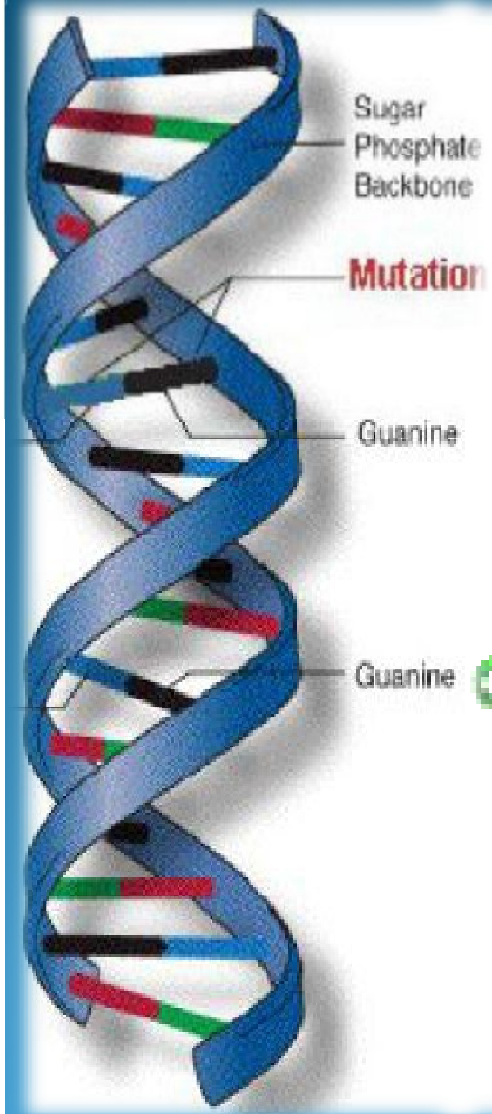
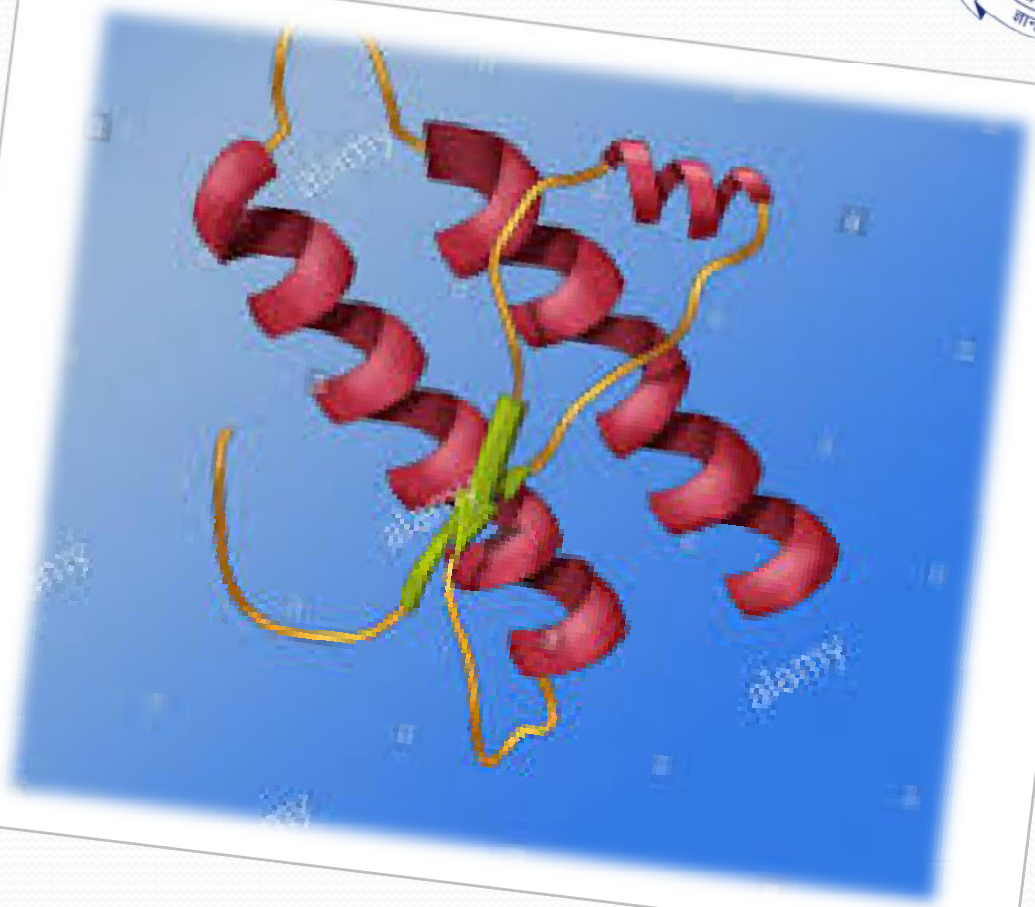
Prion Diseases



Dr. Kaushal Kumar
Assistant Professor & Head
Department of Veterinary Pathology
Bihar Veterinary College
Bihar Animal Sciences University,Patna

Outline of Presentation

- Prion
- Prion Diseases
- History
- Transmission
- Pathogenesis
- Diagnosis



Historical background

1920- Creutzfeldt and Jakob described first cases of progressive neurological disorder in young patients

The eponyme- 'Creutzfeldt-Jakob Disease'(CJD

1950- Disease known as 'kuru', in Papua New Guinea discovered; neuropathological findings were similar to CJD

1960- the term transmissible spongiform encephalopathy (TSE) applied after discovery of the transmissible ability of both kuru and CJD diseases to chimpanzees

1990-Outbreak of BSE in cattle in UK raised public concern and spawned vigorous research efforts to understand mechanism underlying TSE.

