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(v)CJD and reprocessing of Medical Products

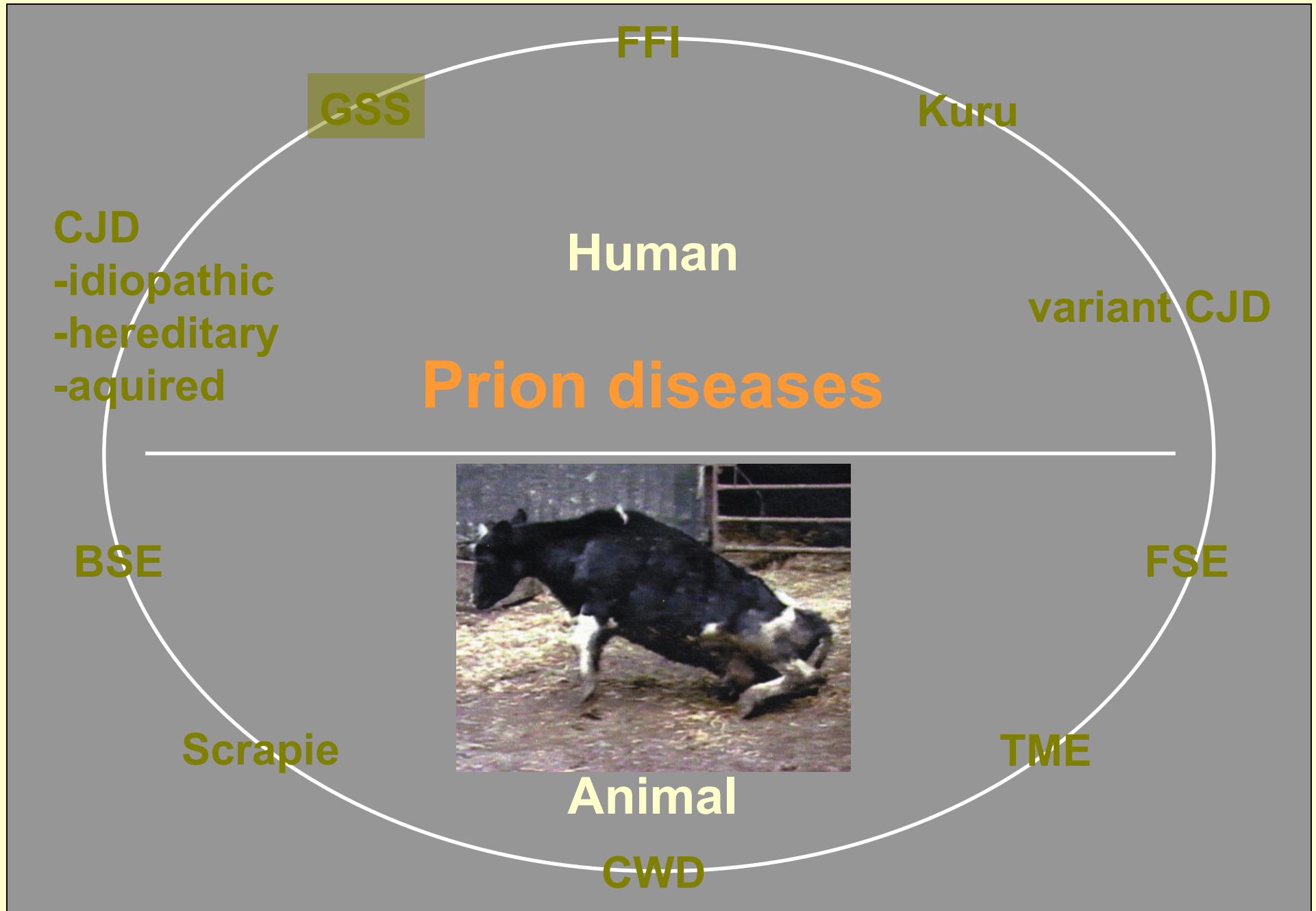
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ÖGSV annual conference and wfhss-Congress
Baden, 4. Mai 2007



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New occurring agents of diseases that are potentially transmissible to humans are causing serious concern especially in case they were able to propagate in production animals because they hold an incalculable risk of infection.



