

# **Slow Viral Diseases**

1. All known mammalian prion diseases are caused by the so-called prion protein, [PrP](#). The endogenous, properly folded form is denoted PrP<sup>C</sup> (for *Common* or *Cellular*), whereas the disease-linked, misfolded form is denoted PrP<sup>Sc</sup> (for [Scrapie](#), after one of the diseases first linked to prions and neurodegeneration. The precise structure of the prion is not known, though they can be formed by combining PrP<sup>C</sup>, polyadenylic acid, and lipids in a [Protein Misfolding Cyclic Amplification](#) (PMCA) reaction.
2. An isoform of PrP known as PrP<sup>res</sup> because of its resistance to proteolytic digestion by [Proteinase K](#), a [surrogate marker](#) of prion infectivity. PrP<sup>res</sup> may be infectious.
3. The infectious [isoform](#) of PrP, known as PrP<sup>Sc</sup>, is able to convert normal PrP<sup>C</sup> proteins into the infectious isoform by changing their [conformation](#), or shape; this, in turn, alters the way the proteins interconnect. PrP<sup>Sc</sup> always causes prion disease.
4. A prion in the Scrapie form (PrP<sup>Sc</sup>) is an infectious agent composed of protein in a misfolded form. This is the central idea of the Prion Hypothesis, which remains debated.
5. PRNP gene .

# Persistent infections

- As those in which the virus is not cleared but remains in specific cells of infected individuals.
- Involve stages of both silent and productive infection without rapidly killing or even producing excessive damage of the host cells.
- There are three types of overlapping persistent virus-host interaction that may be defined as latent, chronic and slow infection.

# Types

- Latent infection - by the lack of demonstrable infectious virus between episodes of recurrent disease.
- Chronic infection - by the continued presence of infectious virus following the primary infection and may include chronic or recurrent disease.
- Slow infection is characterized by a prolonged incubation period followed by progressive disease. Unlike latent and chronic infections, slow infection may not begin with an acute period of viral multiplication.

# Pathogenesis

- Both modulation of virus and cellular gene expression
- Modification of the host immune response.
- Reactivation of a latent infection may be triggered by various stimuli,  
including changes in cell physiology  
superinfection by another virus  
physical stress or trauma.  
Host immunosuppression is often associated with reactivation of a number of persistent virus infections.

# Pathogenesis

- ❖ Limitation of recognition molecules on infected cells:
  - Restricted expression of viral antigens (e.g., HIV, measles virus in subacute sclerosing panencephalitis)
  - Antiviral antibody-induced internalization and modulation of viral antigens (e.g., measles virus)
  - Blocking antibody that prevents the binding of neutralizing antibody (e.g., measles virus)
  - Viral antigenic variation (e.g., HIV)
  - Decreased expression of cell MHC recognition molecules (e.g., CMV, adenoviruses)
  - Restricted expression of the cell adhesion molecules LFA-3 and ICAM-1 (e.g., EBV, CMV).

# Pathogenesis

- Altered lymphocyte and macrophage functions, including modified production of cytokines and immunosuppression (e.g., HIV-1, HIV-2, EBV).
- Compromise non-specific defenses (e.g., interferon)
- Modulation of viral gene expression

# Associated diseases

- AIDS, AIDS-related complexes,
- Chronic hepatitis
- Subacute sclerosing panencephalitis (chronic measles encephalitis),
- Chronic papovavirus encephalitis (progressive multifocal leukoencephalopathy)
- Spongiform encephalopathies (caused by prions),
- Herpes virus-induced diseases



# Slow viral infections - Definition

- It is applied to a group of infections in animals and human beings, characterised by a very long incubation period and a slow course, terminating fatally.
- It was proposed by Sigurdsson (1954), a veterinary pathologist for slowly progressive infections of sheep such as Scrapie, Visna & Maedi.

# Characteristics

- Incubation period – months to years
- Course of illness lasting for months or years, with remissions and exacerbations.
- Predilection for involvement of the central nervous system
- Absence of immune response or an immune response that does not arrest the disease, but may actually contribute to pathogenesis
- Genetic predisposition
- Invariable fatal termination

# Classification

## Group A

- Slowly progressive infections of sheep, caused by lentivirus

## Group B

- Prion diseases of CNS (Transmissible spongiform viral encephalopathies)

## Group C

- Subacute sclerosing panencephalitis
- Progressive multifocal leukoencephalopathy

Disease	Agent	Hosts	Incubation period	Nature of disease
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## Disease of humans

Subacute sclerosing panencephalitis	Measles virus variant	Humans	2-20 years	Chronic sclerosing panencephalitis
Progressive multifocal leukoencephalopathy	Polyomavirus JCV	Humans	Years	Central nervous system demyelination
Creutzfeldt – Jakob disease	Prion	Humans, chimpanzees, monkeys	Months to years	Spongiform encephalopathy
Kuru	Prion	Humans, chimpanzees, monkeys	Months to years	Spongiform encephalopathy

Disease	Agent	Hosts	Incubation period	Nature of disease
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## Disease of animals

Visna	Retrovirus	Sheep	Months to years	Central nervous system demyelination
Scrapie	Prion	Sheep, goats, mice	Months to years	Spongiform encephalopathy
Bovine spongiform encephalopathy	Prion	Cattle	Months to years	Spongiform encephalopathy
Transmissible mink encephalopathy	Prion	Mink, other animals	Months	Spongiform encephalopathy
Chronic wasting disease	Prion	Mule deer, elk	Months to years	Spongiform encephalopathy

# Subacute sclerosing panencephalitis

- The rare late complication of measles infection.
- Young adults
- Incidence – 1:300,000 cases.
- It begins 5-15 years after a case of measles.
- Progressive demyelination in the CNS.
- Large number of viral nucleocapsid structures are produced in neurons and glial cells.
- Restricted expression of the viral genes that encode envelope proteins, so the virus in persistently infected neural cells lack protein needed for the production of infectious particles.

# Subacute sclerosing panencephalitis

## ➤ Clinical features-

- Progressive mental deterioration
- Involuntary movements
- Muscular rigidity and coma
- Fatal within 1-3 years after onset

➤ Pt. with SSPE have high titre of antimeasles Ab except that the Ab to M protein is lacking.

✓ Reduced efficiency of measles virus transcription in differentiated brain cells is imp. in maintaining the persistent infection that lead to SSPE.

# Progressive multifocal leukoencephalopathy

- JC virus (member of Polyomaviridae)
- CNS complication in immunosuppressed patients
- About 5% of patients with AIDS
- Demyelination of CNS occurs due to oligodendrocyte infection by polyomavirus.
- Progressive deterioration of motor function, vision and speech.
- Death occurs in 3-4 months



# Visna and Maedi viruses

- Retroviruses of genus lentivirus
- It was recognised in Iceland 1935 & eradicated in 1951.
- Long incubation periods (months to years).
- Cause slowly developing infections in sheep.
- Visna virus infects all the organs of body but pathologic changes are confined to brain, lungs and RES.
- Insidious onset with paresis, progressing to total paralysis and death.
- Virus can be recovered for whole of life of animals.
- Can be grown in sheep choroid plexus tissue culutres from CSF, blood and saliva of affected animals.
- High level of neutralising antibody can be detected.

# Maedi virus

- Slowly progressive fatal haemorrhagic pneumonia of sheep
- Incubation period of 2-3 years
- Visna and Maedi virus are variant of single strain of virus.

# Prions

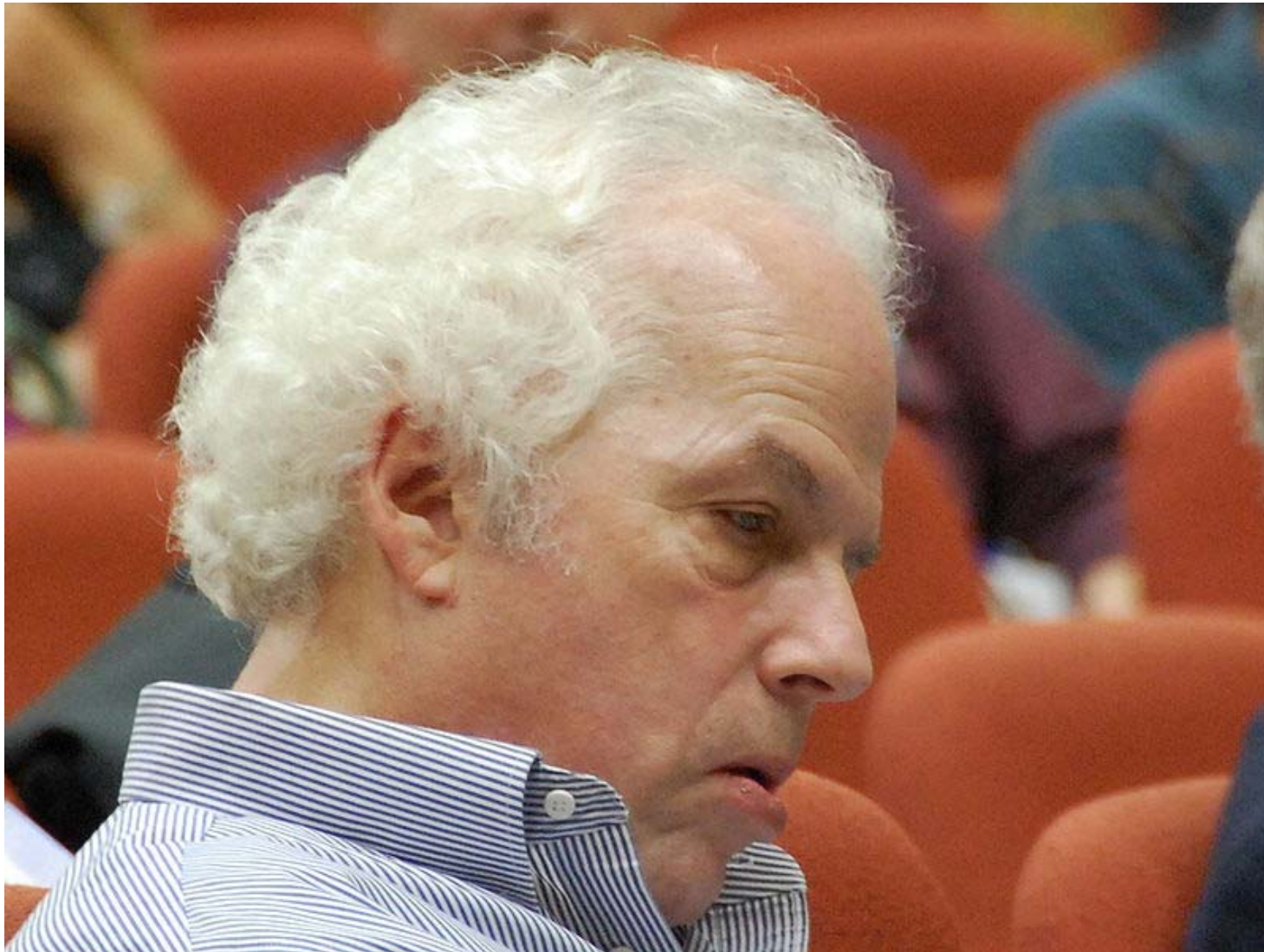
The actual infectious principle consists merely of protein and is capable of replicating and transmitting infections without the need for informational nucleic acids.