1997- Stanley B Prusiner was awarded Nobel Prize in Medicine for his work on 'protein-only' hypothesis and prions.

Prions

- ✓An acronym for 'Proteinaceous Infectious Particle.'
- ✓Prions are novel transmissible pathogens
- ✓No nucleic acid
- ✓Resistance to protease treatment (proteinase K)
- ✓Non-degradable by typical sterilization
- ✓Insensitive to irradiation such as UV 254nm (suggests that nucleic acids are not present)
- ✓Existing somewhere in the border zone between living things and non-living matter

Prions

How are prions different from viruses?

A. Prions can exist in multiple molecular forms whereas viruses exist in a single form with a distinct ultrastructural morphology (prion infectivity detected in prion particles with a wide range of sizes)

B. Prions are non-immunogenic because the normal protein PrPC renders the host tolerant to PrPSc, viral proteins are seen as "foreign" and hence immunogenic.

Structutre of Prions Protien

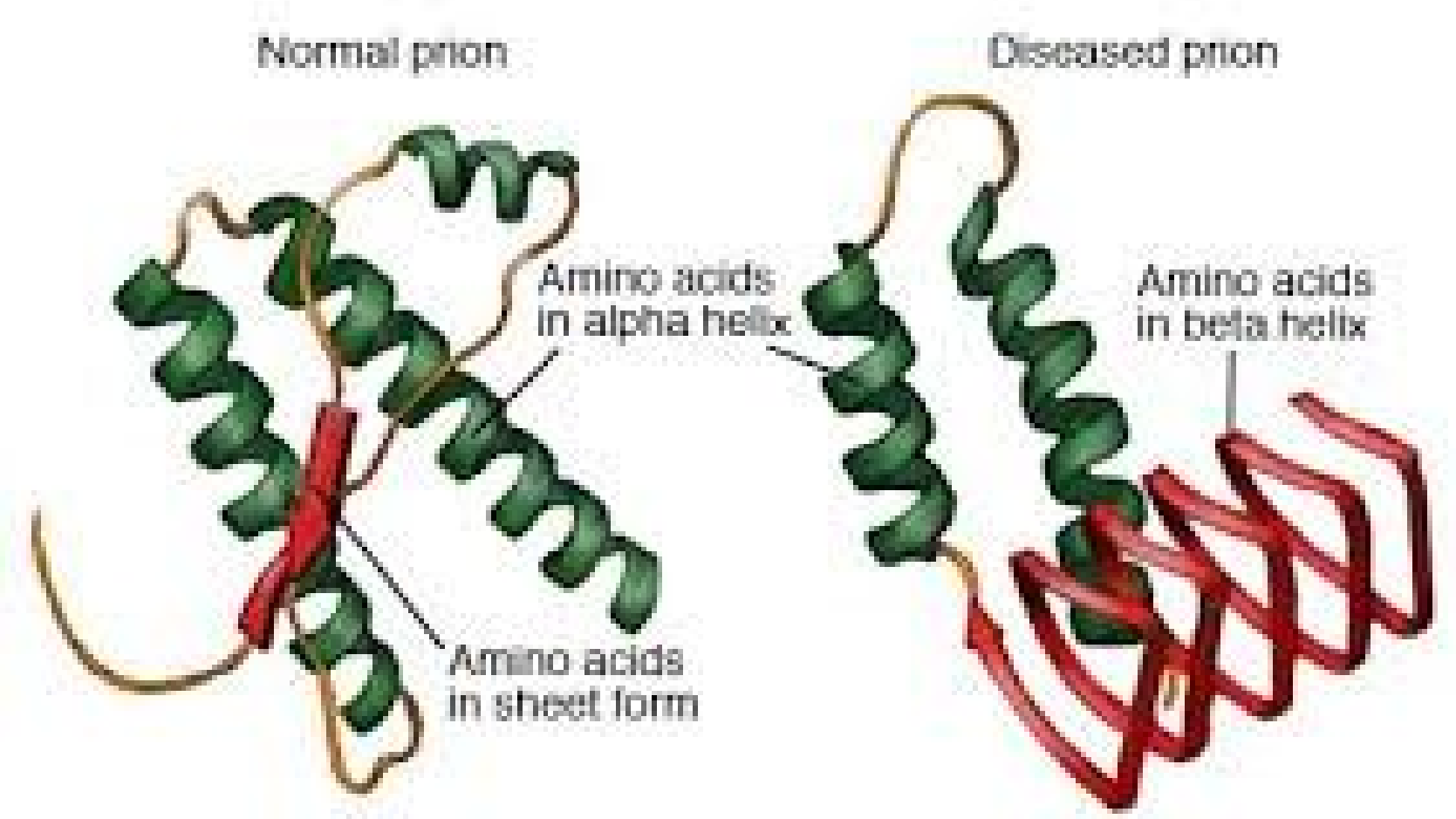
- The prions are exclusively composed of glycoprotein called prion protein (PrP).
- PrP^{c} is a normal protein found in the membrane of cells (the c refers to cellular or common).
- Pr P^{sc} is the infections form (the sc refer to scrapie)

