Prions

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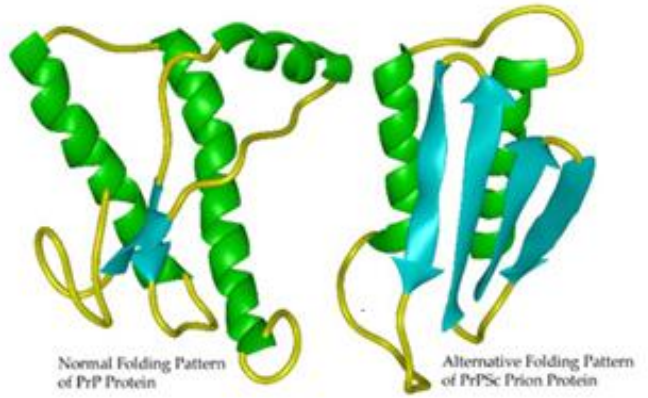
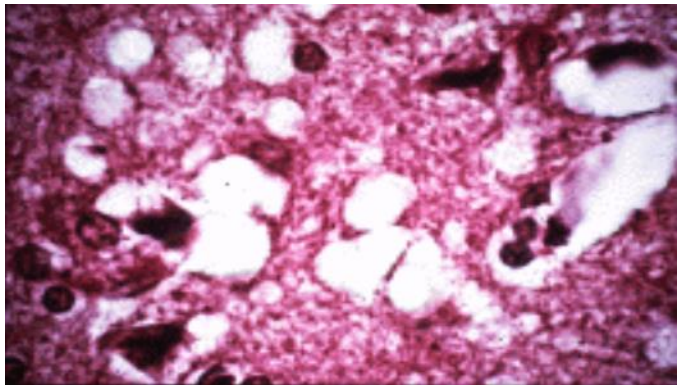
PRIONS



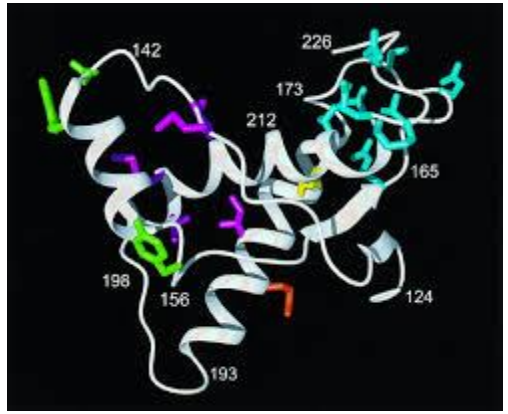
- Small proteinaceous infectious particles
- Transmissible Encephalopathies (TSEs)
- Post mortem appearance of the brain with large vacuoles in the cortex and cerebellum
- Fatal neuro- degenerative disorders:

  Humans

  Animal (mamals)



Introduction



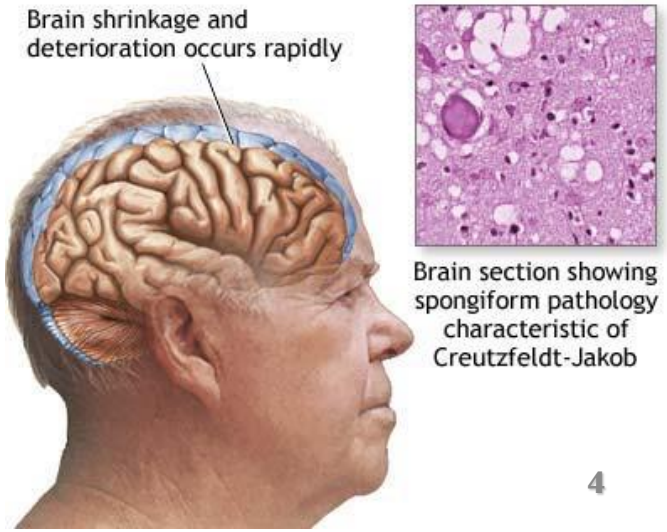
- All are transmissible portions without nucleic acid :
  Infectious/transmissible

- Deposition of abnormal isoform of the host-encoded prion protein (PrP)

