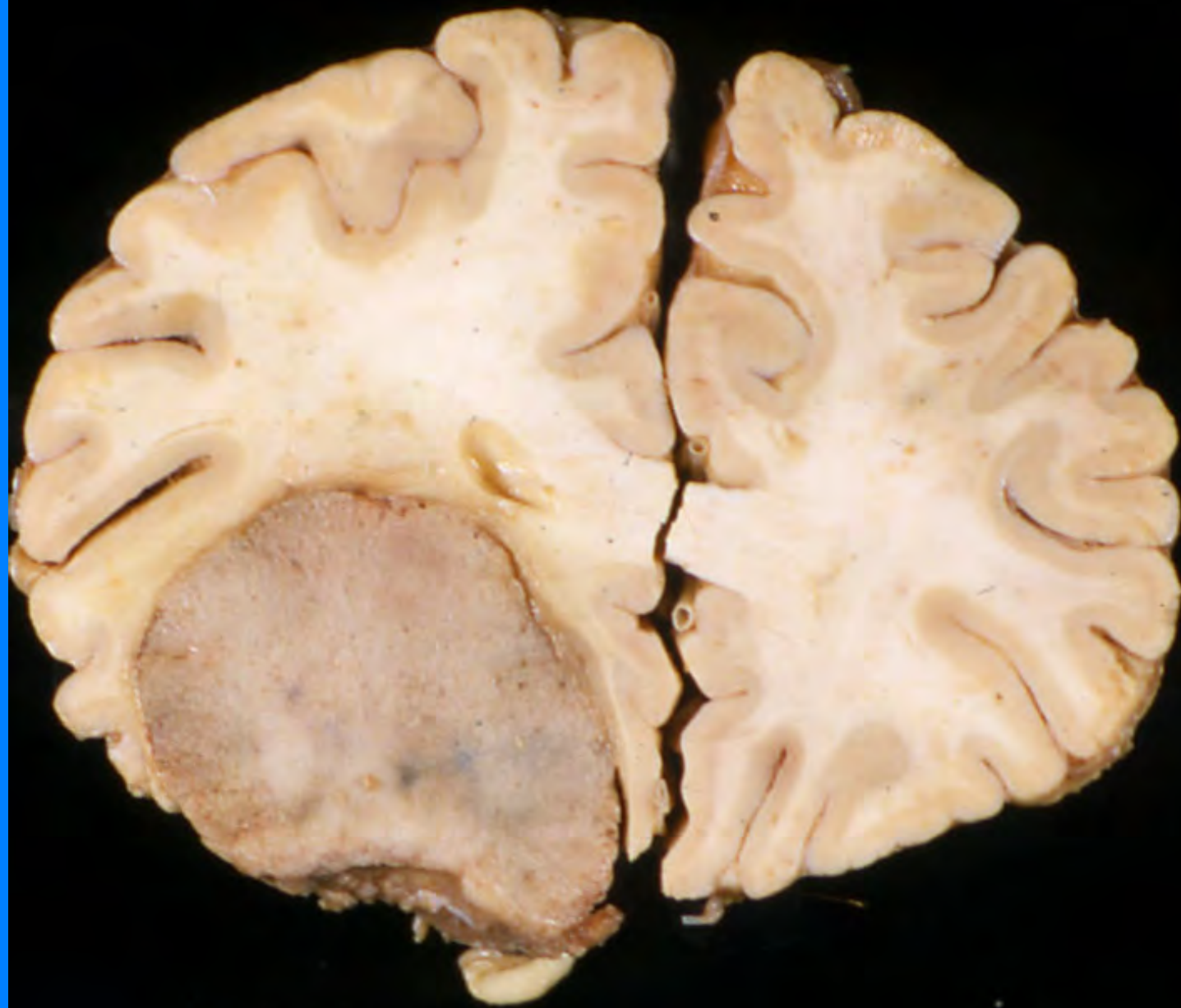
Types of Pathological Changes in Epileptic Brain Tissue

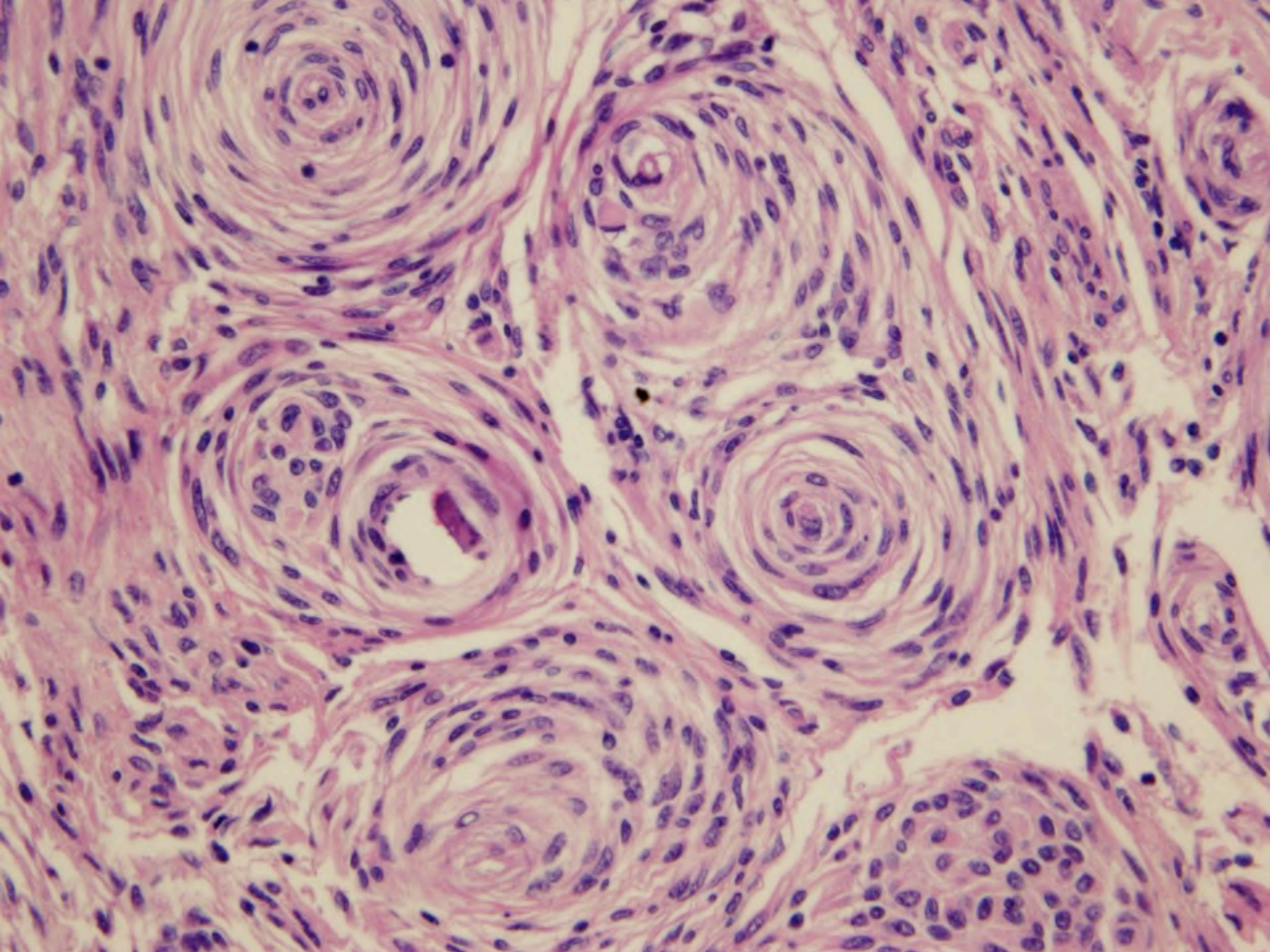
- 1. Lesions thought to cause epilepsy, or at least be causally associated with it:
 - Tumors (Meningiomas; Dysembryoplastic Neuroepithelial Tumors; Gangliogliomas; Oligodendrogliomas, mixed gliomas, and related neurocytic tumors; astrocytomas)
 - Vascular Malformations (AVM, cavernous hemangioma; special case of Sturge-Weber Disease)
 - Hamartomas (including tubers of TSC)
 - Cortical dysplasia, including “focal cortical dysplasia”, cortical hamartias, other evidence for neuronal migration disorders; also hippocampal dysplasia
 - Heterotopic Gray Matter in White Matter: band heterotopias, nodular heterotopias, and excess white matter neurons
 - Inflammatory Lesions: Rasmussen’s Encephalitis; Microglia-Driven Epilepsy; Sarcoidosis
 - Glial scars following infarcts, contusions, neurosurgical procedures, infections
- 2. Lesions/abnormalities thought to be secondary to chronic epilepsy:
 - Chaslin gliosis
 - Hippocampal neuronal loss and gliosis (“medial temporal sclerosis”—note some controversy over cause and effect for this)
 - Diffuse gliosis of cortex and/or white matter
- 3. Lesions/abnormalities thought to be iatrogenic, related to diagnostic and therapeutic procedures for epilepsy:
 - Aseptic chronic meningitis after placement of subdural recording devices
 - Microcavities from depth electrodes
 - Foreign body reactions to surgically implanted materials
 - Pressure necrosis/acute infarcts of cortex following placement of subdural recording devices

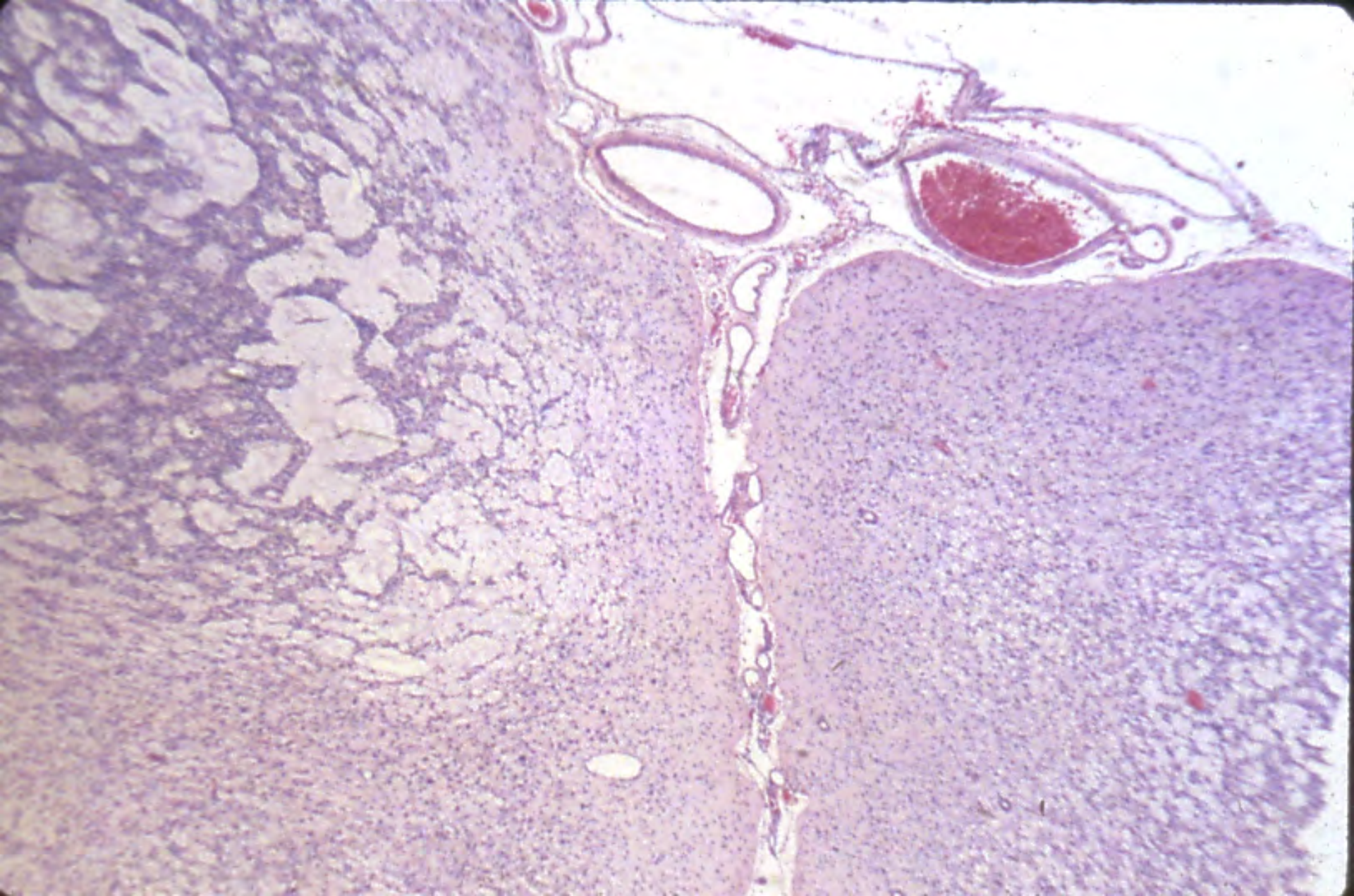
Lesions Thought to Cause Epilepsy, I

- Tumors
 - Meningiomas: Extra-axial, press on and irritate cortex
 - Dysembryoplastic Neuroepithelial Tumors: Typically cortically-based, interrupt normal cortical architecture, have limited local mass effect, are associated with adjacent/intermixed areas of dysplastic cortex; contain neoplastic neurons (neurocytoma-like cells, ganglion cells); ?Connectivity of neoplastic neurons?
 - Gangliogliomas: Often involve cortex as well as white matter; ? Connectivity of neoplastic neurons?
 - Angiocentric Gliomas: Almost always involve cortex; some descriptions say there are neoplastic neuronal elements in these tumors.
 - Other gliomas: Infiltrate cortex, interrupt axonal connections or axonal function, alter ionic environment, have mass effect, possibly induce ischemia, etc