Structutre of Prions Protien

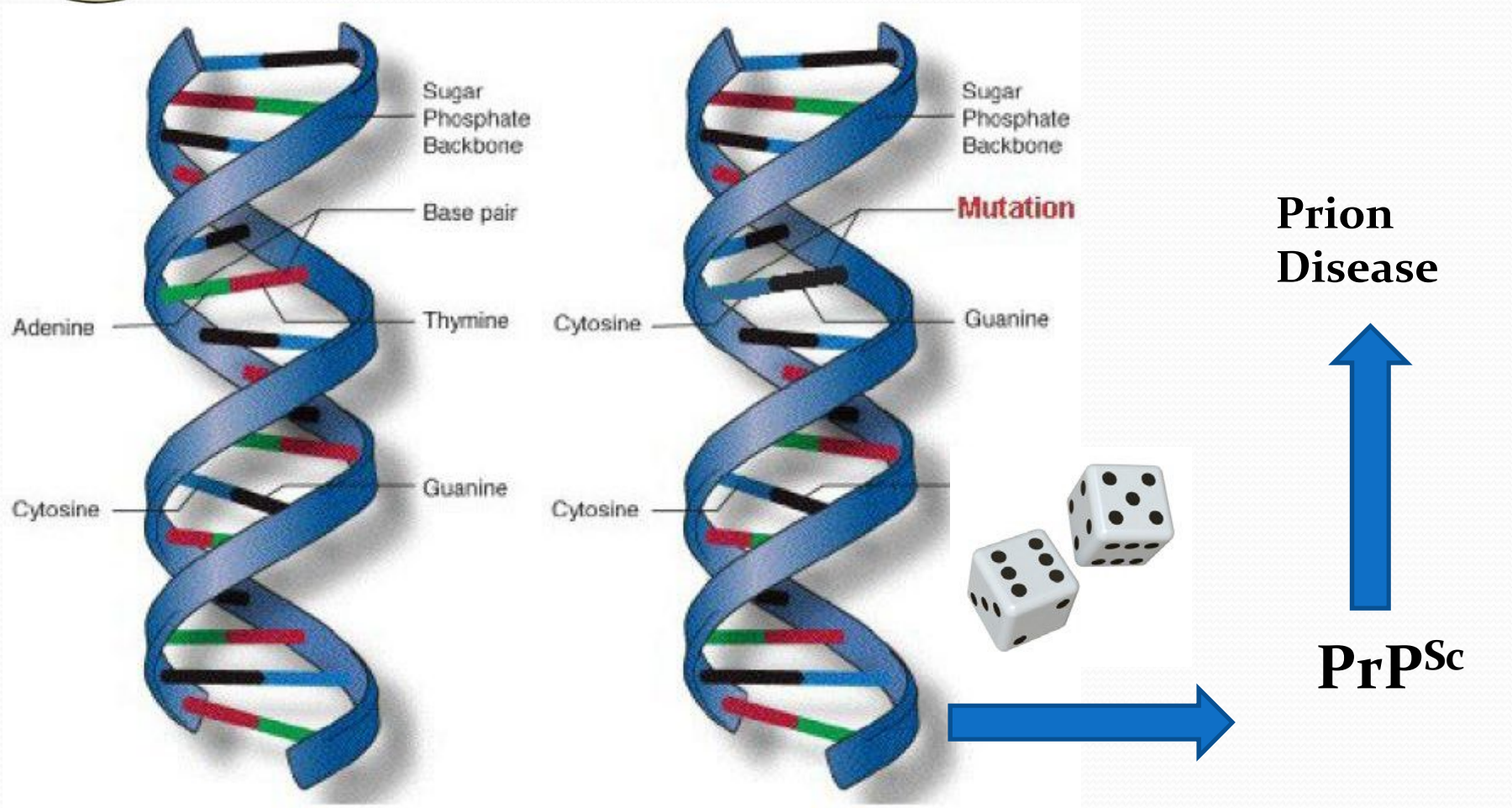
- PrP^{c} has 209 amino acids , one disulfide bond, a molecular mass of 35-36 KDa and a mainly alpha-helical structure.

- Pr P^{sc} is able to convert normal PrP^{c} proteins into infectious isoform by changing their conformation, or shape, this in turn, alters the way, the prion interconnect. It has a higher proportion of B-sheet structure.

Structutre of Prions Protien



Genetic Prion Disease



Multiplication of Prions

- Prions multiply by transmitting a misfold protein state.
- When prion enters a healthy organism, it induces existing properly folded proteins to into disease associated prion form.
- The cellular prion acts as a template to guide misfolding of more proteins into prion form.
- These newly formed prions can then go on to convert more proteins themselves, this triggers a chain of reaction that produces a large amount of the prion forms.

Multiplication of Prions

- To-explain this Heterodimer model is given.