# Prion

- Prion diseases are a large group of related neurodegenerative conditions, which affect both animals and humans
- Proteinaceous infectious particles
- Only known infectious pathogens devoid of nucleic acid
- Glasses in 1950's and 60's
- Carleton Gajdusek proved that they are transmissible
- In 1967 Tikvah Alper found that particles responsible for transmissible spongiform encephalopathies contained no nucleic acids
- In 1982 [Stanley Prusiner](#) - "proteinaceous infectious particles"
- Nobel Prize in 1997

# Historical background

- 1738: First description of scrapie
- 1921: H.G. Creutzfeldt, A.M. Jakob: description of CJD and its neuropathology
- 1950–1960: D.C. Gajdusek: investigation of kuru in Papua New Guinea
- 1959: W.J. Hallow: similarities between kuru and scrapie
- 1976: D.C. Gajdusek: Nobel prize
- 1982: S. Prusiner: animal model
- 1986: BSE outbreak in England
- 1991: S. Prusiner: molecular biology of prions
- 1993: T.G.F. Esmonde: link between BSE and vCJD
- 1997: S. Prusiner: Nobel prize



**Stanley Prusiner**

## USA – 16 yr period

- 2329 prion disease cases have been screened
- 1965 cases of sporadic CJD
- 338 cases of familial CJD
- 5 cases of iatrogenic CJD, and 3 cases of vCJD

# France

- 25 cases of confirmed or probable vCJD have been recorded 1992.
- 1996, 2000, 2001 – one
- 3 in 2002, 2 in 2004, 6 in 2005, 6 in 2006, 3 in 2007, 2 in 2009
- There have been none in 2010 and 2011.



# U.K

- Since 1990, there have been 2833 referrals
- 1259 fatal cases of sporadic CJD,
- 172 cases of vCJD
- 88 cases of familial CJD,
- 65 cases of iatrogenic CJD
- 44 cases of GSS.

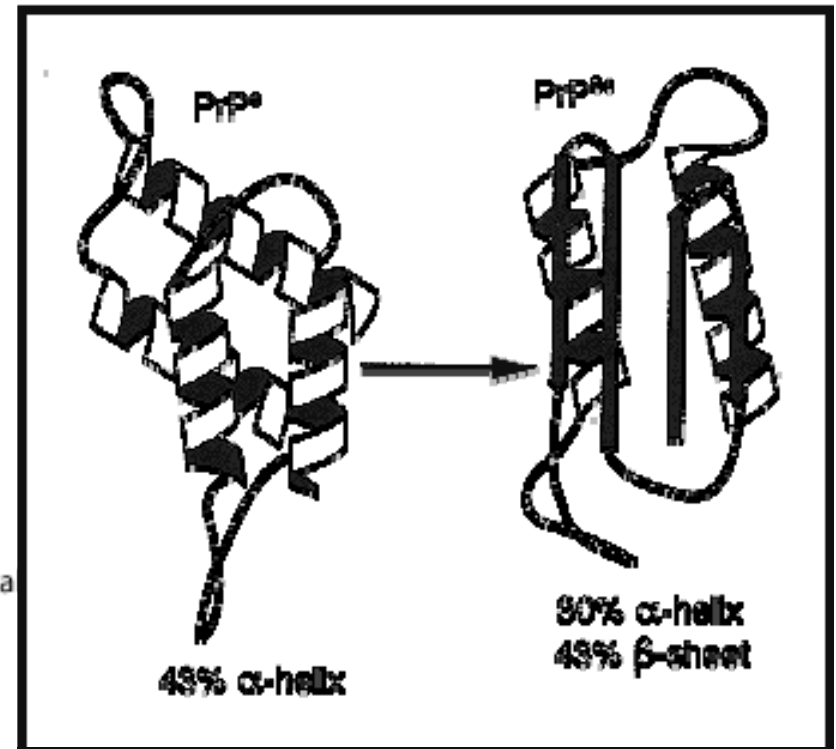
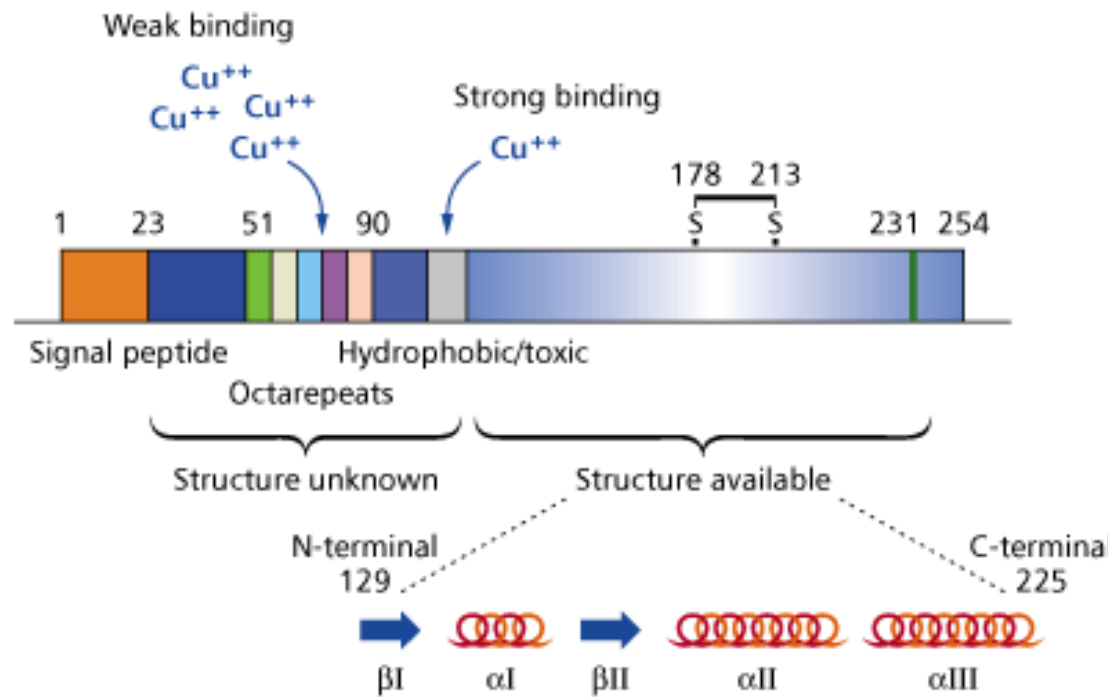
# Prion disease

- Prions are the only known infectious pathogens that are devoid of nucleic acid.
- Prion disease may be manifest as infectious, genetic and sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations.
- Prions disease result from the accumulation of  $\text{PrP}^{\text{sc}}$ , the confirmation of which differs substantially from that of its precursor  $\text{PrP}^{\text{c}}$
- $\text{PrP}^{\text{sc}}$  can exist in a variety of different conformations, each of which seems to specify a particular disease phenotype.

# Prions

- The normal prion protein, designated as **PrP<sup>c</sup>**
- It is encoded by the **PRNP** gene on chromosome 20
- It is a 35kD membrane glycoprotein, which is water-soluble and proteinase-sensitive
- 254 amino acid peptide with several octapeptide repeat sequences toward the N-terminus
- Variable binding affinity for divalent metals such as copper, zinc and Mn, with preferential binding for copper
- PrP<sup>c</sup> is a GPI-anchored cell-surface glycoprotein
- PrP is found in most tissues with highest levels in the CNS, in particular in neurons
- Also expressed widely on the cells of immune system

# Sequence of prion protein



## Resistant

- Formaldehyde (3.7%)
- Urea (8 M)
- Dry heat, boiling
- Ethanol (50%)
- Proteases
- Deoxycholate (5%)
- Ionizing radiation

## Sensitive

- Phenol (90%)
- Household bleach
- Ether
- NaOH (2N)
- Strong detergents (10% Sodium dodecyl sulphate)
- Autoclaving (2 h, 134°C), gravity displacement autoclave.

# Prions

- ❖ Guinidine thiocyanate is highly effective in decontaminating medical supplies and instruments.

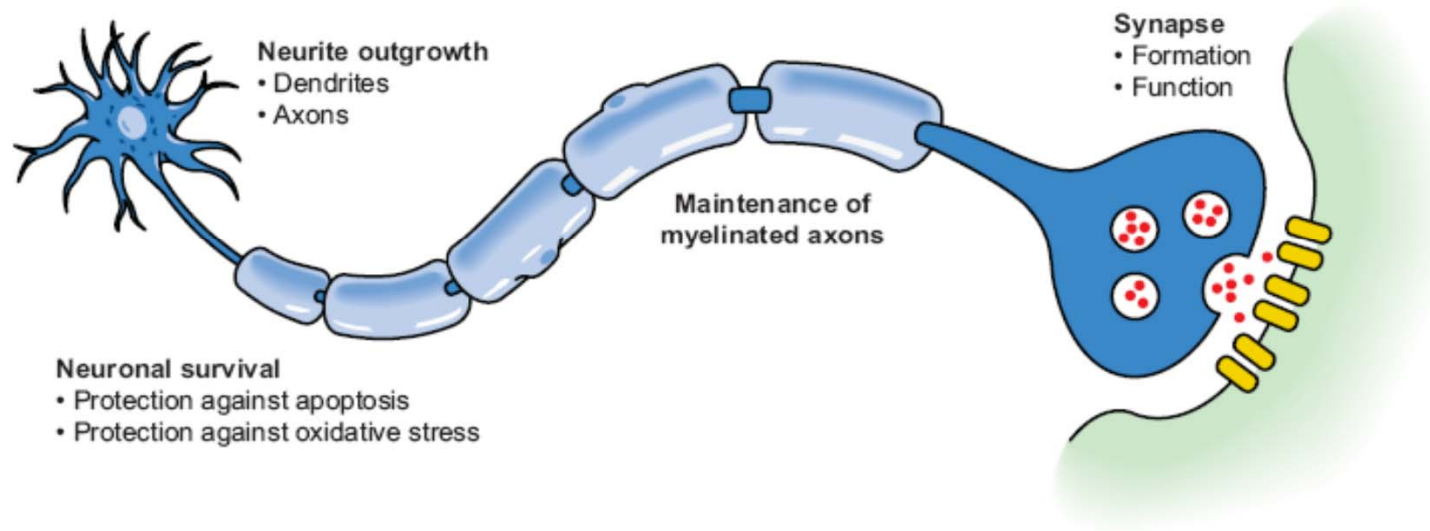
## Functions of PrP

- Signal transducing properties
- Role in cell adhesion
- Role in copper transport or metabolism: Antioxidant properties
- PrP<sup>C</sup> prevents Alzheimer's plaques formation:  
regulates  $\beta$ -secretase cleavage of the Alzheimer amyloid precursor protein
- But still its exact function is unknown

# Function

## \* Neurons

## \* Periphery – Lung, heart, kidney, pancreas



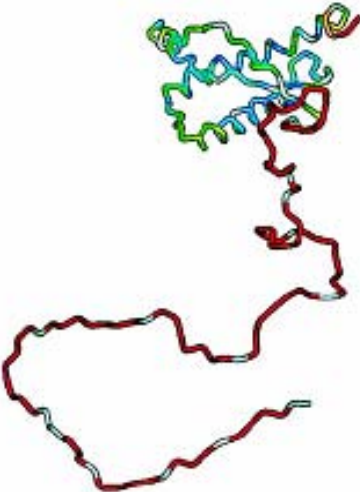
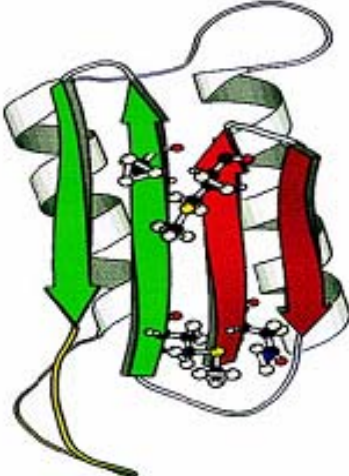