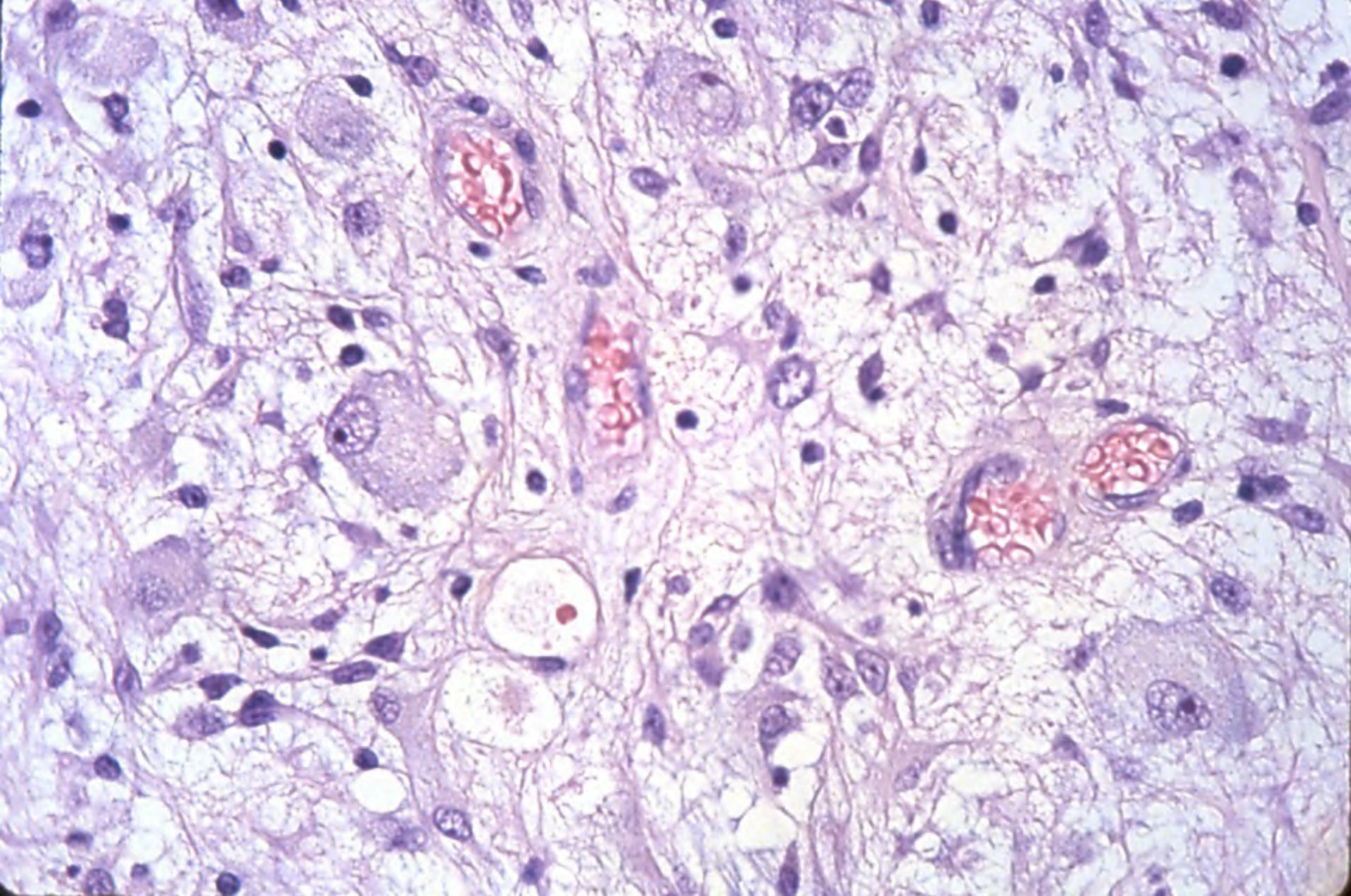
Inferior left
frontal lobe
meningioma,
probably from
olfactory
groove







Dysembryoplastic Neuroepithelial Tumor



Ganglioglioma

Lesions Thought To Cause Epilepsy, II

- Cortical Malformations
 - Hamartomas (including tubers of TSC)
 - Cortical dysplasia, including “focal cortical dysplasia”, cortical hamartias, other evidence for neuronal migration disorders
- Abnormalities of gyration: polymicrogyria, pachygyria

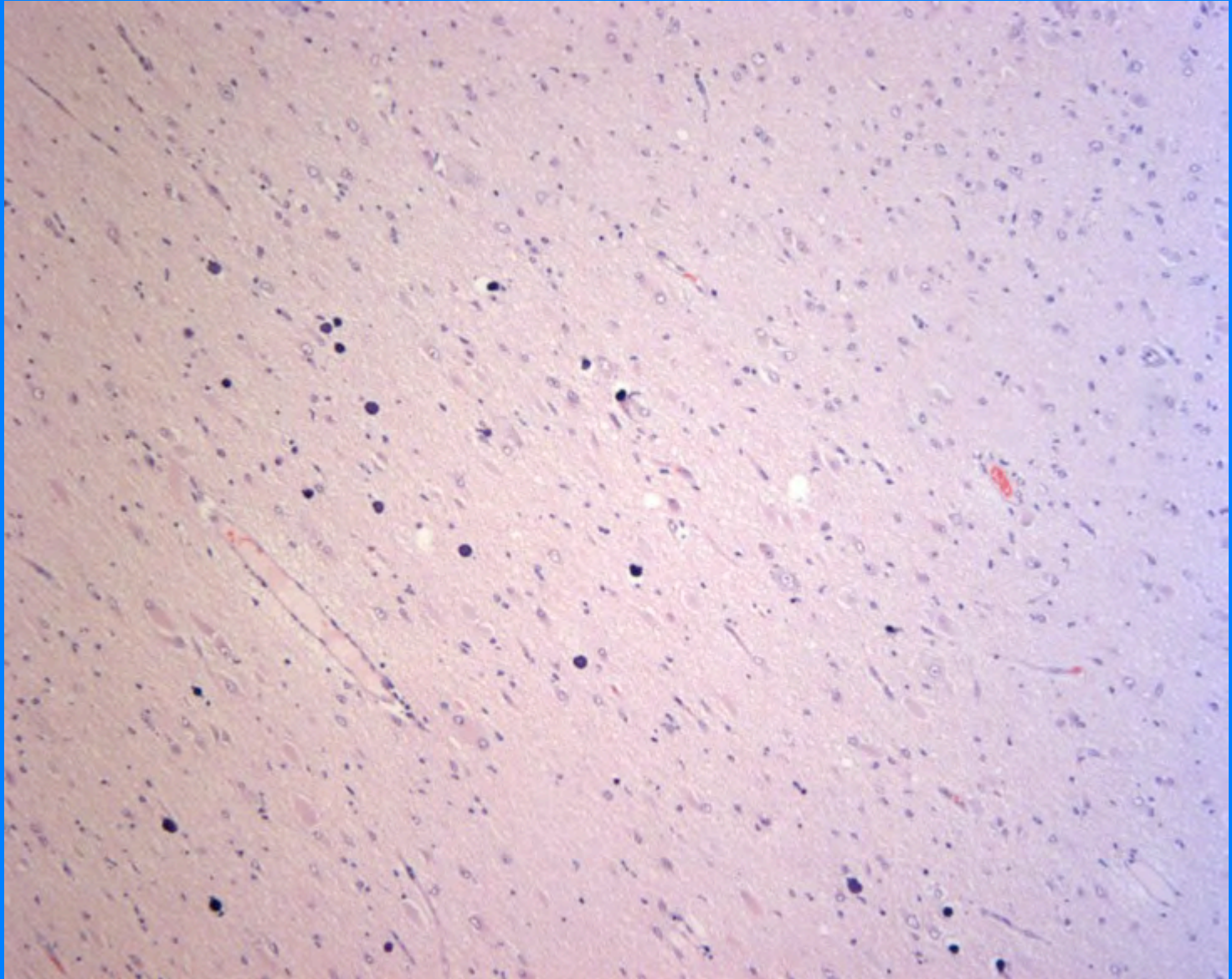
Diffuse Cortical Dysplasia

- “Cortical dysplasia” describes a group of abnormalities of the organization of the neocortex, which normally has six distinct layers running horizontally in parallel with the pial surface, and columns of cells organized orthogonally to the laminae. Dysplasia can be diffuse or focal, it can be mild, moderate, or severe, and it can involve considerable linear zones of cortex, in one lobe or in multiple lobes; it may be unilateral or bilateral. Some forms of cortical dysplasia are detectable in good quality MRI scans, particularly if the abnormal cortex is unusually thick. Surgical treatment is not an option for extensive bilateral dysplasia. Extensive unilateral dysplasia characterizes a few conditions, notably Hemimegalencephaly, and in young children this can be treated with “functional” hemispherectomy

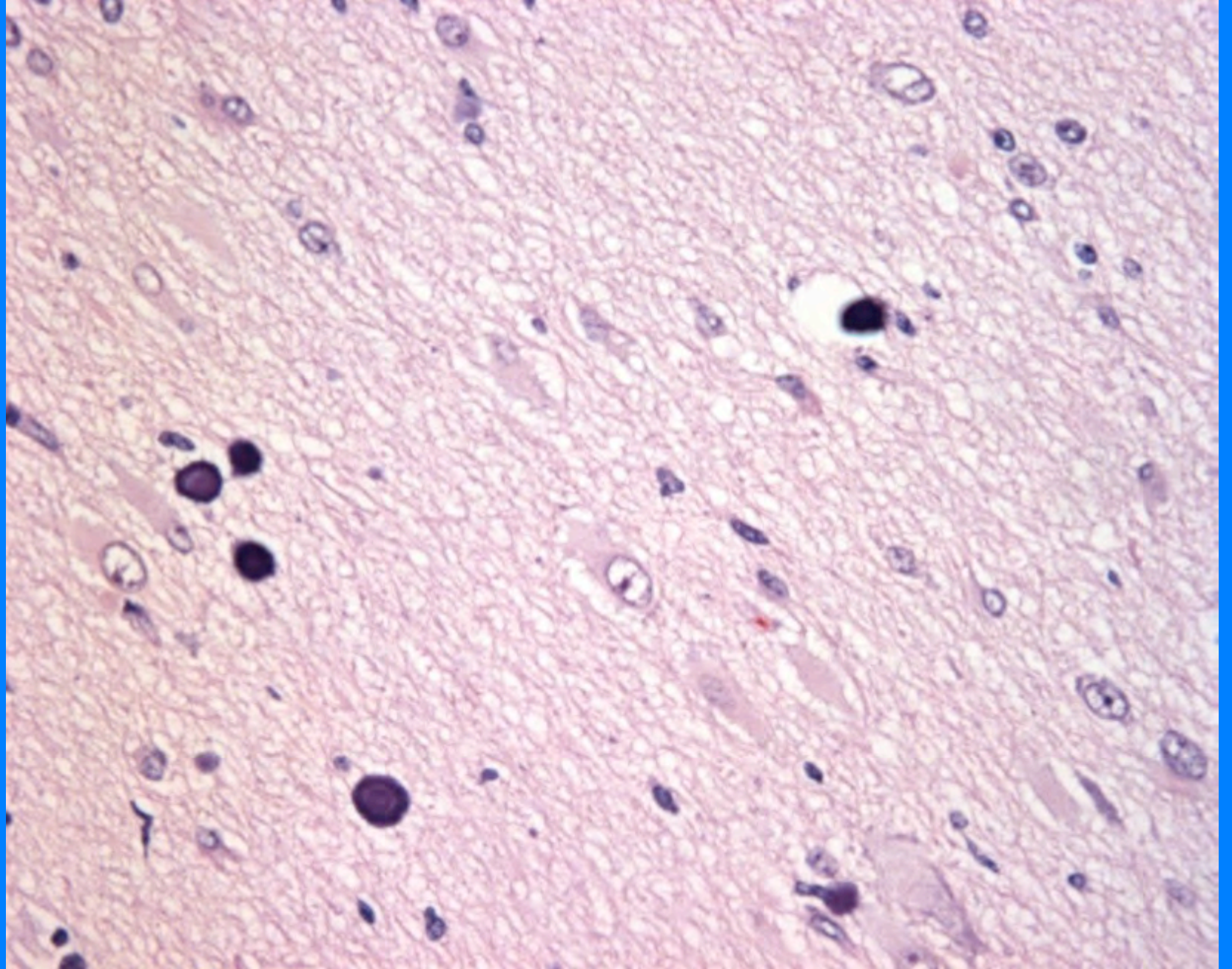


Bilateral insular region polymicrogyria associated with cortical dysplasia in an autopsy specimen. The patient had epilepsy most of his life.