- Unique category of infectious protein-misfolding

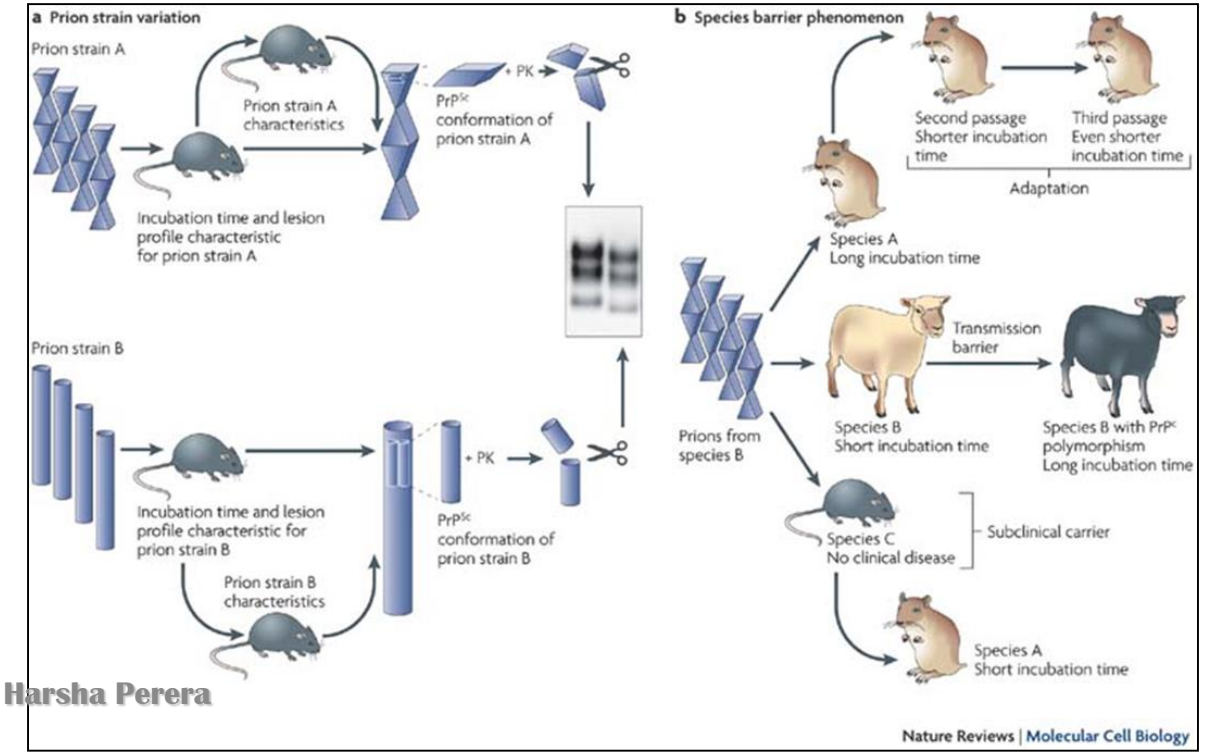
Introduction

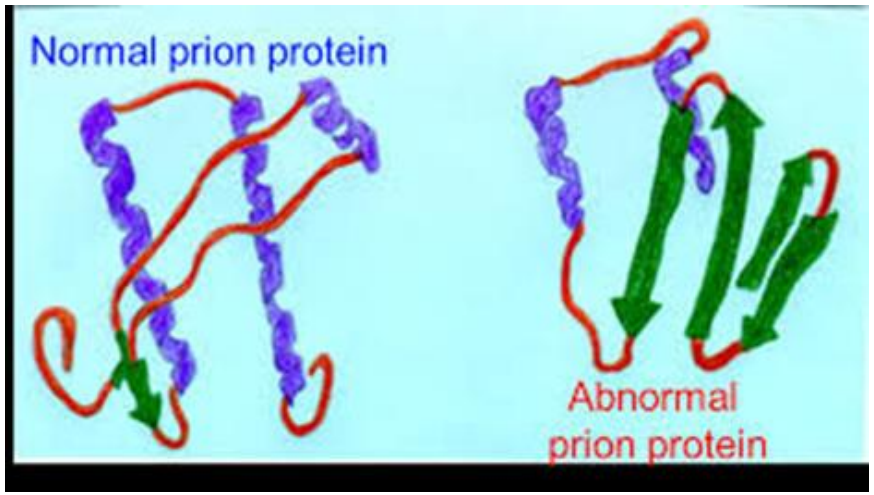
- Affect a wide variety of animal species
- Display limited zoonotic potential
- Prolonged incubation periods
- Clinically recognized via progressive neurological deterioration
- No evidence of a conventional host immune reaction



PrP^C

- Normal protein found on the membranes of cells
- It has 209 amino acids/in humans
- Highly conserved/amino acid sequences vary
- Several topological forms exist