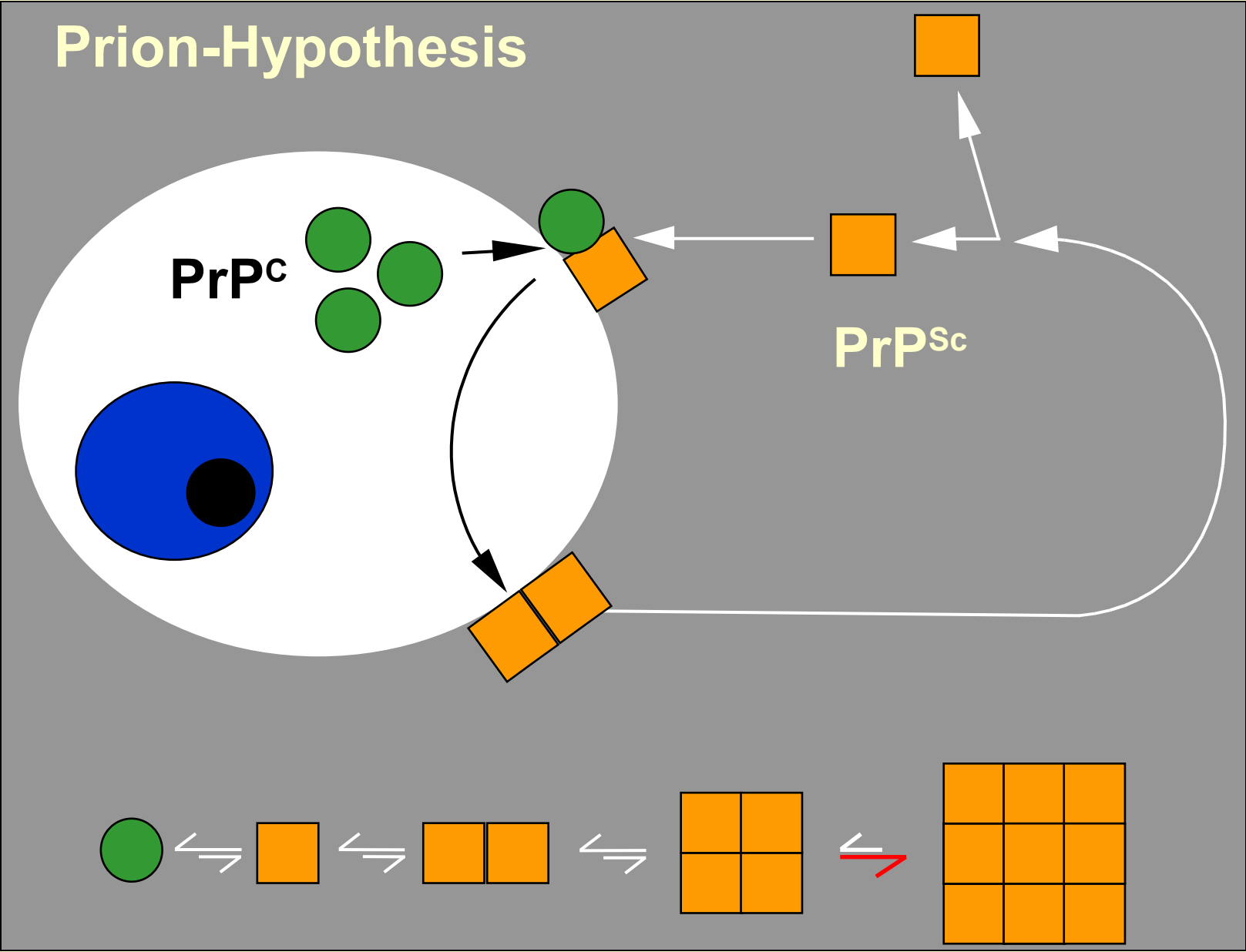
Prion diseases

- Neurodegenerative disease; always fatal
- Long incubation time – short disease course
- Transmissible in general
- Unusual characteristics of the agent:
 - resistant against nucleic acid-destroying treatments
 - inactivation by protein-denaturing measures
 - isolation results in the prion protein scrapie fraction
- Pathological prion protein deposits in the brain tissue



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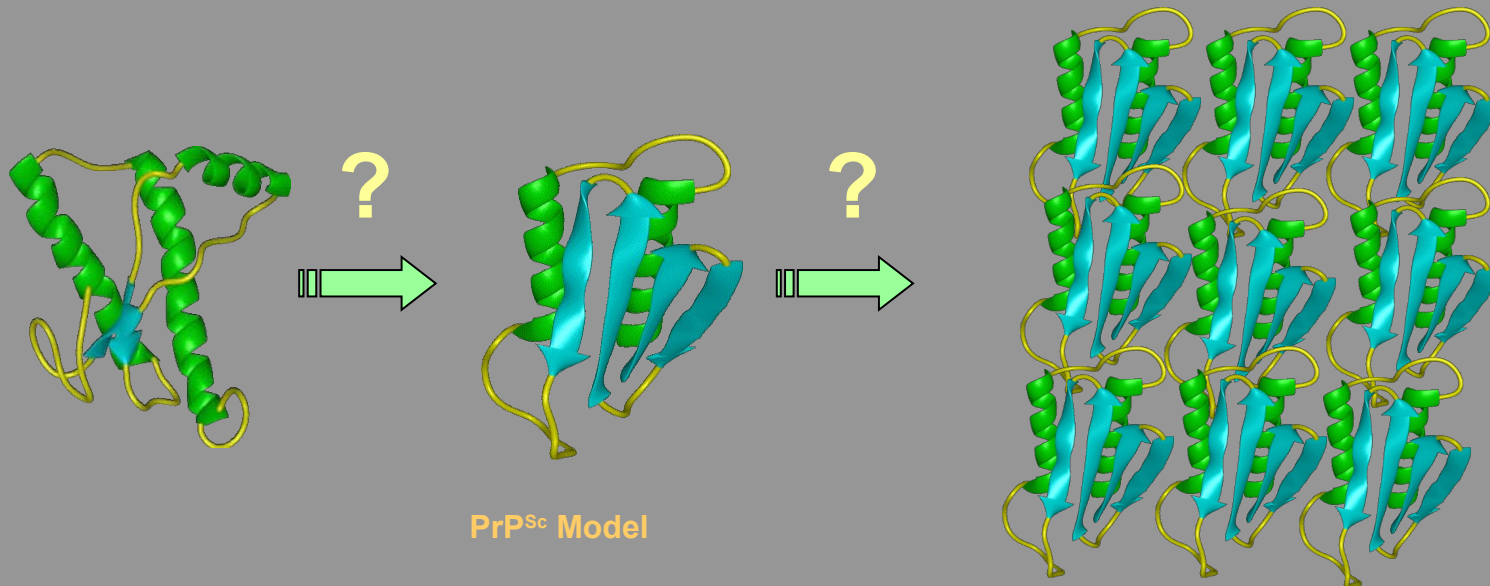
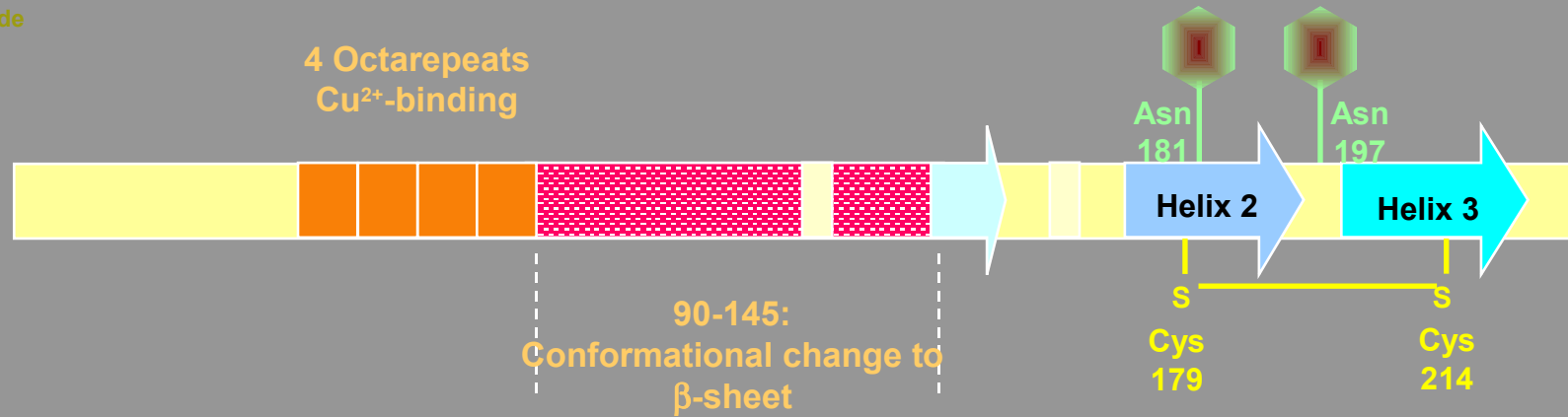
Prion-Hypothesis



