Human Prion Diseases
Past, Present and Future
Pierluigi Gambetti M.D.
National Prion Disease Pathology Surveillance Center
Case Western Reserve University
Human Prion Diseases: History

- **1921-1923** Alfons Maria Jakob published five cases, included a sixth case by Hans Gerhard Creutzfeldt signaled to him by Walther Spielmeyer and coined the name *spastic pseudo-sclerosis, disseminated encephalo-myelopathy*;
- **1922** Spielmeyer proposed the eponym of Creutzfeldt-Jakob disease (CJD);
- Only three of the Jakob’s cases are likely to belong to CJD; Creutzfeldt’s case definitely is not CJD.

![Alfons Maria Jakob (1884-1931)](image1)
![Hans Gerhard Creutzfeldt (1885-1964)](image2)
![Walther Spielmeyer (1879-1935)](image3)
Human Prion Diseases: History (Cont)

• 1936 Original report of the now known Gerstmann-Sträussler-Scheinker disease (GSS), which
• 1957 First report of kuru, a disease affecting the Fore tribe of New Guinea that practiced ritualistic cannibalism, by Carlton Gajdusek and Vincent Zigas;
• 1959 Veterinary pathologist William J. Hadlow suggests that transmissibility of kuru be tested in primates based on the similarity between kuru and scrapie of sheep known to be transmissible since 1939;
• 1963-1980 These experiments are successfully carried out by Carlton Gajdusek, Joe Gibbs and colleagues who reported transmission to primates of kuru, sporadic and inherited CJD and at least one form of GSS, definitely establishing that all these diseases belonged to the same group and were transmissible. The label of transmissible spongiform encephalopathies was introduced (TME). Carlton Gajdusek is awarded the Nobel Prize in 1976;
• 1967 John Stanley Griffith and Tikvah Alpers propose that the infectious agent consisted solely of a protein...
In the 80s Stanley Prusiner and co-workers identified the infectious agent as a protein and put forward the *prion or protein only* hypothesis coining the new word *prion* or *proteinaceous infectious particle*. Now TSE are also called prion diseases. Stanley Prusiner was awarded the Nobel Prize in 1997. Therefore, to date two Nobel Prizes have been awarded for studies on prion diseases.
Understanding Prion Diseases...

- Basic Pathogenetic Mechanisms
- Human prion diseases: Mechanisms of diversity... Classification... Non invasive diagnosis... The infectivity threat
- Similarities & differences of prion diseases with other conformational diseases
- Possible role of the prion protein in Alzheimer’s and other conformational diseases
- Novel prion disease: How does it fit within the existing prion diseases and other neurodegenerative diseases
Understanding Prion Diseases...

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Prion Protein (Hamster)

a. Translational product
   - SP
   - G-P Repeats
   - TM
   - AH
   - SS

b. Postranslational product
   - CHO
   - CHO
   - GPI
   - S-S

SP: 22AA Signal Peptide
G-P Repeats: Gly-Pro-rich 5 octa- and 2 hexarepeats
STE: Stop-transfer effector
TM: Transmembrane α-helix
AH: Amphipathic helix
SS: Hydrophobic signal sequence
X: Unknown modifications
CHO: Glycosylation Sites
GPI: Glycosylphosphatidyl inositol Anchor
S-S: Disulfide bonds
PrP^c Normal Processing
Prion Protein Membrane Association
Proposed Biological Functions of the Normal Prion Protein (PrP\textsuperscript{C})

- Copper binding (copper serving as a co-factor for an undetermined PrP\textsuperscript{C} enzymatic activity)
- Signaling receptor (binding to neural cell adhesion molecule or NCAM)
- Signal transduction (caveolin1-dependent coupling to tyrosine kinase Fyn)
- Role in neuronal growth and survival (protection against Bax-mediated cell death)
- Synaptic regulation (as a receptor or receptor-related in GABA\textsubscript{A}-ergic inhibitory synapses)
- Sleep and circadian rhythms regulator
- Anti apoptotic factor
- Receptor for Aβ in Alzheimer’s disease (acting as mediator of dementia) and possibly other amyloidoses (Lauren et al 2009; Resenbergerger et al 2011)
Pathogenesis of Prion Diseases

Familial Forms
- Inherited

Sporadic Forms
- Spontaneously Occurring

Abnormal PrP

Conformational Change

Induced by Contamination

Normal PrP

Transmitted Forms (iatrogenic)
Normal PrP(PrP\textsuperscript{C})
Protease sensitive

Scrapie isoform(PrP\textsuperscript{Sc}/PrP\textsuperscript{re})
Protease resistant, insoluble, pathogenic

Adapted from http://www.empirum.ucsf.edu/cohen/research/gallery/aw_prion.gif
Prion Protein (Hamster)

A. Translational product
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Codon Numbers
PrP Propagation in the Acquired Form

PrP^Sc Exogenous

PrP^c Endogenous

First Interaction

First Conv.

