CNS II
Microbiology Lecture IV

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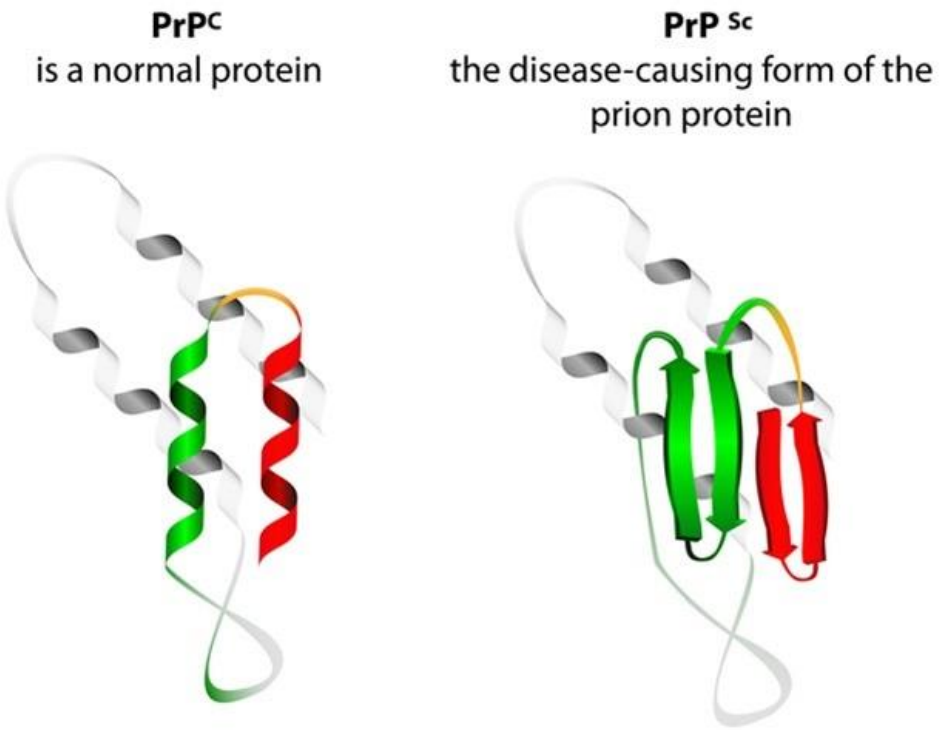
Prions “pree-ons”

- **Introduction**
  - **Prion diseases** are a group of neurodegenerative diseases caused by the conversion of the normal prion protein (PrP^{C}) with a primarily α-helical structure into an abnormal form of the protein called the prion (PrP^{Sc}) which has a primarily β-pleated sheet structure.
  - Stanley Prusiner received the 1997 Nobel Prize in Physiology or Medicine in part for isolating the scrapie agent and confirming it was a misfolded protein, which he called a “proteinaceous infectious particle,” or prion.