# Pathogenesis

- Hallmark of all prion diseases is that they result from aberrant metabolism and lead to accumulation of the prion protein
- $\text{PrP}^{\text{C}} \longrightarrow \text{PrP}^{\text{Sc}}$  (the abnormal disease-causing isoform)
- Involves a conformation change
  - $\alpha$  helical content diminishes
  - amount of  $\beta$  sheet increases
- Protein X may facilitate  $\beta$  sheet formation
- It can be a molecular chaperone that binds to  $\text{PrP}^{\text{C}}$  and assists in altering its conformation

# Changes in properties

- This structural transition leads to profound changes in the properties of the protein
- PrP<sup>C</sup> is soluble in nondenaturing detergents, whereas PrP<sup>Sc</sup> is not
- Resistant to inactivation by many physical & chemical agents
- Proteinase K cannot completely digest PrP<sup>Sc</sup> (PrP-res)
- PrP 27-30 is the protease resistant domain of PrP<sup>Sc</sup>
- PrP-res half-life >48 hours compared to 3-6 hours of normal cellular protein

	PrP <sup>C</sup>	PrP <sup>Sc</sup>
Structure		
$\alpha$ -helix	~43%	~34%
$\beta$ -sheet	~3%	~43%
Solubility	+	-
Protease resistance	-	+

## Cellular prion protein (PrP<sup>c</sup>)

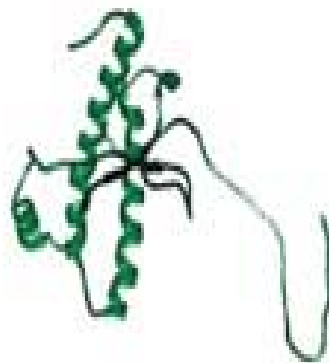
non-infectious

monomer

soluble (in mild detergents)

structure: predominantly  $\alpha$ -helical

Proteinase K (PK) sensitive



## Scrapie-associated prion protein (PrP<sup>Sc</sup>)

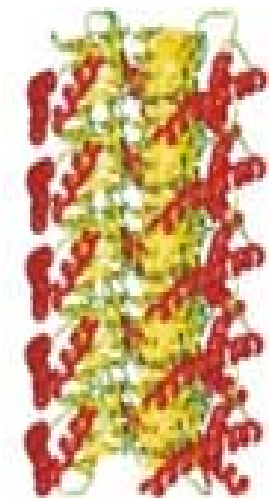
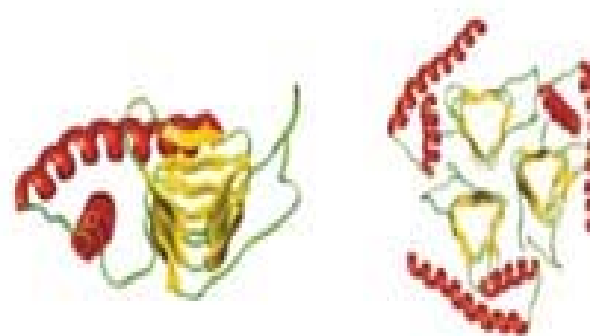
infectious

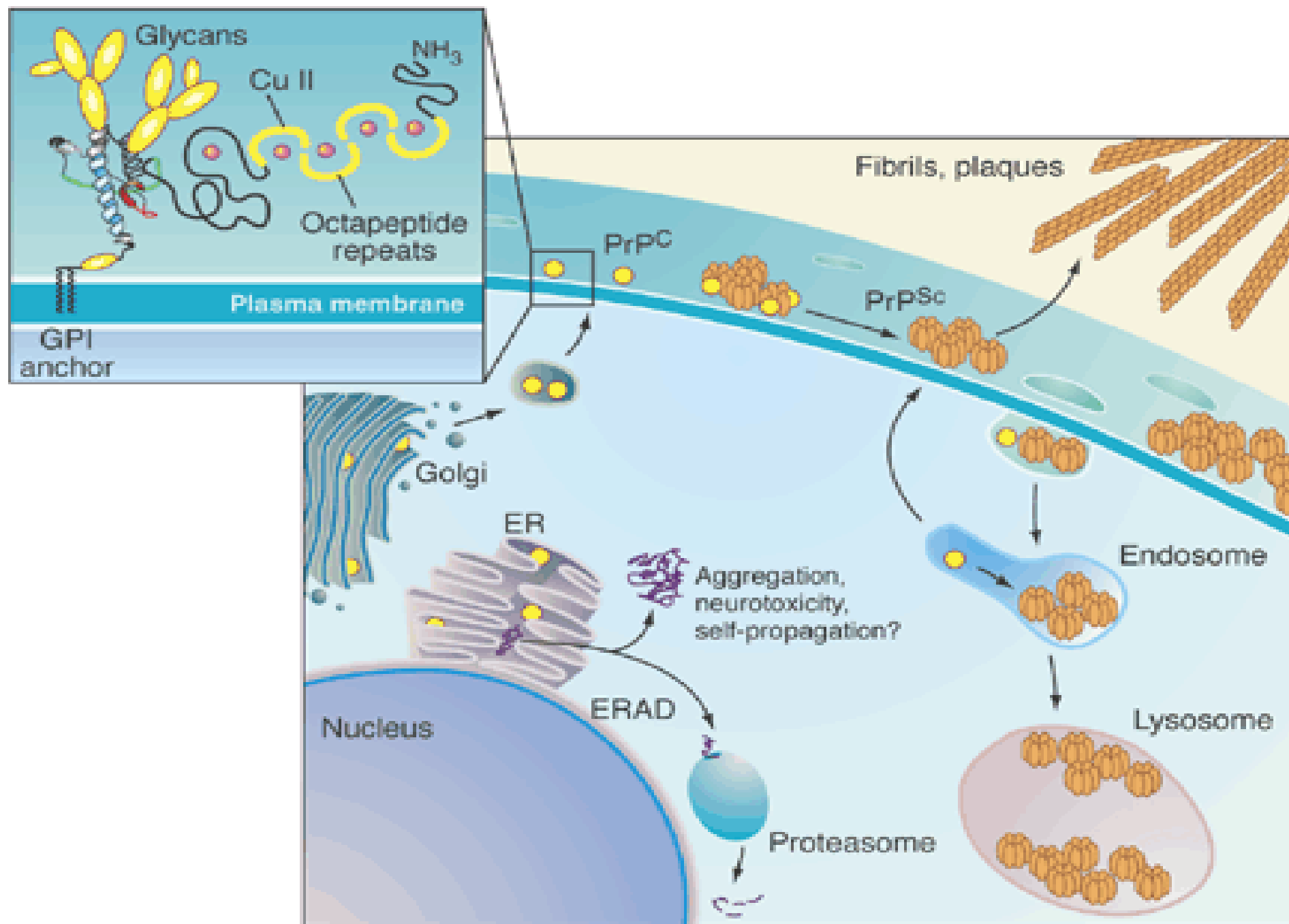
aggregate

insoluble

structure: rich in  $\beta$ -sheets

partial PK-resistant





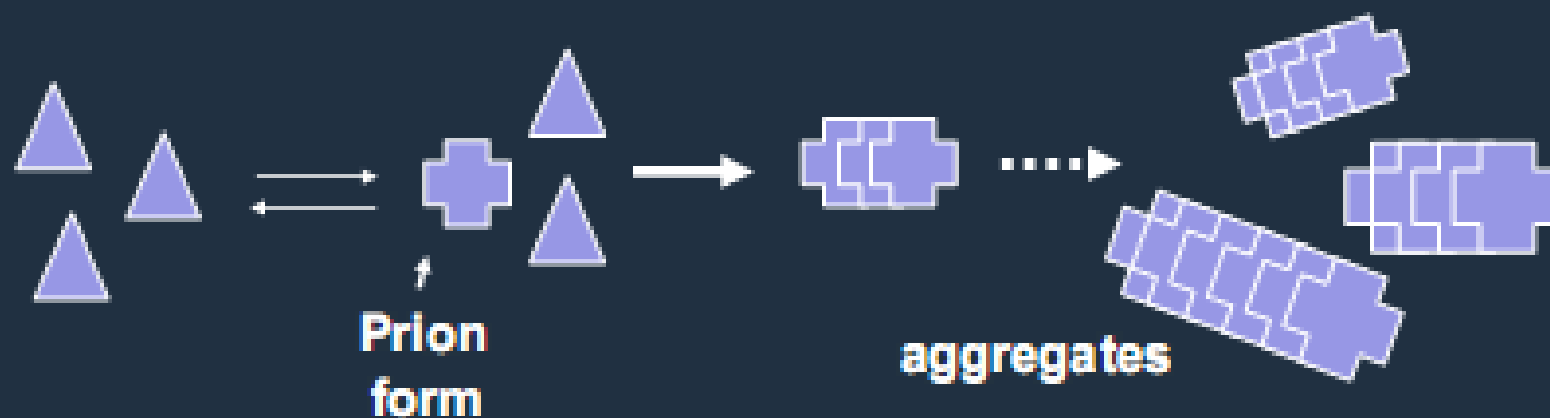
# Pathogenesis

- The replication of prions involves recruitment of the normally expressed prion protein, into a disease-specific conformation
- $\text{PrP}^{\text{Sc}}$  binds to the normal cellular isoform of  $\text{PrP}^{\text{C}}$
- Causes conversion of  $\text{PrP}^{\text{C}}$  into  $\text{PrP}^{\text{Sc}}$ , initiating a self-perpetuating vicious cycle
- In **familial prion diseases**, conformation change is due to mutations of the *PRNP* gene
- In **infectious diseases**, extrinsic abnormal prions are introduced into the body

# Pathogenesis

- How sporadic prion disease arises, is a mystery ?
- The initial seed of PrP<sup>Sc</sup> is caused by
  - somatic mutations
  - posttranslational modifications
  - methionine/valine polymorphism at codon 129 of the *PRNP* gene
- This polymorphism influences susceptibility, clinical phenotype, and pathology of prion diseases
- PrP<sup>Sc</sup> exist in different conformations, each of which specify a particular disease phenotype
- There is a species barrier but not absolute, e.g. emergence of new variant CJD (vCJD)

## Prion Formation





# Prion diseases

- Unique as they can be inherited, infectious or occur sporadically
- Long incubation periods
- Typically rapidly progressive
- Always fatal
- No effective form of treatment
- No evidence of conventional immune reactions found in these diseases

# Prion diseases

- **Animals**

- Bovine spongiform encephalopathy (BSE)
- Scrapie in sheep and goats
- Transmissible mink encephalopathy
- Chronic wasting disease of deer, elk

- **Humans**

- Creutzfeldt-Jacob disease (CJD)
- Fatal familial insomnia (FFI)
- Gerstmann-Straussler syndrome (GSS)
- Kuru

# Types

- Sporadic
  - 85-90% of all cases
  - sCJD
- Familial
  - Due to autosomal dominant mutation of PrP
  - 10-15% of cases
  - fCJD, FFI, GSS
- Iatrogenic/ environmental
  - kuru, iCJD, vCJD

Disease	Mechanism of pathogenesis
Kuru (Fore people)	Infection through ritualistic cannibalism
Iatrogenic CJD	Infection from prion-contaminated HGH, dura mater grafts, and so forth
Variant CJD	Infection from bovine prions?
Familial CJD	Germline mutations in PrP gene
GSS	Germline mutations in PrP gene
Fatal familial insomnia	Germline mutation in PrP gene (D178N and M129)
Sporadic CJD	Somatic mutation or spontaneous conversion of PrP <sup>C</sup> into PrP <sup>Sc</sup> ?

