MJF COLLEGE OF VETERINARY AND ANIMAL SCIENCE, CHOMU, JAIPUR

DEPARTMENT OF VETERINARY PATHOLOGY

TSE

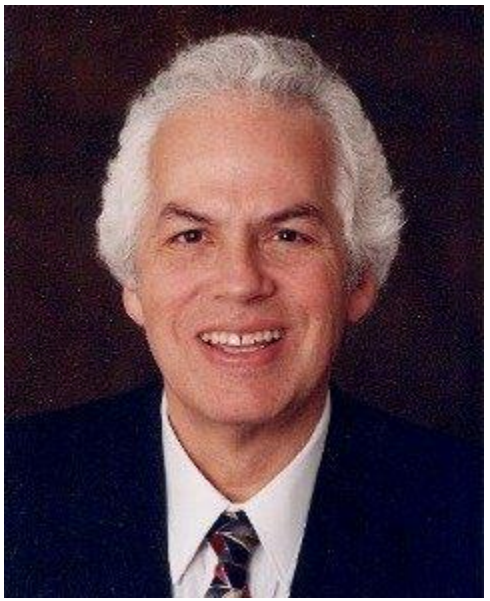
Transmissible Spongiform Encephalopathies

- Transmissible Spongiform Encephalopathies

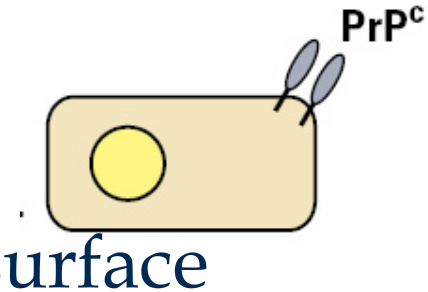
- Encephalopathies :
  - Non inflammatory conditions
  - No infiltration of inflammatory cells
  - Degenerative process

- Encephalitis
  - Inflammation of the parenchyma of the brain
  - Infiltration of inflammatory cells

- **Prions**
- Short form of " Proteinaceous Infectious Particle "
- Smaller than smallest known virus
- Not yet completely characterized
- Most widely accepted theory
- The word prion, coined in 1982 by **Stanley B. Prusiner -** Awarded the Nobel Prize for Medicine in 1997