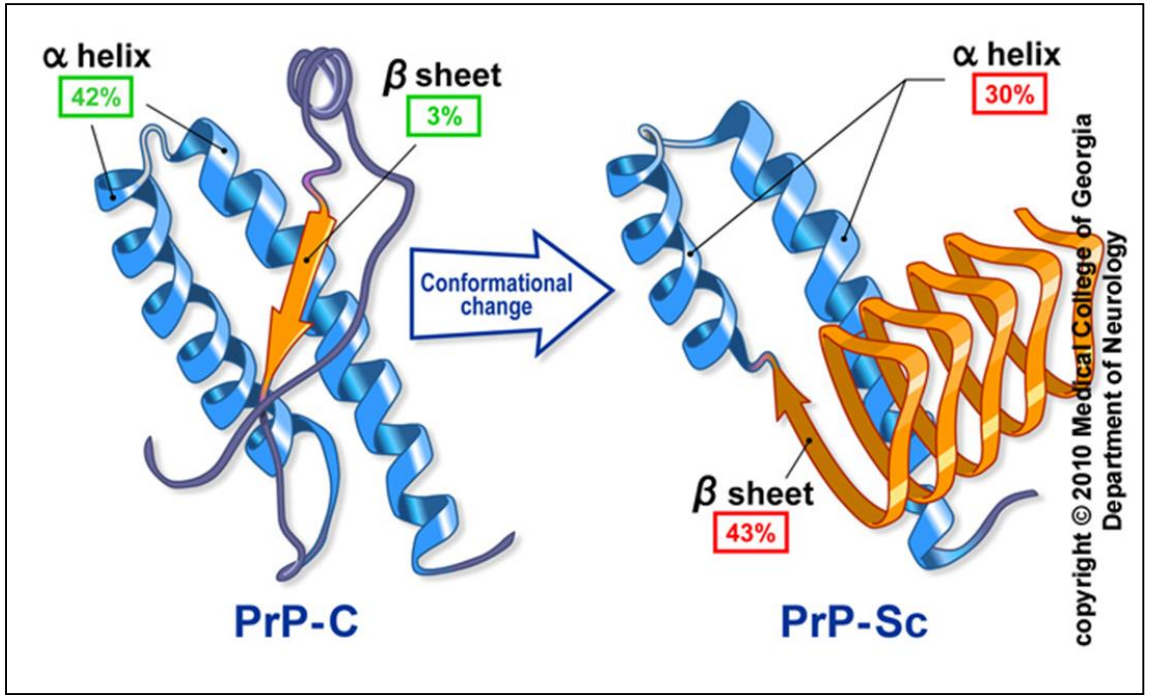


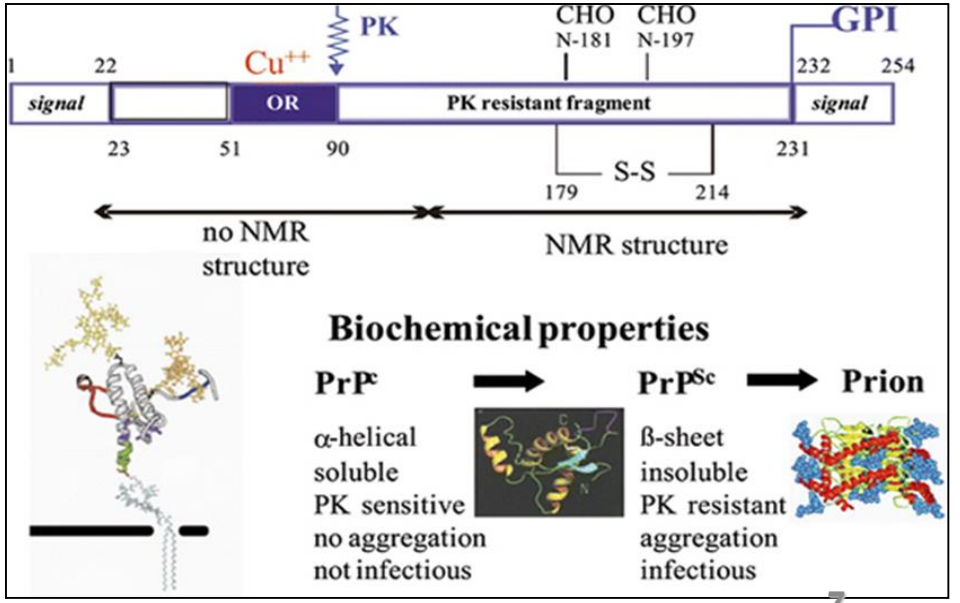
Physiological function of PrP^c

- The physiological function not clear
- Readily digested by proteinase K
- May act as a copper binding protein

PrP^{sc} (scrapie)

- PrP^{c} undergoes conformational changes
- Beta plated sheet formation
- Resistant to Protinase K
- Allow to aggregate amyloid
- The precise molecular mechanism conversion is not completely understood



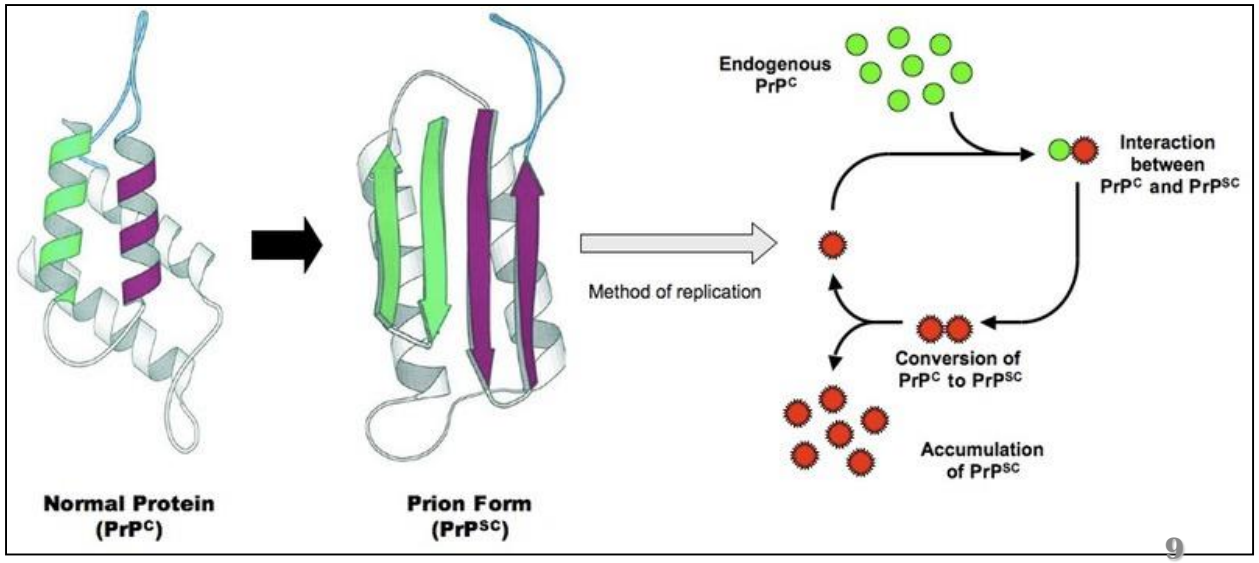


Differences between PrPc and PrPsc

PrP^{C}	PrP^{SC}
Solubility	
Soluble	Non soluble
Structure	
Alpha-helical	Beta-sheeted
Configuration	
Monomeric	Multimeric
Infectivity	
Non infectious	Infectious
Proteinase K	
Susceptible	Resistant