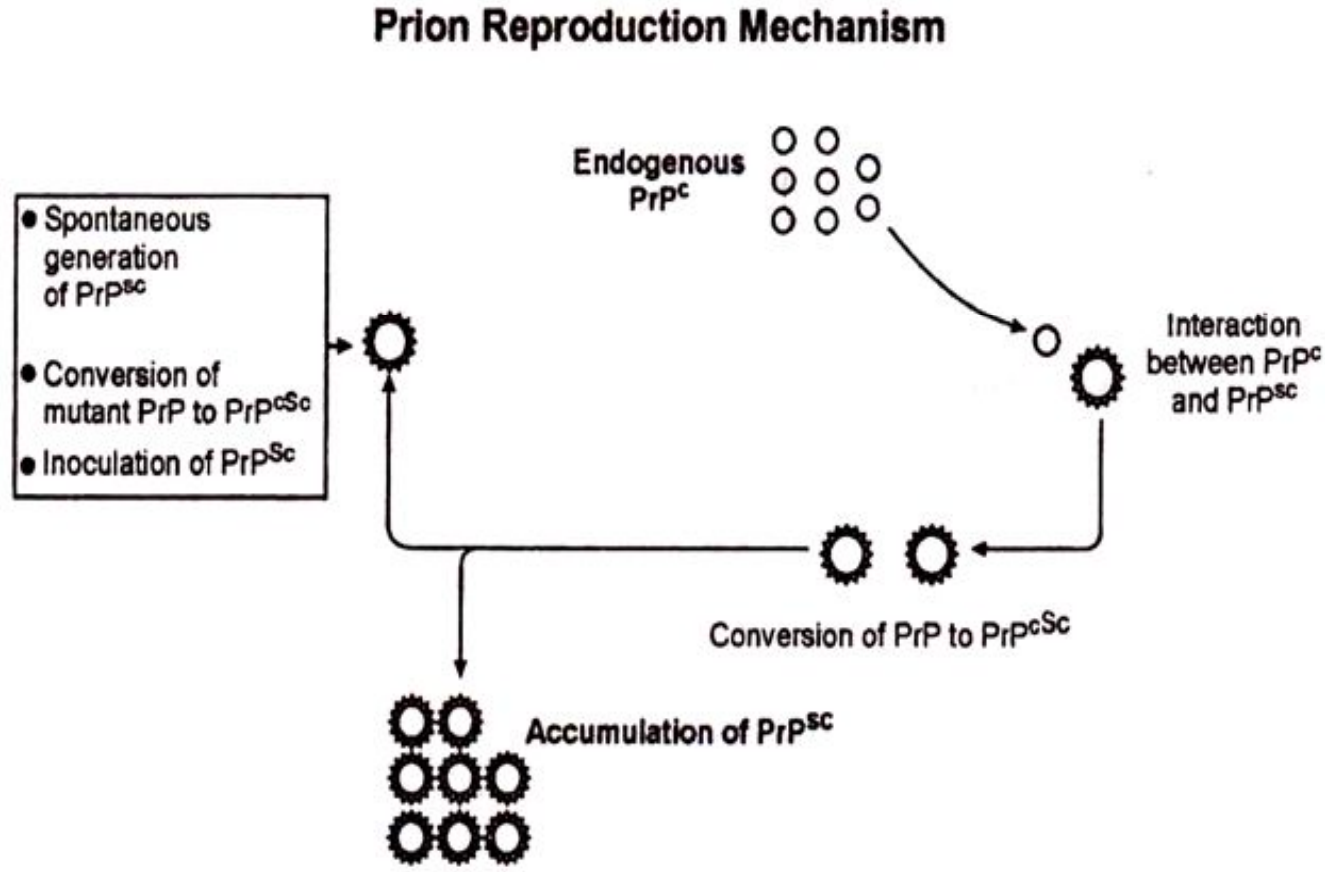
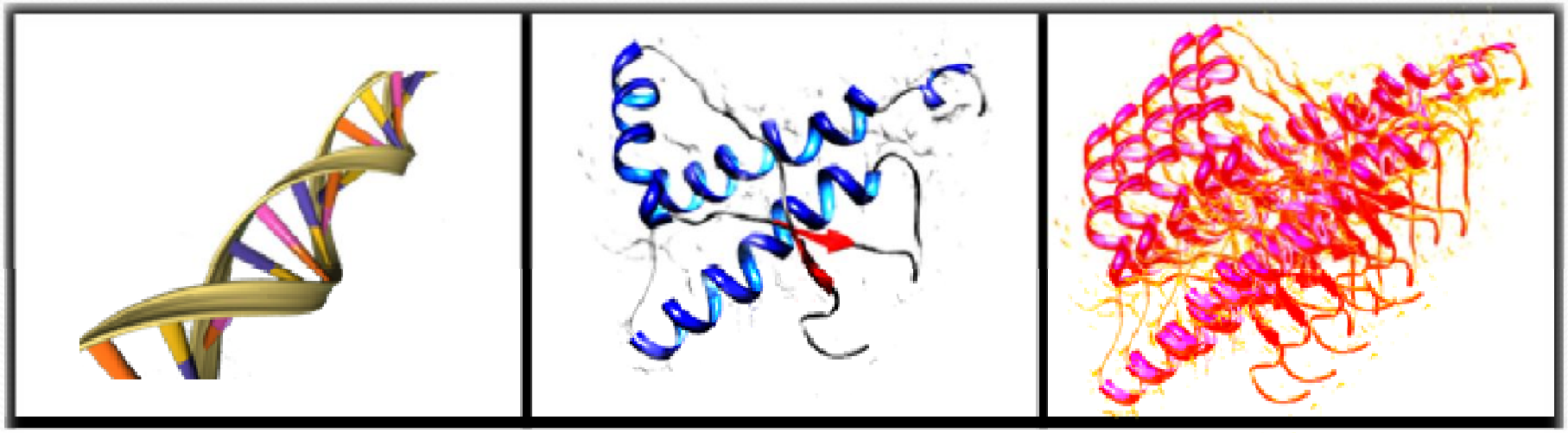


Fig. 3. Heterodimer model of prion propagation.

Prion Protien



PRNP is a gene in your DNA which encodes for prion protein

Prion protein or **PrP** is a protein on the surface of your cells

A **prion** is an infectious particle made up of misfolded prion proteins

Prion diseases

- **A group of invariably fatal neurodegenerative diseases**
- **Can present as a genetic, infectious, or sporadic (spontaneous) disorders**
- **All are believed to involve modifications of the prion protein (PrP^c)**
- **Incidence of all human prion diseases: 1 in 1,000,000**

Prion diseases

Human: Creutzfeldt-Jakob disease (CJD)

Gerstmann-Straussler-Scheinker disease (GSS)

kuru

Animals: Scrapie (goats and sheep)

Bovine Spongiform Encephalopathy (BSE or MadCow)

Chronic Wasting Disease (deer and elk)

Transmissible Spongiform Encephalopathy: TSE

Transmission

- Can be transmitted in other individuals of the same or closely related species:

  by injection or

  by ingestion of infected tissue and

- Prions (PrP^{Sc}) sheds from sheep and goats in birth fluids, feces and other excrement.
- Appear to be transmissible between species that are not closely related e.g., between cattle and humans.
- ***Recent studies suggest prions may be spread through urine and persist in the environment for decades***

Scrapie

A fatal, degenerative disease affecting the nervous system of Small Ruminants. It usually affects sheep around 3-5 Yrs of age

✓**CLINICAL SIGNS**

affected animals scrape off their fleeces against rocks, trees or fences.