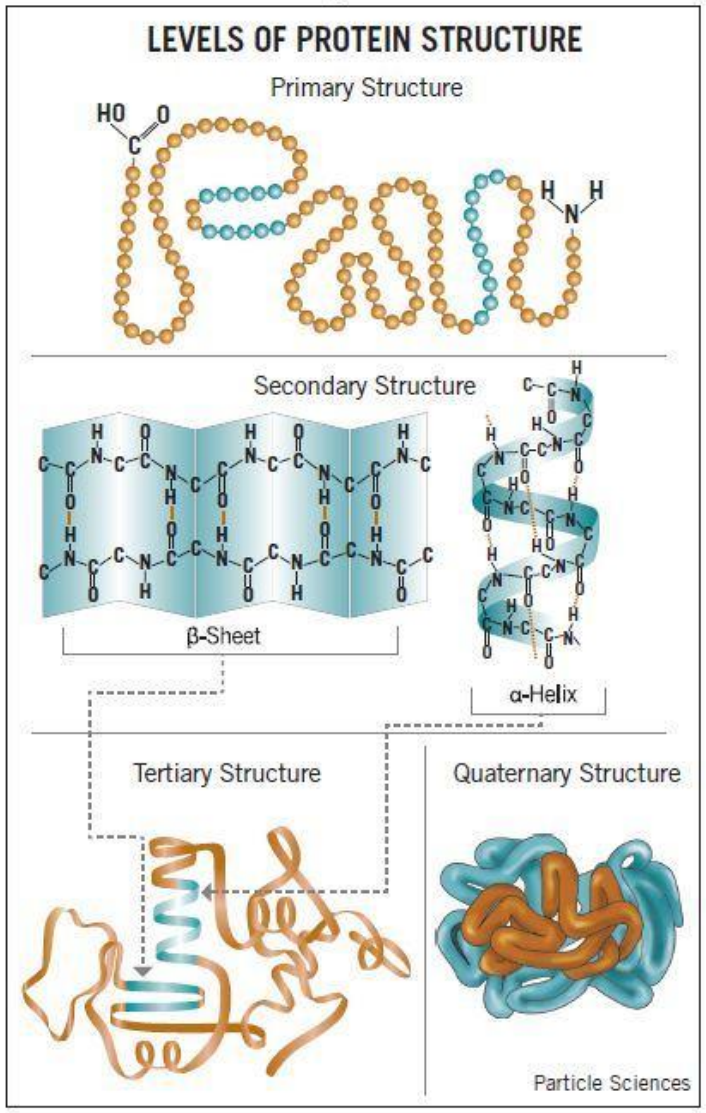


- Normal **Pr**ion **P**rotein
  - **PrP**^{C} (C for cellular)
  - Glycoprotein normally found at cell surface inserted in plasma membrane
  - Highest concentration in brain/neurons
- Function of Normal Prion Protein (PrP^{C})
  - Protection against apoptotic and oxidative stress
  - Binding of copper ions
  - Transmembrane signaling
  - Formation and maintenance of synapses
  - Adhesion to the extracellular matrix



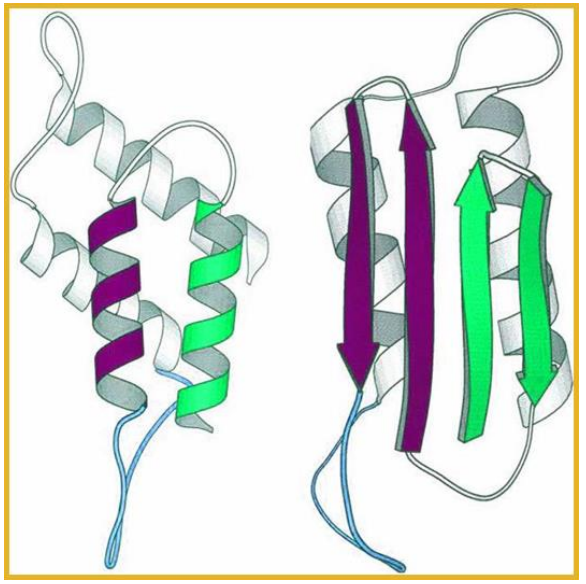
- Secondary structure dominated by alpha helices
- Easily soluble
- Easily digested by proteases
- Encoded by PRNP gene (in humans)
- Located on human chromosome 20

Figure 2



Abnormal Protein

- PrP^{Sc} (Sc for scrapie)
  - Self replication
- Same amino acid sequence and primary structure as normal protein
- Secondary structure dominated by beta conformation
- Insoluble in all but strongest solvents
- Highly resistant to digestion by proteases
- Survives in tissues post-mortem
- Extremely resistant - Heat,, sunlight
- No detectable immune response

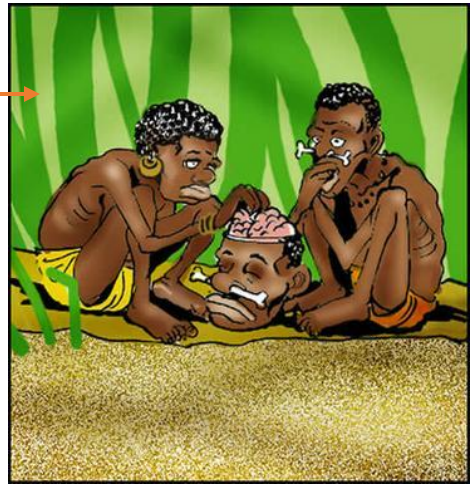


- Scrapie of sheep and goats
- Bovine spongiform encephalopathy (BSE)
- Chronic wasting disease (CWD) of deer and elk,
- Transmissible mink encephalopathy (TME)
- Feline spongiform encephalopathy (FSE)
- Exotic ungulate encephalopathy of captive wild Ruminants