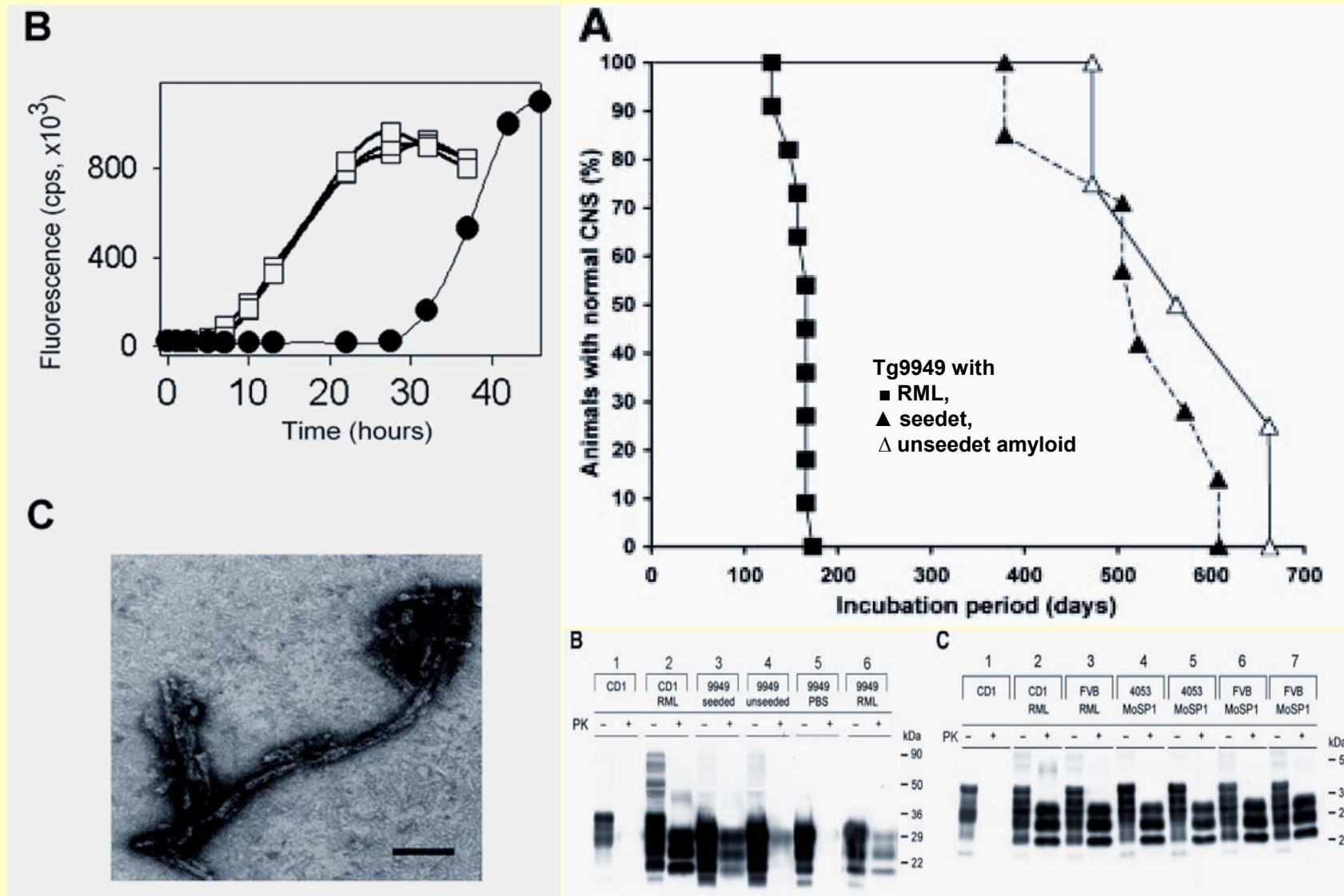


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Conformational change to Scrapie-Prion



Synthetic generated infectiosity



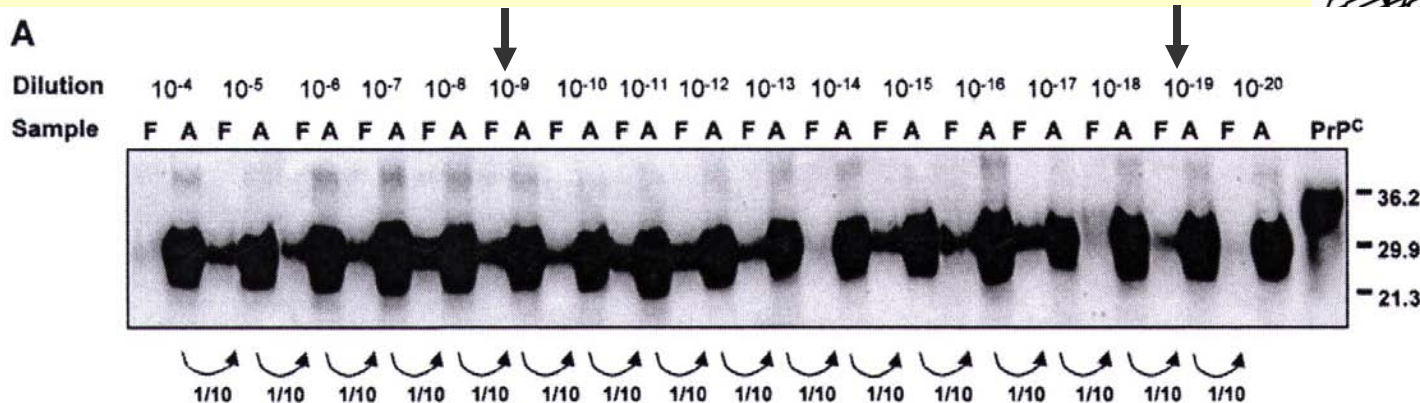
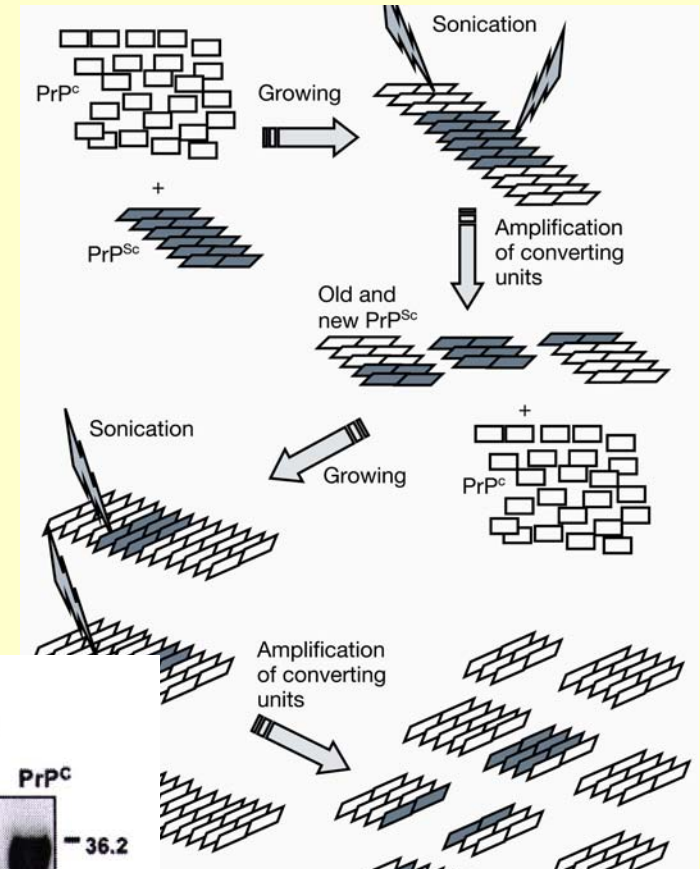
Legname et al. Synthetic mammalian prions. Science 2004;305:673-676