✓The disease apparently causes an itching sensation in the animals.

Other signs include excessive lip smacking ltered gait and convulsive collapse

Ewe with scrapie with weight loss and hunched appearance

Bovine Spongiform Encephalopathy

Also known as **mad cow disease**, is a neurodegenerative diseases of cattle. They are believed to have been infected by being fed meat and–bone meal(MBM) that contained the remains of cattle who spontaneously developed the disease

✓**CLINICAL SIGNS**

abnormal behavior, trouble walking, and weight loss.

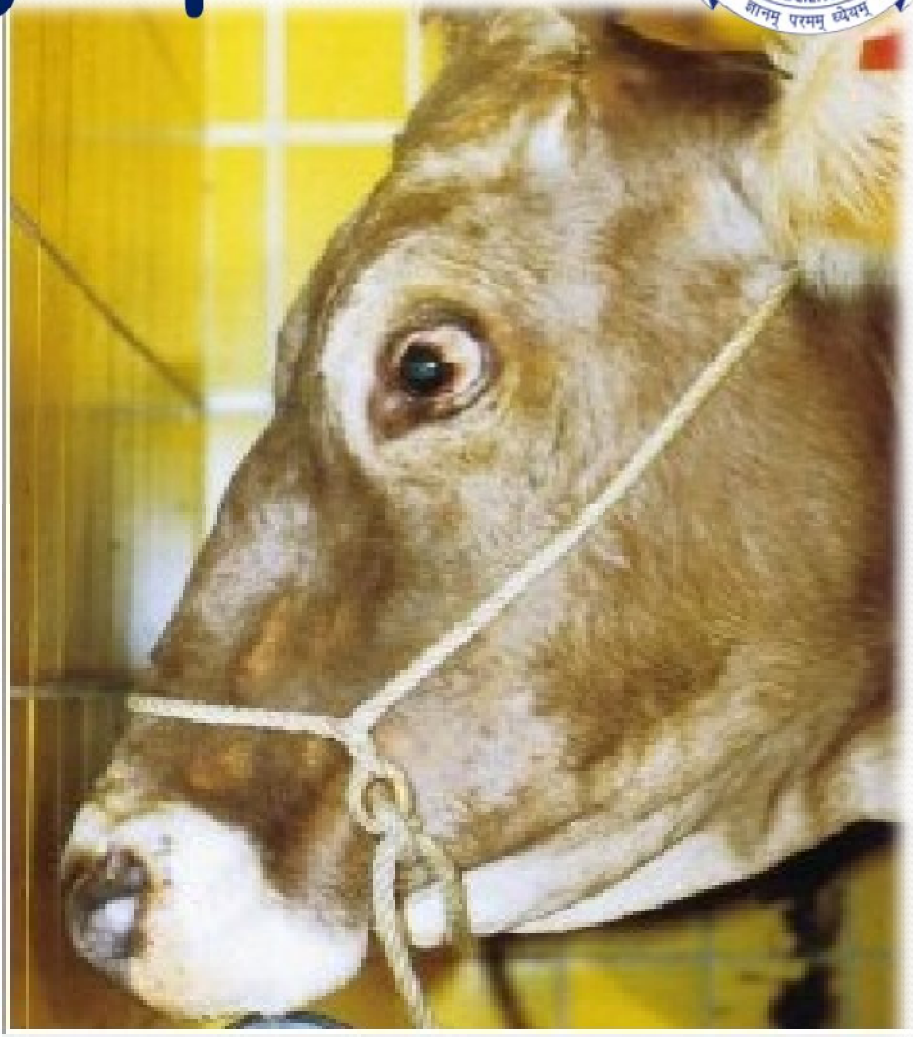
✓The disease apparently causes an itching sensation in the animals.

Other signs include excessive lip smacking ltered gait and convulsive collapse

A cow with BSE which has lost his ability to stand

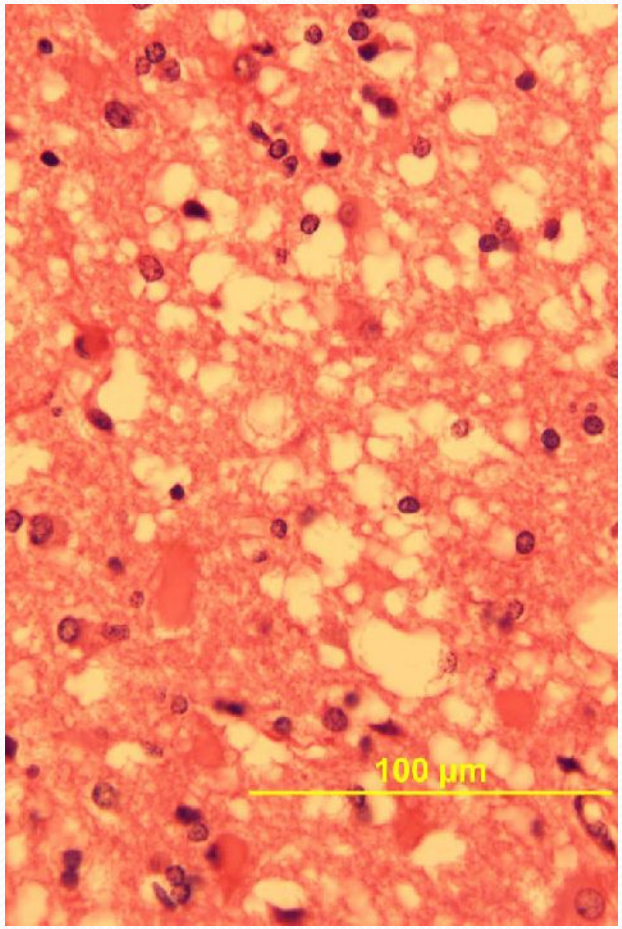
Sign & Symptoms

Ataxia and hypermetria of infected cow.