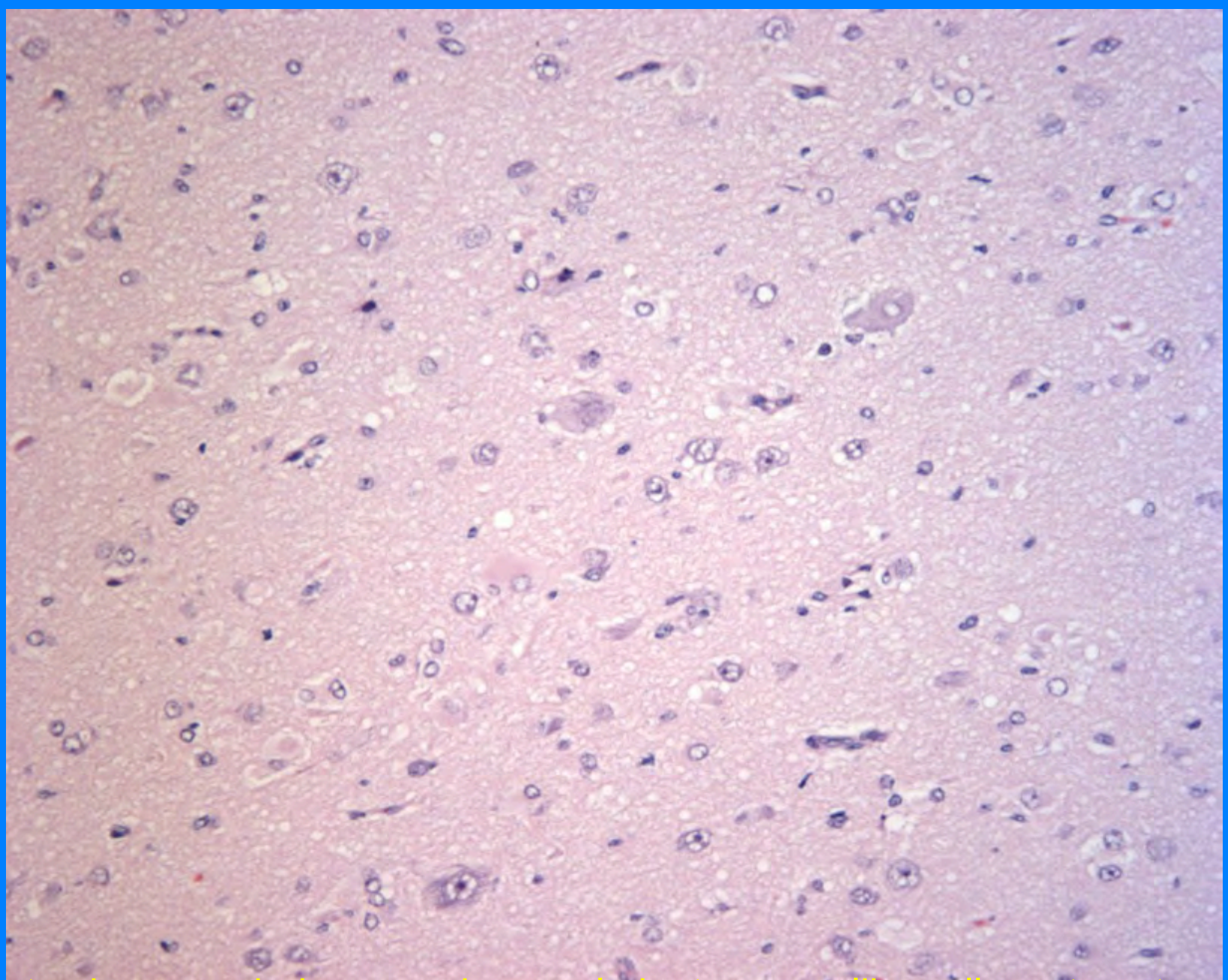
Focal Cortical Dysplasia



Laminar Disarray with associated calcifications accompanying large abnormal cells—astrocytes? neurons? H&E, 10x



Abnormal cells with calcifications in gyrus core: abnormal neurons abnormally placed?



Cortex in expanded gyrus: abnormal giant neuron-like cells, astrocytes, abnormal lamination

Diagnosis

- Focal Cortical Dysplasia, Palmini Type II
(Neuroglial hamartoma/cortical dysplasia
(Histopathologically, the lesion is more or less indistinguishable from those characteristic of Tuberous Sclerosis Complex (tubers))
- These lesions are thought to arise from defective neuronal migration during embryonic and early fetal life, a period in which waves of cells must migrate from the periventricular germinal matrix zones through the developing white matter to reach their pre-programmed sites in the neocortex.

Tuberous Sclerosis Complex

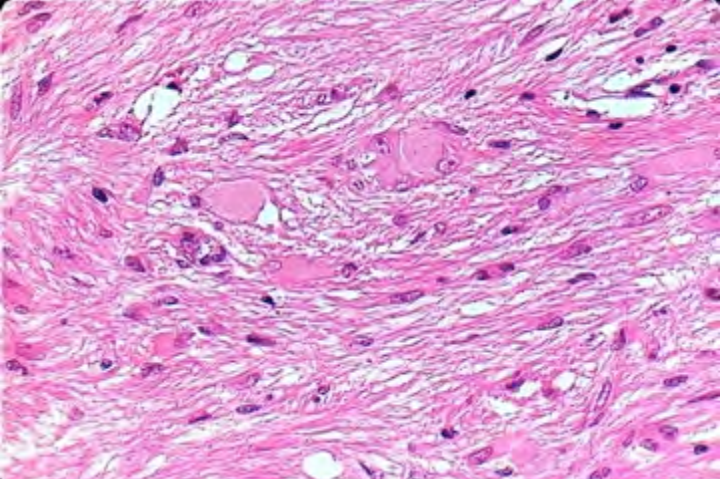
- Complex genetic disorder: 2 different genes, TS1 and TS2, with gene products tuberin and hamartin
- Normal function in development depends on interactions between tuberin and hamartin in regulation of the MTOR pathway
- Also have functions as tumor suppressor genes

TSC, cont.

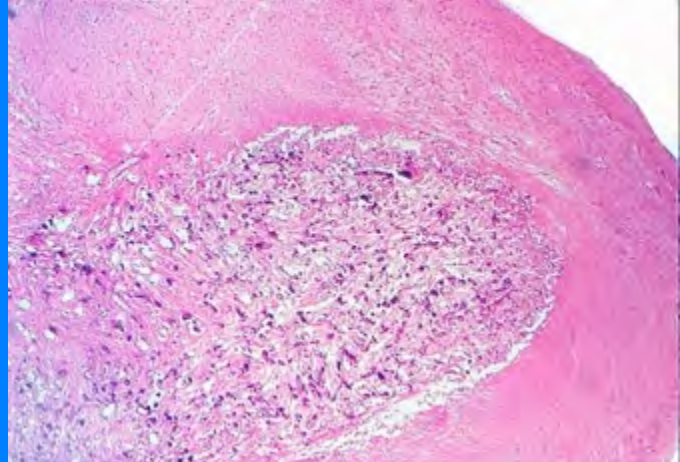
- Epilepsy is a common problem in patients with TSC, whether the TSC is due to a defect in TS1 or TS2 genes.
- Usually this associated with gross evidence of a neuronal migration disorder, with formation in brain development of cortical/subcortical hamartomatous nodules of abnormal glioneuronal cells, the tubers of the disease name



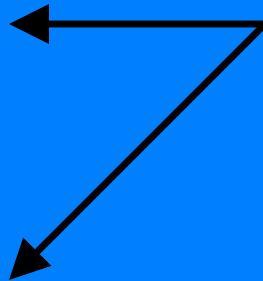
MASS. GENERAL HOSPITAL PATHOLOGY DEPT
METRIC 1 2 3 4 5 6 7 8 9



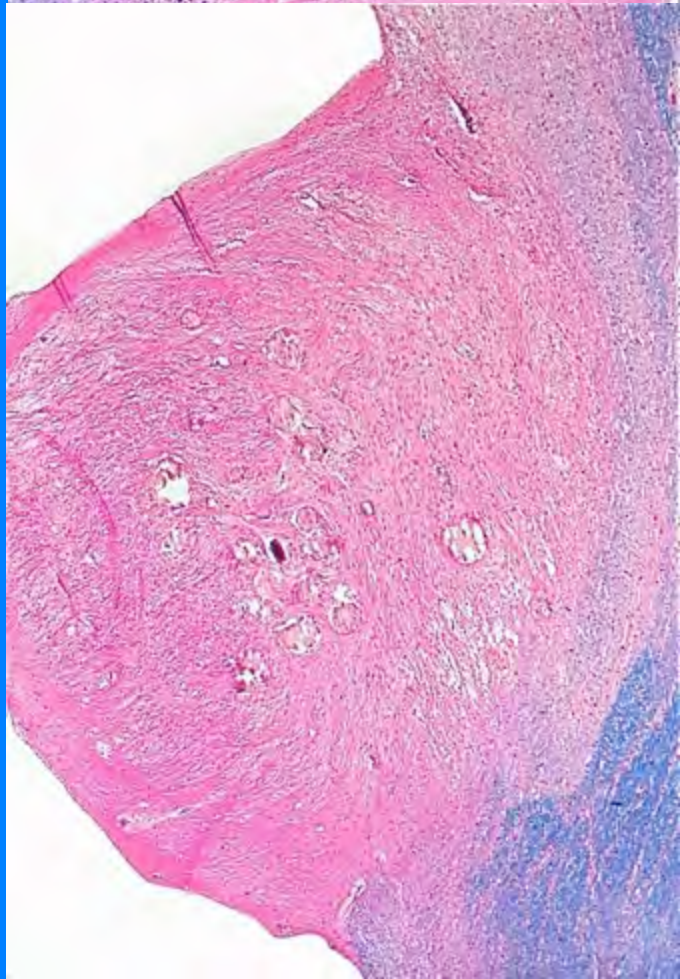
Tuber



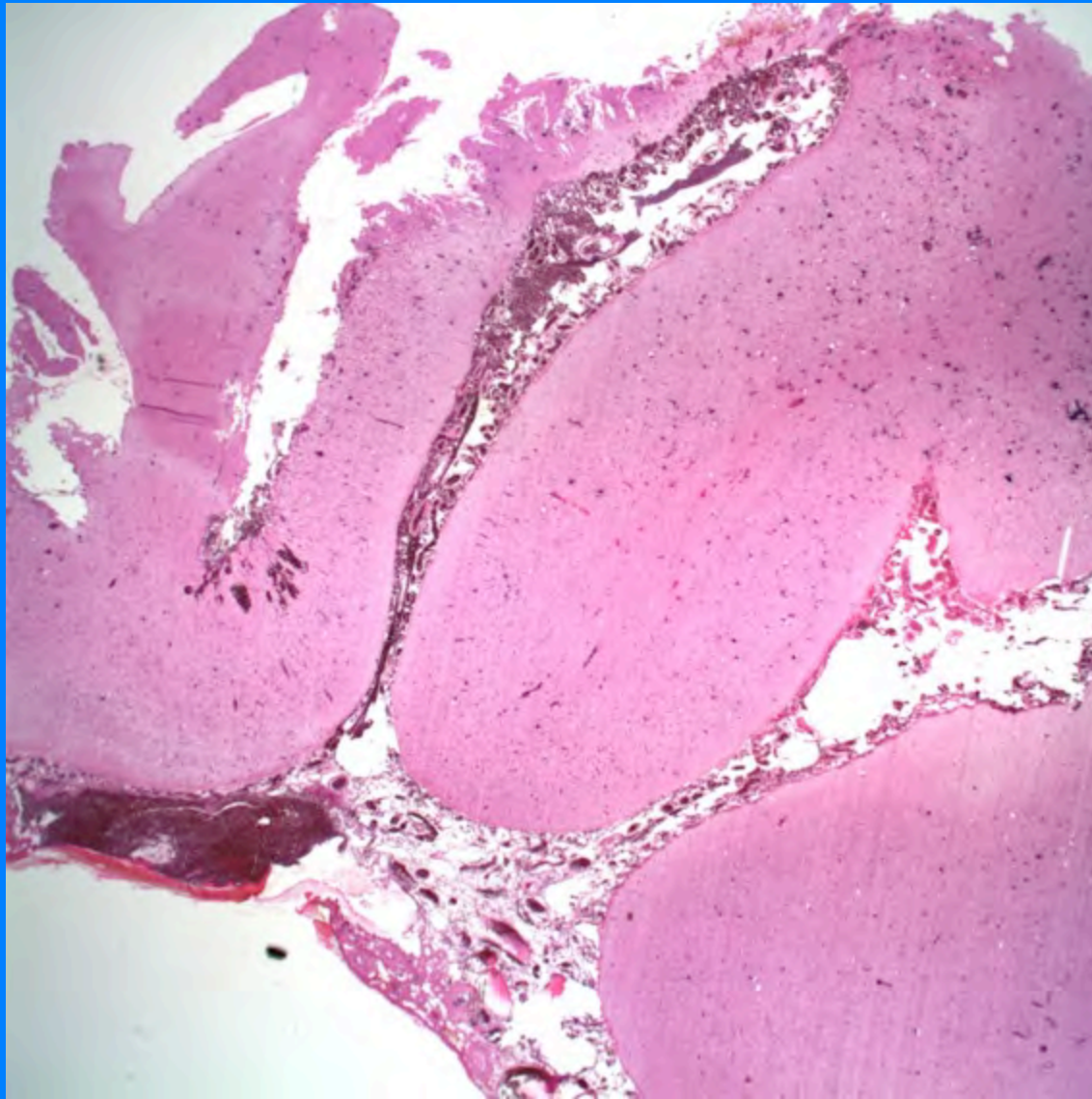
Abnormal
astrocytes in
cortex near
tuber