# Pathology

- A unifying feature of all the prion disease is their neuropathology
- These illnesses tend to affect gray matter of the CNS

Spongiform degeneration

Astrocytic gliosis

Neuronal loss

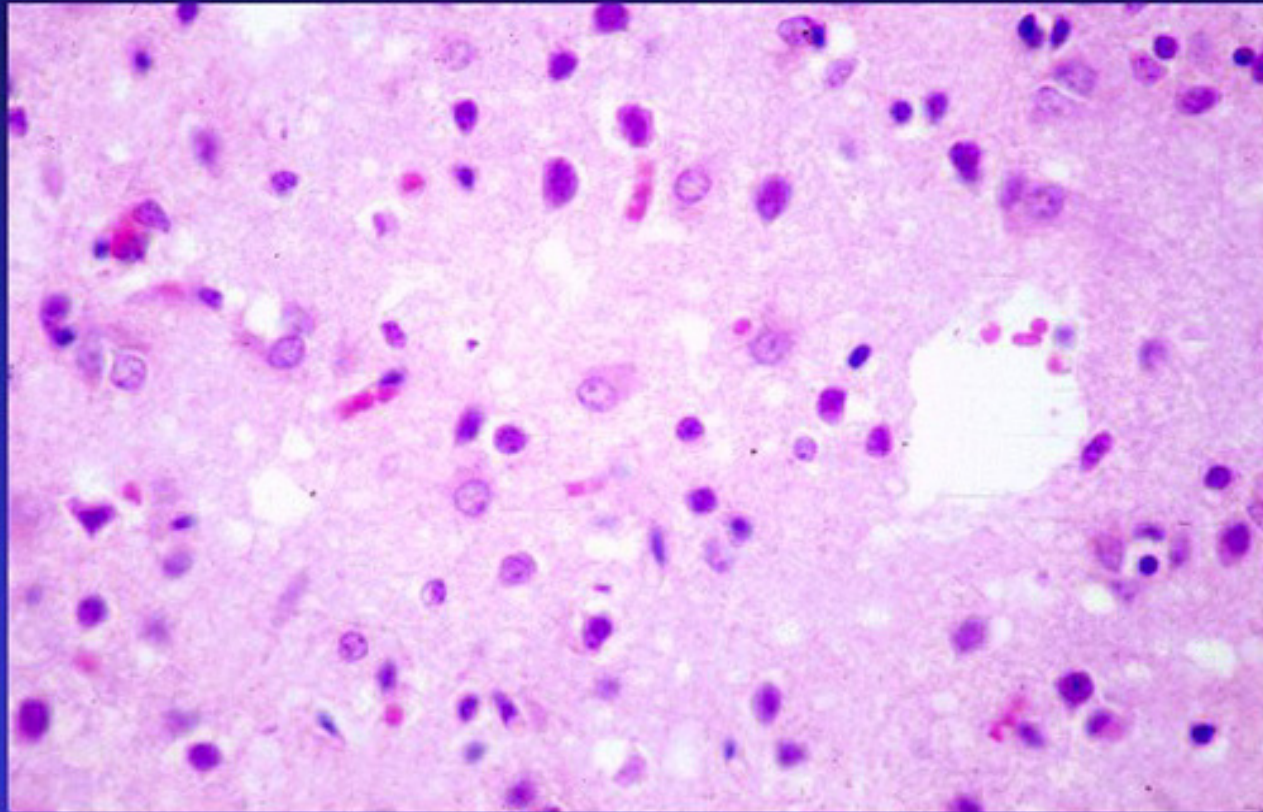
Amyloid plaque formation

Lack of inflammatory response

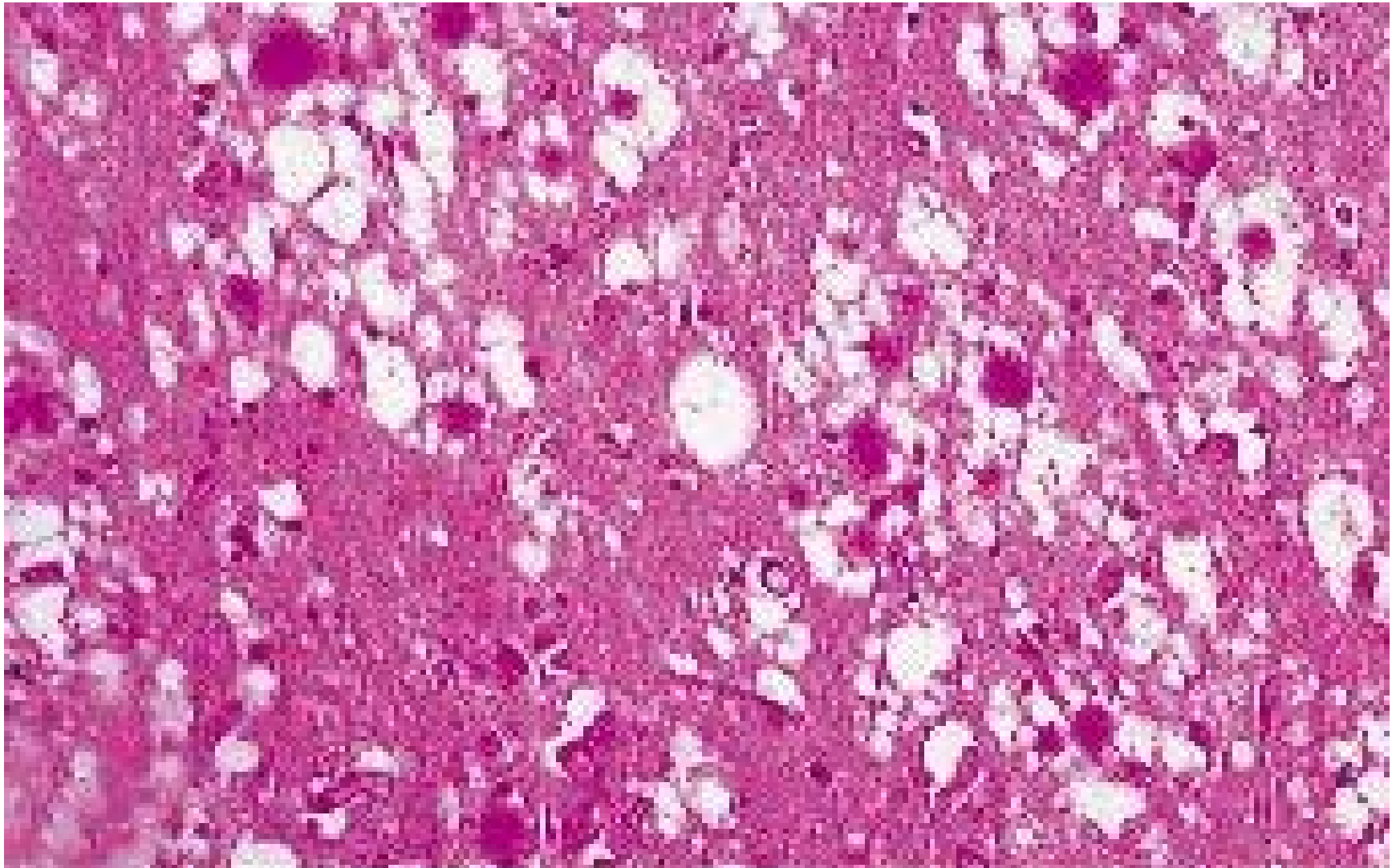
# Spongiform degeneration

- Initially, intracytoplasmic vacuoles (1-5 $\mu$ m) appear in neurons
- As the disease progresses, vacuolization becomes more pronounced
- The cortical neuropil develops a spongy appearance, hence the term **spongiform encephalopathy**
- Cerebral cortex, putamen, caudate nucleus, thalamus & molecular layer of cerebellum

# Spongiform Change in Prion Disease



**Spongiform change in prion disease. This section shows mild parenchymal vacuolation ,prominent reactive astrocytosis and lack of inflammatory response**



**Spongiform encephalopathy**



### ➤ **Astrocytic gliosis**

- Constant but non-specific feature of prion diseases
- Widespread proliferation of fibrous astrocytes found throughout gray matter

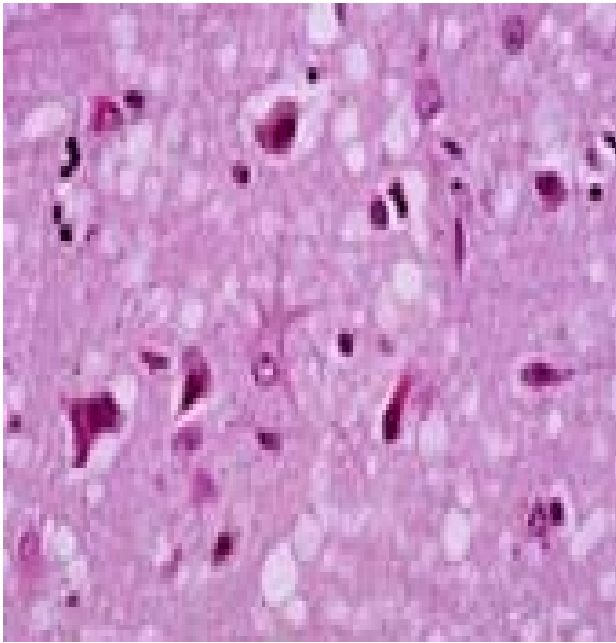
### ➤ **Neuronal loss**

- Advanced cases
- Brain atrophy (cerebellum) is usually severe

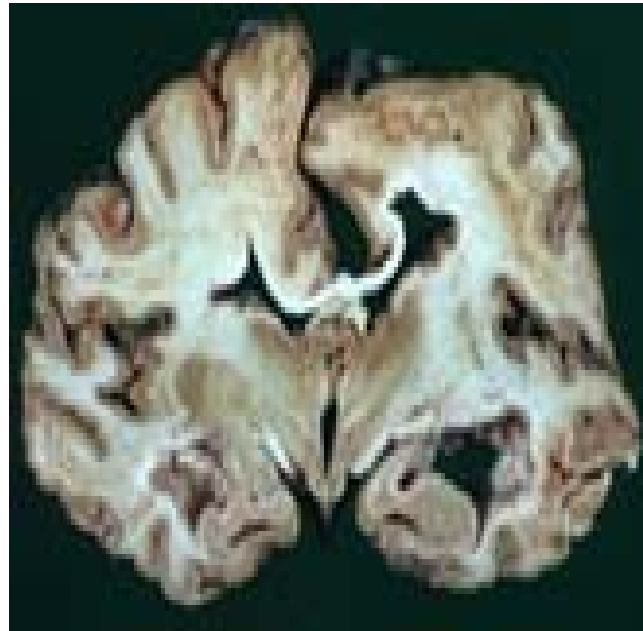
### ➤ **Amyloid plaque formation**

- PrP<sup>sc</sup> precipitates as **amyloid plaques**
- Immunoreactive with antibodies to the prion protein
- Do not immunoreact with antibodies to other amyloidogenic proteins, such as the amyloid-beta