Amplification of prion protein

Infectiousness generated by PrP^{Sc}-amplification

Castilla et al.: In vitro generation of infectious Scrapie prions. Cell 2005;121:195

Saborio, Pemanne, Soto:
Cyclic amplification
of protein misfolding.
Nature 2001;411:811



Human prion diseases

- Idiopathic prion diseases:
Creutzfeldt-Jakob disease 90 %
- Hereditary prion disease:
CJD, Gerstmann-Sträussler-Scheinker syndrome (GSS),
fatal familial insomnia (FFI)
together: 10 %
- Acquired prion disease:
iatrogenic i.e. hormonal extracts from hypophyses <1 %
BSE-related variant CJD (vCJD)

Human prion diseases

Variant Creutzfeldt-Jakob disease:

		Residency in UK:
• United Kingdom	165	165
• France	22	1
• Rep. of Ireland	4	2
• Italy	1	
• The Netherlands	2	
• Portugal	1	
• Spain	1	
• USA	3	2
• Canada	1	1
• Saudi Arabia	1	
• Japan	1	

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Incidence of definite and probable sCJD-cases in european countries

- Expectet numbers:
 - 1 – 2 cases per million inhabitants and year
- Austria, Germany: 0.7 – 1.7 diagnosed sCJD, up to 400 diagnosed BSE cattle (Germany), no vCJD
- France, Italy, Netherlands, Spain: 0,5 – 1,5 diagnosed sCJD, some vCJD, up to 1000 diagnosed BSE cattle
- Switzerland: Incidence of 2,5 in 2001
- UK: additionally up to 28 vCJD per jear (in 2000)
over 180.000 diagnosed BSE cattle



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Diagnostic criteria for sCJD

Probable

- Progressive dementia
- EEG shows PSWC or detection of 14-3-3 protein in CSF
- Two out of four symptoms:
 1. Myoclonus
 2. Visual or cerebellar symptoms
 3. Pyramidal or extrapyramidal signs
 4. Akinetic mutism

• **Possible**

- Progressive dementia
- EEG shows no PSWC
- 14-3-3 protein in the CSF not detectable (Western blot)
- Two out of the four clinical symptoms as described above
- Duration of illness less than two years

CJD-type: M/M^{Cod129}, PrP^{CJD}type 1

- ca. 60-70% of proven CJD cases
- Average of age: 66 years
- Typical clinical disease course with rapid progressive dementia, myoclonus, short disease duration (4months), characteristic EEG changes (PSWC)
- NP: severe cortical pathology predominant in the occipital lobe
- PrP^{CJD}-deposits in cerebral cortex, cerebellum, synaptic distribution

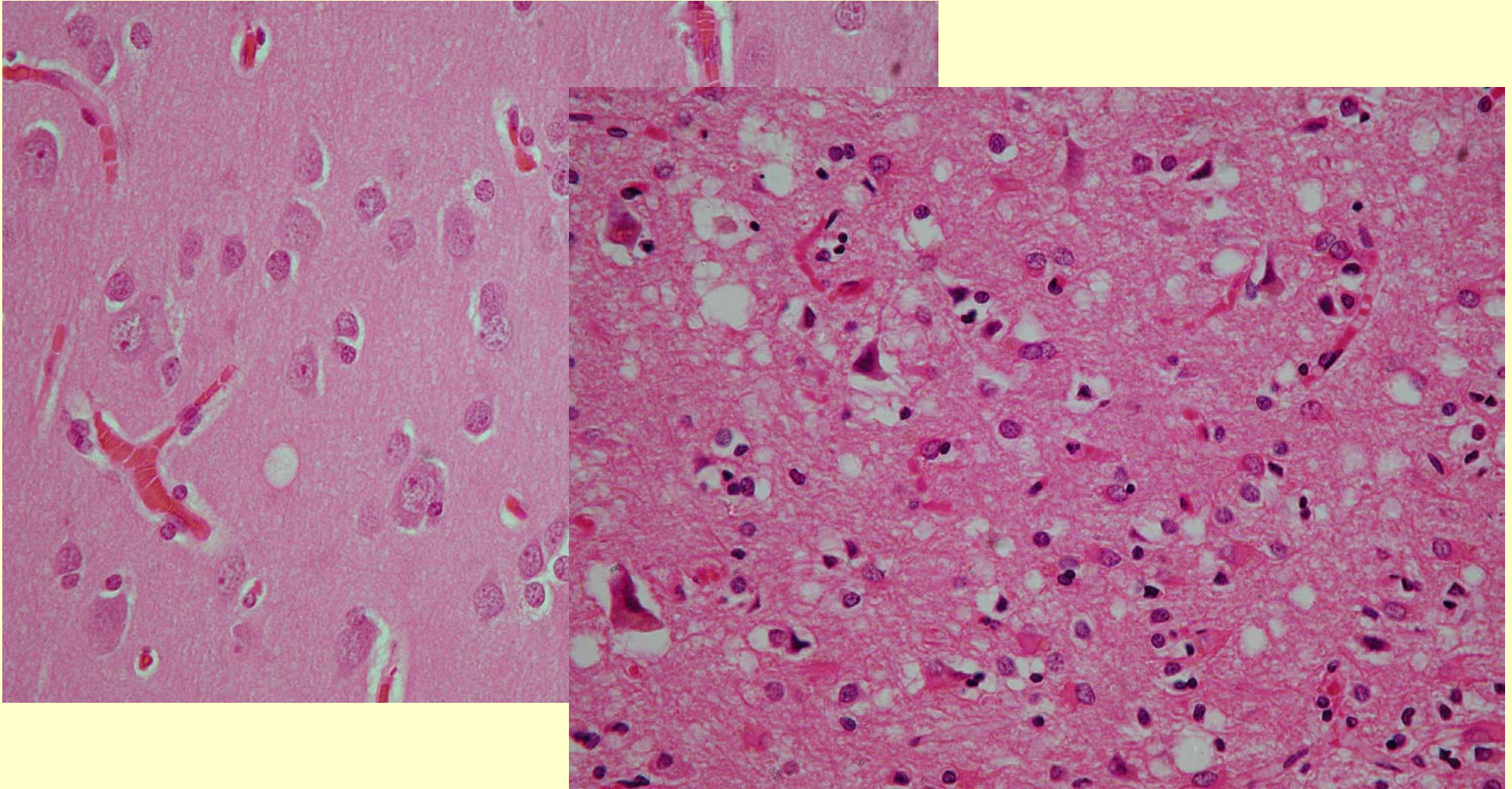
CJD-type: V/V^{Cod129}, PrP^{CJD} type 2

