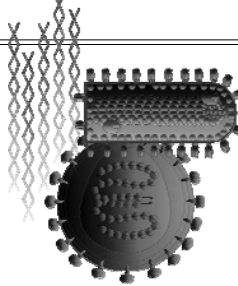



Prion Diseases



Steve Udem, M.D., Ph.D.
VP Wyeth Vaccines Discovery



Amyloid

- Fibrillar tissue deposits that bind dye (Congo Red)
- Some proteins (amyloidogenic proteins) have greater potential to misfold
- The misfolded protein can induce conformational change in normal proteins causing deposition of insoluble toxic aggregates

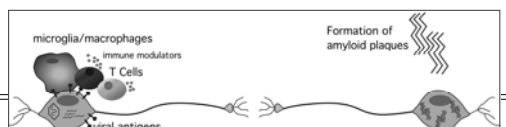
Infectious Agents and Slow Degenerative Diseases of the CNS

Viral Diseases

Measles (Subacute Sclerosing Panencephalitis)
HIV (HIV-D, HIV dementia)
HTLV-I Myelopathy
JC and BK (Progressive multifocal leukoencephalopathy)
Rubella panencephalitis
Rabies
Canine distemper virus

Prion Diseases

Scrapie
Mad Cow
Creutzfeldt-Jakob
Fatal familial insomnia
Gerstmann-Straussler
Scheinker



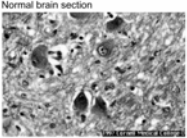
Amyloidosis

A disorder in which insoluble protein fibers are deposited in tissues and organs impairing their function.

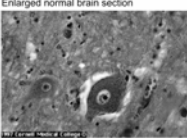
- Caused by deposits of homogeneous proteinase-resistant fibrils
- A stable conformational change in normal cellular protein leads to aggregation:
Soluble ⇒ Insoluble