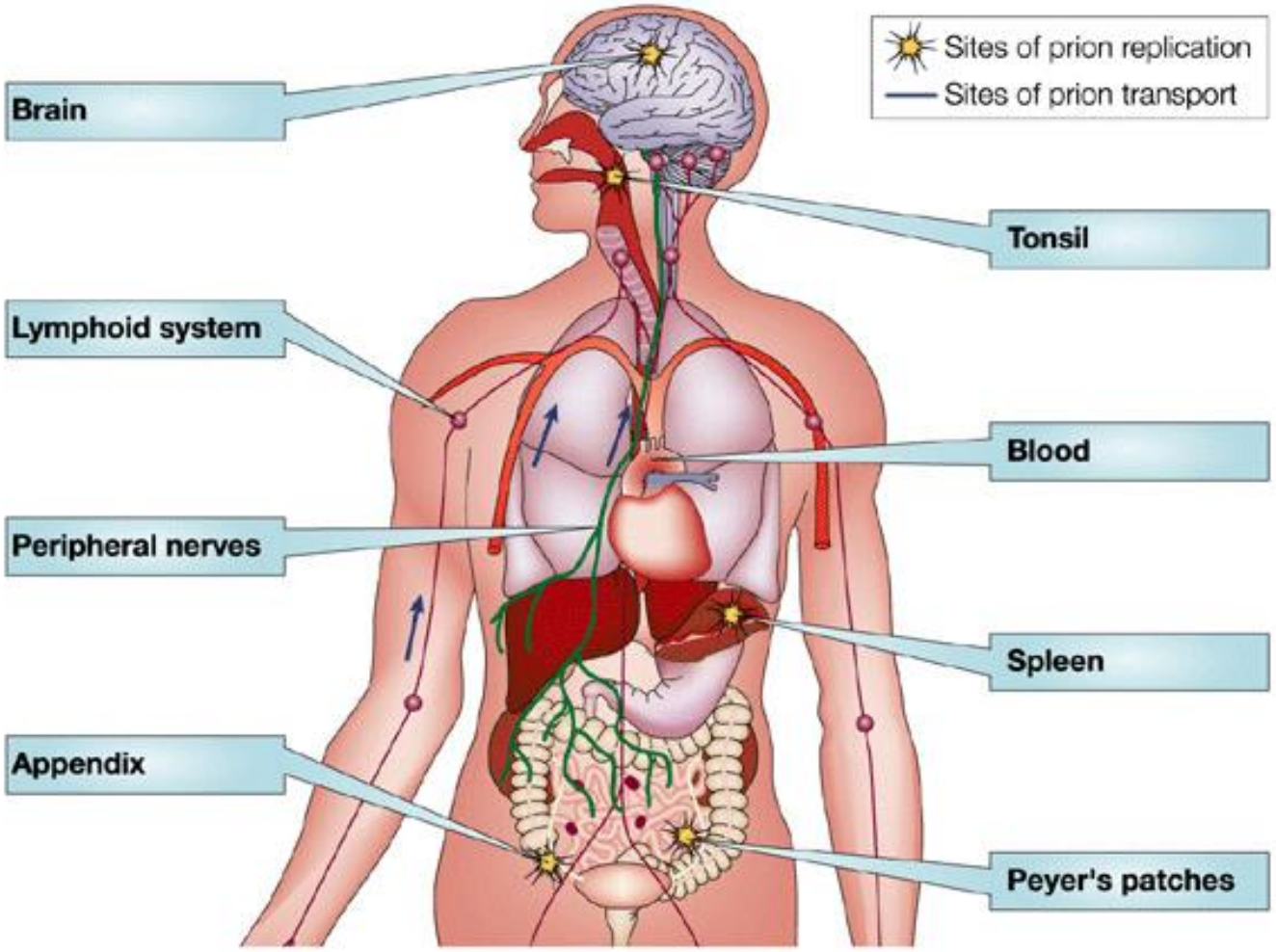
Transformation

- PrPSc in the infectious material interacts with host PrPC
- Catalyzing conversion to the pathogenic form of the protein
- co-factor/s might participate
  in prion replication



Prion hypothesis

- A protein behaves like a living micro-organism to infect an individual by various routes
- Survive metabolic clearance
- Self-replicate in the body
- Reach the target organ and induce a cascade of neurodegenerative damage
- Ultimate death


Sites of prion replication
Sites of prion transport
Brain
Tonsil
Lymphoid system
Blood
Peripheral nerves
Spleen
Appendix
Peyer's patches
Nature Reviews | Microbiology

Prion Diseases in Nature

Human

- Kuru
- Fatal Familial Insomnia (FFI)
- Creutzfeldt-Jakob disease (CJD)
- Variant Creutzfeldt-Jakob disease (vCJD)