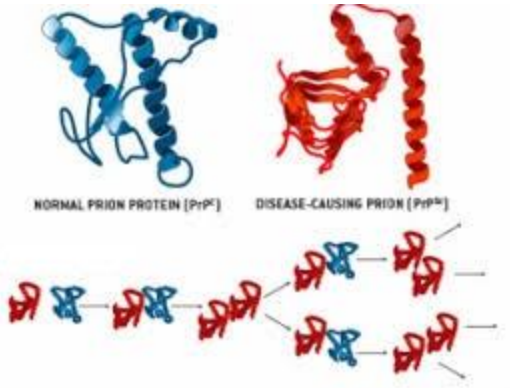


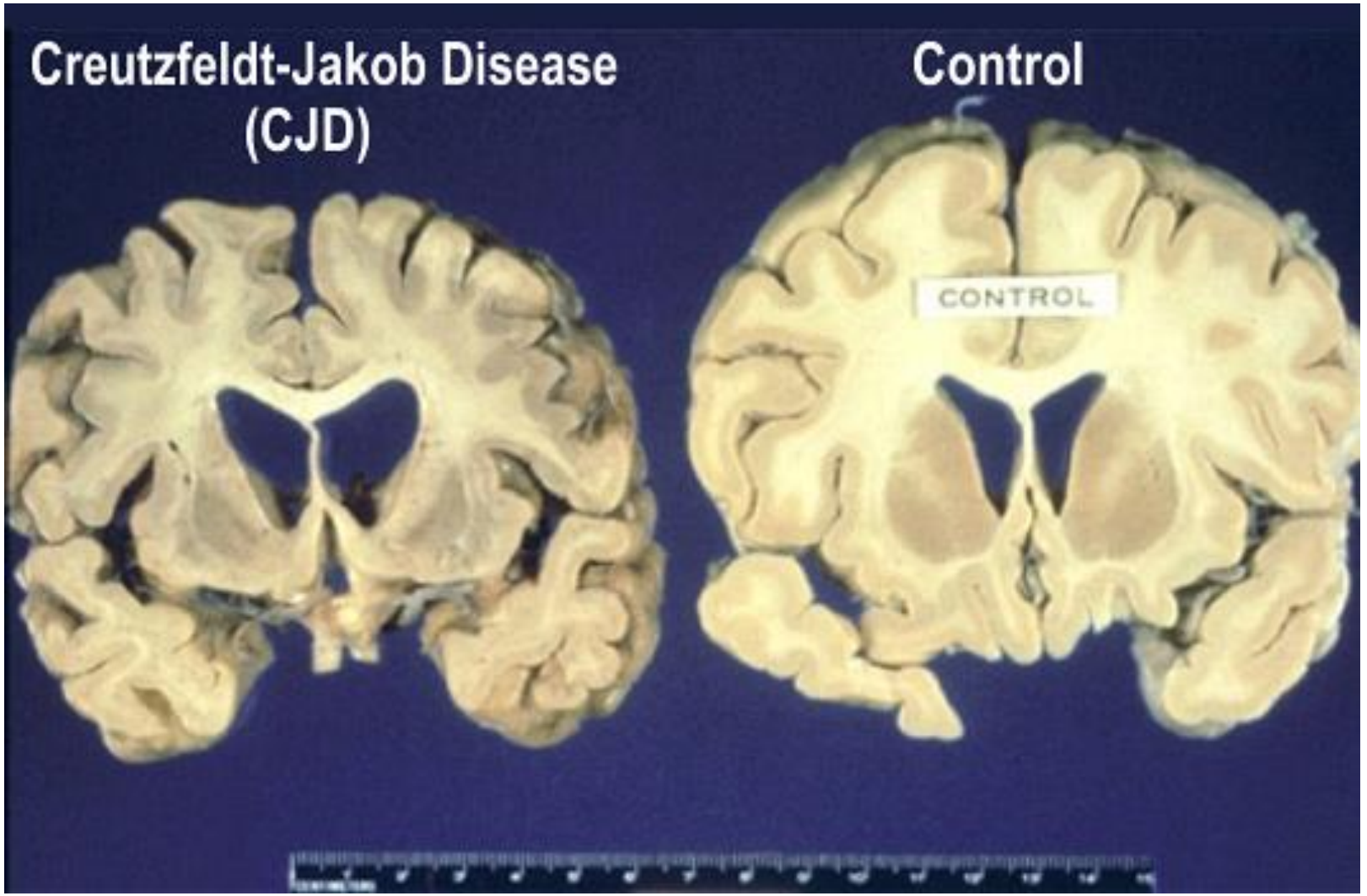
- **PrP^C :** prion-related protein, in which C stands for the cellular form of the protein.
- **PrP^{Sc}:** prion-related protein, in which Sc stands for scrapie, the prion disease of sheep and goats.