Brain Histology

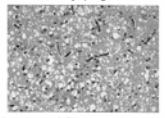
Normal brain section




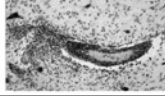
Enlarged normal brain section



Noninflammatory spongiform disease



Lymphocyte infiltrate

Systemic Amyloidoses

Amyloid protein	Precurser	Systemic (S) or localized (L)	Syndrome or involved tissues
AL	Immunoglobulin light chain	S, L	Primary, myeloma-associated
ALl	Immunoglobulin heavy chain	S, L	Primary, myeloma-associated
ATTR	Transthyretin	S	Familial, senile systemic
		L	Tenosynovium
AB ₂ M	β ₂ -microglobulin	S	Hemodialysis
AA	ApoI serum AA	S	Senile
AApoAI	ApoI/serum-AI	S	Secondary, reactive
ApoAII	ApoII/serum-AII	S	Familial
ApoAIII	ApoIII/serum-AIII	S	Familial
ApoAIV	ApoIV/serum-AIV	S	Familial
ApoA	ApoA/serum-A	S	Familial
ApoB	ApoB/serum-B	S	Familial
ApoC	ApoC/serum-C	S	Familial
ApoE	ApoE/serum-E	S	Familial
ApoF	ApoF/serum-F	S	Familial
ApoG	ApoG/serum-G	S	Familial
ApoH	ApoH/serum-H	S	Familial
ApoI	ApoI/serum-I	S	Familial
ApoJ	ApoJ/serum-J	S	Familial
ApoK	ApoK/serum-K	S	Familial
ApoL	ApoL/serum-L	S	Familial
ApoM	ApoM/serum-M	S	Familial
ApoN	ApoN/serum-N	S	Familial
ApoO	ApoO/serum-O	S	Familial
ApoP	ApoP/serum-P	S	Familial
ApoQ	ApoQ/serum-Q	S	Familial
ApoR	ApoR/serum-R	S	Familial
ApoS	ApoS/serum-S	S	Familial
ApoT	ApoT/serum-T	S	Familial
ApoU	ApoU/serum-U	S	Familial
ApoV	ApoV/serum-V	S	Familial
ApoW	ApoW/serum-W	S	Familial
ApoX	ApoX/serum-X	S	Familial
ApoY	ApoY/serum-Y	S	Familial
ApoZ	ApoZ/serum-Z	S	Familial
ApoAA	ApoAA/serum-AA	S	Familial
ApoAB	ApoAB/serum-AB	S	Familial
ApoAC	ApoAC/serum-AC	S	Familial
ApoAD	ApoAD/serum-AD	S	Familial
ApoAE	ApoAE/serum-AE	S	Familial
ApoAF	ApoAF/serum-AF	S	Familial
ApoAG	ApoAG/serum-AG	S	Familial
ApoAH	ApoAH/serum-AH	S	Familial
ApoAI	ApoAI/serum-AI	S	Familial
ApoAJ	ApoAJ/serum-AJ	S	Familial
ApoAK	ApoAK/serum-AK	S	Familial
ApoAL	ApoAL/serum-AL	S	Familial
ApoAM	ApoAM/serum-AM	S	Familial
ApoAN	ApoAN/serum-AN	S	Familial
ApoAO	ApoAO/serum-AO	S	Familial
ApoAP	ApoAP/serum-AP	S	Familial
ApoAQ	ApoAQ/serum-AQ	S	Familial
ApoAR	ApoAR/serum-AR	S	Familial
ApoAS	ApoAS/serum-AS	S	Familial
ApoAT	ApoAT/serum-AT	S	Familial
ApoAU	ApoAU/serum-AU	S	Familial
ApoAV	ApoAV/serum-AV	S	Familial
ApoAW	ApoAW/serum-AW	S	Familial
ApoAX	ApoAX/serum-AX	S	Familial
ApoAY	ApoAY/serum-AY	S	Familial
ApoAZ	ApoAZ/serum-AZ	S	Familial
ApoBA	ApoBA/serum-BA	S	Familial
ApoBB	ApoBB/serum-BB	S	Familial
ApoBC	ApoBC/serum-BC	S	Familial
ApoBD	ApoBD/serum-BD	S	Familial
ApoBE	ApoBE/serum-BE	S	Familial
ApoBF	ApoBF/serum-BF	S	Familial
ApoBG	ApoBG/serum-BG	S	Familial
ApoBH	ApoBH/serum-BH	S	Familial
ApoBI	ApoBI/serum-BI	S	Familial
ApoBJ	ApoBJ/serum-BJ	S	Familial
ApoBK	ApoBK/serum-BK	S	Familial
ApoBL	ApoBL/serum-BL	S	Familial
ApoBM	ApoBM/serum-BM	S	Familial
ApoBN	ApoBN/serum-BN	S	Familial
ApoBO	ApoBO/serum-BO	S	Familial
ApoBP	ApoBP/serum-BP	S	Familial
ApoBQ	ApoBQ/serum-BQ	S	Familial
ApoBR	ApoBR/serum-BR	S	Familial
ApoBS	ApoBS/serum-BS	S	Familial
ApoBT	ApoBT/serum-BT	S	Familial
ApoBU	ApoBU/serum-BU	S	Familial
ApoBV	ApoBV/serum-BV	S	Familial
ApoBW	ApoBW/serum-BW	S	Familial
ApoBX	ApoBX/serum-BX	S	Familial
ApoBY	ApoBY/serum-BY	S	Familial
ApoBZ	ApoBZ/serum-BZ	S	Familial
ApoCA	ApoCA/serum-CA	S	Familial
ApoCB	ApoCB/serum-CB	S	Familial
ApoCC	ApoCC/serum-CC	S	Familial
ApoCD	ApoCD/serum-CD	S	Familial
ApoCE	ApoCE/serum-CE	S	Familial
ApoCF	ApoCF/serum-CF	S	Familial
ApoCG	ApoCG/serum-CG	S	Familial
ApoCH	ApoCH/serum-CH	S	Familial
ApoCI	ApoCI/serum-CI	S	Familial
ApoCJ	ApoCJ/serum-CJ	S	Familial
ApoCK	ApoCK/serum-CK	S	Familial
ApoCL	ApoCL/serum-CL	S	Familial
ApoCM	ApoCM/serum-CM	S	Familial
ApoCN	ApoCN/serum-CN	S	Familial
ApoCO	ApoCO/serum-CO	S	Familial
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ApoCQ	ApoCQ/serum-CQ	S	Familial
ApoCR	ApoCR/serum-CR	S	Familial
ApoCS	ApoCS/serum-CS	S	Familial
ApoCT	ApoCT/serum-CT	S	Familial