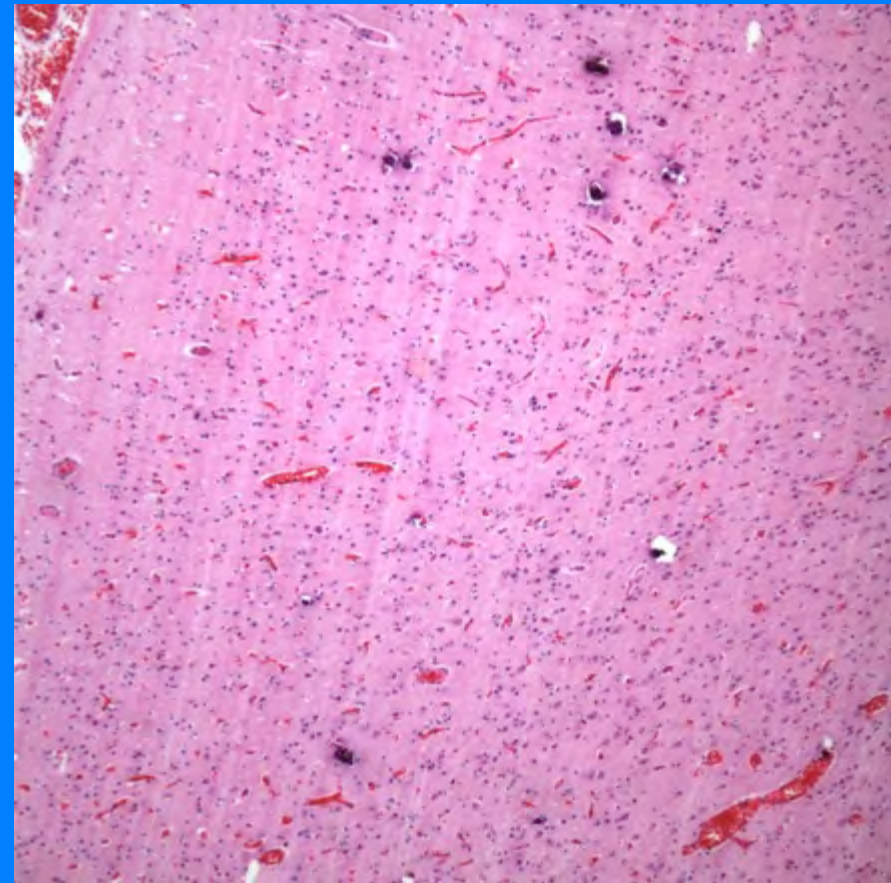
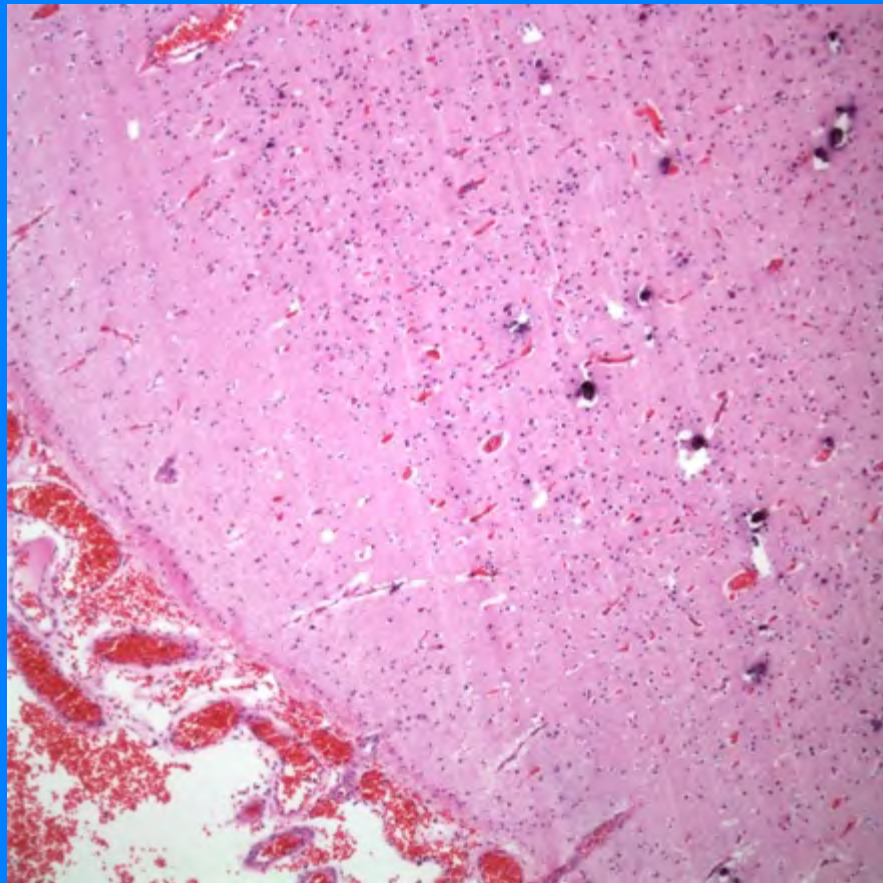
Subependymal
heterotopic
nodule



Sturge-Weber Disease: This genetically determined brain malformation combines an angiomatous proliferation in the leptomeninges with diffuse dysplasia of the underlying cortex, which also contains scattered lines of mineralization (calcification).



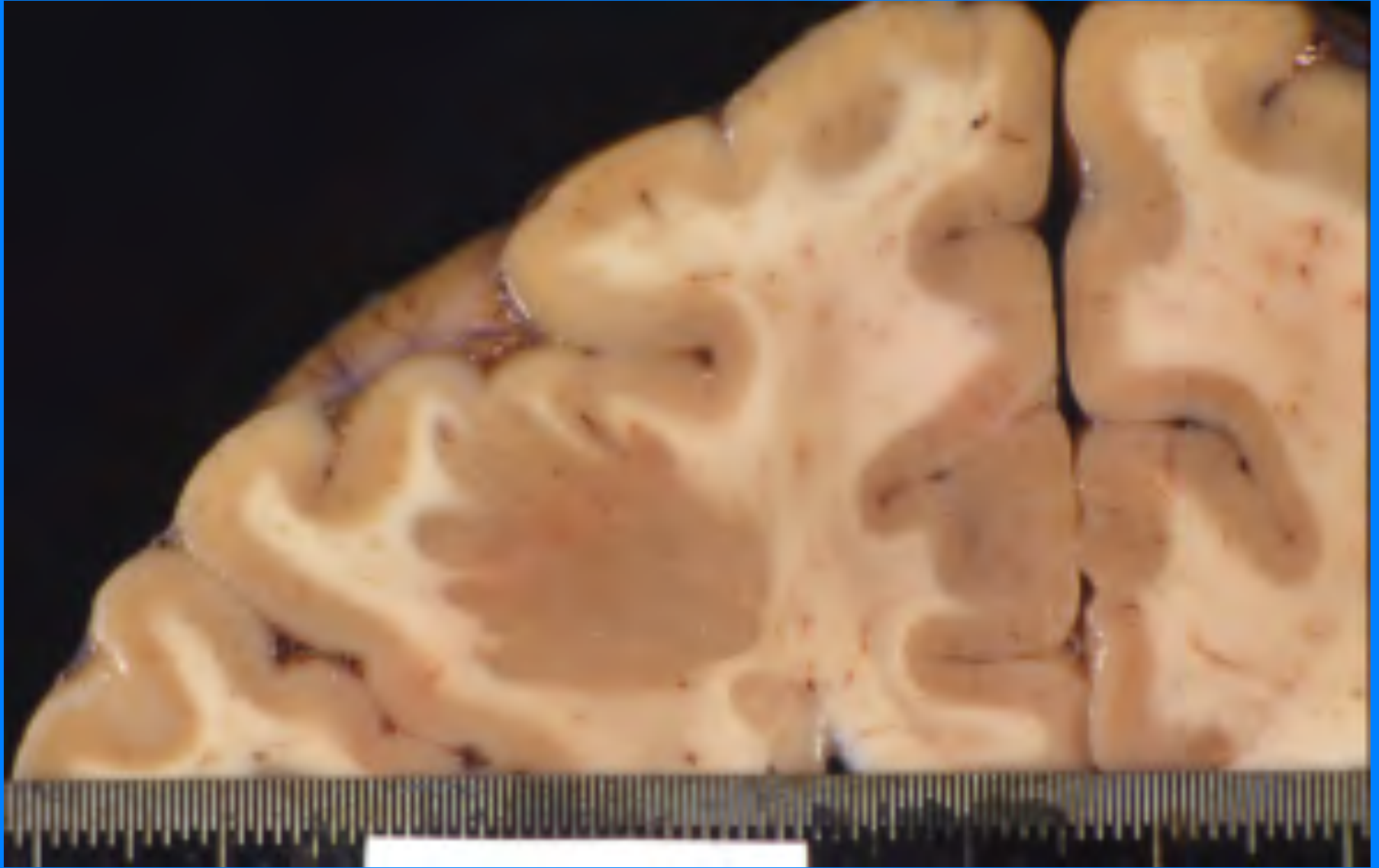
Sturge-Weber Disease



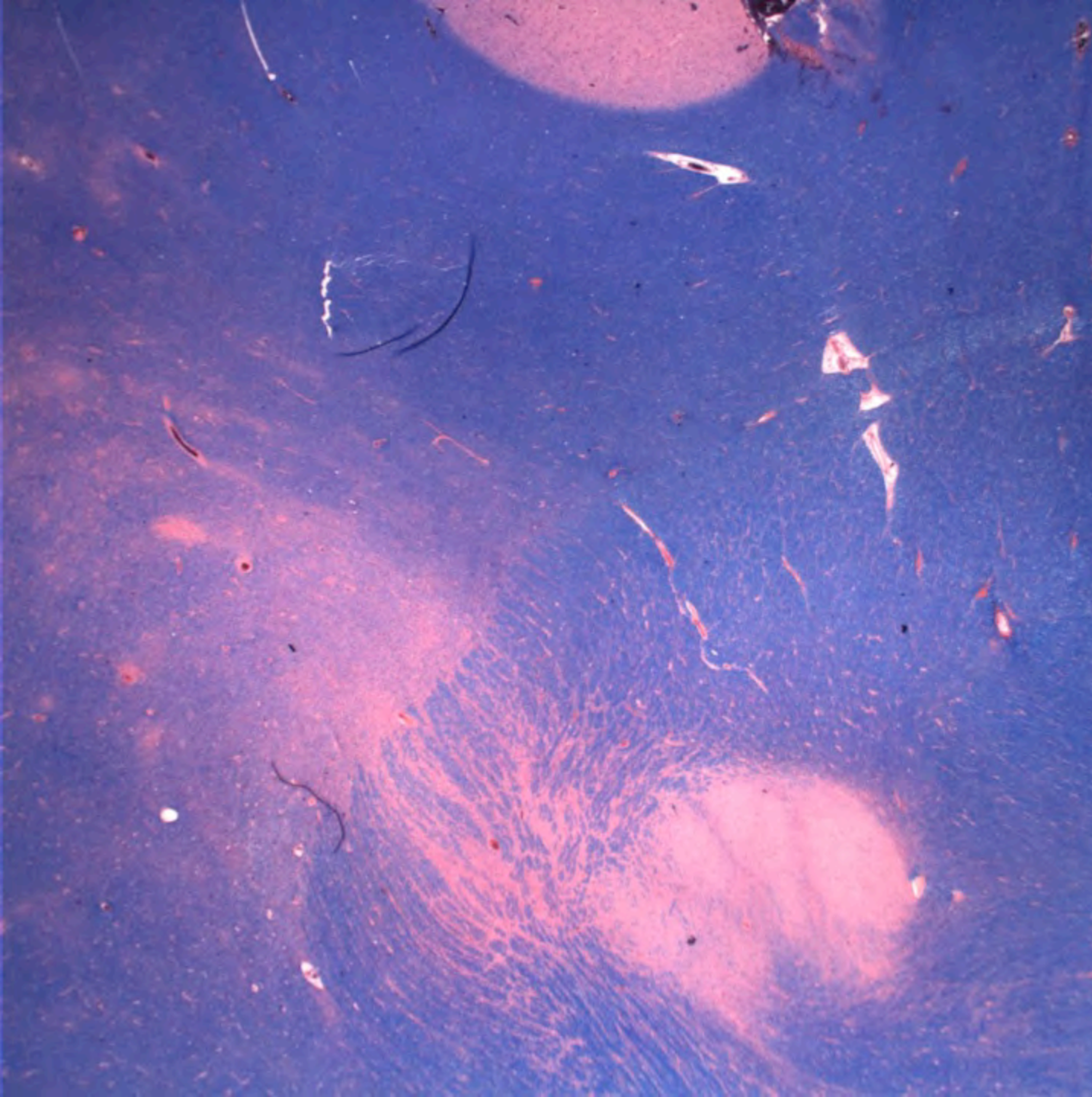
Lesions Thought to Cause Epilepsy, III: Gray Matter Heterotopias