- The incubation periods for these diseases are **months to years**, and their courses are protracted and inevitably **fatal**.
- A prion is not inactivated by procedures that destroy nucleic acids and are resistant to ionizing radiation, boiling, and many common disinfectants.
- They can remain viable even in formalinized brain tissue for many years.
- They have not been grown in cell culture.
- The amino acid sequence of different prion proteins in different animal species differ from one another and transmission across species usually **does not** occur. Tissue from infected cows did, however, transmit variant Creutzfeldt-Jakob disease.

Pathogenesis

- The model of prion disease is that the pathologic disease-causing misfolded form of the prion protein PrP^{Sc}, acts as a template, such that when it comes into contact with a prion protein, PrP^{C}, it transforms PrP^{C} into PrP^{Sc}, resulting in two prions. These two prions, in turn, transform two more PrP^{C} into PrP^{Sc}, which then transform four more, and so forth, leading to an exponential transformation and accumulation of prions.
- Varying degrees of neuronal loss and astrocyte proliferation occur. The diseases are known as “spongiform” encephalopathies or transmissible spongiform encephalopathies because of the vacuolar changes in the cortex and cerebellum.




Creutzfeldt-Jakob Disease
(CJD)
Control
CONTROL

Prion Diseases

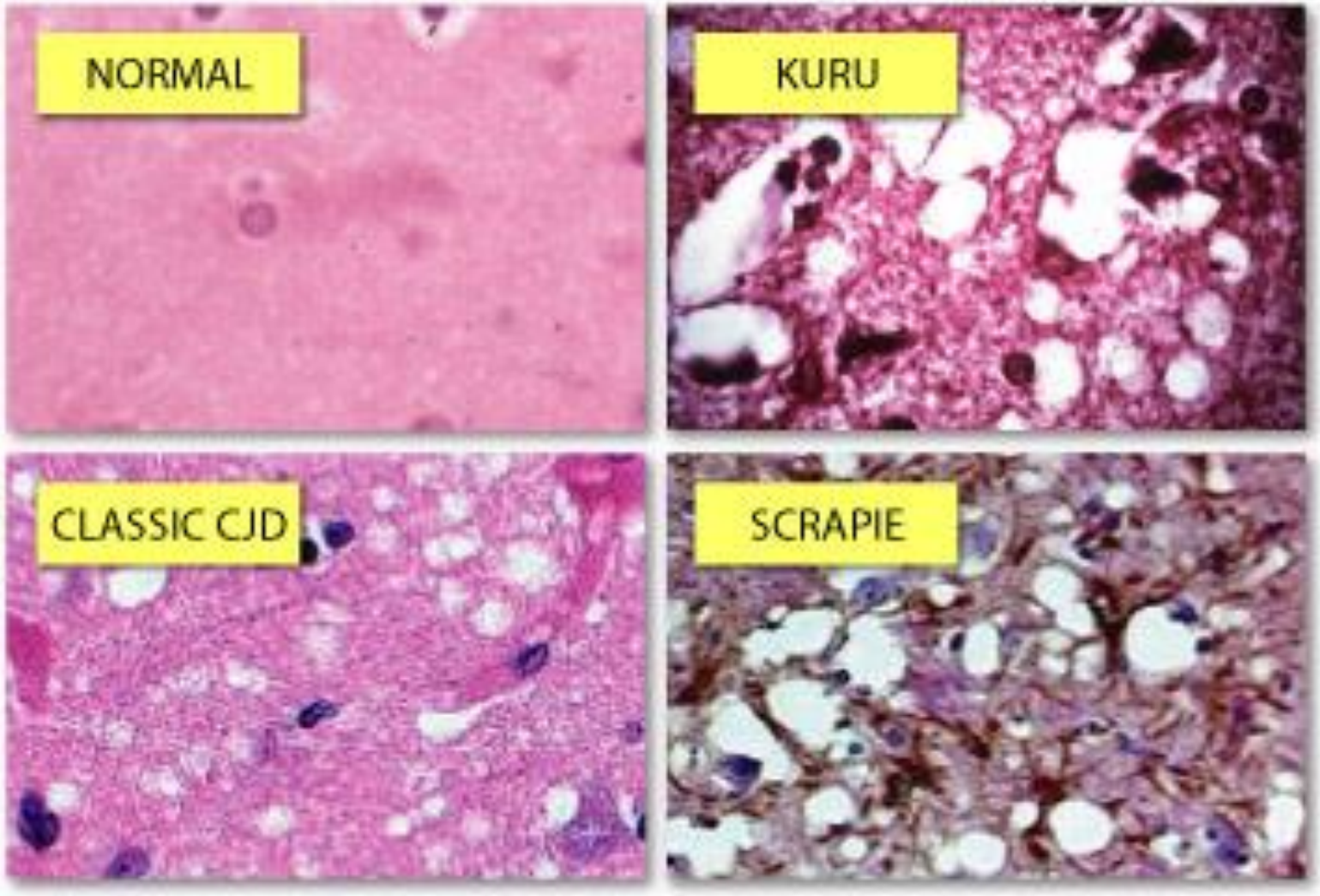
TABLE 20–2 Unconventional Virus (Prion) Diseases[a]