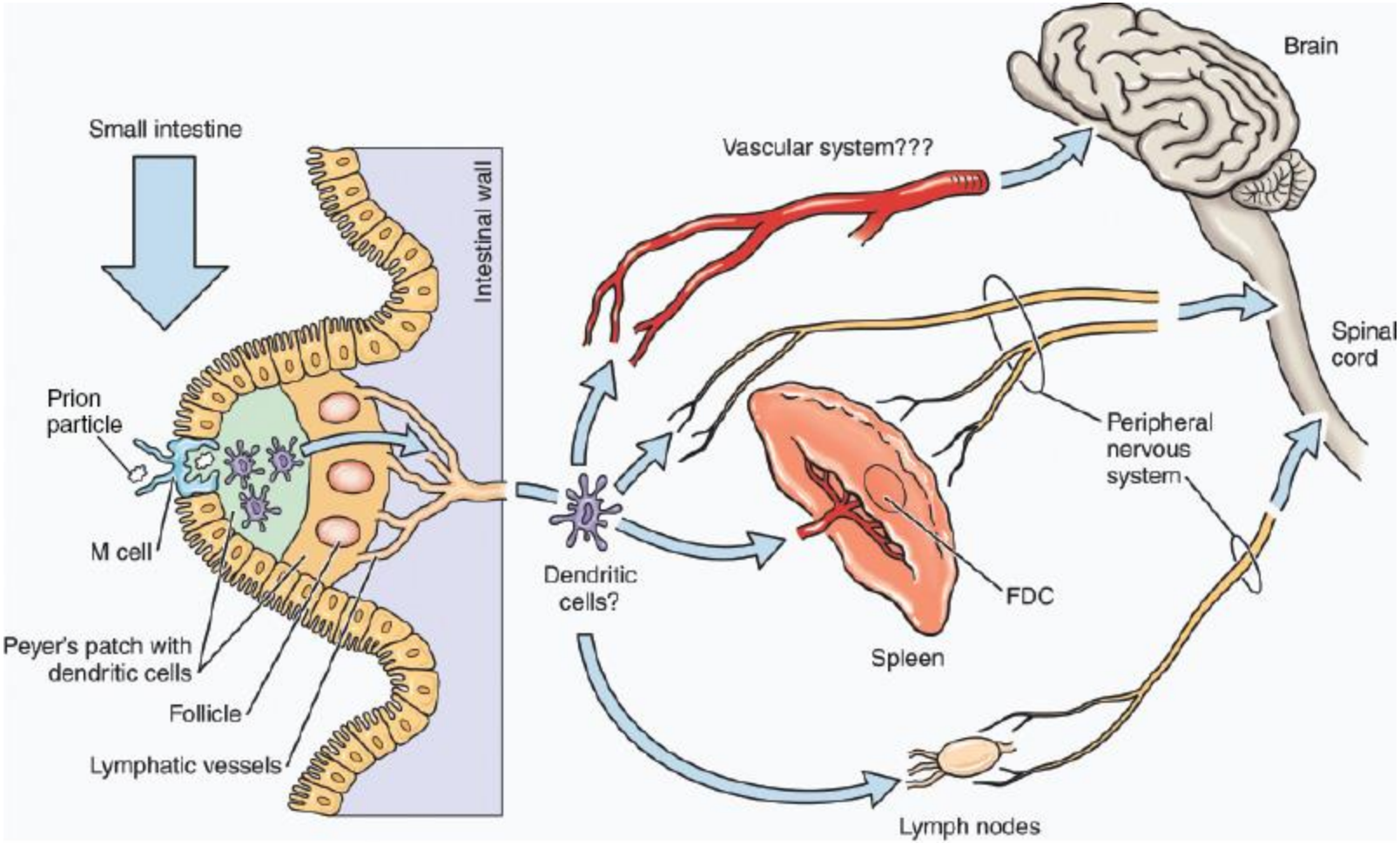
- Kuru
- Creutzfeldt-Jacob disease (CJD) – 4 types
  - Sporadic CJD
  - Familial CJD
  - Iatrogenic CJD
  - Variant CJD (vCJD)
- Gerstmann-Straussler-Scheinker disease (GSS)
- Fatal familial insomnia (FFI).