ApoCU	ApoCU/serum-CU	S	Familial
ApoCV	ApoCV/serum-CV	S	Familial
ApoCW	ApoCW/serum-CW	S	Familial
ApoCX	ApoCX/serum-CX	S	Familial
ApoCY	ApoCY/serum-CY	S	Familial
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ApoDG	ApoDG/serum-DG	S	Familial
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ApoDI	ApoDI/serum-DI	S	Familial
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ApoDK	ApoDK/serum-DK	S	Familial
ApoDL	ApoDL/serum-DL	S	Familial
ApoDM	ApoDM/serum-DM	S	Familial
ApoDN	ApoDN/serum-DN	S	Familial
ApoDO	ApoDO/serum-DO	S	Familial
ApoDP	ApoDP/serum-DP	S	Familial
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ApoDS	ApoDS/serum-DS	S	Familial
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ApoDW	ApoDW/serum-DW	S	Familial
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ApoDY	ApoDY/serum-DY	S	Familial
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ApoEB	ApoEB/serum-EB	S	Familial
ApoEC	ApoEC/serum-EC	S	Familial
ApoED	ApoED/serum-ED	S	Familial
ApoEE	ApoEE/serum-EE	S	Familial
ApoEF	ApoEF/serum-EF	S	Familial
ApoEG	ApoEG/serum-EG	S	Familial
ApoEH	ApoEH/serum-EH	S	Familial
ApoEI	ApoEI/serum-EI	S	Familial
ApoEJ	ApoEJ/serum-EJ	S	Familial
ApoEK	ApoEK/serum-EK	S	Familial
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ApoEM	ApoEM/serum-EM	S	Familial
ApoEN	ApoEN/serum-EN	S	Familial
ApoEO	ApoEO/serum-EO	S	Familial
ApoEP	ApoEP/serum-EP	S	Familial
ApoEQ	ApoEQ/serum-EQ	S	Familial
ApoER	ApoER/serum-ER	S	Familial
ApoES	ApoES/serum-ES	S	Familial
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ApoEU	ApoEU/serum-EU	S	Familial
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ApoFI	ApoFI/serum-FI	S	Familial
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ApoFK	ApoFK/serum-FK	S	Familial
ApoFL	ApoFL/serum-FL	S	Familial
ApoFM	ApoFM/serum-FM	S	Familial
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ApoFP	ApoFP/serum-FP	S	Familial
ApoFQ	ApoFQ/serum-FQ	S	Familial
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ApoGC	ApoGC/serum-GC	S	Familial
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ApoGG	ApoGG/serum-GG	S	Familial
ApoGH	ApoGH/serum-GH	S	Familial
ApoGI	ApoGI/serum-GI	S	Familial
ApoGJ	ApoGJ/serum-GJ	S	Familial
ApoGK	ApoGK/serum-GK	S	Familial
ApoGL	ApoGL/serum-GL	S	Familial
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ApoHE	ApoHE/serum-HE	S	Familial
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ApoHH	ApoHH/serum-HH	S	Familial
ApoHI	ApoHI/serum-HI	S	Familial
ApoHJ	ApoHJ/serum-HJ	S	Familial
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ApoHN	ApoHN/serum-HN	S	Familial
ApoHO	ApoHO/serum-HO	S	Familial
ApoHP	ApoHP/serum-HP	S	Familial
ApoHQ	ApoHQ/serum-HQ	S	Familial
ApoHR	ApoHR/serum-HR	S	Familial
ApoHS	ApoHS/serum-HS	S	Familial
ApoHT	ApoHT/serum-HT	S	Familial
ApoHU	ApoHU/serum-HU	S	Familial
ApoHV	ApoHV/serum-HV	S	Familial
ApoHW	ApoHW/serum-HW	S	Familial
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ApoHY	ApoHY/serum-HY	S	Familial
ApoHZ	ApoHZ/serum-HZ	S	Familial
ApoIA	ApoIA/serum-IA	S	Familial
ApoIB	ApoIB/serum-IB	S	Familial
ApoIC	ApoIC/serum-IC	S	Familial
ApoID	ApoID/serum-ID	S	Familial
ApoIE	ApoIE/serum-IE	S	Familial
ApoIF	ApoIF/serum-IF	S	Familial
ApoIG	ApoIG/serum-IG	S	Familial
ApoIH	ApoIH/serum-IH	S	Familial
ApoII	ApoII/serum-II	S	Familial
ApoIJ	ApoIJ/serum-IJ	S	Familial
ApoIK	ApoIK/serum-IK	S	Familial
ApoIL	ApoIL/serum-IL	S	Familial
ApoIM	ApoIM/serum-IM	S	Familial
ApoIN	ApoIN/serum-IN	S	Familial
ApoIO	ApoIO/serum-IO	S	Familial
ApoIP	ApoIP/serum-IP	S	Familial
ApoIQ	ApoIQ/serum-IQ	S	Familial
ApoIR	ApoIR/serum-IR	S	Familial
ApoIS	ApoIS/serum-IS	S	Familial
ApoIT	ApoIT/serum-IT	S	Familial
ApoIU	ApoIU/serum-IU	S	Familial
ApoIV	ApoIV/serum-IV	S	Familial
ApoIW	ApoIW/serum-IW	S	Familial
ApoIX	ApoIX/serum-IX	S	Familial
ApoIY	Apo		