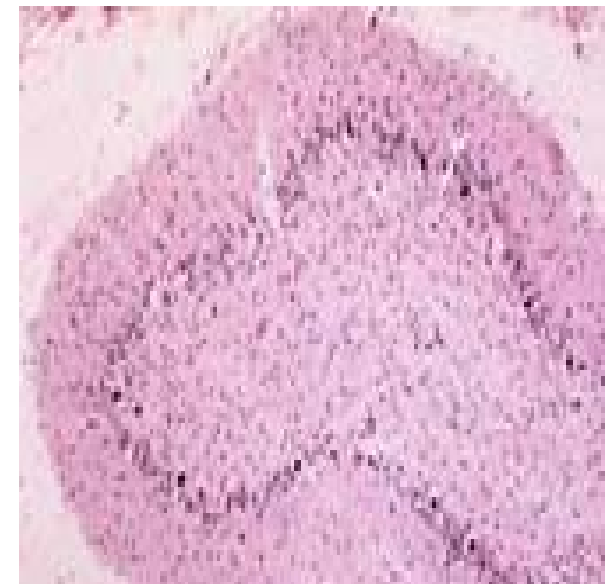
### ➤ **There is no inflammation**



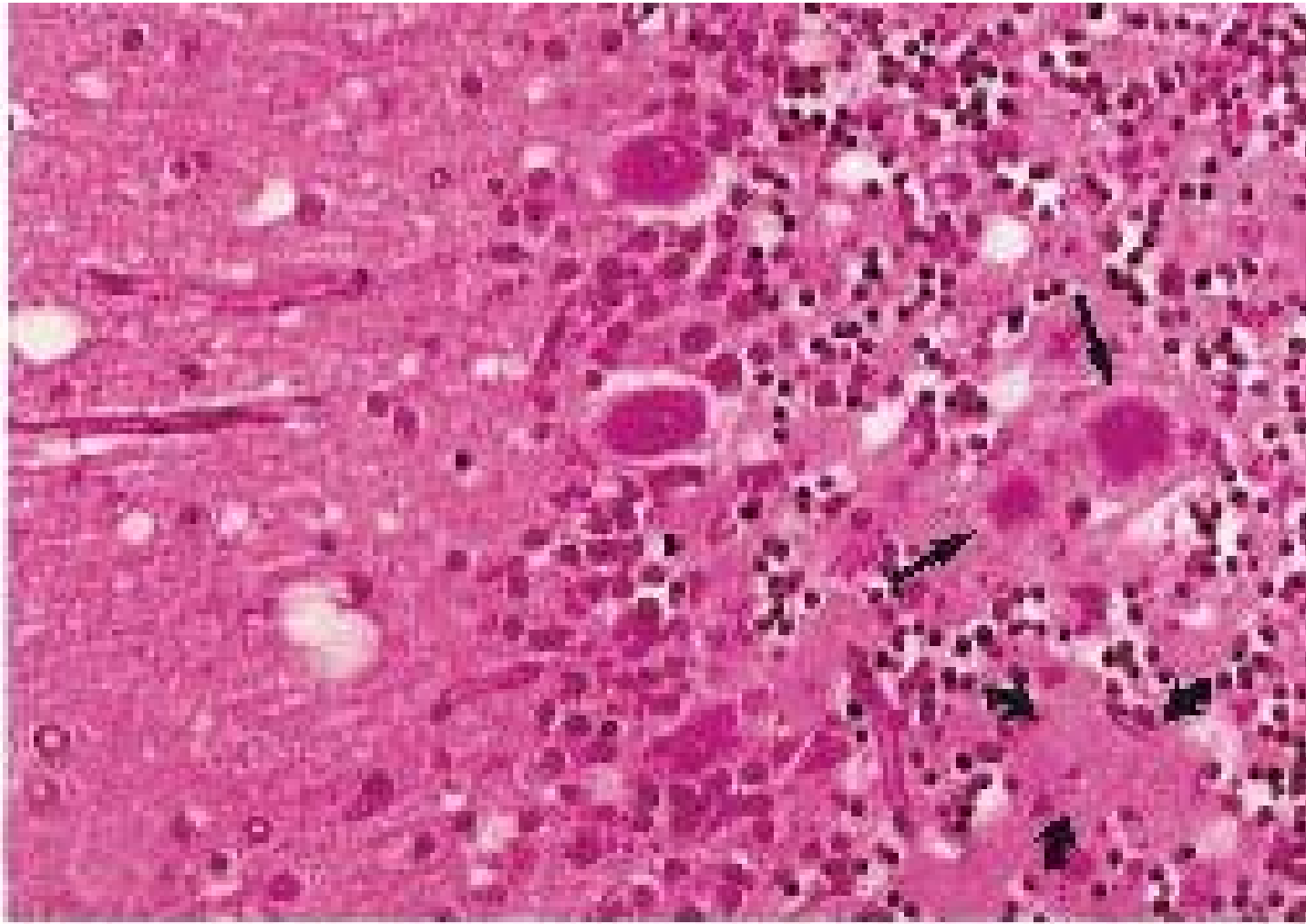
**Spongiform encephalopathy**



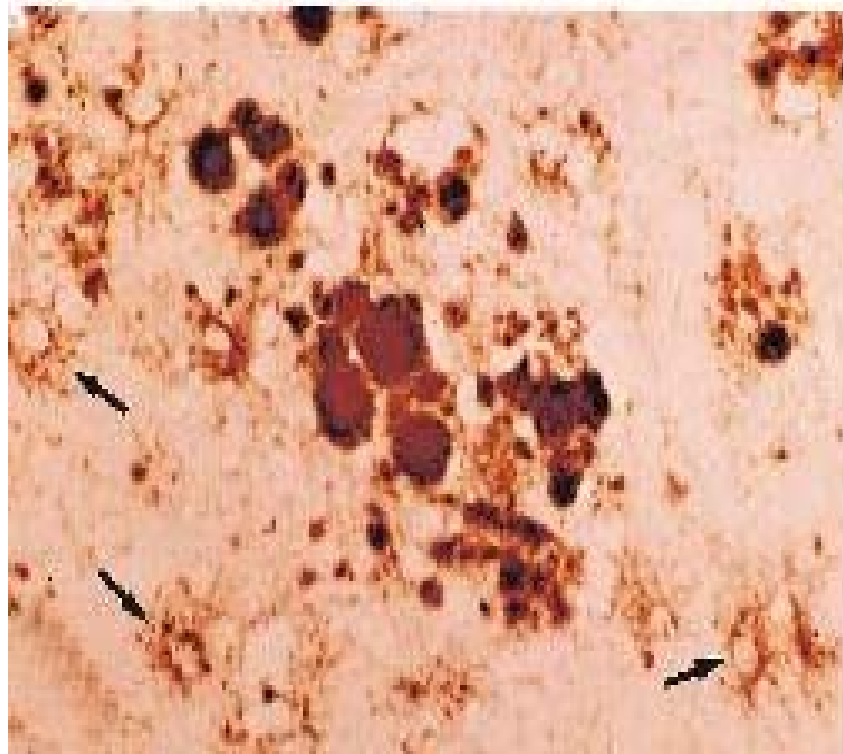
**CJD: severe brain atrophy**



**Cerebellar degeneration**

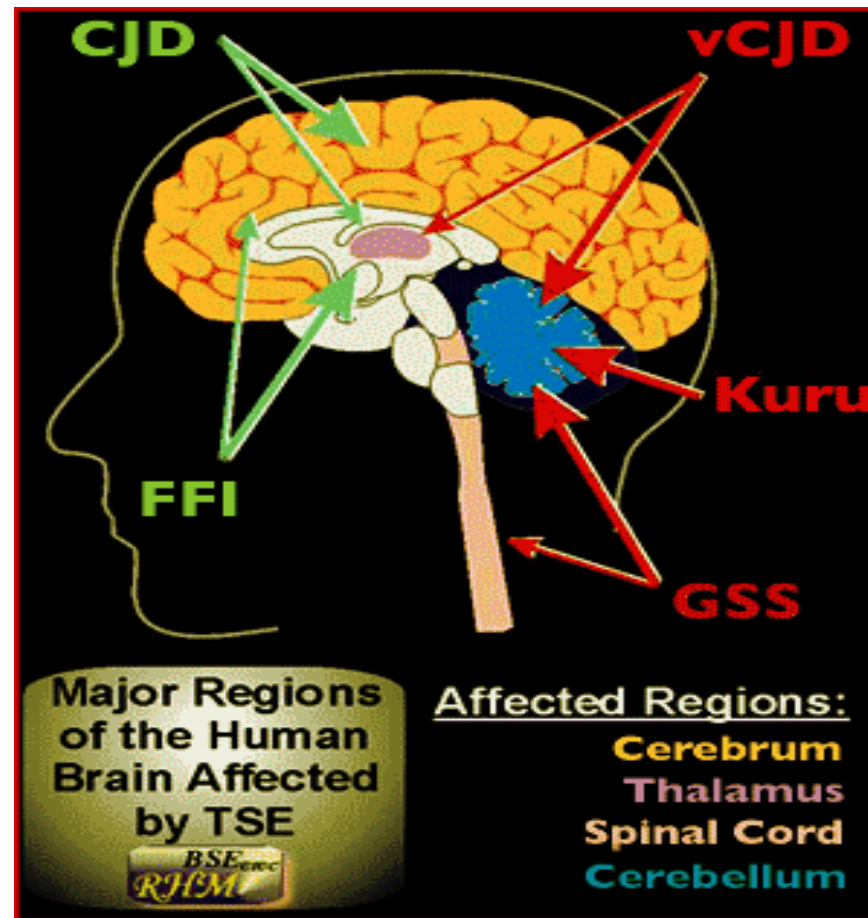


**kuru plaques**



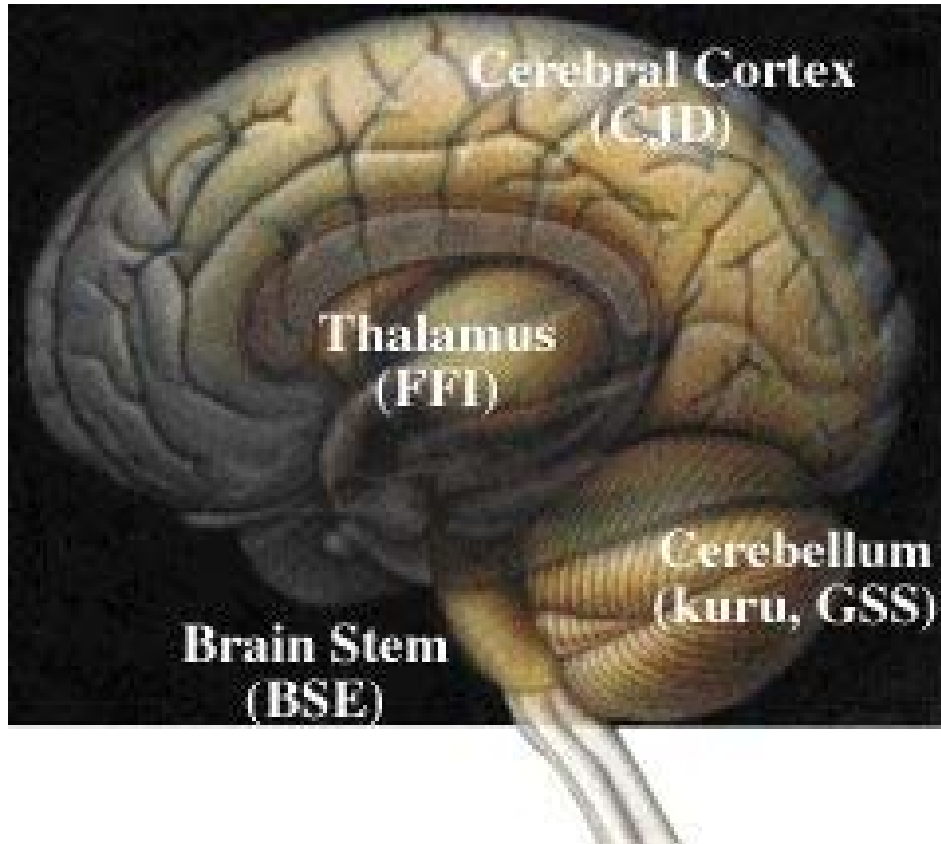
**The masses of prion stained with relevant antibody**

# Different prions affect different parts of brain



# Different prions affect different parts of the brain

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**Cerebral cortex** When the cerebral cortex is affected, the symptoms include loss of memory and mental acuity, and sometimes also visual impairment (CJD).