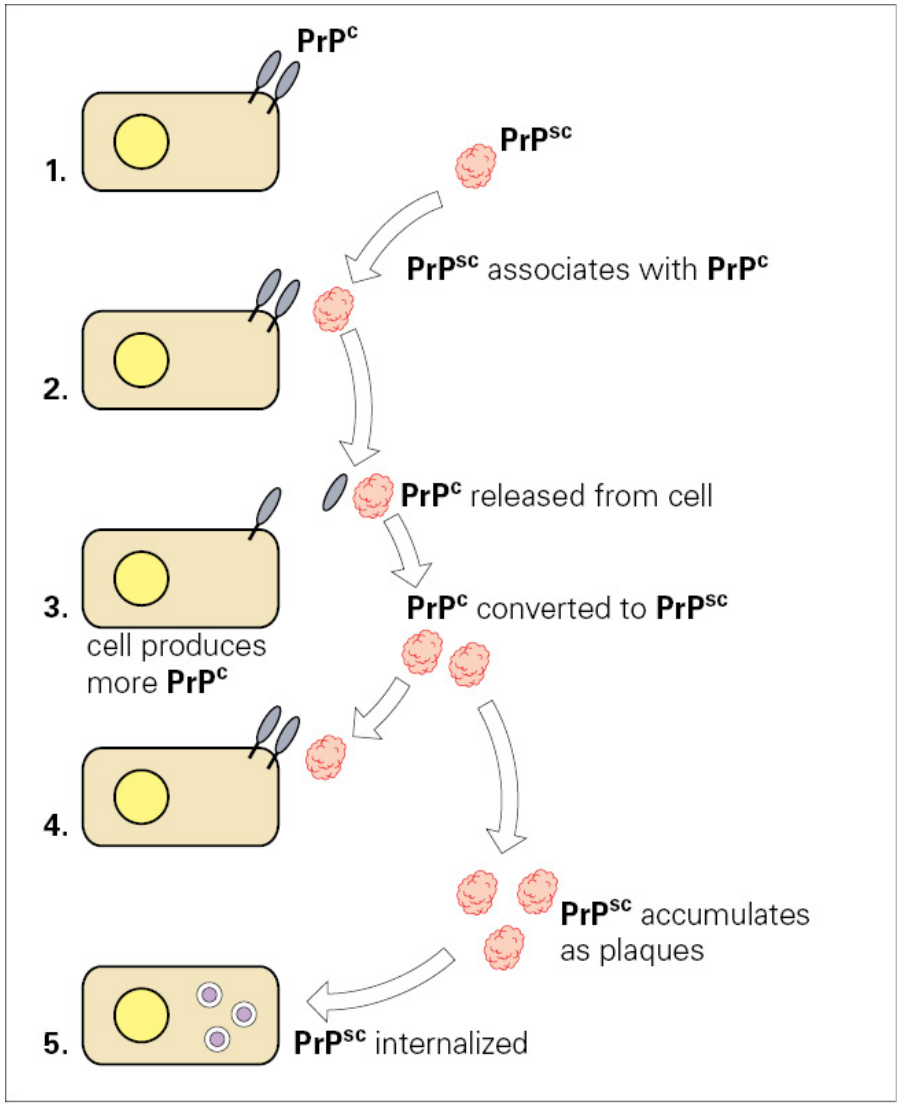
Not completely understood

- **Feed contaminated with PrP^{sc}**
- Spontaneous mutation
- Changes in feed processing
- Maternal transmission
- Likely spread ingestion of BSE contaminated feed
- Kuru - ritualistic cannibalism
- vCJD - BSE contaminated feed



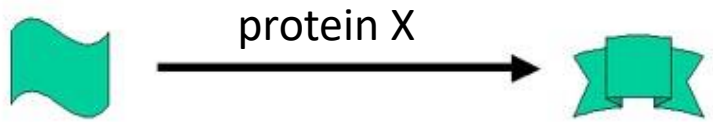
- **<u>Not completely understood - Hypothesis</u>**
- Following ingestion PrP^{sc} attached to epithelial cells → Infects M cells and APC cells → spread systemically via leukocyte trafficking → Infect follicular dendritic cells and B lymphocytes → PrP^{sc} replication and accumulation (may be up to 2 years) → PrP^{sc} infect/enter nerve ending present in lymphoid tissue → Travel through nerve, reach to spinal cord and brain → localizes in the medulla oblongata and diencephalon → Infect and enter to the various neurons → in lysosomes PrP^{sc} replicate and acts as a template and catalyst for the abnormal folding and polymerization of PrP^{c} → PrP^{c} converted to PrP^{sc} (with help of protein X)→ PrP^{sc} resistance to endogenous proteases → In neurons accumulate and polymerize into plaques of scrapie-associated fibrils (SAF) →