Amyloidosis - Examples

•Systemic

- Immunoglobulin light chain - deposits found in kidney, heart, skeletal muscle, nerves. Patients often present with kidney dysfunction. Associated with myeloma.
- Serum amyloid A - deposits in kidney, liver, spleen. Associated with chronic inflammation (inflammatory arthritis, granulomatous bowel disease, tuberculosis, leprosy...)

• Hereditary

- Transthyretin (prealbumin) - deposits in nervous tissue, gastrointestinal, kidney, heart.

•Cerebral

- Alzheimer's Disease - deposits of A- β peptide in brain (plaques)
- Prion Diseases - deposits of PrP^C protein in brain (plaques)

•Endocrine

- Amylin - Normally packaged with insulin in secretory granules - deposits occur in islets of type 2 diabetes patients (islet amyloid polypeptide, IAPP)

An infectious disease

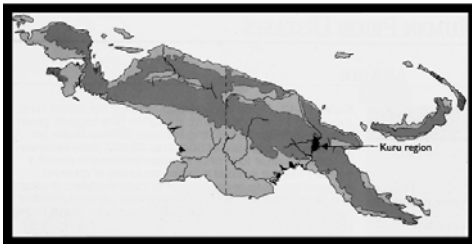
Kuru



Disease strikes children

Kuru

Papua New Guinea



Kuru



Mother & daughter

Kuru



Walking Sticks

Kuru

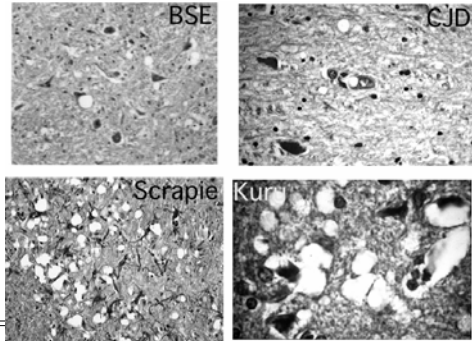


Disease affects the Tribe

Clinical features of Kuru

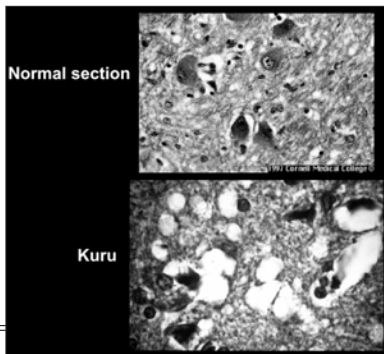
Transmission	Autoinoculation/ingestion of infected brain material
Prevalence	Fore linguistic group of Papua New Guinea
Clinical features	Cerebellar ataxia, tremor, movement disorders Mental impairment, emotional lability, frontal release signs (snout, suck, root, grasp reflexes)
Course	Fatal 9-24 months after onset

Spongiform Encephalopathies



Center for Animal Health and Productivity - U. Penn

Spongiform Encephalopathy - Histology



“Slow Viral Diseases” - ?