Animal

- Scrapie (sheep)
- Bovine Spongiform Encephalopathy (BSE)
- Chronic Wasting Disease (CWD) of deer, elk

Prions in Humans

- First identified with “Spongiform encephalopathies”
- Presentation/s
  - Loss of motor control
  - Dementia
  - Paralysis
  - Encephalitis
  - Widespread neuronal loss
- Possible ways of infection:
  - Infectious (diet, surgical procedures)
  - Hereditary (autosomal dominant)

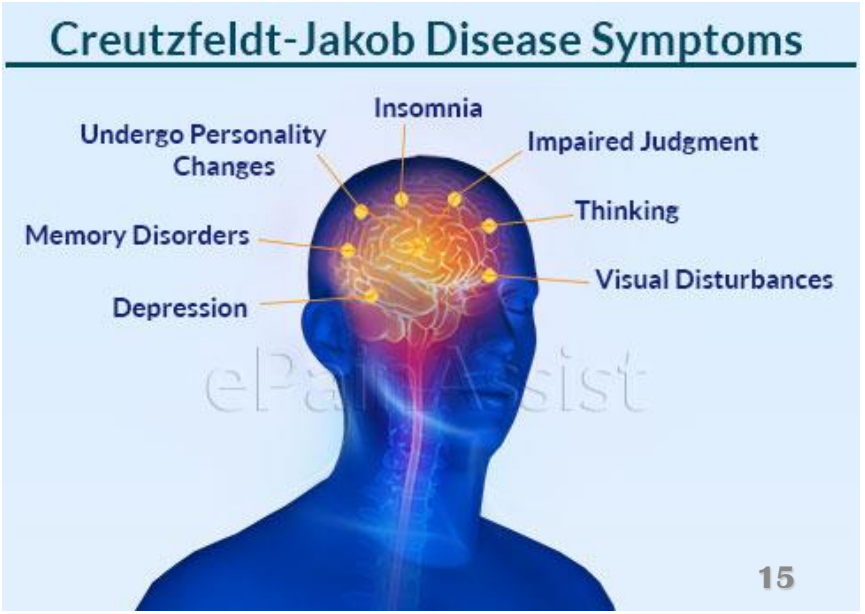
Classification of Human Prion Diseases

- **Idiopathic form**
  - Sporadic CJD (90%)
  - Familial CJD (10%) autosomal dominant
  - Gerstmann-Straussler-Scheinker Syndrome
    GSS Syndrome
  - Fatal familial insomnia

- **Transmitted form**
  - Kuru
- **Person to person transmitted form**
  - Intragenic CJD
- **Transmitted from bovines to humans form**
  - Variant CJD

CREUTZFELDT-JAKOB DISEASE (CJD)
SPORADIC FORM

- German neurologists Creutzfeldt and Jakob in 1920s
- >90% of all CJD cases.
- 1/1 million population per year/equal sex ratio.
- peak age of onset between 55-75.
- Induced by somatic mutation or spontaneous conversion of PrPc into PrPsc.
- **Clinical Features ??????**



CREUTZFELDT-JAKOB DISEASE
FAMILIAL FORM

- 10% of CJD patients
- Autosomal dominant inheritance pattern with a family history
- Presented with personality changes followed by progressive dementia and a Parkinsonian syndrome.
- The mean age at onset was 44 years.

CREUTZFELDT-JAKOB DISEASE
IATROGENIC FORM

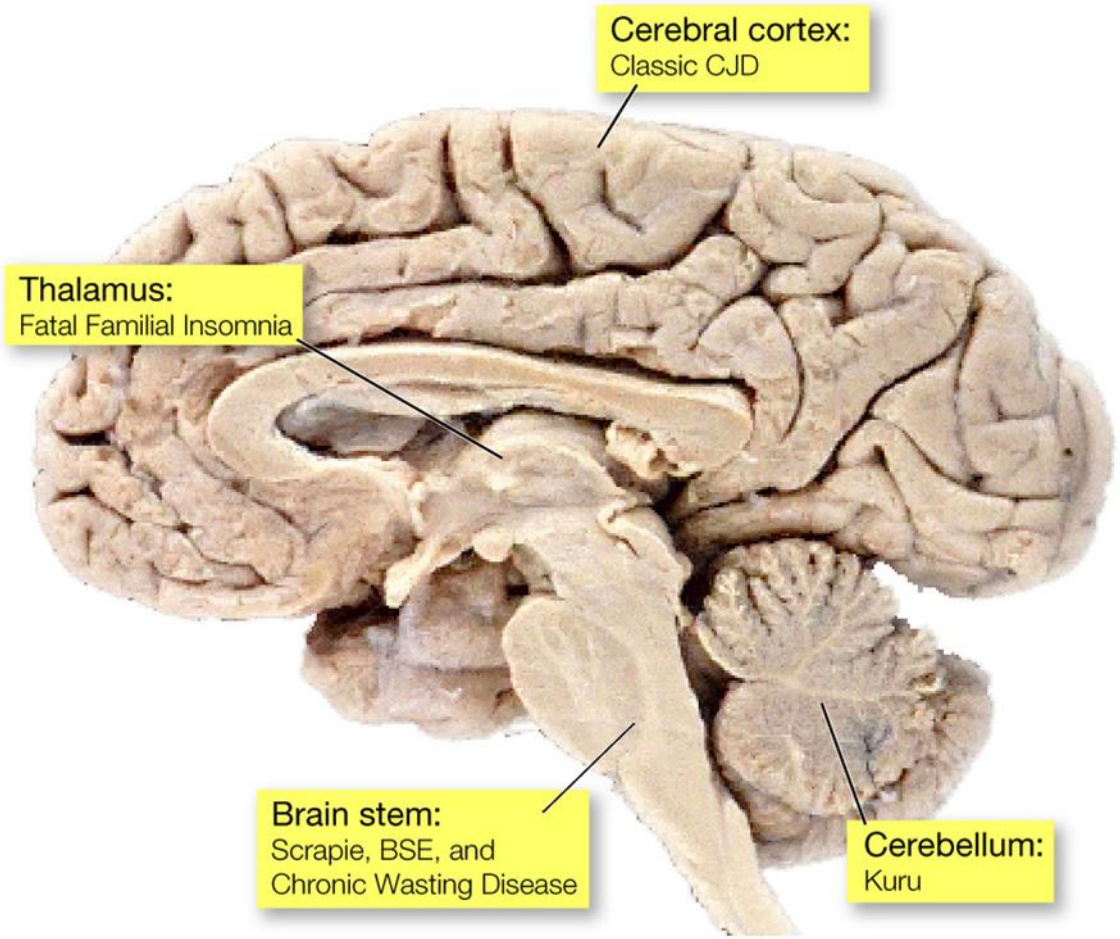
- The transmissible CJD was first described in 1968