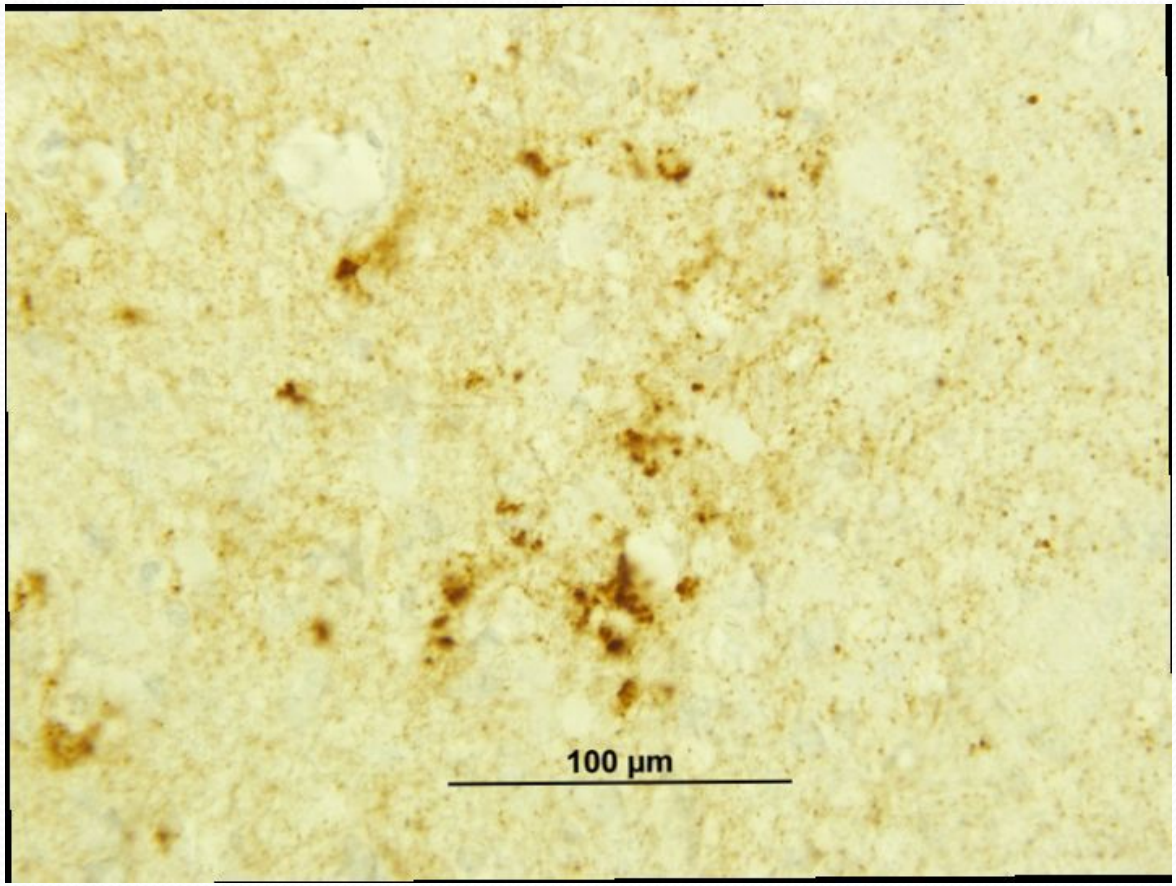


Nervousness when confronted with obstacles.