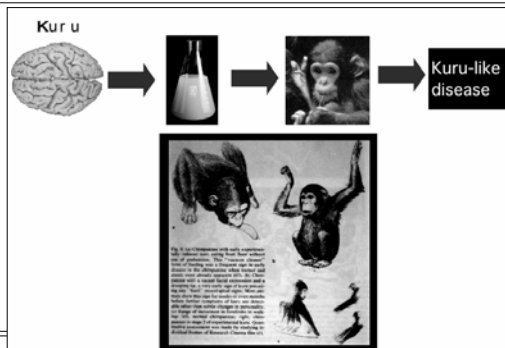
Suggestion that Scrapie is an Infectious Disease

Mid 1930s - vaccine prepared against Louping-ill

- ▶ Infectious encephalomyelitis of Sheep
- ▶ Viral disease spread by ticks (Flavivirus)
- ▶ Formalin-inactivated viral vaccine prepared from sheep brain
- ▶ No adverse effects caused by vaccination for 2 years
- ▶ Subsequently, some sheep herds developed Scrapie
- ▶ Realized that Scrapie was an infectious agent found in some batches of Louping-ill vaccine

Gordon, W.S., PhD. Advances in Veterinary Research. The Veterinary Record: 1946 November 23. Presented at the National Veterinary Medical Association of Great Britain and Ireland Annual Congress, 1946.

Linking Kuru to an Infectious Agent (Gajdusek)



Prion Diseases

Disease	Natural Host	Prion	Pathogenic PrP Isoform
Scrapie	Sheep and goats	Scrapie Prion	OvPrP ^{Sc}
Transmissible mink encephalopathy (TME)	Mink	TME Prion	MkPrP ^{Sc}
Chronic wasting disease (CWD)	Deer and elk	CWD Prion	MdePrP ^{Sc}
Bovine spongiform encephalopathy (BSE)	Cattle	BSE Prion	BoPrP ^{Sc}
Feline spongiform encephalopathy (FSE)	Cats	FSE Prion	FePrP ^{Sc}
Exotic ungulate encephalopathy (EUE)	Nyala & greater kudu	EUE Prion	UngPrP ^{Sc}
Kuru	Humans	Kuru Prion	HuPrP ^{Sc}
Creutzfeldt-Jakob disease (CJD)	Humans	CJD Prion	HuPrP ^{Sc}
Gerstmann-Strausler-Scheinker syndrome (GSS)	Humans	GSS Prion	HuPrP ^{Sc}
Fatal familial insomnia (FFI)	Humans	FFI Prion	HuPrP ^{Sc}



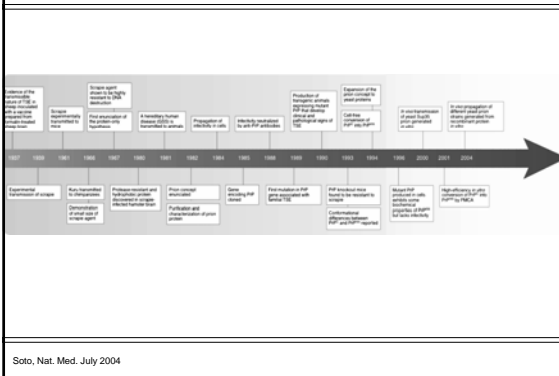
Milestones in Development of the Prion Hypothesis

- ▶ Kuru transmitted to Chimps (Gajdusek, Gibbs, Alpers 1966)
- ▶ Scrapie agent is resistant to radiation inactivation - suggests an unusual infectious agent that does not contain nucleic acid (Alpers et al., 1967)
- ▶ Hypotheses develop for transmission of scrapie agent (Griffith, 1967)
 - A protein that induces transcription of its own gene
 - A protein that acquires a pathogenic conformation
- ▶ Creutzfeldt-Jakob Disease transmitted to chimps (Gibbs, Gajdusek et al., 1968)
- ▶ Scrapie agent purified - predominately protein; infectivity insensitive to nucleases and other agents that inactivate viruses (Prusiner 1982)

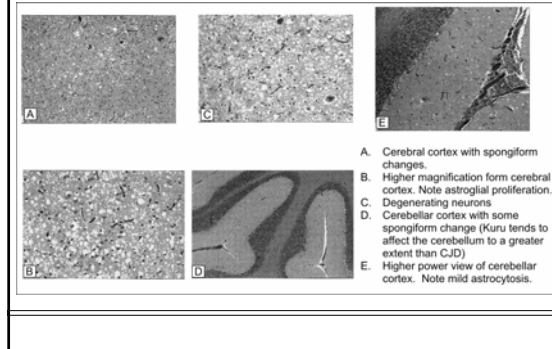
Creutzfeldt-Jakob Disease

- Most common human TSE - about 1 case/million/yr
- Three forms traditionally recognized
 1. sCJD - sporadic, about 85% of cases
 2. fCJD - familial, about 10% of cases
 3. iCJD - iatrogenic, about 5% of cases
- In 1996 a new variant emerged in the U.K. - vCJD
 - ▶ Associated with eating beef infected with BSE agent (Mad Cow)
 - ▶ In contrast with traditional forms of CJD, vCJD strikes young adults
 - ▶ Crossed species barrier