Second Interaction

Second Conv.

Cycling

Accumulation

Break Down or Dispersion

PrP^Sc Endogenous
Possible Mechanism of PrP Propagation

PrP<sub>c</sub>

Interaction

Conversion

PrP<sub>Sc</sub>

Cycling

Accumulation
Understanding Prion Diseases...

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<td>Iatrogenic CJD</td>
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Underlined: Diseases discovered by our group
Original Subtypes of Sporadic CJD Identified Based on Clinical and/or Pathological Features

- Typical or myoclonic
- Amyotrophic
- Visual or Heidenhain
- Thalamic
- Ataxic or cerebellar
- Cortico-striatal
- Pan-encephalopathic
- Long duration

We tried to determine whether the 129 M/V polymorphism at codon 129 and the PrP^Sc type could explain this heterogeneity.
Human Prion Protein Gene
Codon 129 Polymorphism (Normal)

Allele from Mother:
37%

Allele from Father:
51%

129 Codon
Met
Met

129 Codon
Val
Val

129 Codon
Met
Val

129 Codon
Immunoblotting of human PrP$^C$ and PrP$^{Sc}$ for diagnosis and PrP$^{Sc}$ type determination

PAGE and Membrane Transfer

PK

- + + +

Normal and CJD

Normal PrP$^C$

CJD PrP$^{Sc}$

CJD PrP$^{Sc}$

Type 1

Type 2
PrP<sup>Sc</sup> Type 1 and 2
Size of PK-resistant fragment

<table>
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<tr>
<th>PNGase</th>
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<th>+</th>
<th>+</th>
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<tbody>
<tr>
<td>32.5</td>
<td>-</td>
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<td></td>
<td></td>
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<tr>
<td>27.5</td>
<td>-</td>
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<tr>
<td>18.5</td>
<td>-</td>
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</table>

Sugars removed by PNGase

Full Length PrP<sup>Sc</sup> Type 1 and 2
with Protease Cleavage Site

Amino acid 82
PK

Amino acid 97
PK

Type 1

Type 2
We collected 300 cases of sporadic CJD, subdivided them into six groups based on the combination of the genotype at codon 129 and the PrP\textsuperscript{Sc} type according to the diagram below, and compared the disease phenotypes of the individual groups.

<table>
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<tr>
<th>Codon 129</th>
<th>PrP\textsuperscript{Sc} Type</th>
</tr>
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<tbody>
<tr>
<td>Met/Met</td>
<td>1 &amp; 2</td>
</tr>
<tr>
<td>Met/Val</td>
<td>1 &amp; 2</td>
</tr>
<tr>
<td>Val/Val</td>
<td>1 &amp; 2</td>
</tr>
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The six possible combinations of codon 129 alleles and PrP\textsuperscript{Sc} types correlated with distinct disease phenotypes in patients with sporadic prion diseases.
Classification of Sporadic Creutzfeldt-Jakob Disease Based on Molecular and Phenotypic Analysis of 300 Subjects

Piero Parchi, MD,* Armin Giese, MD,† Sabina Capellari, MD,* Paul Brown, MD,‡ Walter Schulz-Schaeffer, MD,‡ Otto Windl, PhD,‡ Inga Zerr, MD,§ Herbert Budka, MD, Nicolas Kopp, MD,§ Pedro Piccardo, MD,§ Sigrid Poser, MD,§ Amyn Rojiani, MD, PhD,** Nathalie Streichemberger, MD,§ Jean Julien, MD,‡‡ Claude Vital, MD,‡‡ Bernardino Ghetti, MD,# Pierluigi Gambetti, MD,* and Hans Kretzschmar, MD†