HUMANS	ANIMALS (PRIMARY HOSTS)
Creutzfeldt-Jakob disease	Scrapie (sheep)
Variant Creutzfeldt–Jakob disease[b]	Transmissible mink encephalopathy (mink)
Gerstmann-Straüssler-Scheinker syndrome	Chronic wasting disease (mule deer, elk)
Kuru	Bovine spongiform encephalopathy (BSE; cows)[b]
Fatal familial insomnia	

[a]Subacute spongiform encephalopathies.

[b]Prion agents of variant Creutzfeldt–Jakob disease and bovine spongiform encephalopathy (BSE) are identical.

Prions cause bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep, and five fatal CNS diseases in humans


NORMAL
KURU
CLASSIC CJD
SCRAPIE

Classification

- **Spontaneous (sporadic):**
  - Incidence: 80-95% of prion diseases.
  - The conversion of PrP^{C} to PrP^{Sc} is thought to occur spontaneously or due to a somatic mutation in the prion protein gene, ***PRNP***.
  - Example: Creutzfeldt-Jakob disease

- **Genetic (familial):**
  - Incidence: 10-15% of prion diseases.
  - **Mutations** in ***PRNP*** make the PrP^{C} more susceptible to misfolding into PrP^{Sc}
  - Examples:
    1. Genetic Creutzfeldt-Jakob disease.
    2. Gerstmann-Sträussler-Scheinker syndrome.
    3. fatal familial insomnia.

- **Acquired (infectious or transmitted):**
  - Incidence is less than 1%; although the least common, they are the most notorious.
  - PrP^{Sc} is accidentally transmitted to a person, causing their endogenous PrP^{C} to misfold.
  - Examples:
    1. Kuru
    2. Variant Creutzfeldt-Jakob disease
    3. Iatrogenic Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease

- The mode of acquisition is unknown, but it occurs **sporadically** (85%), in a **familial** pattern (15%) and **acquired** (Iatrogenic or variant CJD) in less than 1% of the cases.
- There is **no** evidence of transmission by direct contact or airborne spread.

Sporadic Creutzfeldt-Jakob disease

- A progressive, fatal illness of the CNS that is seen most frequently in the sixth and seventh decades of life.

Presentation

- The initial clinical manifestations are a change in cerebral function, usually diagnosed initially as a psychiatric disorder.
- Forgetfulness and disorientation progress to overt dementia and the development of changes in gait, increased tone in the limbs, involuntary movement, and seizures.
- The disorder usually runs a course of 4 to 7 months, eventually leading to paralysis, wasting, pneumonia, and death (85% to 90% of patients dying within 1 year).