- Nodular Heterotopias
- Band Heterotopias
- Diffuse Excess White Matter Neurons

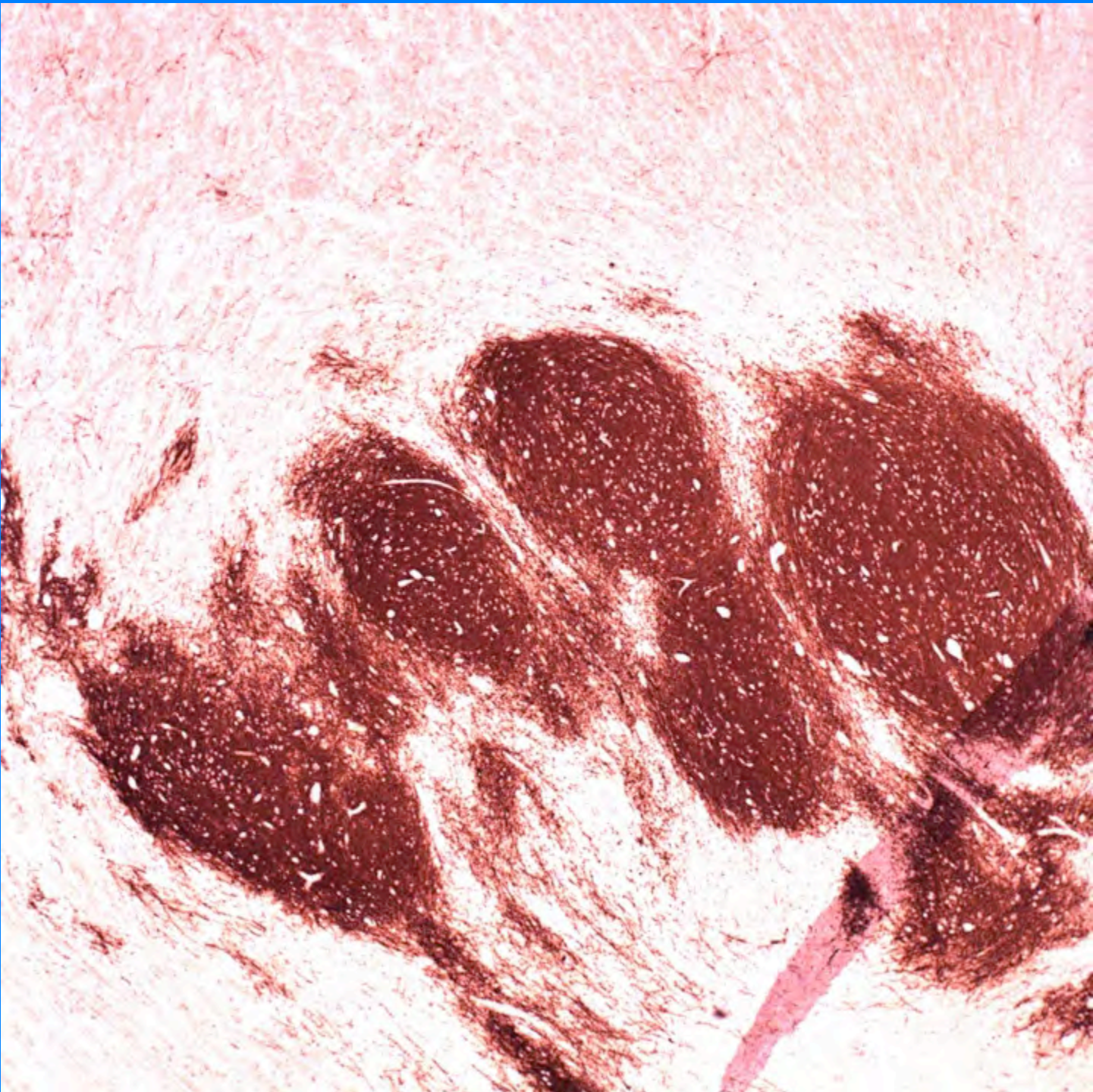
Nodular Heterotopias



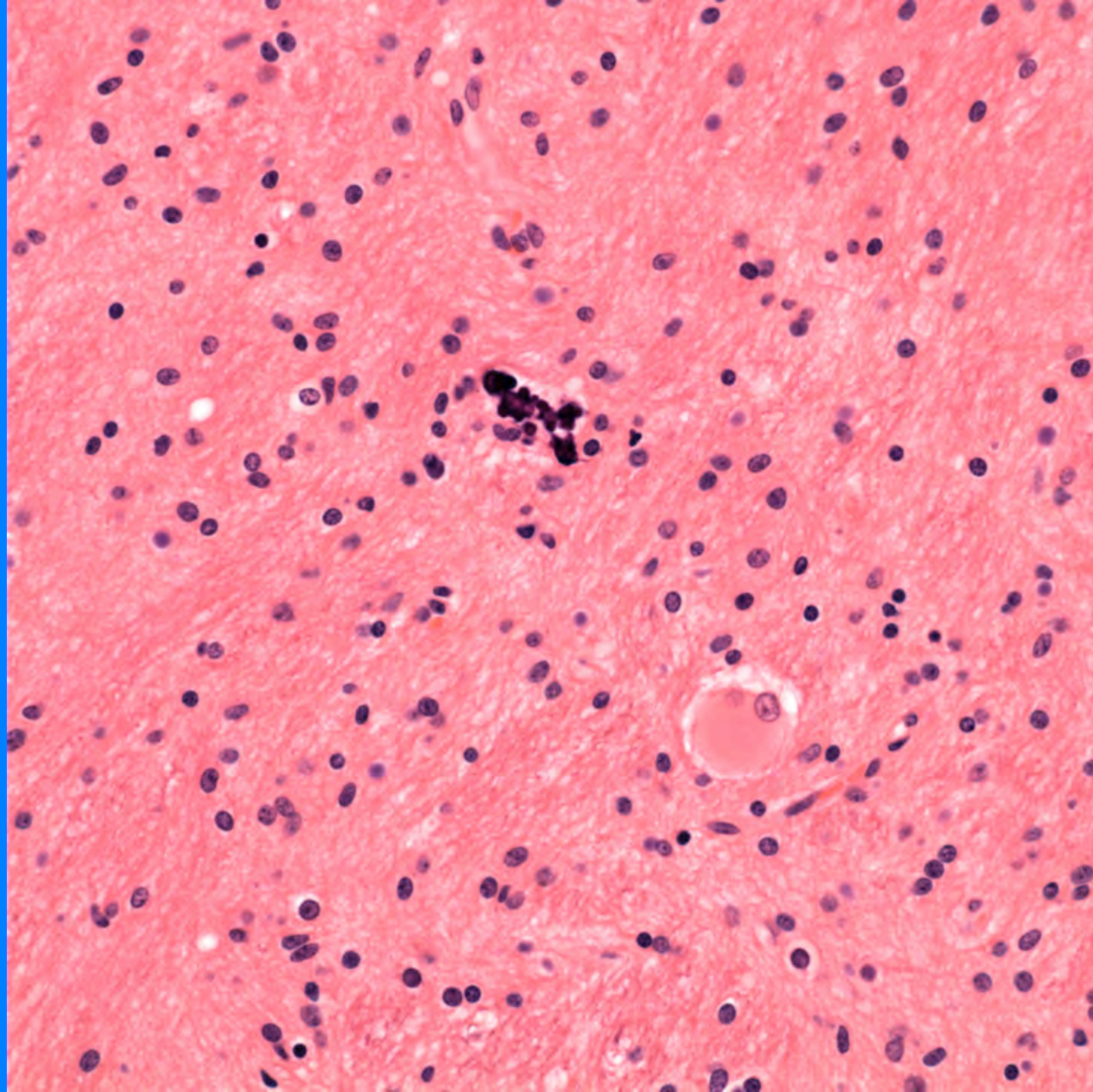
Nodular gray matter heterotopia in subcortical white matter, from an autopsy



Nodular Gray Matter Heterotopia in Parietal White Matter from a surgical specimen: This was solely a histological discovery, not seen by MRI or grossly, although the seizure focus was identified by invasive monitoring to this region. Luxol Fast Blue/H&E combination stain.