Neuropathology

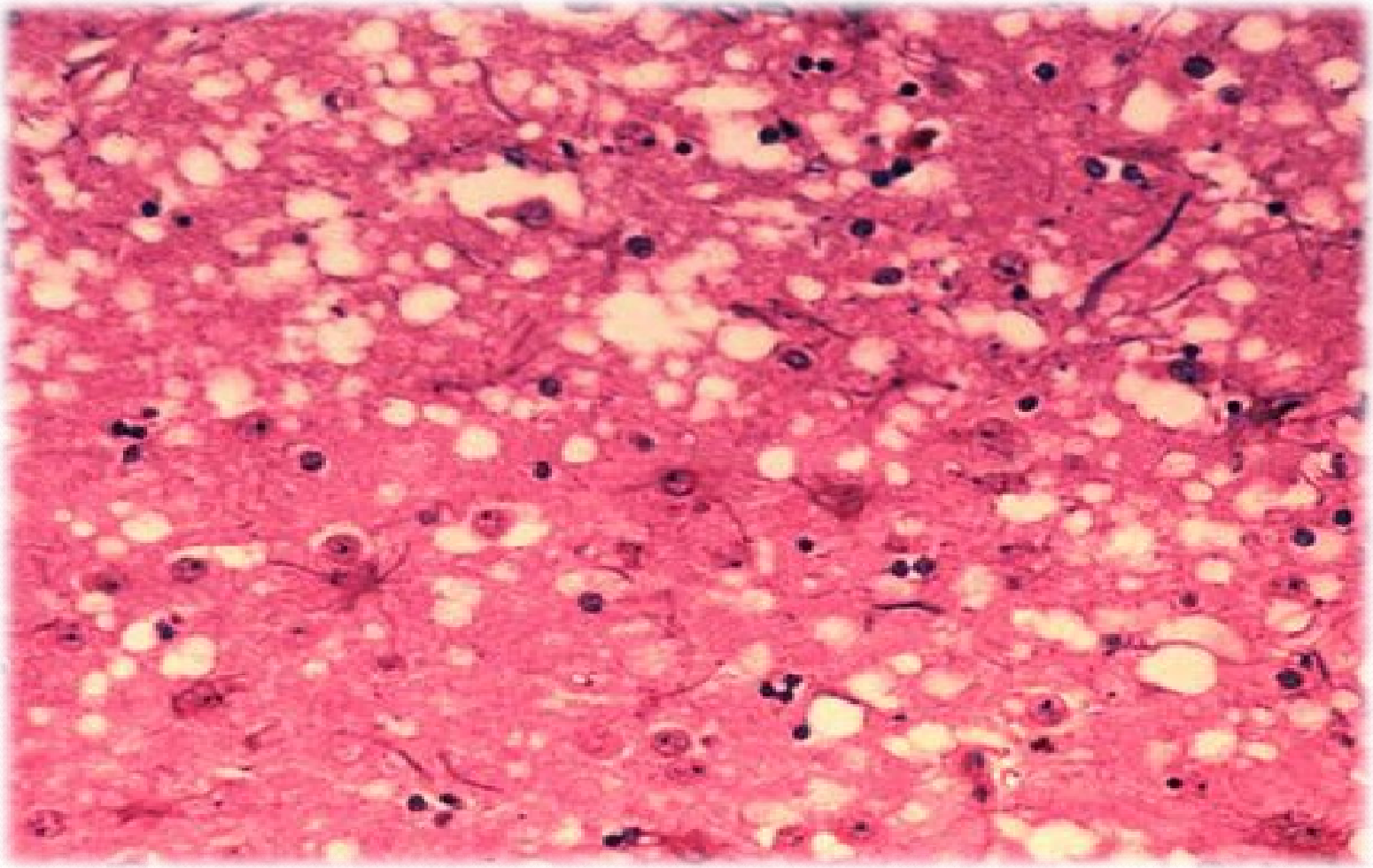


H & E Staining
(spongiform changes)



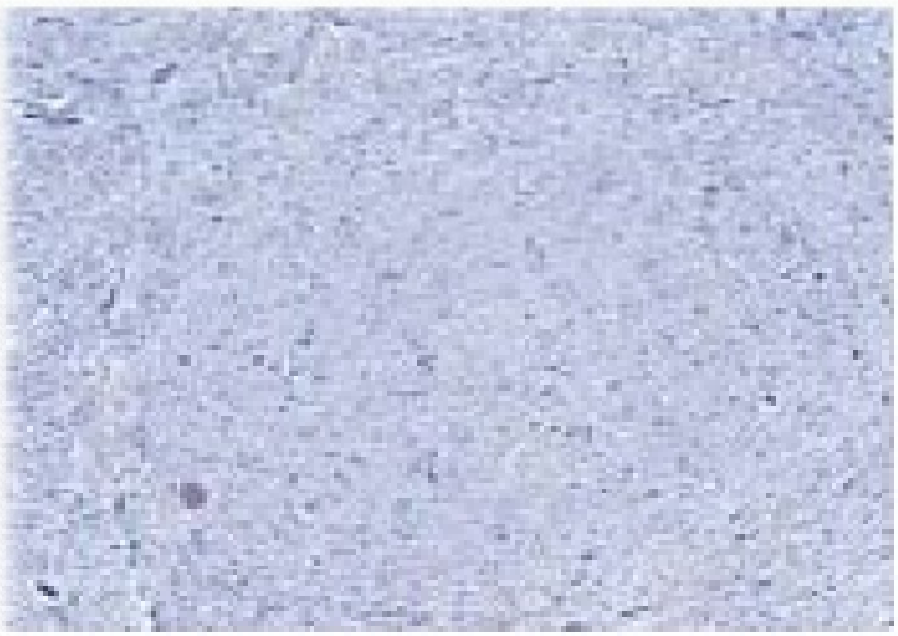
Immunohistochemistry
(abnormal prion protein)