Iatrogenic Creutzfeldt-Jakob disease

- Dura mater grafts and corneal transplants
- By contact with contaminated electrodes or instruments used in neurosurgical procedures
- Pituitary-derived human growth hormone

Prevention

- Stereotactic neurosurgical equipment, especially which was used in patients with undiagnosed dementia, should not be reused.
- Organs from patients with undiagnosed neurologic disease should not be used for transplants.
- Growth hormone from human tissue has now been replaced by a recombinant genetically engineered product.
- Recommendations for disinfection of potentially infectious material include treatment for 1 hour with NaOH or by autoclaving at 132°C for 60 to 90 minutes.

Variant Creutzfeldt-Jakob Disease

- **History:**
  - **Bovine Spongiform Encephalopathy "Mad Cow Disease"** was identified in 1986, after it began striking cows in the United Kingdom, causing them to become uncoordinated and unusually apprehensive. The cows also exhibited hyperesthesia, hyperreflexia, muscle fasciculations, tremors, and weight loss.
  - The source of the emerging epidemic was soon traced to a food supplement that included meat and bone meal from dead sheep (infected with scrapie).
  - To combat BSE, the British government banned the use of animal-derived feed supplements in 1988, and the epidemic among cattle, which peaked at nearly 40,000 cases in 1992. By February 2002, new infections have ceased as a result of imposing tight controls on cattle feed.
  - Unfortunately, the prion that causes BSE survived the heat of cooking and was transmitted to humans who inadvertently consumed infected bovine neural tissue or bone marrow (both are sometimes found in processed meats).

Presentation

- Compared to sporadic Jakob-Creutzfeldt disease, the median age of onset of patients with variant Jakob-Creutzfeldt disease is much younger than most sporadic Jakob-Creutzfeldt disease cases, about 27 years (range 12 to 74 years), with a longer median disease duration of **14.5 months**.
- The cases frequently present in young adults as psychiatric problems progressing to neurologic changes and dementia, with death.
- It appears that destruction of diseased cattle and the changes in livestock feeds have prevented further cases. Since 2000, variant Jakob-Creutzfeldt disease cases have steadily declined, with no new cases with onset after 2012.

- **Diagnosis:**
  - CSF analysis shows high protein level but is non-specific.
  - EEG may show some changes.
  - Pathologic examination of brain tissue is the only definitive diagnostic test.
- **Therapy:** There is no effective therapy for Creutzfeldt-Jakob disease, and all cases have been fatal.