History of TSE



Creutzfeldt-Jakob Disease



Human Prion Diseases

DISEASE	SYMPTOMS	ACQUISITION	DISTRIBUTION	DISEASE COURSE
Kuru	Loss of coordination followed by dementia	Infection (Cannibalism)	2600 cases identified in Papua New Guinea	3 mo - 1 yr
Creutzfeldt-Jakob Disease	Dementia followed by loss of coordination	Usually unknown (Sporadic disease) 15% of cases involve an inherited mutation in the PrP gene Rarely infection through contaminated surgical instrument or organ transplant	Sporadic: 1/1,000,000 Inherited: 100 extended families identified Infectious: 80 cases identified	Usually 1 yr but as short as 1 mo and as long as 10 yrs
Gerstmann-Straussler-Scheinker disease	Loss of coordination followed by dementia	Inheritance of a mutation in the PrP gene	50 extended families identified	2-6 yrs
Fatal familial insomnia	Trouble sleeping and disturbance of the autonomic nervous system. Followed by dementia and loss of coordination	Inheritance of a mutation in the PrP gene	9 extended families identified	About 1 yr

BSE

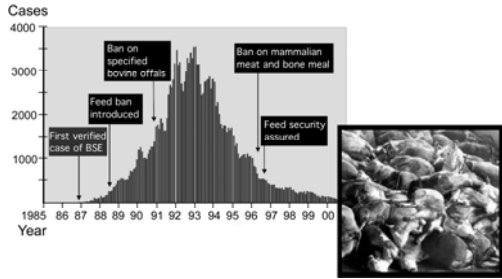
Reported cases of bovine spongiform encephalopathy as of December 2000(a)

Country	Native cases	Imported cases	Total cases
United Kingdom	180,376(b)	0	180,376
Republic of Ireland	487	12	499
Portugal	446	6	452
Switzerland(c)	363	0	363
France	150	1	151
Belgium	18	0	18
Netherlands	6	0	6
Liechtenstein	2	0	2
Denmark	1	1	2
Luxembourg	1	0	1
Germany	3	6	9
Oman	0	2	2
Italy	0	2	2
Spain(d)	0	2	2
Canada	0	1	1
Falklands (UK)	0	1	1
Azores (Portugal)(e)	0	1	1

a Data from Organization of International Epizootics (Paris) and Ministry of Agriculture, Fisheries, and Food (UK).
 b Includes 1,287 cases in offshore British islands.
 c Includes cases detected by active surveillance with immunologic methods.
 d Origin and dates of imported cases are under investigation.
 e Case imported from Germany.

Table adapted from: <http://www.cdc.gov/ncidod/diseases/tse/bse.htm>

BSE Epidemic in UK

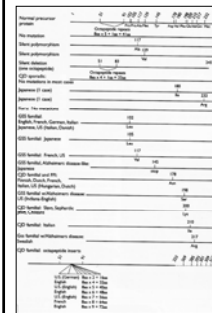


What is Normal PrP^C?

- ▶ Glycoprotein ~250 amino acids
- ▶ Membrane associated through a C-terminal glycosylphosphatidylinositol (GPI) linkage
- ▶ Role in membrane trafficking has been proposed - possibly involved in some endocytic pathways
- ▶ Knockout mice develop and behave normally, but perhaps prone to seizures
- ▶ Interacts with laminin, which plays a role in cell adhesion and neurite formation
- ▶ Also interacts with the laminin receptor resulting in internalization of membrane-bound PrP^C
- ▶ Binds Cu²⁺ - may have an antioxidant function that promotes neuron survival
- ▶ Abundant in brain - also detected in: spleen, lymph node, lung, heart, kidney, skeletal muscle, uterus, adrenal gland, parotid gland, intestine, proventriculus, abomasum and mammary gland.

vCJD in U.S.