- ca. 15-20% of proven CJD cases
- Average of age 58 years
- Clinical course: ataxia initially, later development of dementia, disease course longer, no typical EEG changes, 14-3-3 positive
- NP: spongiform changes predominant in lower cortical layers
- pericellular und granular PrP^{CJD}-deposits in cortex, plaque-like deposits in cerebellum

Diagnosis of prion diseases

- Immunohistochemical detection of pathological PrP deposits in the brain; (vCJD: additionally in tonsils and appendix)
- Western blot: detection of PrP^{Sc}
- Electron microscopy: detection of scrapie-associated fibrils (SAF)
- Transmission of the disease to animals

Prionerkrankungen - Pathology





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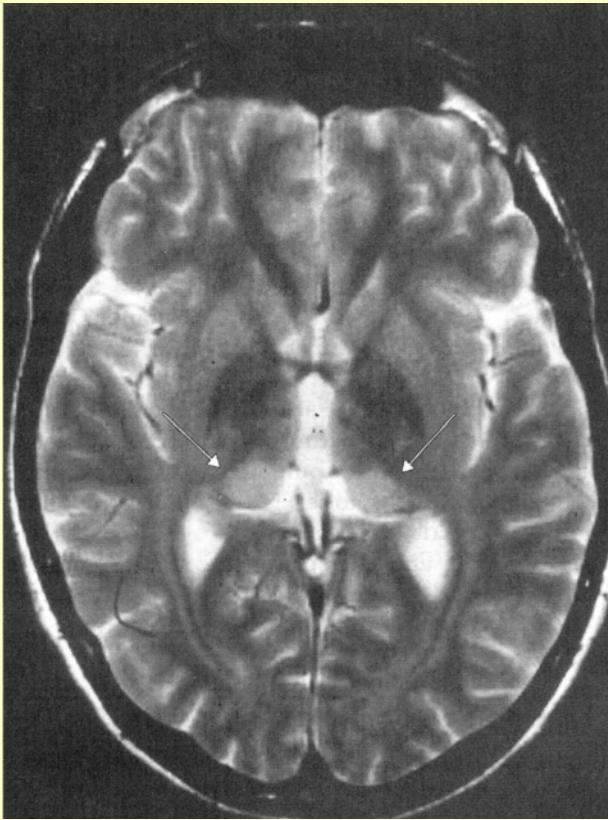
Clinical picture of vCJD

- Mean age at time of death: 29 years (16 – 74 years)
- Mean disease course: 14 months (8 – 38 months)
- M:F: insignificantly more women
- Initial psychiatric symptoms (depression)
- First neurological symptoms frequently painful dysesthesia or paresthesia
- Movement disorder and ataxia approximately 6 months after disease onset
- Consequent rapid progressive dementia; finally akinetic mutism.