(From Goering R, Dockrell H, Roitt I, et al: *Mims' medical microbiology*, ed 4, St. Louis, 2008, Mosby.)
Zachary and McGavin: Pathologic Basis of Veterinary Disease, 5th edition.

PRION PROTEIN (PrP)

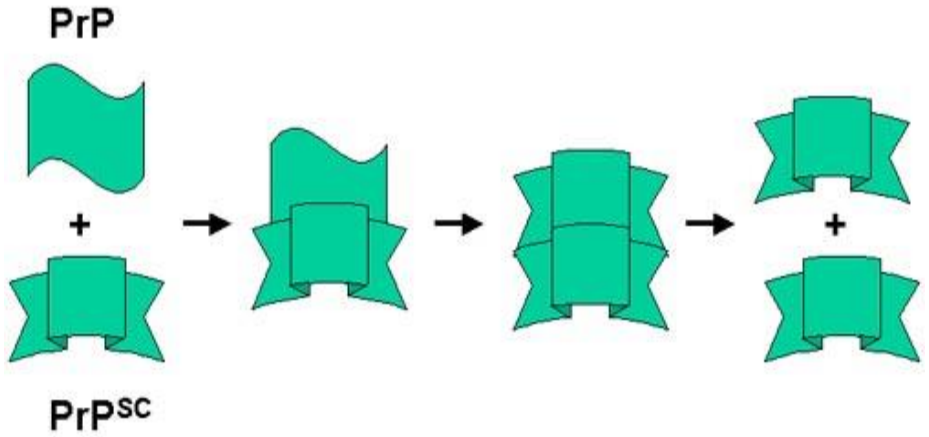


PrP
alpha-helical
protease sensitive

Helical - Happy

PrP^RES or PrP^SC
beta-pleated sheet
protease resistant

Beta-pleated sheet - Bad



- Accumulated PrP^{sc} in neurons leads to
  - Mechanical destruction of nerve cell membranes from the excessive accumulations
  - Lysosomal accumulation of PrP^{sc} may trigger apoptosis
  - PrP^{sc} may be a direct neurotoxin
- This may leads to neuronal vacuolation and nervous signs
- Leads to death