Corneal transplant
- Contaminated EEG depth electrodes
- Neurosurgical instruments
- Cadaveric pituitary-derived gonadotropin
- Human growth hormone (hGH)
- Dura mater grafts
- Blood transfusion?

Kuru

- In the 1950's and 60's among the South Fore people of New Guinea
- Transmitted through ritual mortuary cannibalism
- Deceased individuals were consumed by their relatives to honor them
- Incubation period 5-15 years

Location of predominant lesion



Diagnosis

EEG: Pattern

CSF: presence of high protein

Histopathology:Biopsy/Autopsy (confirmatory diagnosis):

Spongiform changes,

Gliosis, and neuronal loss in the absence of inflammatory reaction.

Amyloid plaques

PrP^{sc} :The presence of PrPsc in biopsy or autopsy

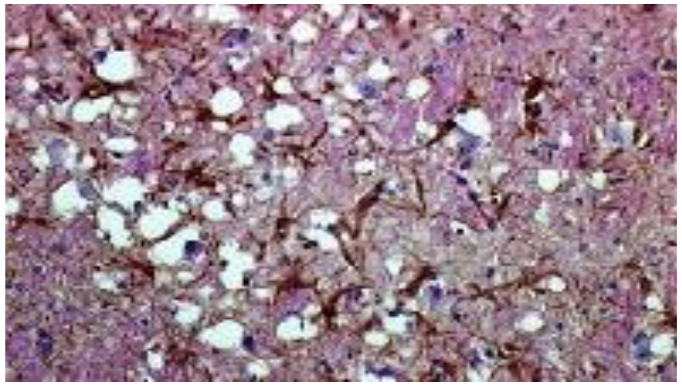
a) immunohistochemical staining.

b) Western blot techniques

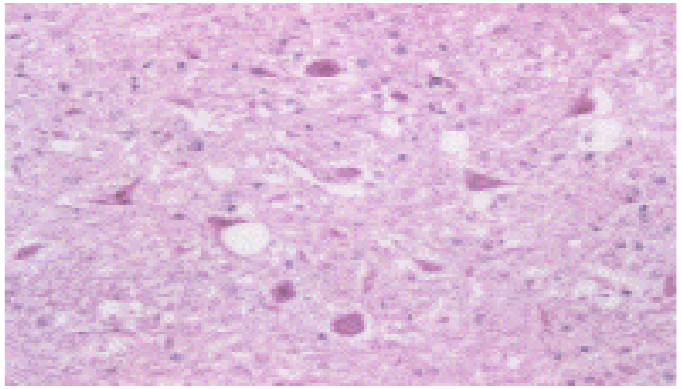
c) Conformation-dependent immunoassay(CDI)