**Thalamus** Damage to the thalamus may result in insomnia (FFI).

**Cerebellum** Damage to the cerebellum results in problems to coordinate body movements and difficulties to walk (kuru, GSS).

**Brain stem** In the mad cow disease (BSE), the brain stem is affected.

# Scrapie

- Fatal, degenerative disease that affects the nervous systems of sheep, goats.
- Identified in 18th century (1732)
- Does not appear to be transmissible to humans.
- It causes an itching sensation in the animals.
- Excessive lip-smacking, altered gaits, and convulsive collapse.

# Scrapie

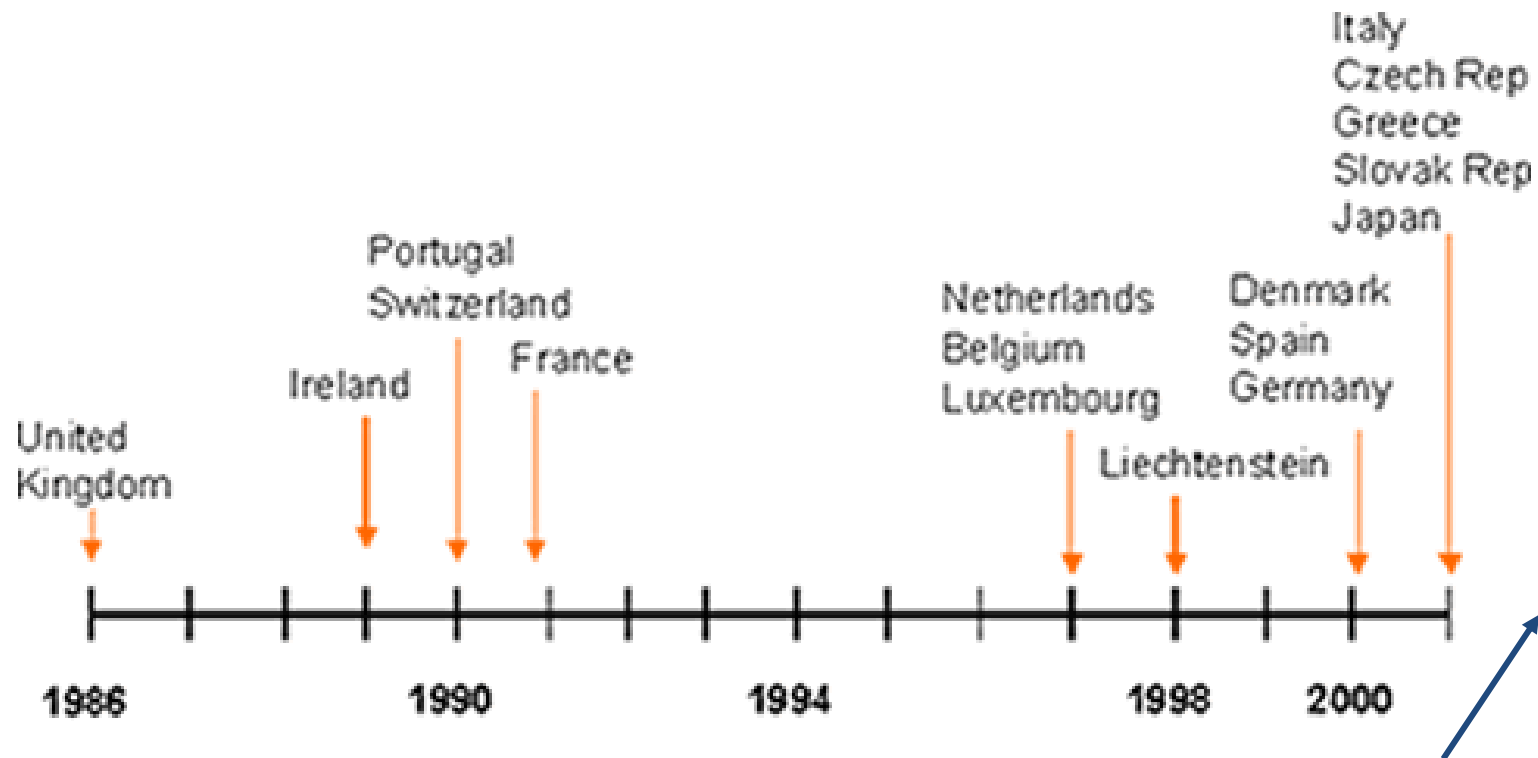


Courtesy of Dr. Michelle L. Crocheck, USDA-APHIS-US-MVSL



# Bovine spongiform encephalopathy (BSE)

- Incubation (30 months-8 yrs)
- All breeds
- Symptoms - slow in onset-motor dysfunction
- 4.4 million cattle infected



**First occurrence of indigenous BSE cases**

BSE continues to spread to other areas, but has not become epidemic as it was in Great Britain. It is a major concern because finding it may result in quarantines against beef from the country in which it is found.

# Bovine spongiform encephalopathy (BSE)



# Chronic wasting disease

- Identified in 1967
- Not transmissible to humans
- Transmissible spongiform encephalopathy (TSE) deer, elk and moose.
- Symptoms – chronic weight loss



# Prion disease of human

**Table 1.** Clinical Phenotypes of Prion Disease

Disease	Primary features	Age at Onset (Range)	Duration	Pathology
Kuru	Ataxia, then dementia	40 years (29-60)	3 months–1 year	Kuru plaques
sCJD	Dementia, ataxia, myoclonus	61 years (17-83) rare <40	<1 year	Generalized grey matter vacuolation and gliosis
fCJD	Dementia, ataxia, myoclonus	Typically <55 years (20s to 80s) <sup>a</sup>	1–5 years	Generalized grey matter vacuolation and gliosis
GSS	Ataxia, then dementia	Typically <55 years (20s to 60s) <sup>a</sup>	2–6 years	PrP-plaques, gliosis, less vacuolation
FFI	Insomnia, dysautonomia, ataxia, dementia	45 ± 10	~1 year	Focal thalamic and olivary gliosis, neuronal dropout
vCJD	Behavioral changes, later dementia	Teens/young adults	~1.5 years	Florid plaques and diffuse spongiosis

Abbreviations: fCJD, familial Creutzfeldt-Jakob disease; FFI, familial fatal insomnia; GSS, Gerstmann-Sträussler-Scheinker syndrome; sCJD, Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

<sup>a</sup> Large variability in some mutations versus others results in a broad range in disease onset.

# Kuru

- In 1957 Kuru was the first human disease identified as a prion disease
- Kuru was reported among the Fore tribe people in Papua New Guinea
- Caused by a ritual cannibalism
- Women were affected more than men
- Present with cerebellar deficits, progressive loss of coordination.
- Associated with uncontrollable and inappropriate episodes of laughter
- Hence Kuru was named "laughing death" by the Fore people



**Legend:**

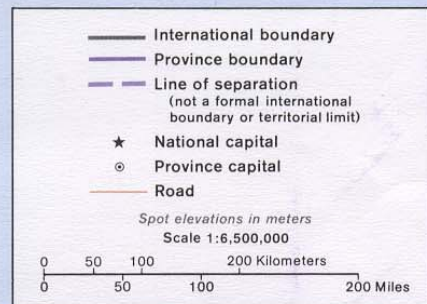
- International boundary
- Province boundary
- Line of separation (not a formal international boundary or territorial limit)
- National capital
- Province capital
- Road

Spot elevations in meters  
Scale 1:6,500,000

0 50 100 200 Kilometers  
0 50 100 200 Miles

**Geographical Features and Regions:**

- South Pacific Ocean** (North)
- Bismarck Sea** (Northwest)
- Solomon Sea** (East)
- Gulf of Papua** (Southwest)
- Milne Bay** (Southeast)
- Coral Sea** (South)
- Provinces:** West Sepik, East Sepik, Madang, Morobe, Western, Northern, Central, New Ireland, New Britain, West New Britain, East New Britain, Bougainville, Northern Solomons, Solomon Islands.
- Islands and Archipelagos:** Admiralty Islands, Manus, Palakau, New Hanover, Kavieng, New Ireland, Feni Islands, Lihir Island, Namatanai, Rabaul, Gazelle Peninsula, Silur, Lemankoa, Hutjena, Sohano, Kunua, Arawa, Panguna, Kietia, Taki, Buin, Choiseul Island, Shortland Island, Treasury Islands, Gizo, Trobriand Islands, D'Entrecasteaux Islands, Fergusson Island, Normanby Island, Alotau, Ahioma, Misima Island, Tagula, Rossel Island, Woodlark Island.
- Mountains and Ranges:** Central Range, Finisterre Range, Krayke Range, Owen Stanley Range.
- Rivers and Lakes:** Sepik River, Mamberamo River, Wapenamundi, Ulu River, Lake Murray, Lake Hagen, Lake Kani.
- Other Features:** Torres Strait, Great Barrier Reef, Oriomo Plateau, Weim, Morehead, Mari, Boigu Island, Saibai Island, Daru, Baimuru, Kikori, P. L. A. I. N., Balimo, Weam, Bama, Weipa, Australia.
- Capitals:** Port Moresby (National Capital), Rabaul (Province Capital), Honiara (National Capital).



# Kuru





# Creutzfeldt-Jacob disease (CJD)

- CJD is the most common form of human prion diseases
- Initially described by Jacob in 1921
- Most patients with sCJD and iCJD are Methionine homozygotes for the Methionine/Valine polymorphism at codon 129

❖ **Sporadic (sCJD)** - most common ( 85-90%)

❖ **Familial (fCJD)** - 15%

❖ **Iatrogenic (iCJD)**- <1%

# Sporadic CJD

- Incidence: one case per 1 million people per year
- Affects middle aged or old persons (60-65 yrs)
- Rapidly worsening global cognitive status
- An important and universal physical feature is the presence of *myoclonus*
- May present with initial cortical blindness
- 40% have cerebellar dysfunction
- Virtually, any unexplained or unusual neurological sign or symptom can be a manifestation of CJD
- CJD is inexorably progressive and fatal within months up to 1 to 2 years

## ❖ Familial CJD

- Autosomal dominant
- Clinically indistinguishable from sCJD

## ❖ Iatrogenic CJD

- Sources :
  - improperly sterilized depth electrodes
  - transplanted corneas
  - human growth hormone
  - dura mater grafts
  - gonadotropin derived from cadaveric pituitaries
  - surgical instruments
  - blood transfusion

# Case definition

- When evaluating a patient for possible sporadic CJD, the clinician should be guided by published case definitions; they are as follows:
- **Definite CJD**
  - Characteristic neuropathology
  - Protease-resistant PrP by Western blot
- **Probable CJD**
  - Progressive dementia
  - Typical findings on EEG
  - At least 2 of the following - Myoclonus, visual impairment, cerebellar signs, pyramidal or extrapyramidal signs, or akinetic mutism