Gerstmann-Straüssler-Scheinker Disease

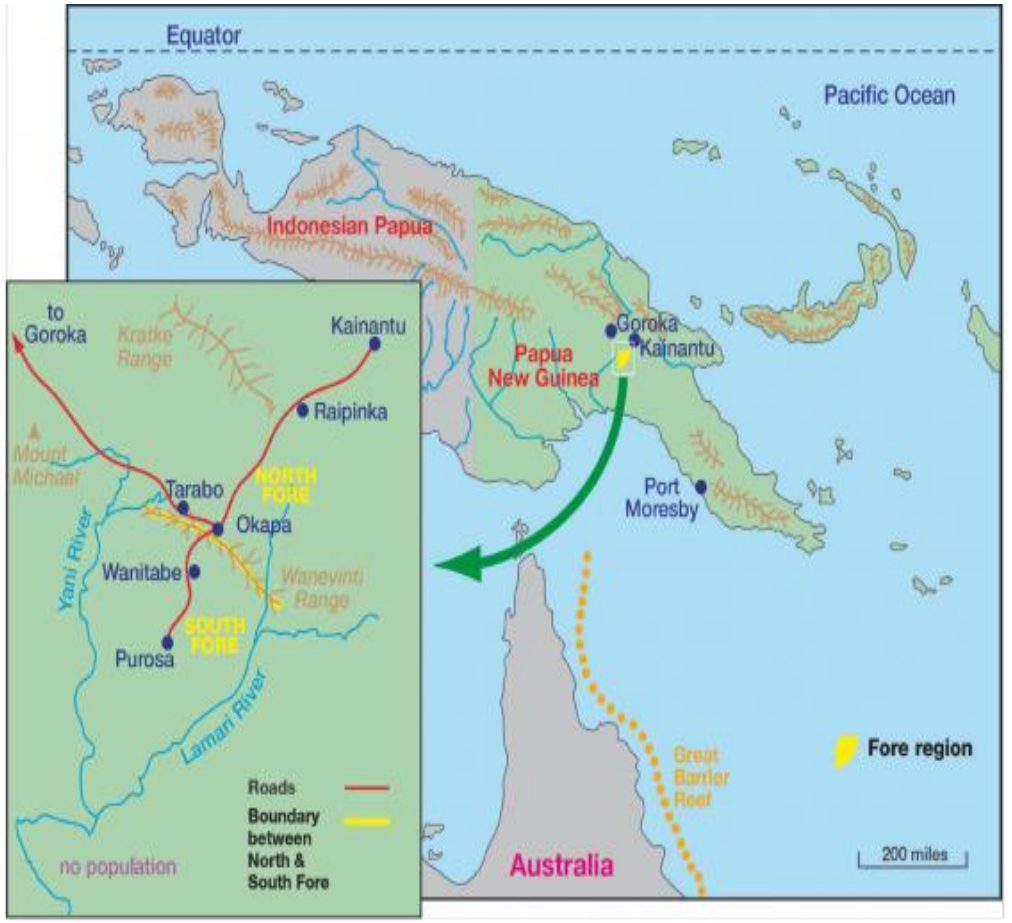
- A disease is similar to Creutzfeldt-Jakob disease, but occurs at a **younger age** (fourth to fifth decade).
- **Cause:** a dozen *PRNP* mutations can cause Gerstmann-Sträussler-Scheinker syndrome.
- **Presentation:** Cerebellar ataxia and paralysis are common, but with a late-onset dementia.
- The disease evolves over an average of 5 years.

Fatal Familial Insomnia

- This is a recently recognized very rare genetic prion disease associated with a single *PRNP* point mutation, in which a syndrome of severe progressive insomnia is followed by progressive dementia.
- It occurs in patients aged 35 to 61 years, culminating in death within 13 to 25 months.

Kuru

- Kuru was a subacute, progressive neurologic disease of the **Fore people** in New Guinea.
- The disease was brought to the attention of the Western world in **1957**.
- Kuru usually afflicted adult **women**, or children of either sex.



- **History:**

  Epidemiologic studies indicated that transmission of the disease in humans was associated with ingestion of a soup made from the brains of dead relatives and eaten in honor of the deceased. The Fore women cut up, divided, shared, and consumed the body. The men rarely partook in the dismemberment and consumption of the corpse. They took great care to consume all parts, even drying and crushing the bones and all used cooking utensils and mixing it in with vegetables so that nothing was missed. Women and children would most often consume the brains of the deceased, which were the most likely body part to contain the infectious prion agent, while the men preferentially consumed muscle tissue.

- The symptoms and signs were ataxia, hyperreflexia, and spasticity, which led to progressive dementia, starvation, and death.
- Pathologic examination revealed changes only in the CNS, with diffuse neuronal degeneration and spongiform changes of the cerebral cortex and basal ganglia.
- Clinical disease developed 4 to 20 years after exposure.
- Since the elimination of cannibalism from the Fore culture, kuru has disappeared.

Treatment of Prion Diseases

- Although some of the symptoms of human prion disease can be temporarily treated, unfortunately, three randomized double-blinded placebo-controlled trials have failed to modify disease outcome, and currently no cures are available, although many laboratories are working in this area.

Thank you ☺