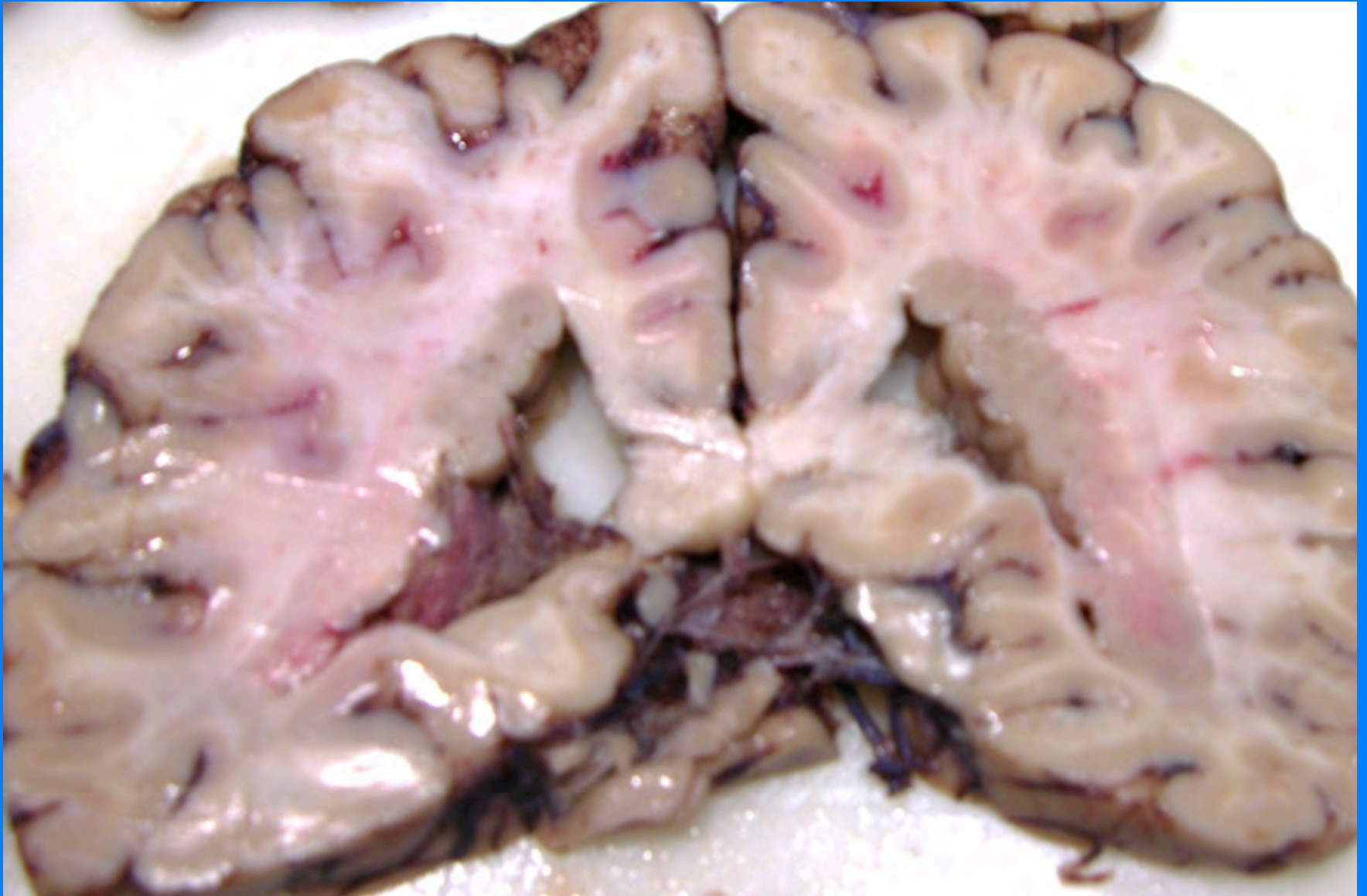


The heterotopic gray matter is intensely immunoreactive for synaptophysin



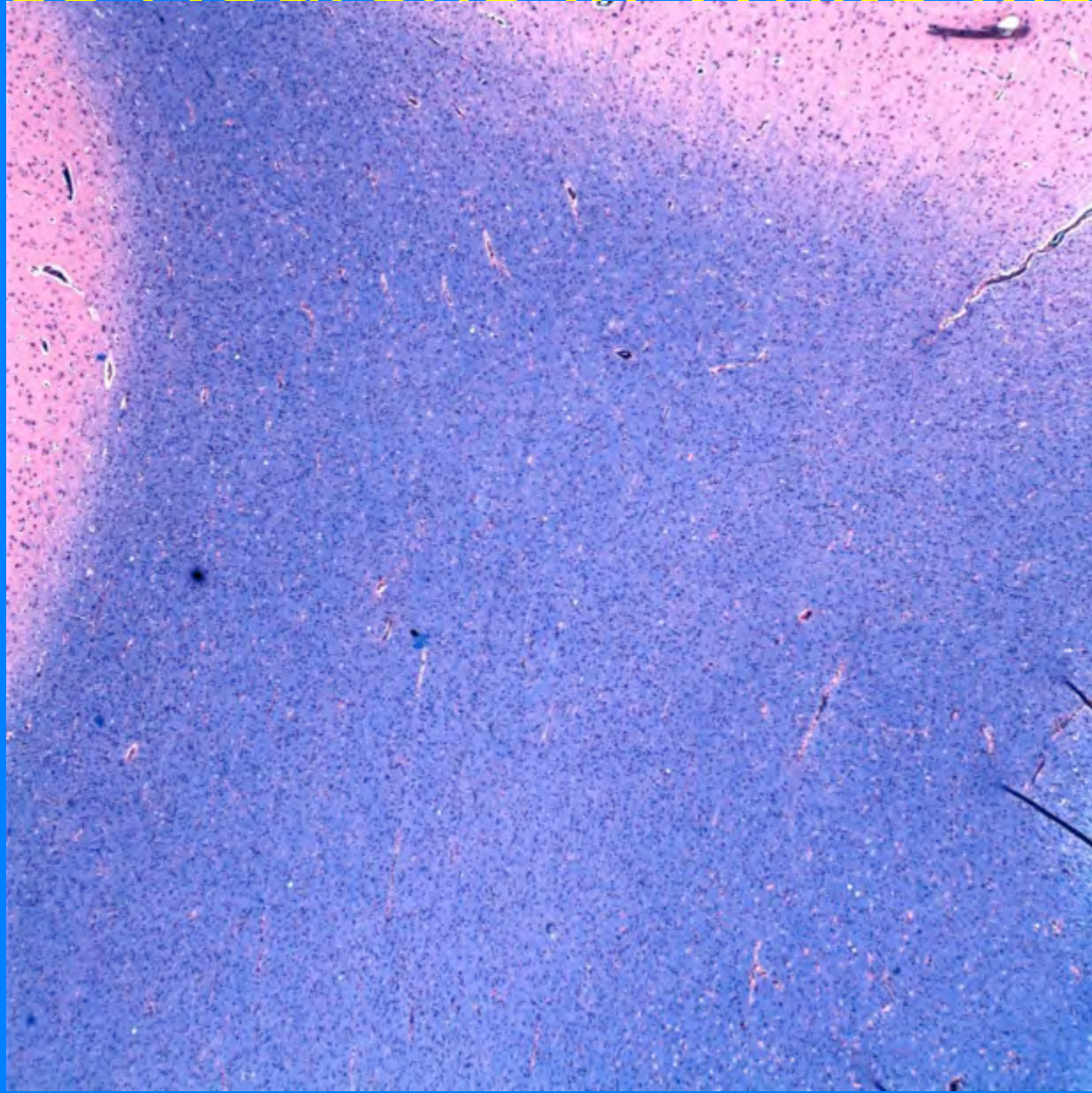
The nodular heterotopic gray matter includes some ballooned neurons and scattered mineral deposits (probably calcium)

Band Heterotopias



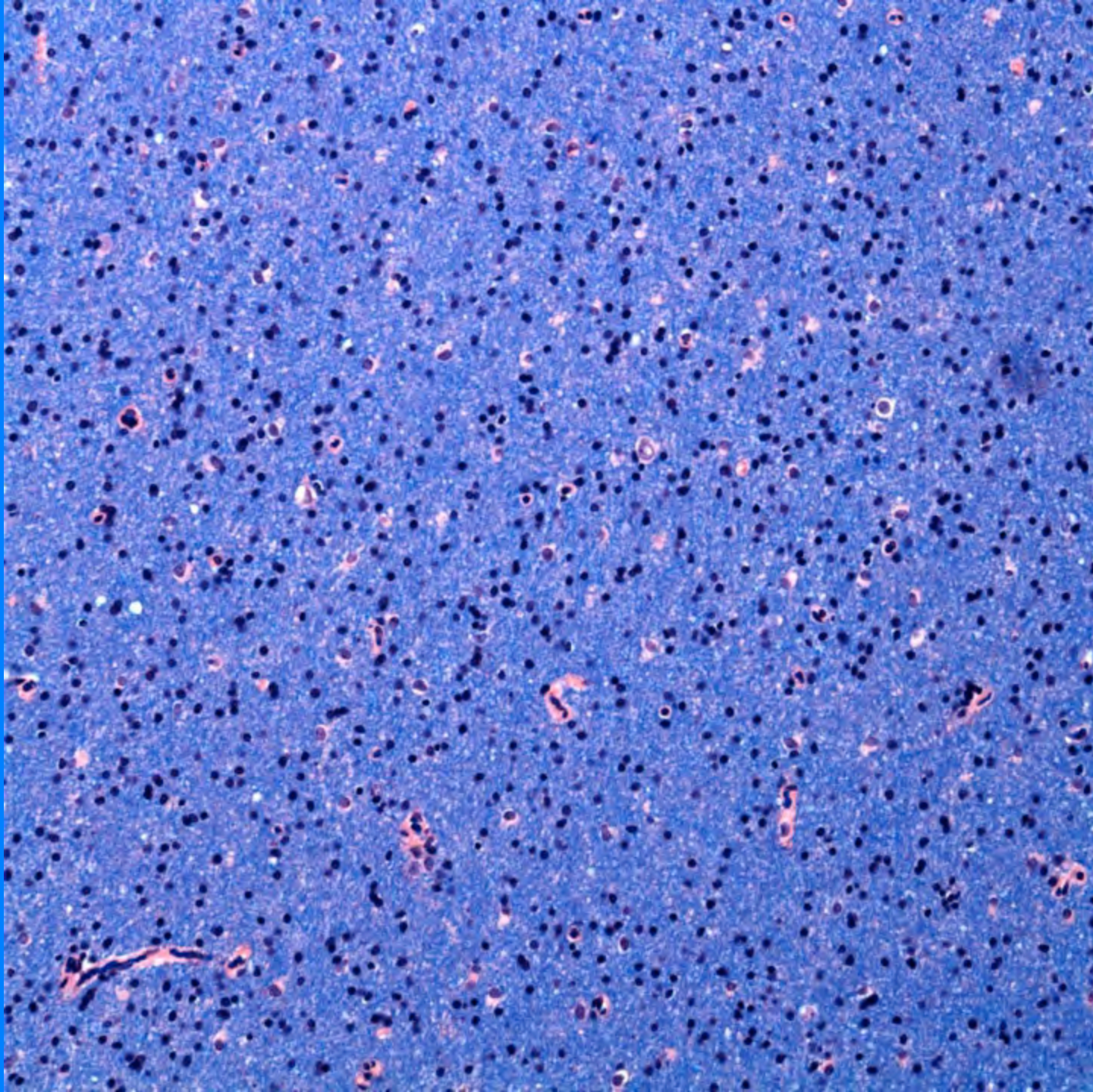
Autopsy specimen showing bilateral periventricular lines of heterotopic gray matter

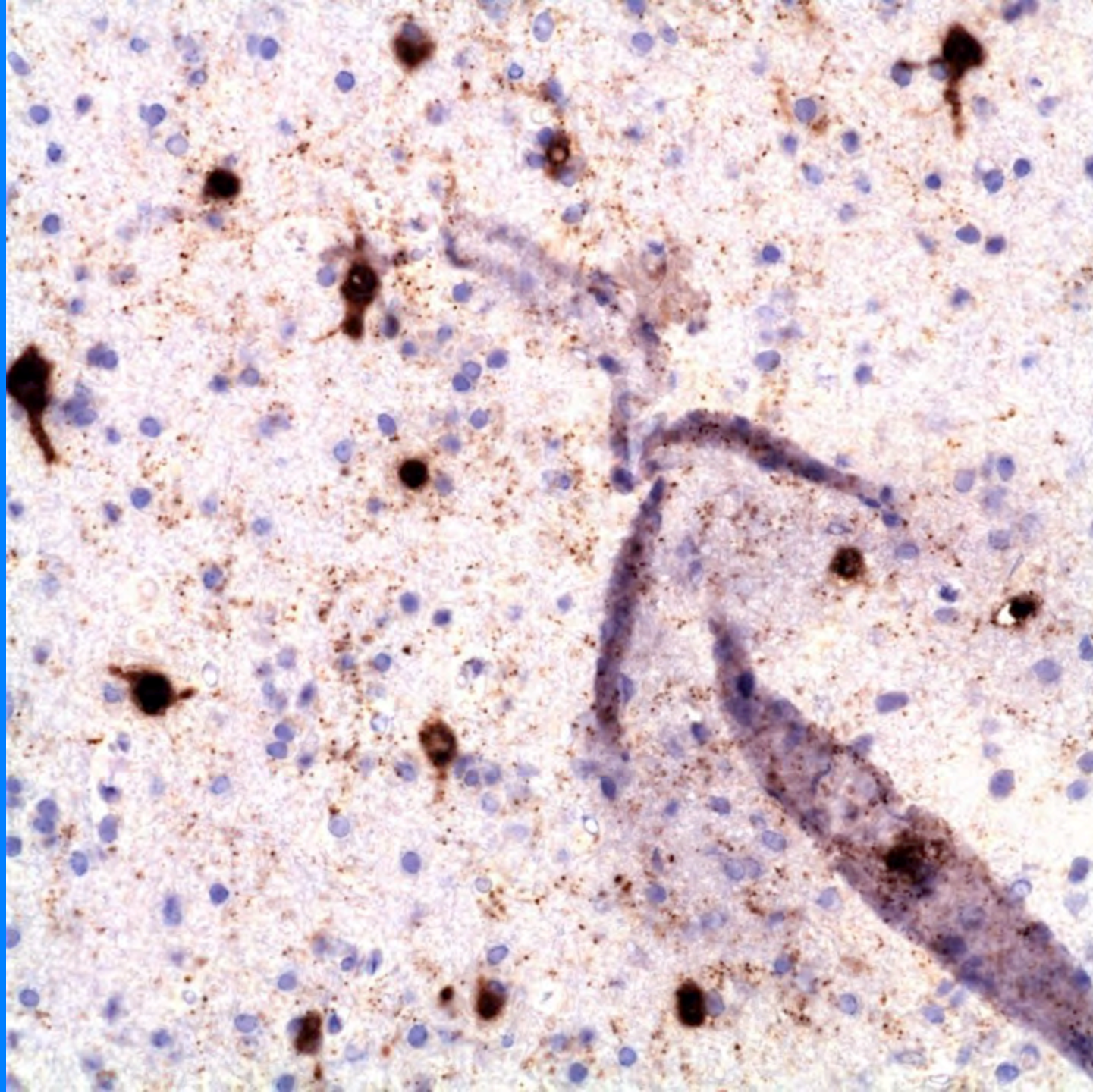
Excess Neurons In White Matter



Luxol Fast Blue/H&E-stained section of surgically resected tissue: large pale “dots” in white matter are neurons.