### Classification of sporadic prion diseases according to molecular features and according to previous criteria

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Distinctive Features</th>
<th>Onset (yrs)/ Durat.(mo)</th>
<th>Distribution %(^1)</th>
<th>Previous Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sCJD</strong></td>
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</tr>
<tr>
<td>M/M 1</td>
<td>Typical CJD clinically and pathologically. Typical EEG (83%). “Synaptic” immunostaining pattern</td>
<td>63.2 / 3.9</td>
<td>58</td>
<td>Myoclonic Heidenhain</td>
</tr>
<tr>
<td>M/V 1</td>
<td>Early onset. No typical EEG. Cerebellum spared. Weak “synaptic” immunostaining</td>
<td>46.0 / 15.3</td>
<td>4</td>
<td>Not described</td>
</tr>
<tr>
<td>M/M 2</td>
<td>No typical EEG. Coarse spongiosis and immunostaining. Cerebellum spared</td>
<td>60.3 / 15.7</td>
<td>9</td>
<td>Not described</td>
</tr>
<tr>
<td>M/V 2</td>
<td>Ataxia at onset. Rarely typical EEG. No cerebellar atrophy but Kuru plaques. Plaque-like pattern of immunostaining.</td>
<td>60.3 / 17.0</td>
<td>14</td>
<td>Cerebellar or ataxic</td>
</tr>
<tr>
<td>V/V 2</td>
<td>As M/V2 but no kuru plaques and cerebellar atrophy.</td>
<td>60.3 / 6.6</td>
<td>15</td>
<td>Cerebellar or ataxic</td>
</tr>
<tr>
<td><strong>sFI</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>M/M 2</td>
<td>Clinically and pathologically indistinguishable from FFI</td>
<td>60.3 / 14.0</td>
<td>1</td>
<td>Thalamic</td>
</tr>
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\(^1\) Based on 609 cases examined by the National Prion Disease Pathology Surveillance Center
Microscopic View of the Cerebral Cortex

Normal  sCJDMM1  sCJDMM2
Prion Protein Immunostain
Cerebral Cortex

Normal  sCJDMMM1  sCJDMMM2

sCJDVV2 and sCJDMV2  sCJDMV2 only
Western blot of protease resistant PrP in sCJD

<table>
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<th>Lanes</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
<td>kDa</td>
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<td>21</td>
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<tr>
<td>19</td>
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sCJD MM1 | sCJD VV2 | sCJD MM2
sCJD: Non invasive diagnosis...

• CSF protein levels of:
  14-3-3  94% sensitivity; 27% specificity (230 autopsy cases)
  Tau  83% sensitivity; 71% specificity (318 autopsy cases)

• MRI (DWI & Flair):  88% sensitivity; 92% specificity (385 subjects)

Definitions

*Sensitivity*: Percentage of prion-affected patients correctly diagnosed
*Specificity*: Percentage of prion-free patients correctly diagnosed
sCJD: Non invasive diagnosis...

- CSF protein levels of:
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  - Tau 83% sensitivity; 71% specificity (318 autopsy cases)

- MRI (DWI & Flair): 88% sensitivity; 92% specificity (385 subjects)

Therefore, by combining the results of the 14-3-3 test and MRI we should achieve over 90% accuracy i.e. if both are positive, the patient has 92% chances to have CJD

Definitions

- **Sensitivity**: Percentage of prion-affected patients correctly diagnosed
- **Specificity**: Percentage of prion-free patients correctly diagnosed
Florid Plaques in human brain faithfully reproduced in the brain of transgenic mice expressing human PrP following intracerebral inoculation of brain from variant CJD (vCJD or human “Mad Cow” d.)
Infectivity:
Precautions and decontamination
(Unofficial in-house procedures)

- CJD Specimen Handling
- Decontamination: General
- Autopsy Suite Decontamination
- Precautions for Prion Diseases Autopsies
- Decontamination: Microtome
- Aerosol

Comments on aerosol contamination:
Potential aerosol exposure in prion research rather than treatment as prion infectivity is not detected in blood and urine of sCJD patients
Danger of aerosol exposure in autopsy and in research but respirator, mask and biosafety cabinets and other precautions are required
Recent studies showing no detectable scrapie prion protein or prion infectivity in blood and urine from patients with sporadic CJD

Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay

Julie Ann Edgeworth, Michael Farmer, Anita Sicilia, Paul Tavares, Jonathan Beck, Tracy Campbell, Jessica Lowe, Simon Mead, Peter Rudge, John Collinge, Graham S Jackson

The Lancet 2011

ASSESSING PRION INFECTIVITY OF URINE IN SPORATIC CREUTZFELDT-JAKOB DISEASE

Silvio Notari\textsuperscript{1}\ast, Liuting Qing\textsuperscript{1}\ast, Maurizio Pocchiari\textsuperscript{2}, Ayuna Dagdanova\textsuperscript{1}, Kristin Hatcher\textsuperscript{1}, Arend Dogterom\textsuperscript{3}, Jose F. Groisman\textsuperscript{4}, Ib Bo Lumholtz\textsuperscript{5}, Maria Puopolo\textsuperscript{2}, Corinne Lasmezas\textsuperscript{6}, Shu G. Chen\textsuperscript{1}, Qingzhong Kong\textsuperscript{1}\#\textsuperscript{1}, Pierluigi Gambetti\textsuperscript{1}\#

(Submitted for publication)
Conclusions (Cont.)

- As infectious agents, prions are characterized by low infectivity but high resistance to disinfectants;
- Compared to other infectious diseases, in prion diseases special attention must be paid to limit contamination and carefully identify contaminated areas;
- Decontamination is a demanding procedure different from those used for other infectious diseases; It includes robust treatment with NaOH along with autoclaving for longer time and at higher temperature or incineration whenever possible;
- working with prion disease-contaminated tissue is as safe (or even less risky) as working with tissues from other infectious diseases if appropriate biosafety rules are followed.
Understanding Prion Diseases...