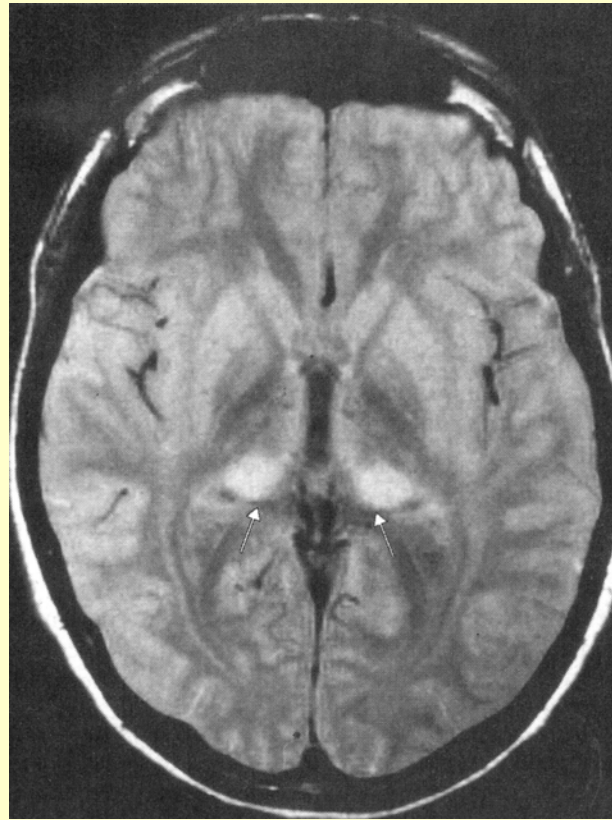


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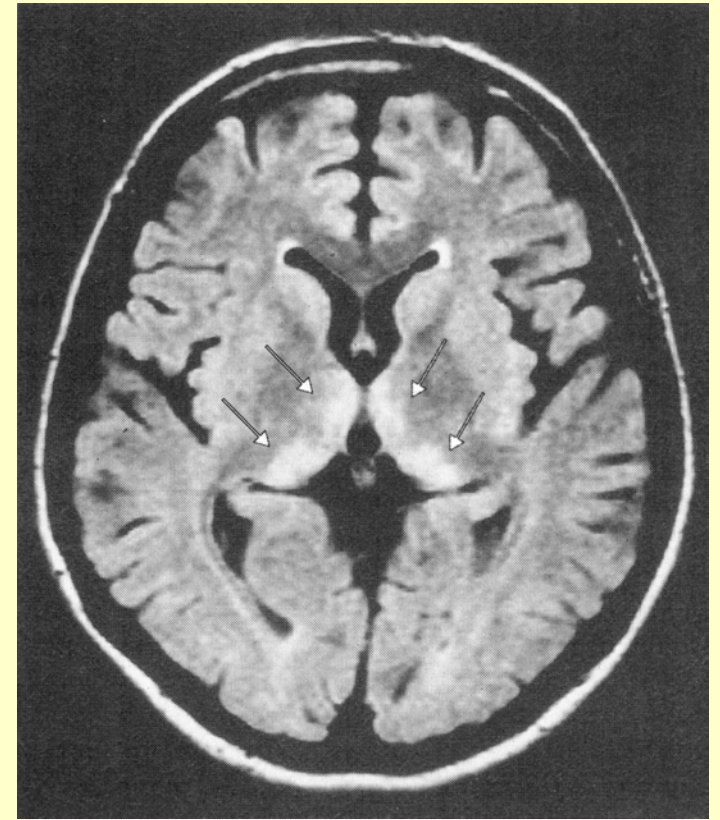
Pulvinar sign in vCJD



MRT: T2



Proton weighted

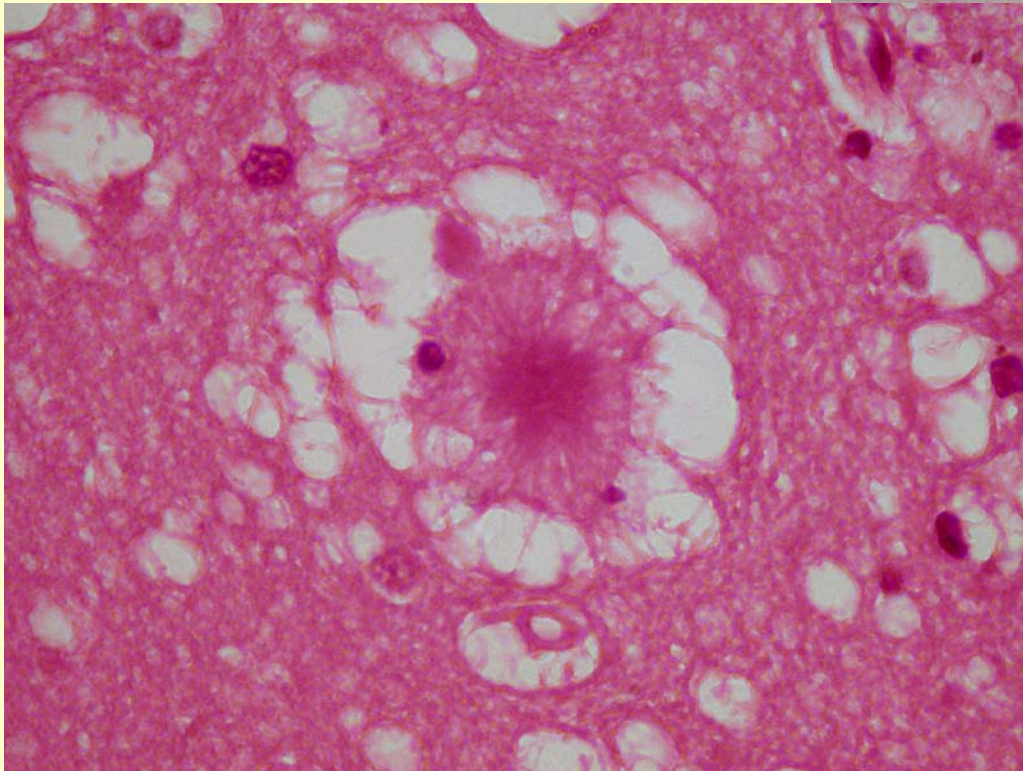
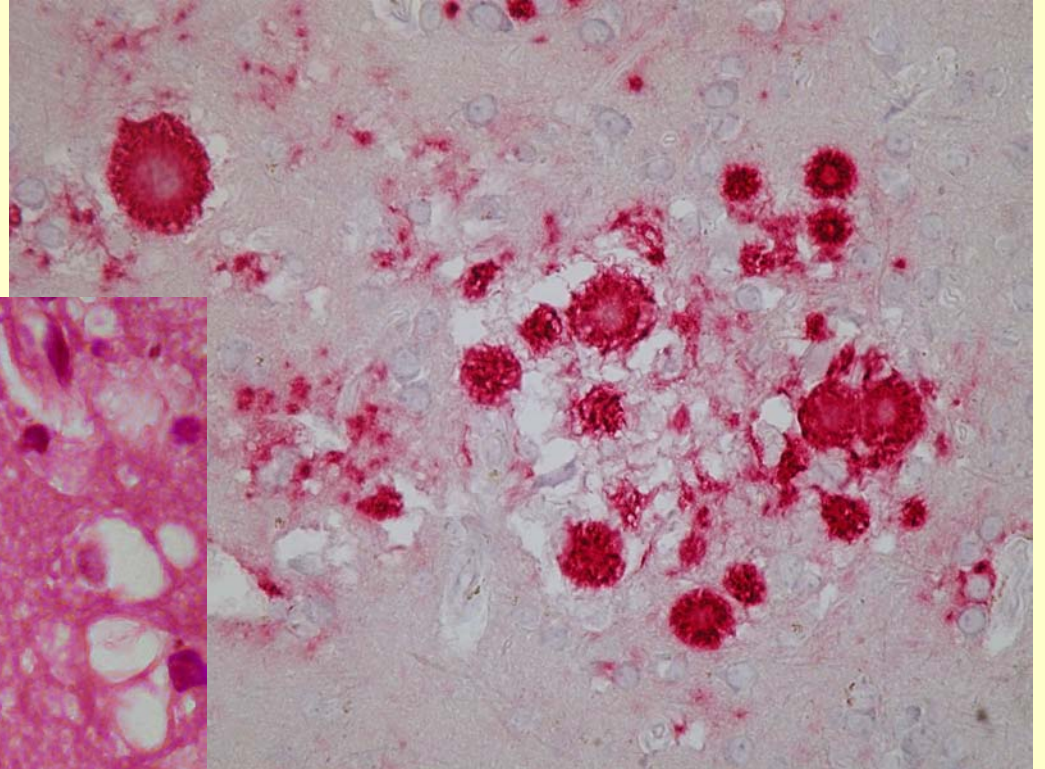