Genetic test: sequencing the PRNP gene

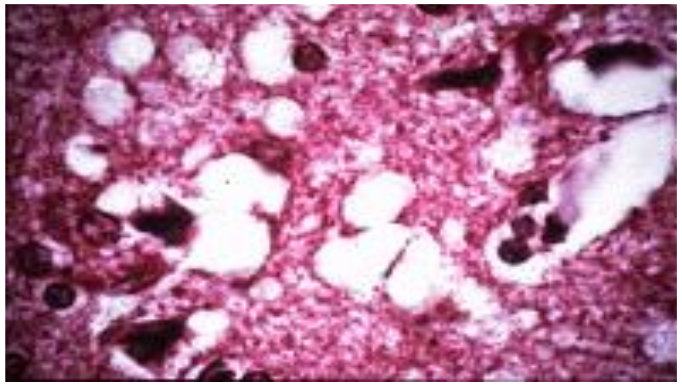
Microscopic appearnce



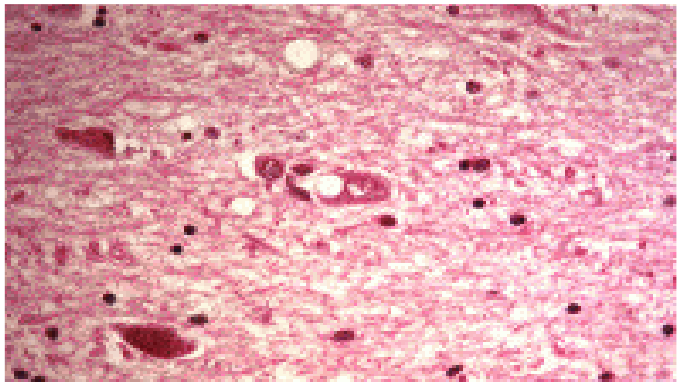
Scrapie



BSE



Kuru

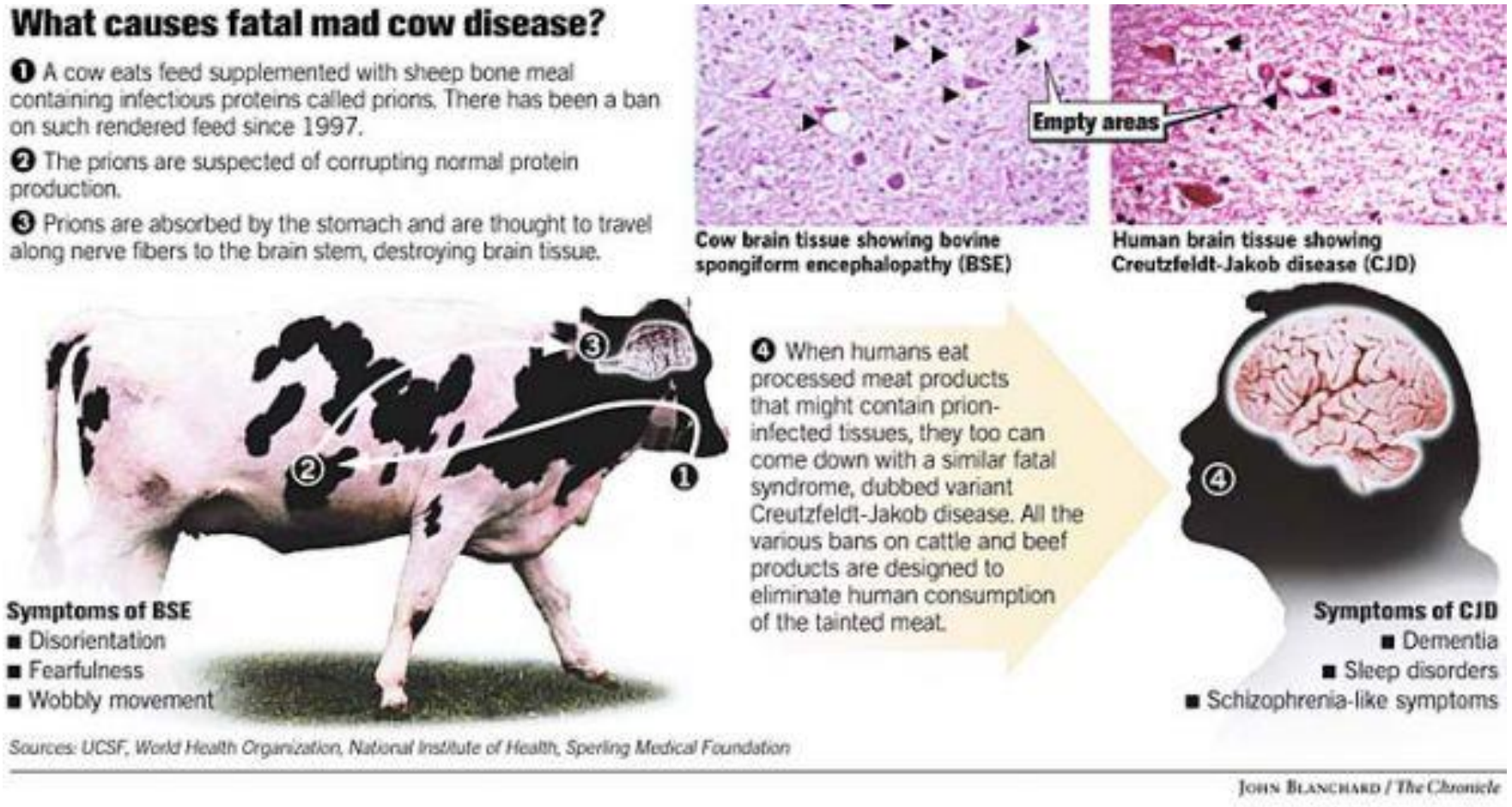


CJD

BSE (MAD COW DISEASE)

- Origin unclear
  - Feed contaminated with scrapie or unknown BSE
  - Spontaneous mutation
  - Changes in feed processing
- Maternal transmission
  - Possible, low risk
  - Retrospective offspring culling
- Likely spread ingestion of BSE contaminated feed

Possible Scenario



Human Transmission

- Humans consuming cattle products infected with BSE can develop vCJD
  - Brain and spinal tissue
- Dose required unknown
- Genetic susceptibility
  - All human cases have been homozygous for methionine at codon 129 of PrPC

Evidence for Relationship between BSE and vCJD

- Since 1996, evidence has been increasing for a causal relationship between ongoing outbreaks of BSE and vCJD.