Excess
neurons in
white matter

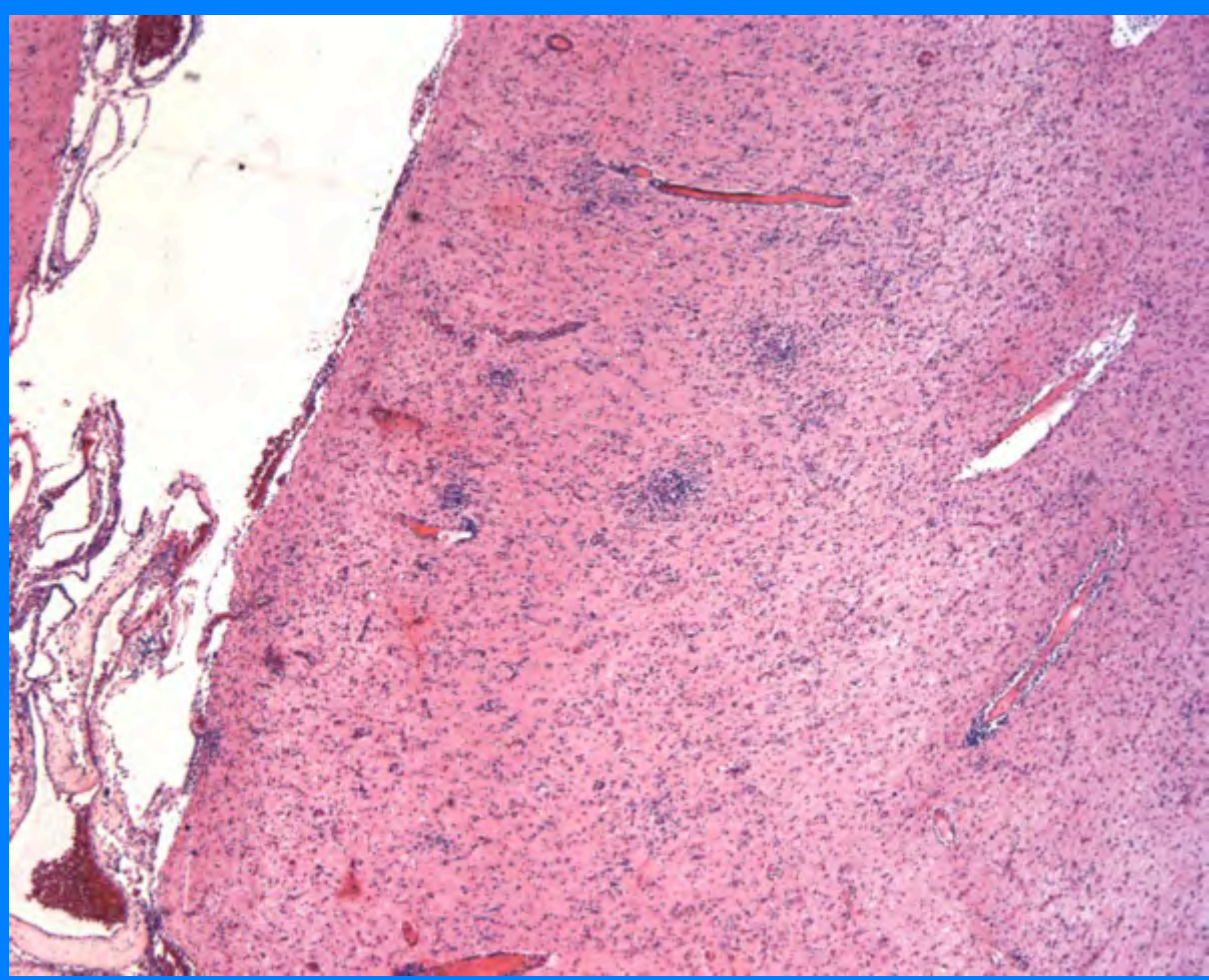
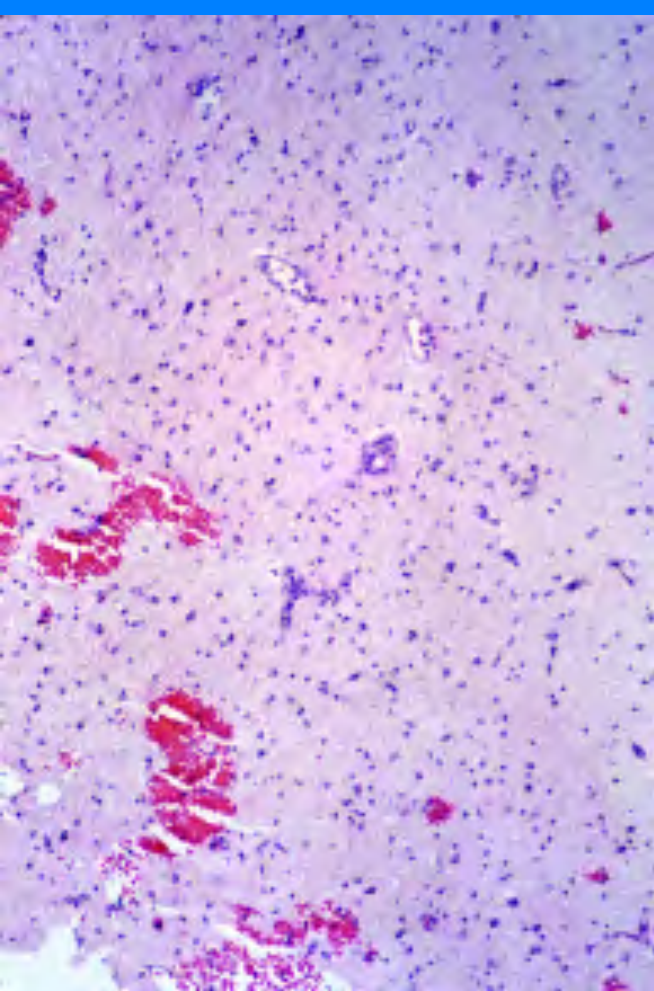




White matter neurons, highlighted by an immunostain for Neu-N

Inflammatory Causes of Epilepsy: Rasmussen's Encephalitis

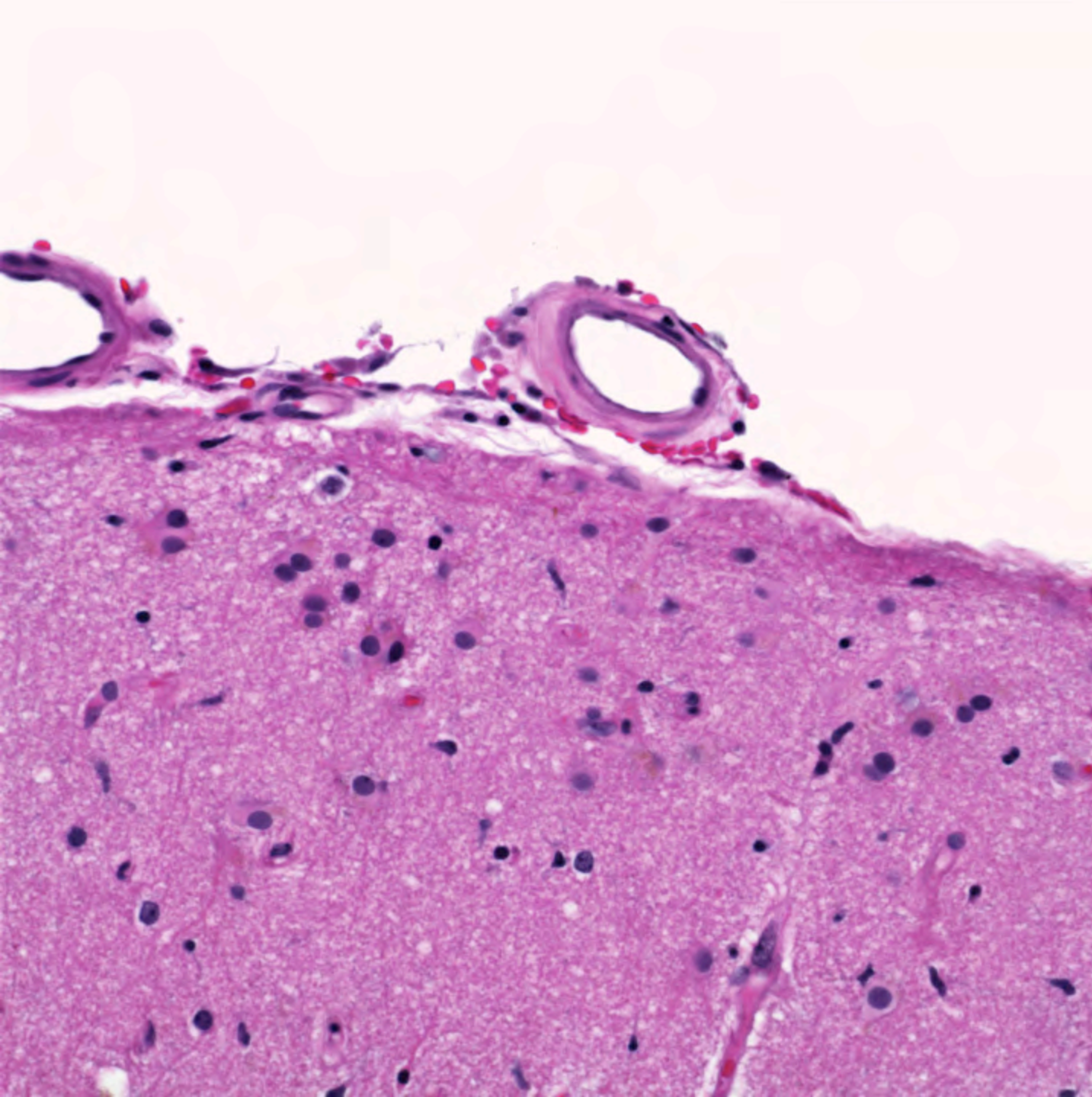
- Idiopathic, possibly viral, encephalitis, typically affecting hippocampus and temporal lobe
- Intense lymphocytic and microglial infiltrates
- Not very responsive to steroids or other anti-inflammatory interventions
- Main treatment is surgical



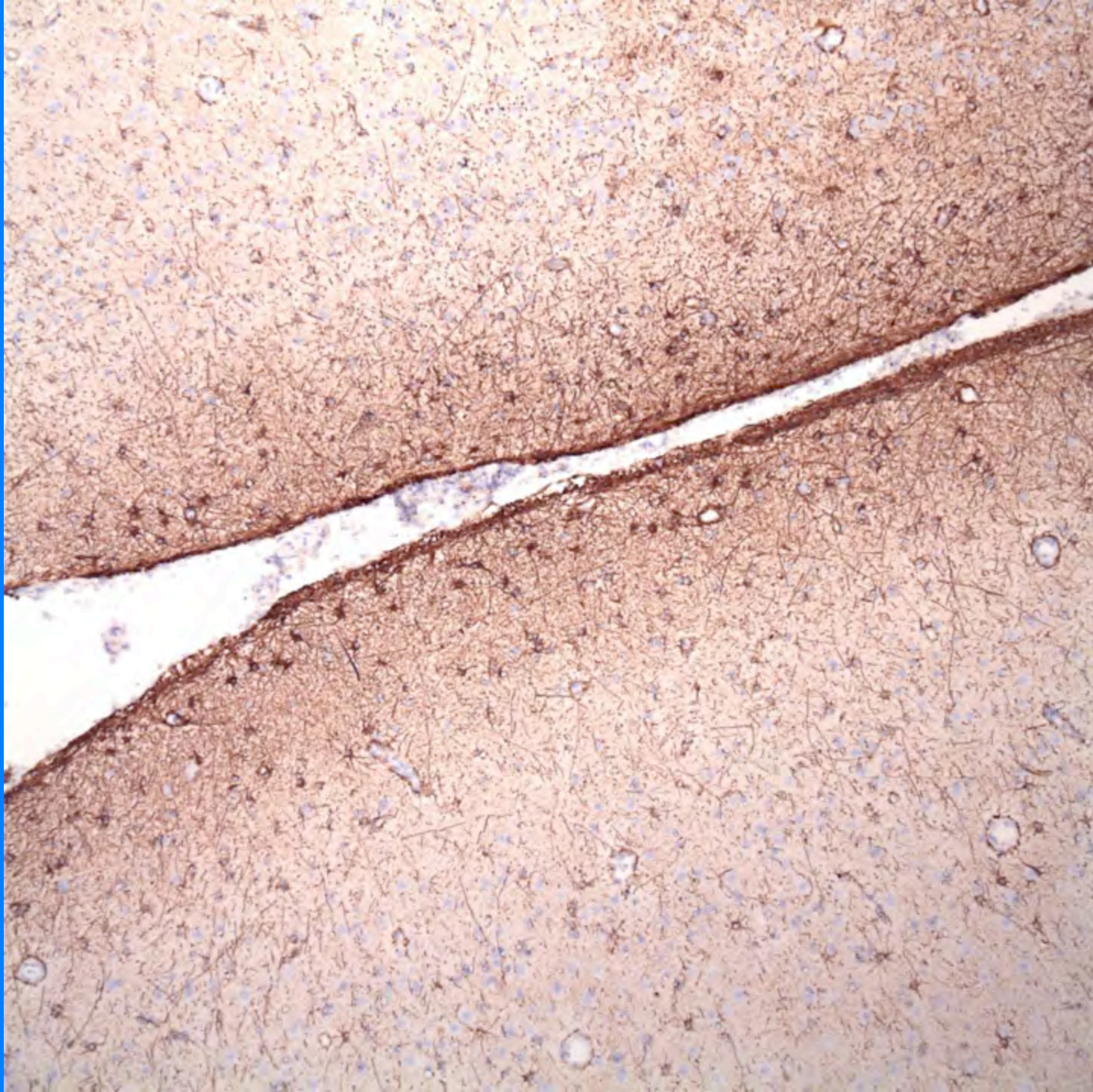
Cortex with lymphocytic infiltrates from Rasmussen's Encephalitis (two different cases)