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- Novel prion disease: How does it fit within the existing prion diseases and other neurodeg. dis.
For many years it was widely believed that the propensity of being transmissible i.e. causing clinical and pathological disease by forming protein aggregates that break and propagate, was unique of prion diseases
Beyond the prion principle

Adriano Aguzzi

It seems that many misfolded proteins can act like prions — spreading disease by imparting their misshapen structure to normal cellular counterparts. But how common are bona fide prions really?

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The abnormal protein forms aggregates recruiting the normal protein isoform and propagates generating specific lesions (prion mechanism) but not the clinical disease (Soto et al Unpublished).

Therefore, at least the prion mechanism if not disease transmissibility is shared by several other diseases.
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A novel human prion disease of long duration and frontotemporal dementia-like clinical signs, with the abnormal prion protein displaying different characteristics from those of classical prion diseases that we called variably protease-sensitive prionopathy (VPSPr). VPSPr accounts for 3-4% of all CJD but probably it is under diagnosed.
Electrophoretic Profiles of the Abnormal PrP in the Three 129 Genotypes of VPSPr and two subtypes of sCJD as well as GSS117, a non-transmissible subtype of GSS

Conclusion: The abnormal PrP Western blot profiles in VPSPr and that of GSS117 are similar evoking a ladder with 5-6 bands, and are very different from the Western blot profile of protease resistant PrP in sCJD
VPSPr Transmissibility to mice genetically modified to be prone to human prion diseases

Experiments are ongoing; inoculated mice of over 700 days post-inoculation are asymptomatic suggesting that, if animal transmission occurs at all, it requires very long incubation times (molecular transmission rather than transmission of the full disease disease?)
...So as for PrP Western blot profile and transmissibility, human prion diseases can be divided into two groups.

Presence of “typical” PrP$^{Sc}$ (PrP27-30) and “easily” transmissible

Presence of “atypical” abnormal PrP and “not easily” transmissible

Creutzfeldt-Jakob disease
- sporadic
- familial
- acquired

Fatal familial insomnia
- sporadic
- familial

Gerstmann-Sträussler-Scheinker disease
- P102L subtype with 8 kDa (PrP-8)$^{1}$
- A117V, H187R and other subtypes

Variably protease-sens. prionopathy (VPSPr)

Gerstmann-Sträussler-Scheinker d.
- P102L subtype with PrP27-30 (PrP-21)$^{1}$

$^{1}$Parchi et al PNAS 1998; Piccardo et al PNAS 2007
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Conclusion: Also some prion diseases may have transmissibility features of other amyloid-forming diseases suggesting that PrP has two patterns of aggregation and propagation.
The latest twist in the prion story...

Model of how the normal prion protein (PrP\textsuperscript{C}) may mediate cell death by binding a number of misfolded proteins such as AD and others. This mechanism is independent of conversion and propagation that is central to conventional prion diseases.

Conclusion: Normal PrP would be the mediator of cell death in a variety of diseases forming amyloids including AD.
Conclusions

• The mechanism of prion diseases is now much better understood;
• Human prion diseases are clearly classified and better diagnosed: The 14-3-3 or tau test combined with MRI seems the most accurate and least invasive in live sCJD patients;
• Classical prion diseases have a unique mechanism of infectivity that challenges public health as well as several aspect of care and research and require the use of careful biosafety procedures;
• However, it is now apparent that a mechanism of abnormal protein formation and propagation similar to that of prion diseases is shared by many other diseases associated with amyloid formation such as Alzheimer’s (AD) and Parkinson diseases. Although the rate of abnormal protein formation and pace of propagation are much slower in the latter diseases, the process seems to be essentially the same;
• This conclusion is supported by the recent discovery of atypical prion diseases which appear to have the same transmissibility characteristics as those of other amyloidoses;
Conclusions (Cont.)

• The disease-causing mechanisms involved in these atypical prion diseases are likely to be either quantitatively or qualitatively different from those of classical prion diseases;
• Several recent and already controversial studies indicate that the normal prion protein (PrP) may act as receptor for the abnormal PrP but also a variety of other amyloids including that of AD mediating cell death;
• This mechanism appears to be distinct from classical PrP conversion and propagation;
• If this recent studies are correct, the prion protein would be a key element in neurodegenerative diseases based on protein misfolding. A surprising twist… or…

Nature has more imagination than man

Lugaro

Ernesto Lugaro, Italian neurologist (1870-1940)
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The CJD Foundation:
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Yvonne Cohen Wei Chen
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Sally Berri