- Strong scientific evidences: agent responsible for BSE(in cattle) and vCJD (in humans), is the same (PrPsc).

Clinical and Pathologic Characteristics
Distinguishing Classic CJD from Variant CJD

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Prominent psychiatric/behavioral symptoms; painful dyesthesiasis; delayed neurologic signs
Periodic sharp waves on EEG	Often present	Often absent
Pulvinar sign on MRI	Not reported	Present in >75% of cases
Presence of "florid plaques" on neuropathology	Rare or absent	Present in large numbers
Immunohitochemical analysis of brain tissue	Variable accumulation	Marked accumulation of protease-resistance prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistance prion protein	Not reported	Marked accumulation of protease-resistance prion protein

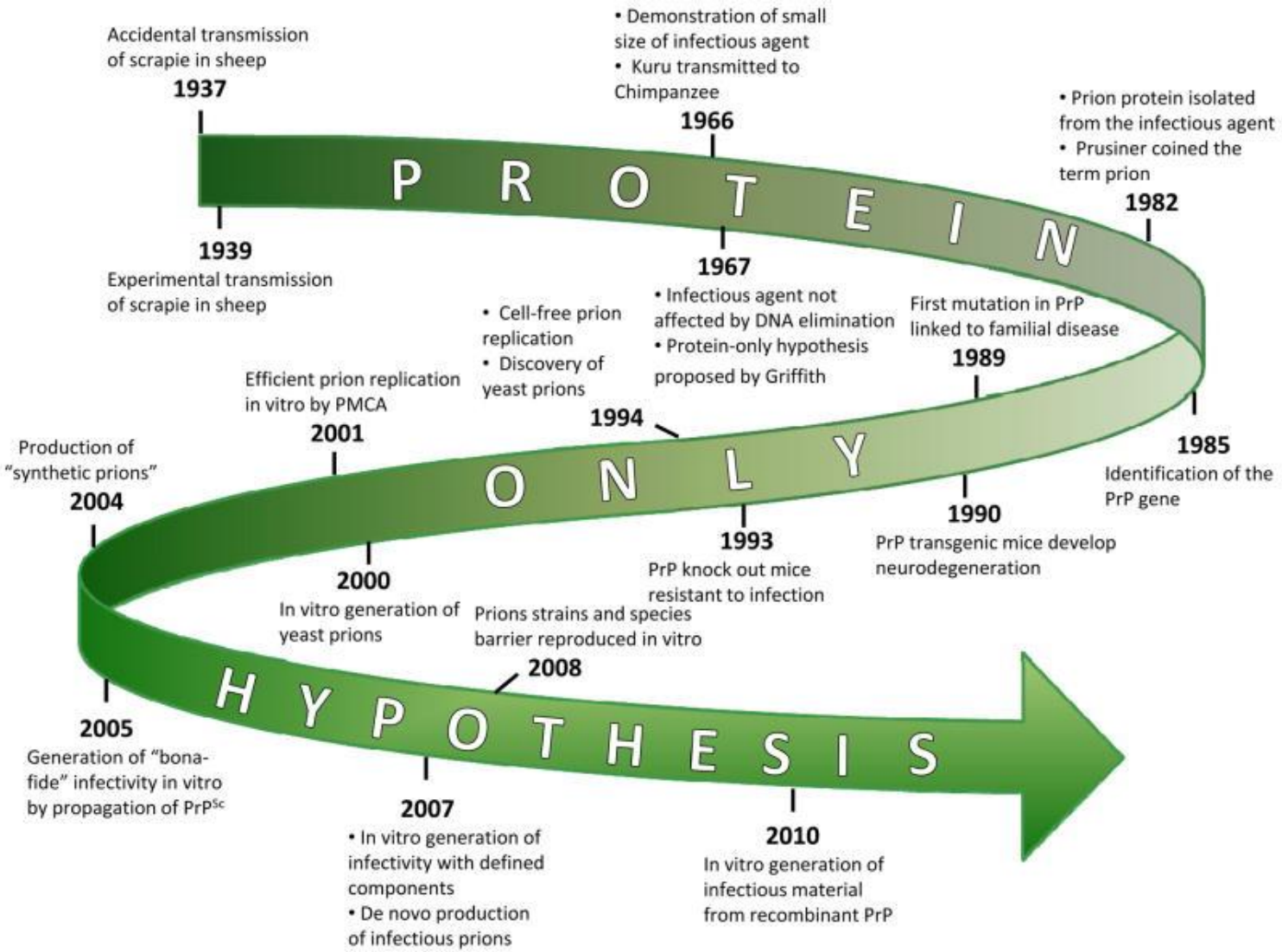
Scrapie

- Fatal, chronic neurodegenerative disease.
- England, France and Germany
  in the 19th century

- Long incubation (2-5 years)

- Affected animals rub their coats against trees, suffer ataxia, convulsions, blindness, anorexia, and eventually death

History of Prions



Soto 2011

DECONTAMINATION OF CJD PRIONS

- Nightmare
- Extremely resistant to common inactivation procedures
- Autoclaving at 132˚ C for 5 h or treatment with 2 *N* NaOH for several hours is recommended for sterilization of prions