Genetic mutations in CJD and other Prion Diseases

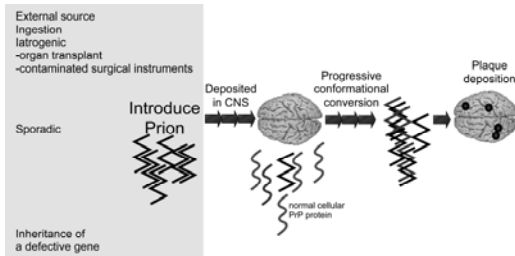


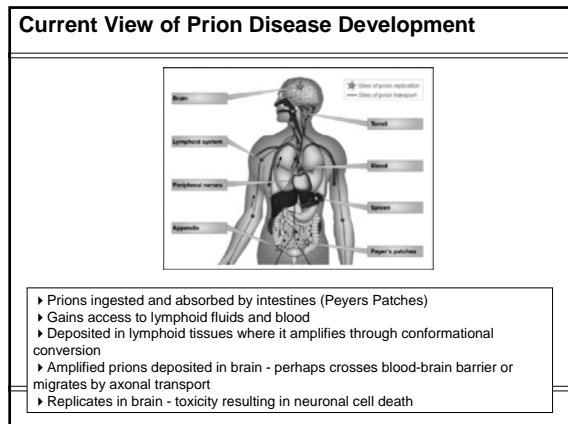
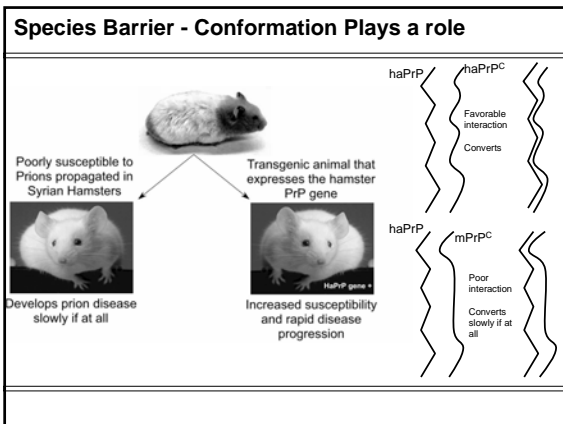
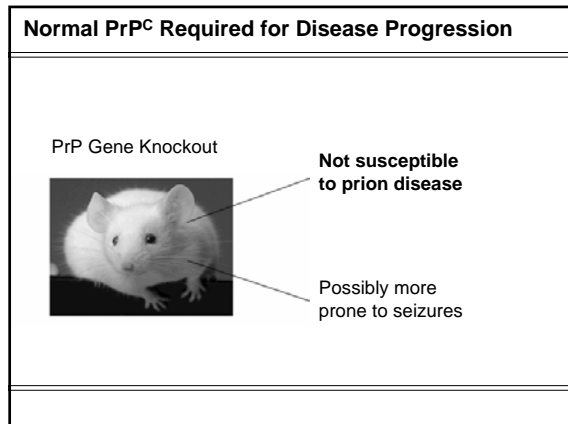
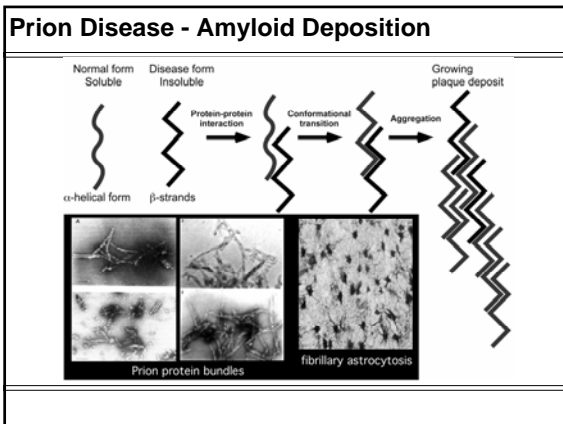
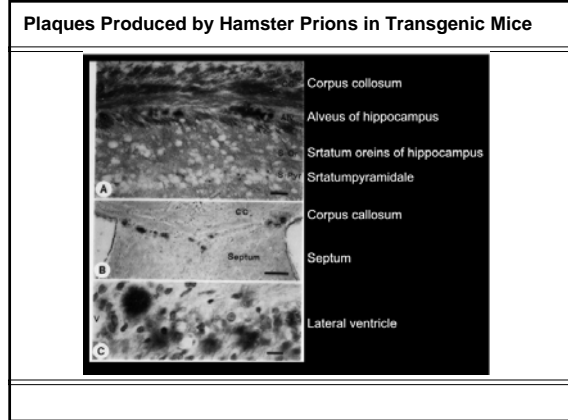
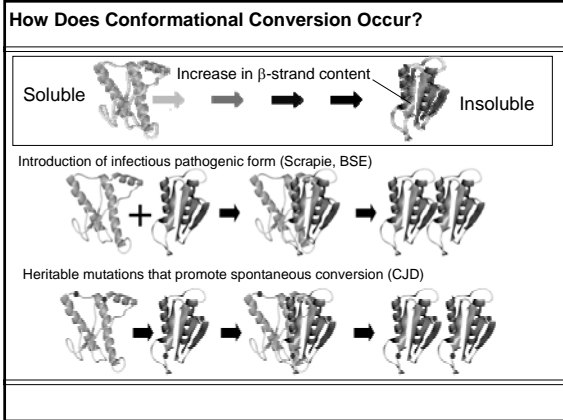
Search for the Agent (Prusiner Lab)