Histologic Changes Secondary to Chronic Epilepsy

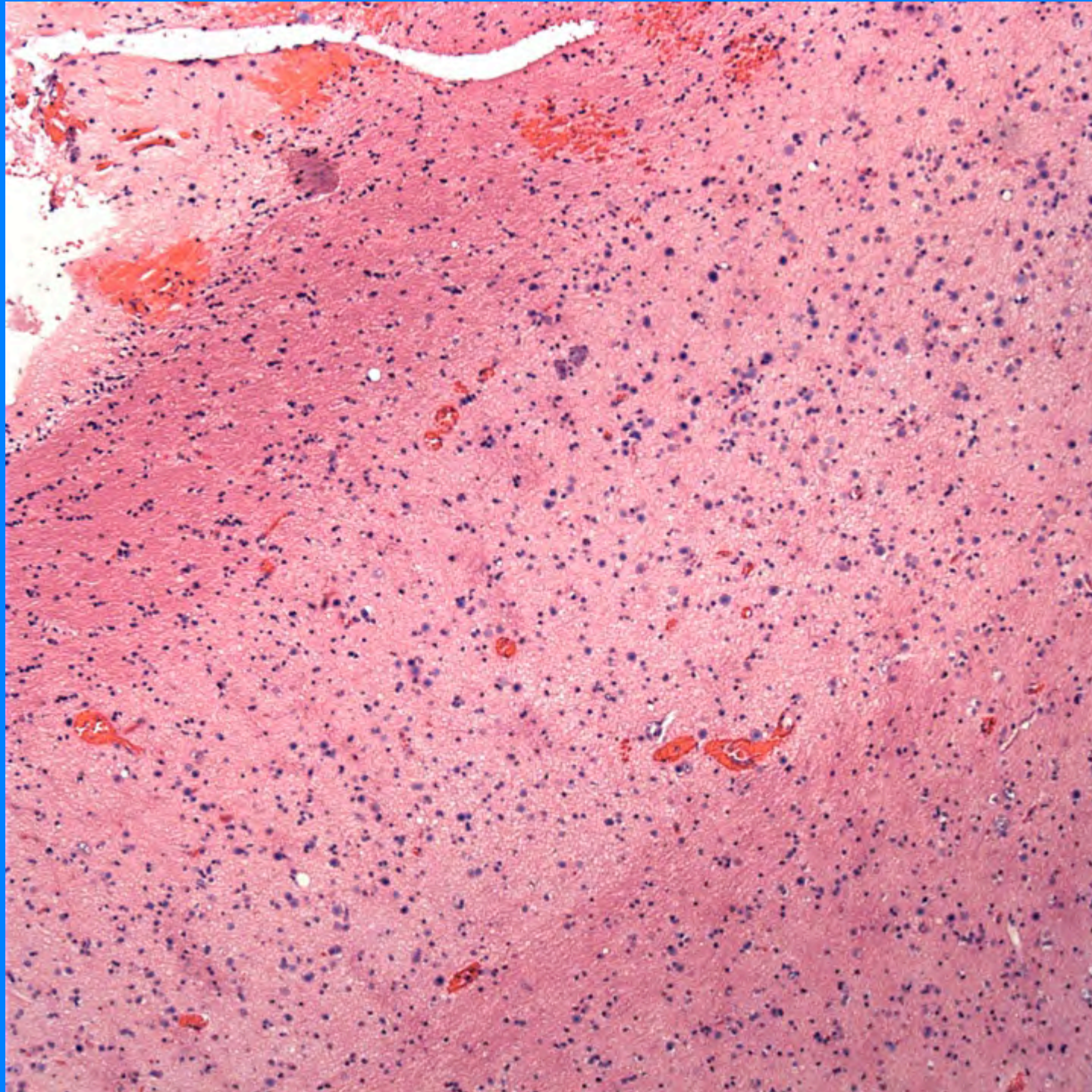
- Chaslin Gliosis
- Diffuse Gliosis, Cortex/White Matter
- Hippocampal Neuronal Loss & Gliosis (“Ammon’s Horn Sclerosis”, “Medial Temporal Sclerosis”, etc)



Chaslin Gliosis is seen as a thickening of the fibrillar matrix at the top of the molecular layer, just below the pia, with associated small astrocytes.



A GFAP
immunostain
highlights the
Chaslin gliosis.

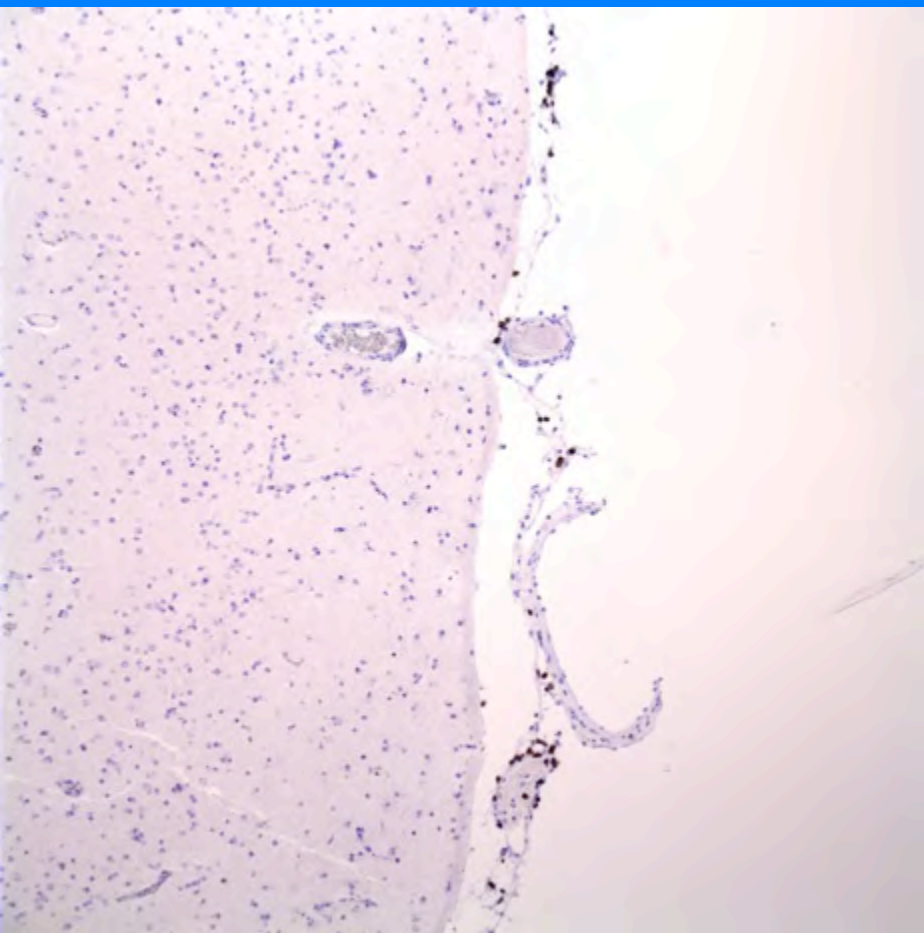


Hippocampal Neuronal Loss and Gliosis: This is the CA1 region (the Sommer Sector) and in this surgically resected hippocampus there is depletion of large pyramidal neurons with associated gliosis. This was originally described as a consequence of neonatal uncal herniation with compression of the posterior choroidal arteries leading to hippocampal ischemia, gliosis, and then later epilepsy. Subsequently it has become clear that some adults who have another cause for temporal lobe seizures, such as a contusion, acquire this as a second lesion. The epileptogenic nature of this abnormality is unproven, but it can clearly be a consequence of poorly-controlled temporal seizures.

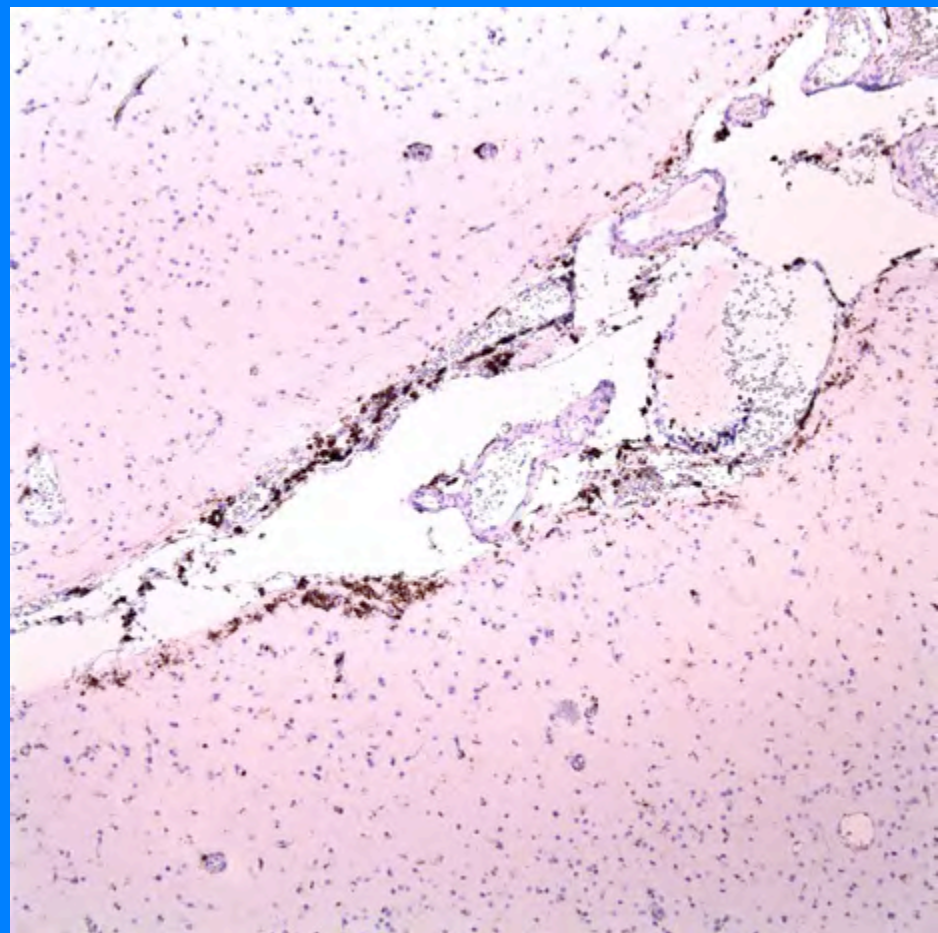
Iatrogenic Changes

- Chronic aseptic meningitis after invasive monitoring
- Linear tracks with macrophages after depth electrodes
- Cortical ischemic changes, infarcts, or contusions after placement of invasive monitoring devices

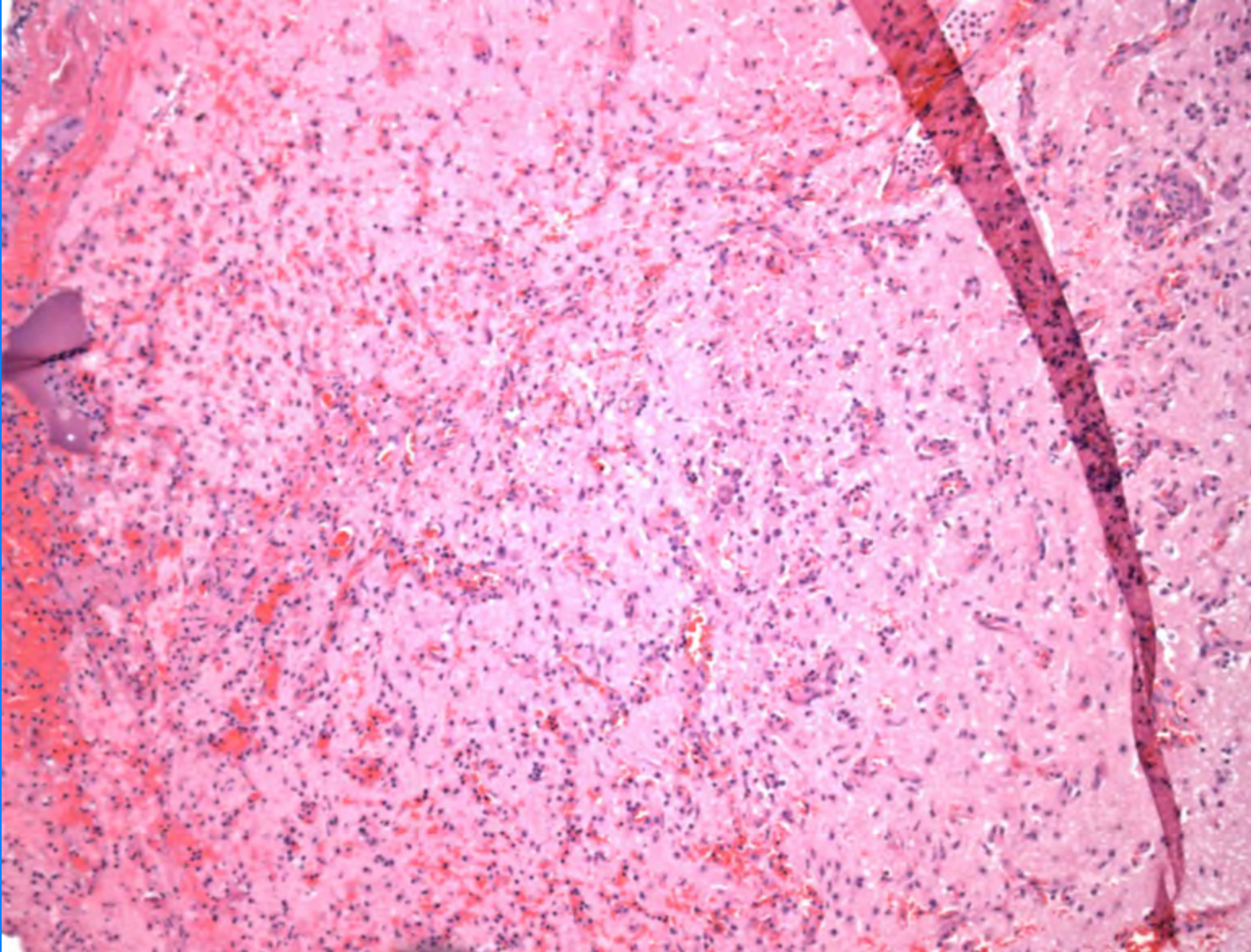
Patchy chronic inflammatory cell infiltrates in leptomeninges following one week of having implanted subdural electrode grids and strips



CD3



CD68



Subacute infarct in cortex under subdural grid, with macrophages in necrotic tissue and with proliferating capillaries.

Conclusion

- This has been a brief survey of the major types of findings one is likely to see in surgically resected brain tissues derived from epilepsy surgery. The depicted abnormalities are by no means the only ones that may be seen, but they are the more common or classic ones.
- My thanks for the opportunity to present this information to this group.