Lesion

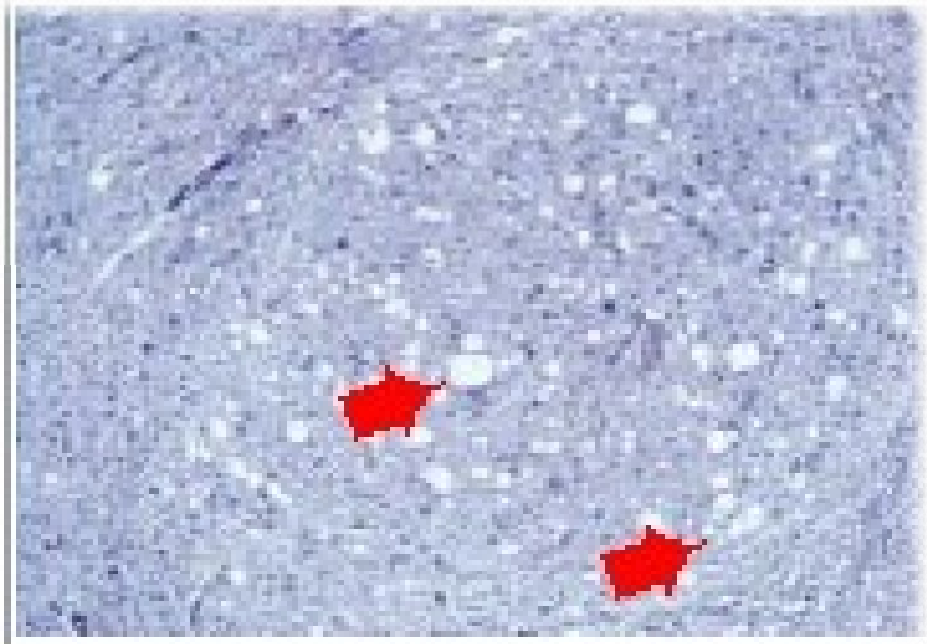


Brain tissue of a cow with BSE showing the typical microscopic "holes" in the grey matter

Lesion



Normal histologic aspect of gray matter.



Vacuolisation of gray matter in BSE affected cow.

Diagnosis

Diagnosis of BSE continues to be a practical problem.

It has an incubation period of months to years, during which no signs are noticed, though the pathway of converting the normal brain prion protein (PrP) into the toxic, disease-related PrP^{Sc} form has started.

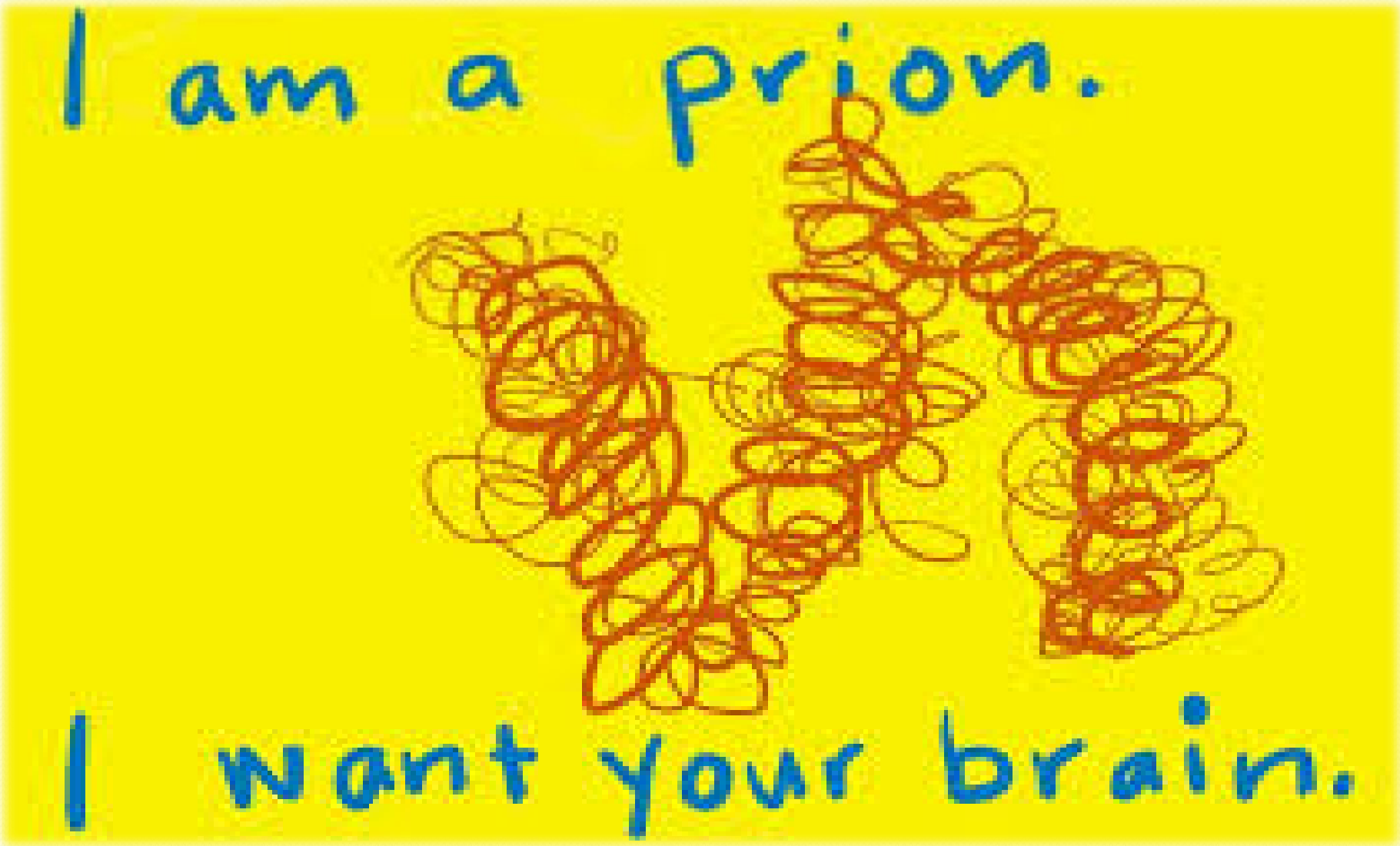
At present, virtually no way is known to detect PrP^{Sc} reliably except by examining *post mortem* brain tissue using neuropathological and immunohistochemical methods.

The traditional method of diagnosis relies on histopathological examination of the medulla oblongata of the brain

Diagnosis

- Accumulation of the abnormally folded PrP^{Sc} form of PrP is a characteristic of the disease, but it is present at very low levels in easily accessible body fluids such as blood or urine.

- Researchers have tried to develop methods to measure PrP^{Sc}, but no methods for use in materials such as blood have been accepted fully


I am a prion.
I want your brain.