- Extremely small, proteinaceous infectious particle
- Resistant to DNase and RNase
- Resistant to limited proteolysis
- Resistant to chemical agents that inactivate conventional viruses

Prion Disease





Criticisms of the Prion Hypothesis are being Addressed

There are different strains of Prions

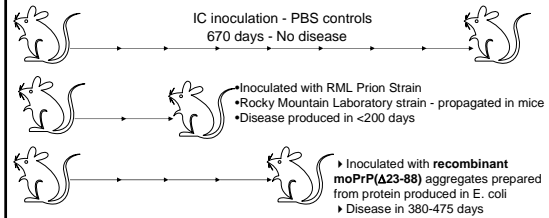
- Differ in incubation time, clinical features, and neuropathology
- How are 'Strains' developed without evolution of nucleic acid genomes?

Can conformational transition be observed in vitro?

A recombinant purified Prion has not been shown to induce disease

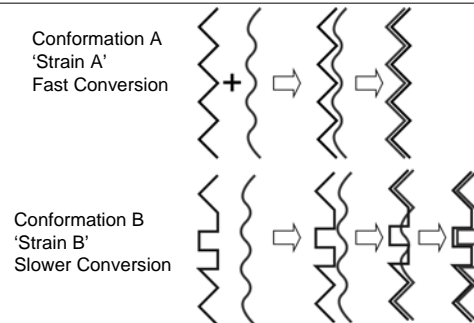
Disease Produced by Synthetic Prions (Prusiner Lab)

- ▶ Transgenic mouse model
- ▶ Mice express low levels of a deleted form of moPrP ($\Delta 23-88$) that aggregates spontaneously
- ▶ These mice do not develop disease spontaneously at rate significantly higher than normal mice
- ▶ But, they are 'seeded' with a protein that is susceptible to misfolding

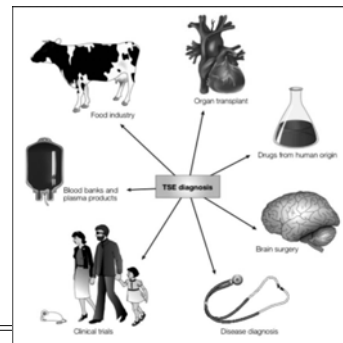


Legname et al., Science (2004) 305:673

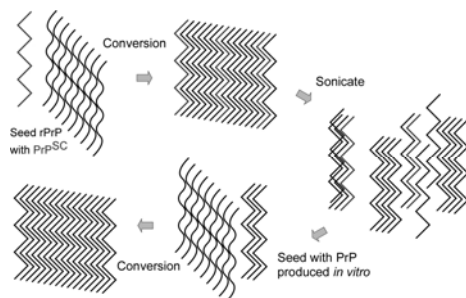
Hypothesis - Conformational Strains



Immediate Need for Prion Diagnostics



Cyclic In Vitro Amplification of a Misfolded Protein



Saborio, Permanne, Soto. Nature 2001

Reading

Soto, C. and Castilla, J. 2004. *The Controversial Protein-Only Hypothesis of Prion Propagation.* Nature Medicine, 10 Supplement: S63-7.

Soto, C. Diagnosing Prion Diseases; Needs, Challenges, and Hopes. Nature Reviews, 2:809-13.

Rhodes, R. *Deadly Feast: Tracking the Secrets of a Terrifying New Plague.* Simon & Schuster 1997