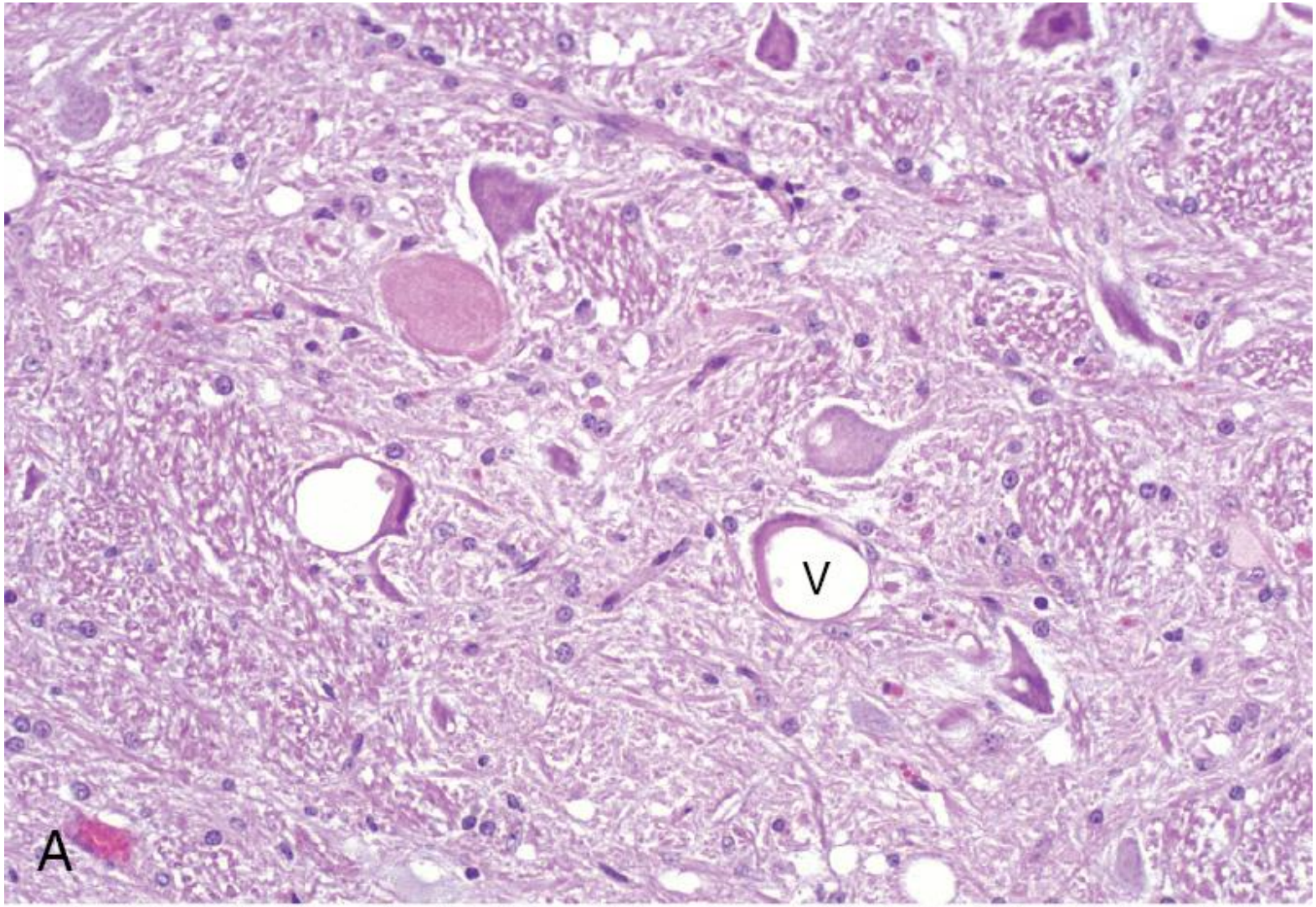
- **First prion disease** to be recognized and described, around 1732 in the UK
- Long incubation period – 2 to 5 years
- **Host**: sheep (and, rarely, of goats)
- **Clinical signs**
  - Seen at 3-5 years of age, signs lasting months to years.
  - Nervousness and excitement; ataxia; head tremors
  - Weight loss; impaired vision; abortion
  - **Pruritus:** agitated rubbing against posts and trees, and nibbling at the feet and legs when lying down behavior that gave rise to the name "scrapie.“
    - May be due to cutaneous paresthesia

Macroscopic

- No gross lesions
- Self-trauma secondary to pruritus

Microscopic

- **Single large or several smaller neuronal intracytoplasmic vacuolation**, degeneration (central chromatolysis), necrosis
- Vacuoles cause neuropil spongiosis.
- Cerebrovascular amyloid deposition, thought to contain prion protein
- Astrocytic proliferation and hypertrophy
- Symmetric lesions occur along brain stem and spinal cord
- No inflammatory reaction or evidence of an immune response



(Courtesy Dr. D. Gould, College of Veterinary Medicine and Biomedical Sciences, Colorado State University; and Dr. M. McAllister, College of Veterinary Medicine, University of Illinois.)
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- **Synonym: Mad Cow Disease**
- Long incubation period – 2 to 8 years
- **Host**: Bovines
- **Clinical signs**
  - Initial neurological signs
    - Often subtle
    - Fear, easily shocked, depressed
  - Final stages
    - Excitable, hyperreflexia, hypermetria, ataxia, muscle tremors
  - Terminal state
    - Loss of body weight and condition despite good appetite
  - Affected herds: 2 to 3% morbidity; 100% mortality