# Case definition

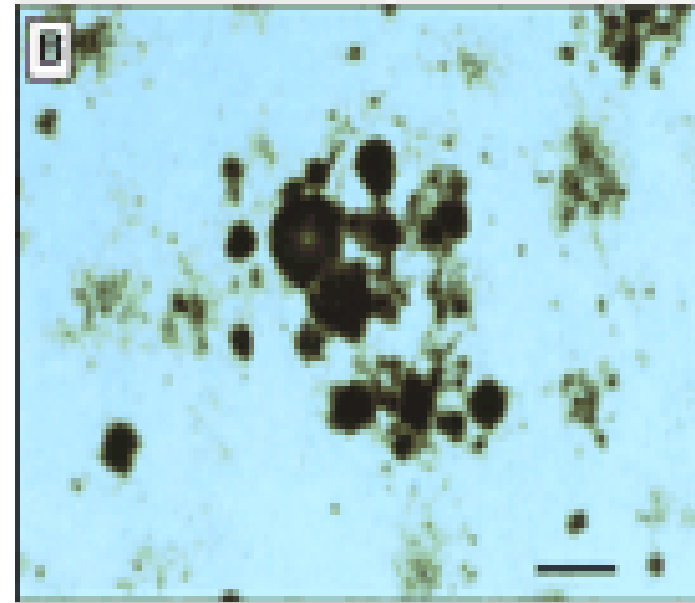
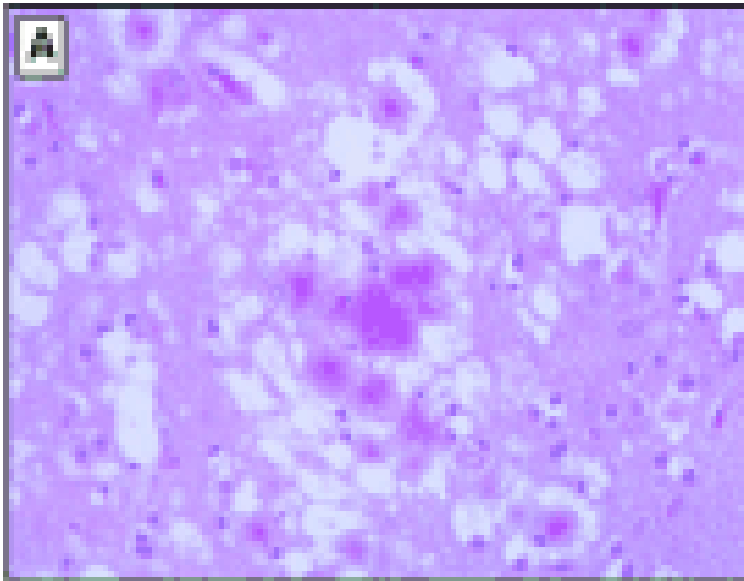
- **Possible CJD**

- Progressive dementia
- Atypical findings on EEG or EEG not available
- At least 2 of the following - Myoclonus, visual impairment, cerebellar signs, pyramidal or extrapyramidal signs, or akinetic mutism
- Duration less than 2 years

# Variant Creutzfeldt-Jakob disease

- The first case of vCJD was reported in 1995
- As of February 2006, 159 cases of vCJD have been diagnosed
- Believed due to ingestion of beef products contaminated by nervous system tissue
- Young age at onset
- Early psychiatric symptoms and sensory symptoms are much more common
- Cerebellar findings are present in all patients with vCJD
- Absence of periodic electroencephalographic activity
- Comparatively prolonged illness
- Distinctive neuropathology : **florid amyloid plaques**, which are reminiscent of kuru-associated PrP amyloid.

# Variant Creutzfeldt-Jakob disease



- a. Field with aggregates of plaques surrounded by spongiform degeneration
- b. Multiple plaques and amorphous deposits are PrP-immunopositive

## Clinical and histopathological features of patients with new variant CJD and typical sporadic CJD

Clinical features	new variant CJD	sporadic CJD
Age at death (yr)	29 (19-41)	65
Duration of illness (mo)	12 (8-23)	4
Presenting signs	Abnormal behavior, dysesthesia	Dementia
Later signs	Dementia, ataxia, myoclonus	Ataxia, myoclonus
Periodic complexes on EEG	None	Most
% with PRNP codon 129 Met/Met	100	83
Histopathologic changes	Vacuolation, neuronal loss, astrocytosis, amyloid plaques (100%)	Vacuolation, neuronal loss, astrocytosis, amyloid plaques (15%)
% with „florid“ PrP plaques	100	10
PrP glycosylation pattern	BSE-like	Not BSE-like

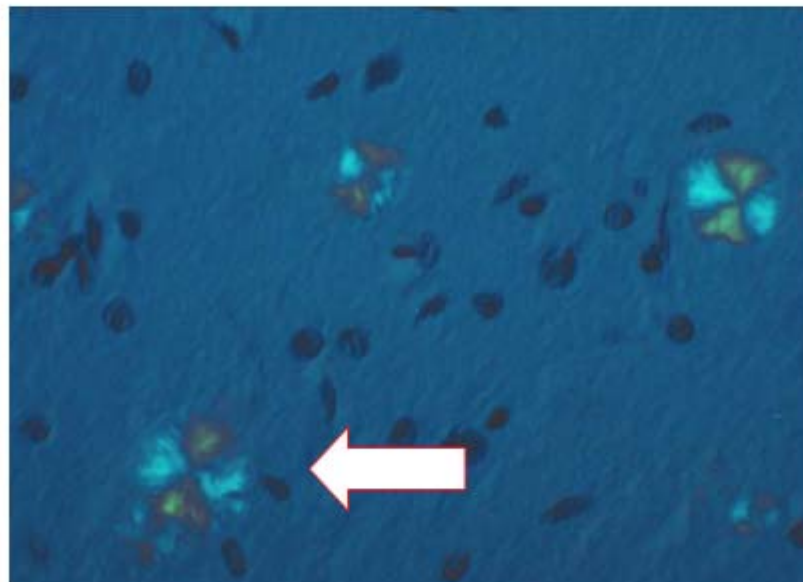


# Gerstmann-Straussler-Scheinker disease

- Autosomal dominant (102 codon, proline to leucine)
- Occurs typically in 4th-5th decade
- Present with a slowly progressive limb and truncal ataxia, as well as dementia
- Prominent involvement of the brainstem degeneration
- Death occurs 3-8 years following presentation
- The neuropathology of GSS is remarkable in that extensive and invariable **amyloid deposition** occurs
- Along with the typical spongiform change, gliosis, and neuronal loss

# GSSD

## *Birefringent amyloid plaques in a prion disease (GSS)*



Congo Red staining of Maltese-cross shaped GSS amyloid plaques.

Plaques can also be stained with thioflavin S, or with PrP-directed antibodies

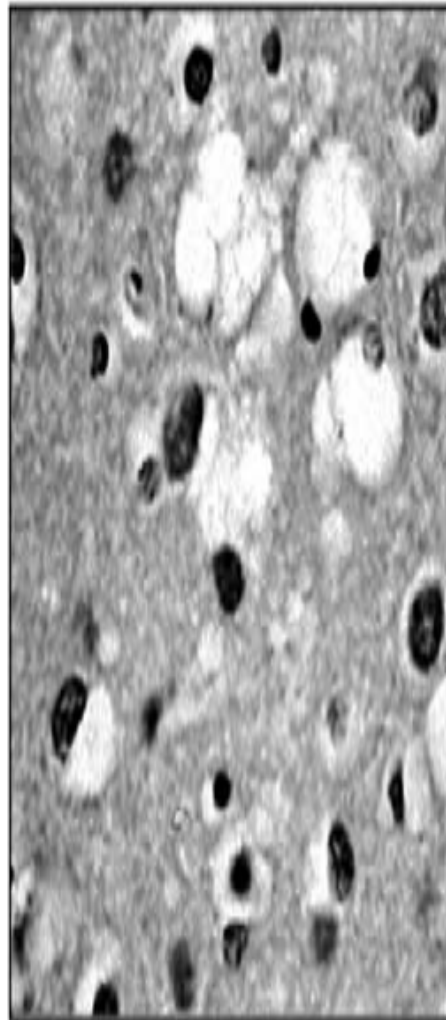
# Fatal familial insomnia

- Age of onset is variable, ranging from 18-60 years
- Missense mutation at codon 178 of the PrP gene where Asn is replaced by Asp
- Coupled with Met at the polymorphic codon 129
- Course ranges from 6 months to 3 years
- Presentation:
  - intractable insomnia
  - dementia
  - motor paralysis
  - dysautonomia (ie, hyperthermia, hypertension, tachypnea, hyperhydrosis)

# Fatal familial insomnia

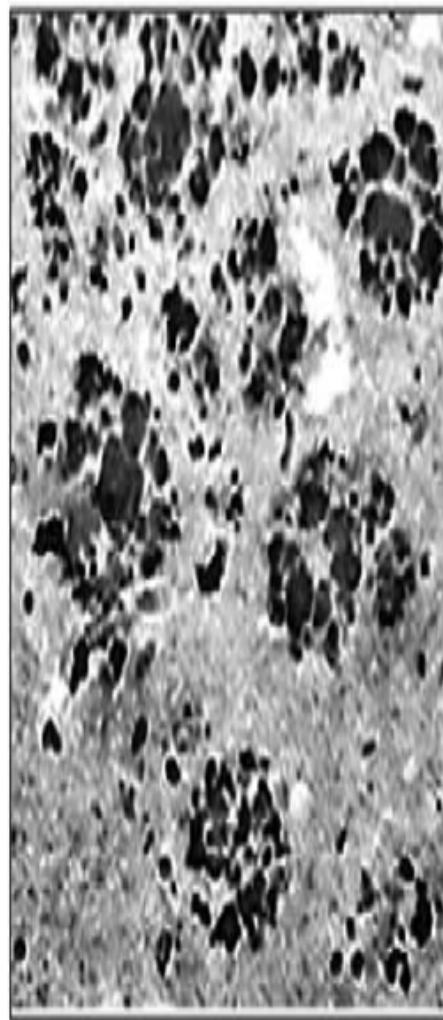
- Because of the diversity of clinical presentations of this disorder, **genotyping** is very important for definitive diagnosis
- Neuropathologically, marked atrophy of the anterior ventral and mediodorsal thalamic nuclei occurs
- Unlike other prionoses, *spongiform change can be a minor feature or can be absent altogether*

CJD



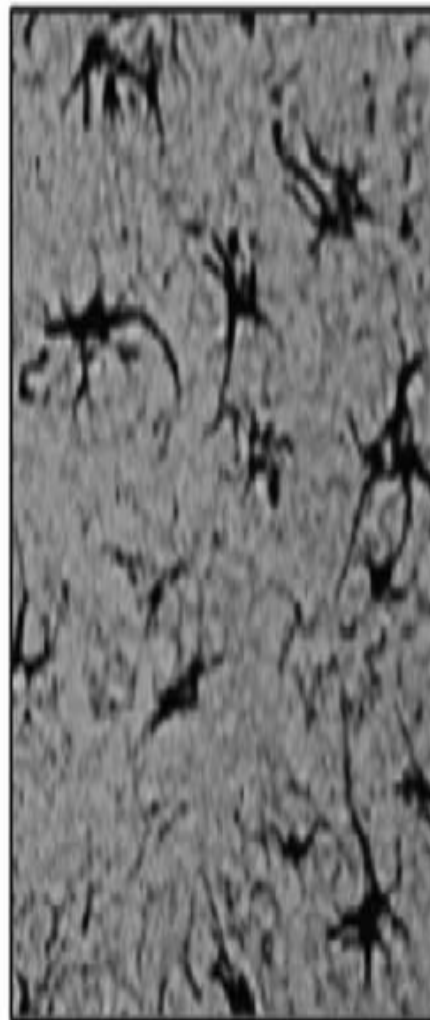
Spongiform Degeneration

GSS



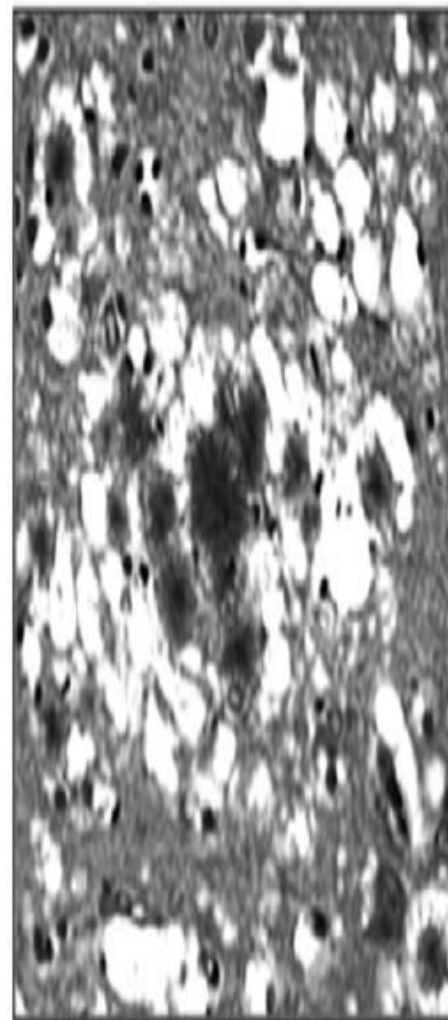
PrP plaques

FI



Gliosis

vCJD



Florid Plaque

# Diagnosis

- Clinical and investigative features, which are included in the diagnosis criteria, may be indicative of the diagnosis of prion diseases but are never definitive