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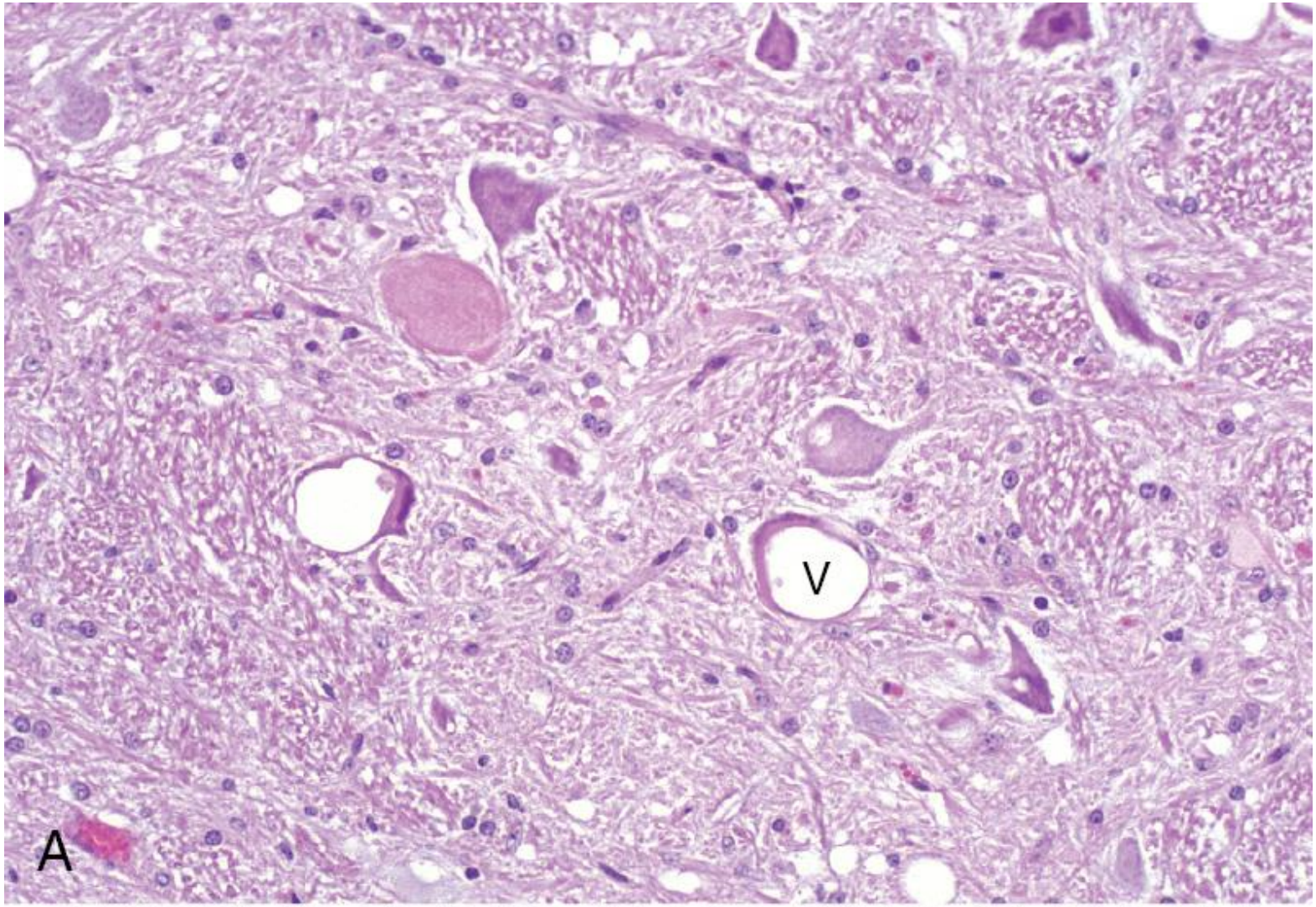

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- Slowly progressive, fatal neurologic disease
- **No antemortem testing available**
  - Brain, medulla, spinal cord, brain stem – Collected at PM
  - Histopathology - Spongiform changes in gray matter
  - **Immunohistochemistry - Gold standard**
- Rapid diagnostic tests
  - Western blotting, ELISA