➤ **Clinical:** features depends on the sites of CNS involved

➤ **Investigations**

## □ EEG

- Shows a typical periodic pattern
- Stereotyped periodic bursts of <200ms duration, occurring every 1-2sec
- 90% cases of sporadic CJD
- Rare in vCJD

# Diagnosis

## □ CSF

- Protein and glucose concentration is normal
- No pleocytosis
- Elevation of **protein 14-3-3**: most useful CSF marker of CJD
- **Protein 14-3-3** is elevated in
  - 90% of cases of sporadic CJD
  - 50% of vCJD cases
- This protein is also elevated in patients with encephalitis, cerebral infarction, and other conditions

## □ CT scan

- Normal/cortical atrophy

# Diagnosis

## □ MRI brain scan

- Shows high signal intensity in
  - basal ganglia 70% of cases of sporadic CJD
  - posterior thalamus in 90% of cases of vCJD

## □ Western blotting of PrP<sup>sc</sup>

- Following proteinase digestion reveals electrophoretic patterns that identify different prion strains
- PrP 27-30 is protease resistant core of PrP<sup>sc</sup>

## □ Conformation dependent immunoassay (CDI)

- Extremely sensitive & quantitative
- Useful for both ante & post mortem detection of prions



# Diagnosis

## □ Brain biopsy

- A definitive diagnosis is made by microscopic examination of brain tissue

	sCJD	vCJD	FFI	GSS
Spongiform degeneration	++	++	+/-	++
Gliosis	+	+	+	+
Amyloid plaques	+	++	+	+++

- Neuronal loss in advance stages

# Diagnosis

- PrP<sup>Sc</sup> can be detected in
  - brain tissue extracts by **ELISA**
  - tissue sections by **immunohistochemistry**
- As PrP<sup>Sc</sup> not uniformly distributed throughout the CNS, absence of PrP<sup>Sc</sup> in limited sample like brain biopsy does not rule out prion disease

## ☐ Brain autopsy

- Only **definitive test** is post-mortem pathology

## ☐ DNA sequencing

- Can be done on extracts from blood, brain, and other tissues
- Detects :
  - Mutations of the *PRNP* gene
  - Codon 129 polymorphism

Disease	Characteristics
Sporadic CJD	<p>Rapidly progressive<sup>a</sup> dementia with two or more of: myoclonus, cortical blindness, pyramidal signs, cerebellar signs, extrapyramidal signs, akinetic mutism</p> <p>Most aged 45–75</p> <p>Serial EEG usually shows pseudoperiodic complexes</p> <p>CSF 14-3-3 protein usually positive</p> <p>CT normal or atrophy, MRI may show high signal in the striatum and/or cerebral cortex in FLAIR or diffusion-weighted images</p> <p><i>PRNP</i> analysis: no pathogenic mutations, most are 129MM (VV and MV may be longer duration, clinically atypical and EEG less often positive)</p> <p>Brain biopsy should be considered in highly selected cases (to exclude treatable alternative diagnoses): PrP immunocytochemistry or Western blot for PrP<sup>Sc</sup> types 1–3<sup>b</sup></p>
Iatrogenic CJD	<p>Progressive cerebellar syndrome and behavioural disturbance or classical CJD-like syndrome with history of iatrogenic exposure to human prions (pituitary-derived hormones, tissue grafting or neurosurgery)</p> <p>May be young</p> <p>EEG, CSF and MRI generally less helpful than in sporadic cases</p> <p><i>PRNP</i> analysis: no pathogenic mutations, most are 129 homozygotes</p> <p>Brain biopsy should be considered in highly selected cases (to exclude treatable alternative diagnoses): PrP immunocytochemistry or Western blot for PrP<sup>Sc</sup> types 1–3<sup>b</sup></p>
Variant CJD	<p>Early features: depression, anxiety, social withdrawal, peripheral sensory symptoms</p> <p>Cerebellar ataxia, chorea or athetosis often precedes dementia</p> <p>Advanced disease resembles sporadic CJD</p> <p>Most in young adults; however, age at onset 12–74 yr seen</p> <p>EEG nonspecific slow waves, CSF 14-3-3 may be elevated or normal</p> <p>MRI: pulvinar sign usually present (particularly using FLAIR sequence) but may be late feature</p> <p><i>PRNP</i> analysis: no mutations, all 129MM to date</p> <p>Tonsil biopsy: characteristic PrP immunostaining and PrP<sup>Sc</sup> on Western blot (type 4t)</p>
Iatrogenic vCJD	<p>Has occurred in recipients of blood transfusion from a donor who subsequently developed clinical vCJD</p> <p>Known recipients of implicated blood or blood products in the UK have been notified of their risk status</p> <p>Clinical features and investigations as for primary vCJD</p>
Inherited prion disease	<p>Varied clinical syndromes between and within kindreds: should consider in all pre-senile dementias and ataxias irrespective of family history</p> <p><i>PRNP</i> analysis: diagnostic, codon 129 genotype may predict age at onset in pre-symptomatic testing</p>

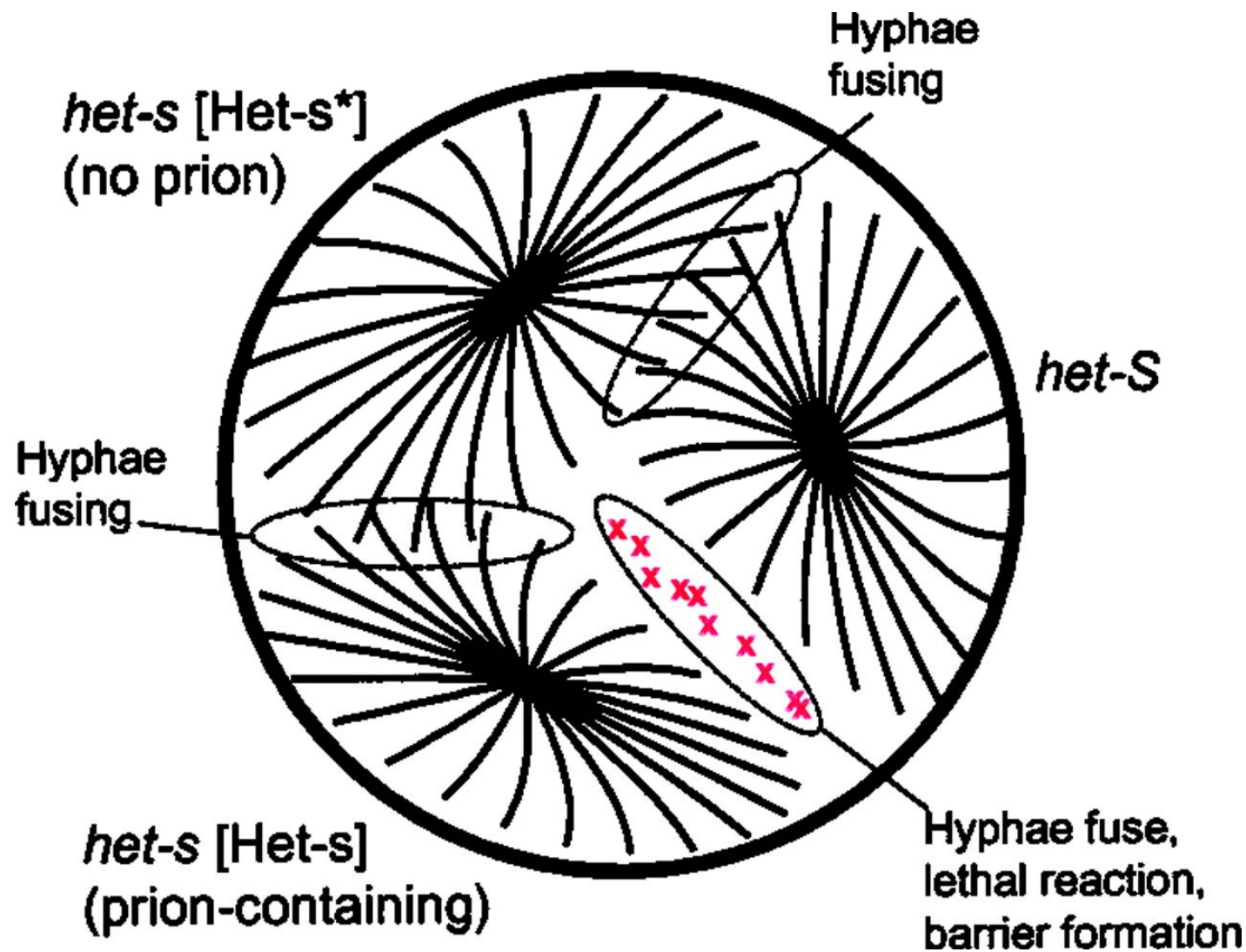
# Prognosis and treatment

- Quinacrine
- Pentosan polyphosphate
- Humanized anti PrP monoclonal antibodies can be given for passive immunizations in early pathogenesis to block the neuroinvasion.

# Prions of yeast and fungi

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- Yeast and filamentous fungi make great experimental tools.
- Prions in yeast first identified by Wickner & associated with nitrogen metabolism [URE3], then as a component of a suppressor tRNA activity [PSI].
- The first prion in filamentous fungi was identified in association with heterokaryon (vegetative) incompatibility in the ascomycete *Podospora anserina*
  - This is the only prion identified to date that is not associated with a diseased state



The [Het-s] prion results in heterokaryon incompatibility in the filamentous fungus *Podospora anserina*.

From Wickner, 1999, J.Biol. Chem. 274: 555

Identity of alleles at the *het-s* locus is required for hyphae of different *Podospora* colonies to fuse. However, an encounter of *het-s* and *het-S* colonies will only result in the lethal reaction that comprises the incompatibility reaction if the Het-s protein is in its prion form (called [Het-s]).

# Future perspectives for Prion Diseases

- Because people at risk for inherited prion diseases can now be identified decades before neurologic dysfunction is evident, the development of an effective therapy for fully penetrant disorders is imperative
- Interfering with the conversion of PrP<sup>C</sup> into PrP<sup>Sc</sup> would seem to be the most attractive therapeutic target
- One reasonable therapeutic strategy would be to stabilize the structure of PrP<sup>C</sup> by binding a drug
- Alternatively, drugs that destabilize the structure of PrP<sup>Sc</sup> might also prove useful
- By modifying the action of protein X, which might function as a molecular chaperone



Thank you