Flair-MRT



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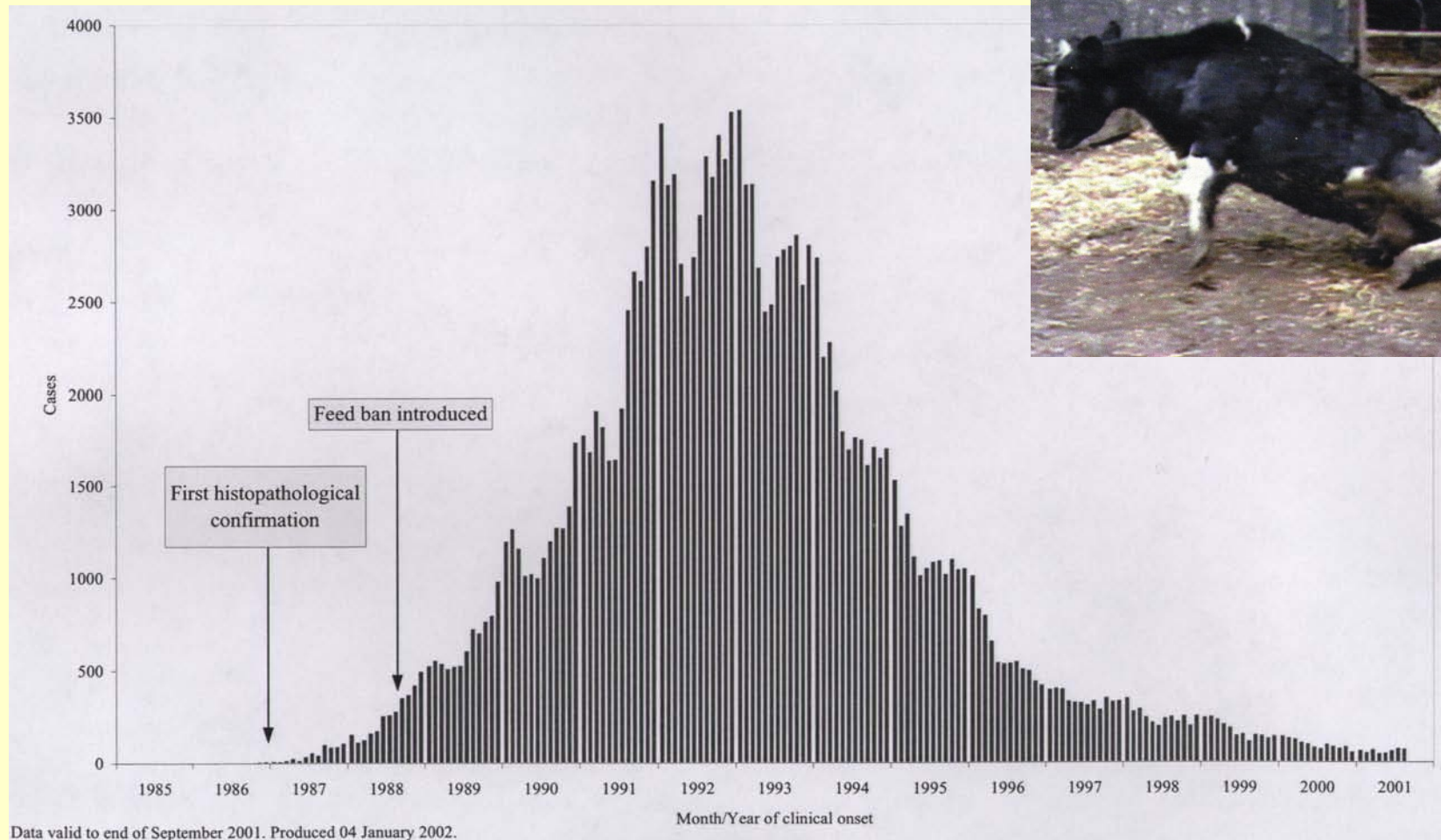
vCJD - Pathology



Evidence that vCJD is caused via transmission of the BSE agent to humans:

- Epidemiology of BSE – vCJD occurs where the most BSE cases were seen
- Transmission of the BSE-agent to macaques – the neuropathological lesion profile is identical with vCJD
- Results of strain typing experiments – BSE and vCJD show identical strain characteristics and can be distinguished from sCJD and scrapie strains
- Transmission of BSE and vCJD to bovin-*PRNP*-transgenic mice – comparable strain characteristics

Epidemiology of BSE



BSE-Cases

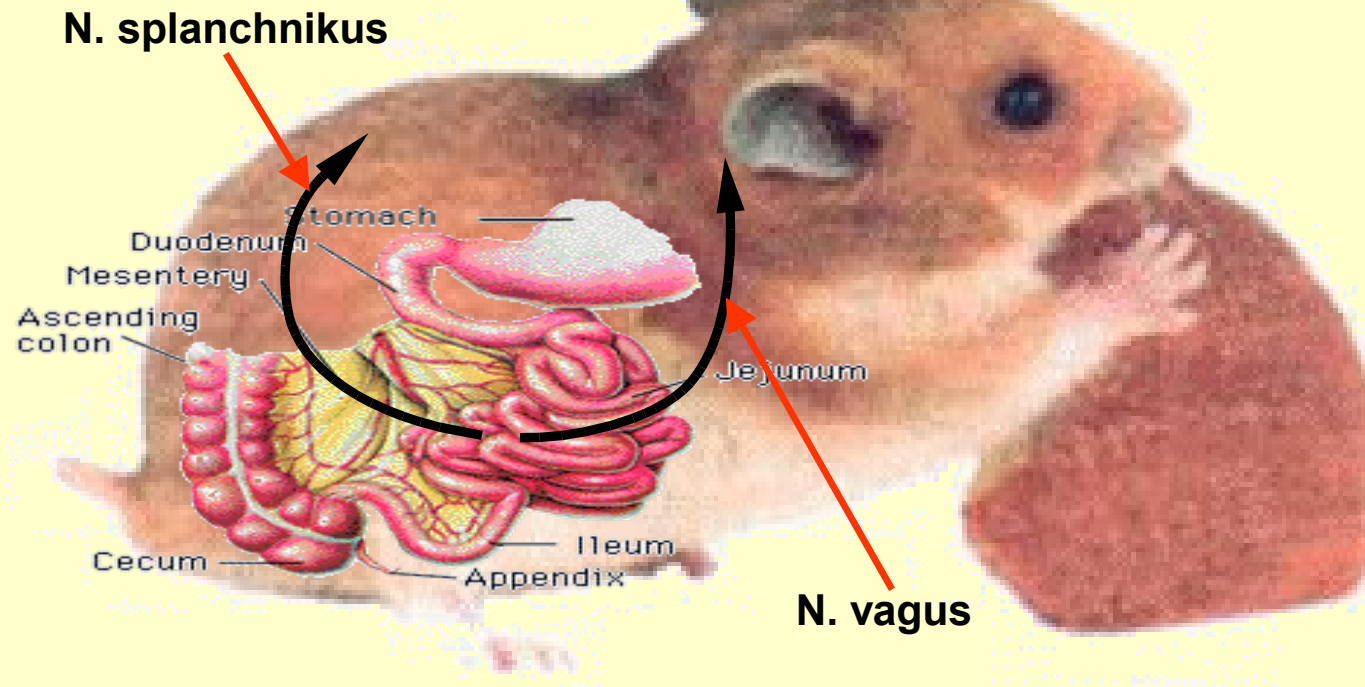
Confirmed BSE cases:

	total	2003	2004	2005	2006
• United Kingdom	182721	611	398	224	124
• Ireland	1590	182	126	69	41
• Portugal	1030	133	92	51	32
• France	986	137	54	31	8
• Spain	678	167	137	98	64
• Switzerland	467	21	3	3	5
• Germany	411	54	65	32	16
• Italy	140	31	7	8	6
• Belgium	133	15	11	2	2
• The Netherlands	82	19	6	3	2
<hr/>					
• Japan	31	4	5	7	10
• Canada	9	1	1	1	5
• USA	3	1	0	1	1



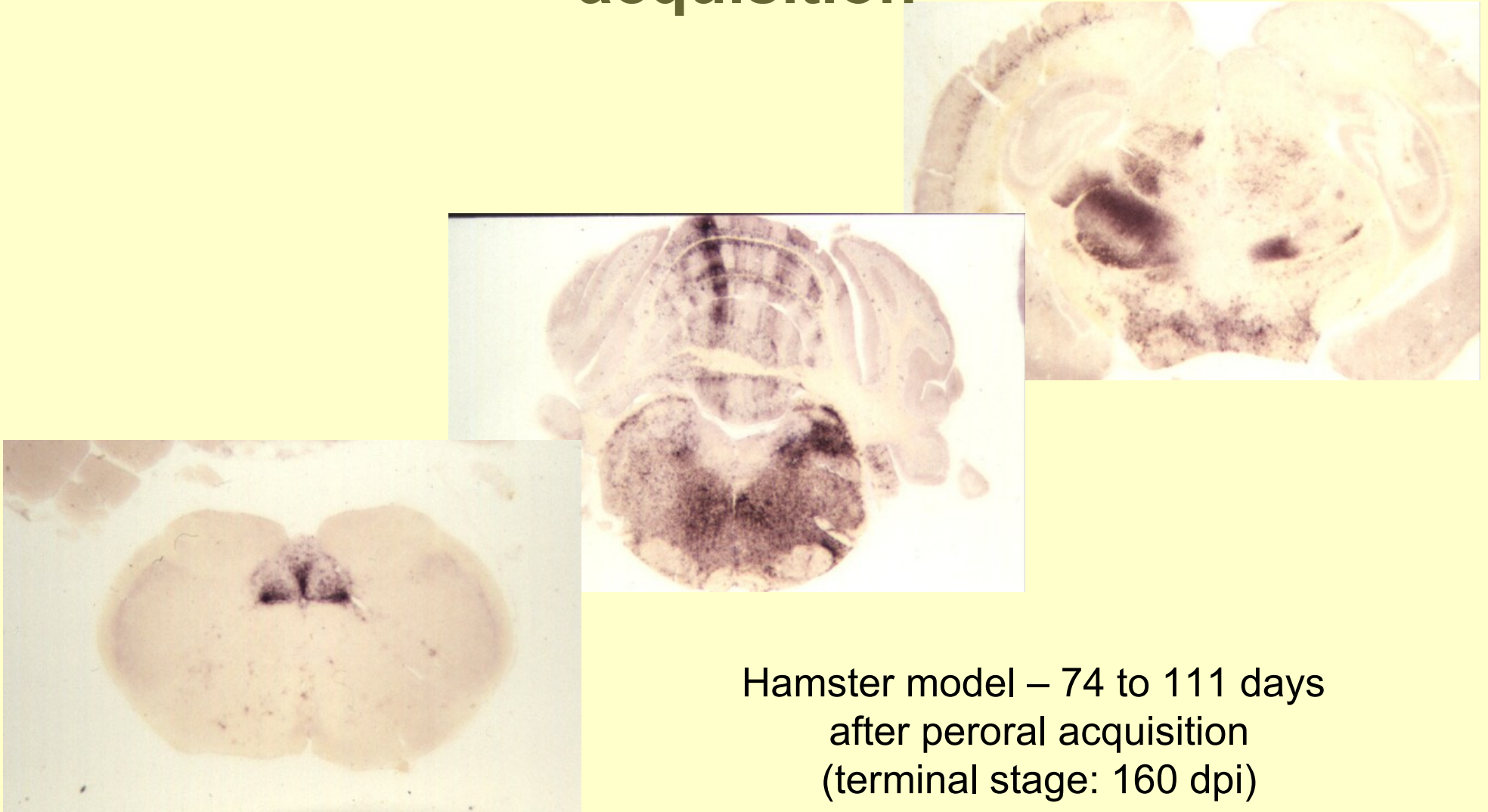
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Spread of PrP^{Sc} after oral acquisition



Pathways and mechanisms in the spread of PrP^{Sc} to the central nervous system.
EU Projekt QL3-CT-2002-81030-nEUROpathways; Coordinator: W. Schulz-Schaeffer

Spread of PrP^{Sc} to the brain after oral acquisition



Hamster model – 74 to 111 days
after peroral acquisition
(terminal stage: 160 dpi)

PrP^{Sc} targeting to the obex in BSE in cattle during incubation

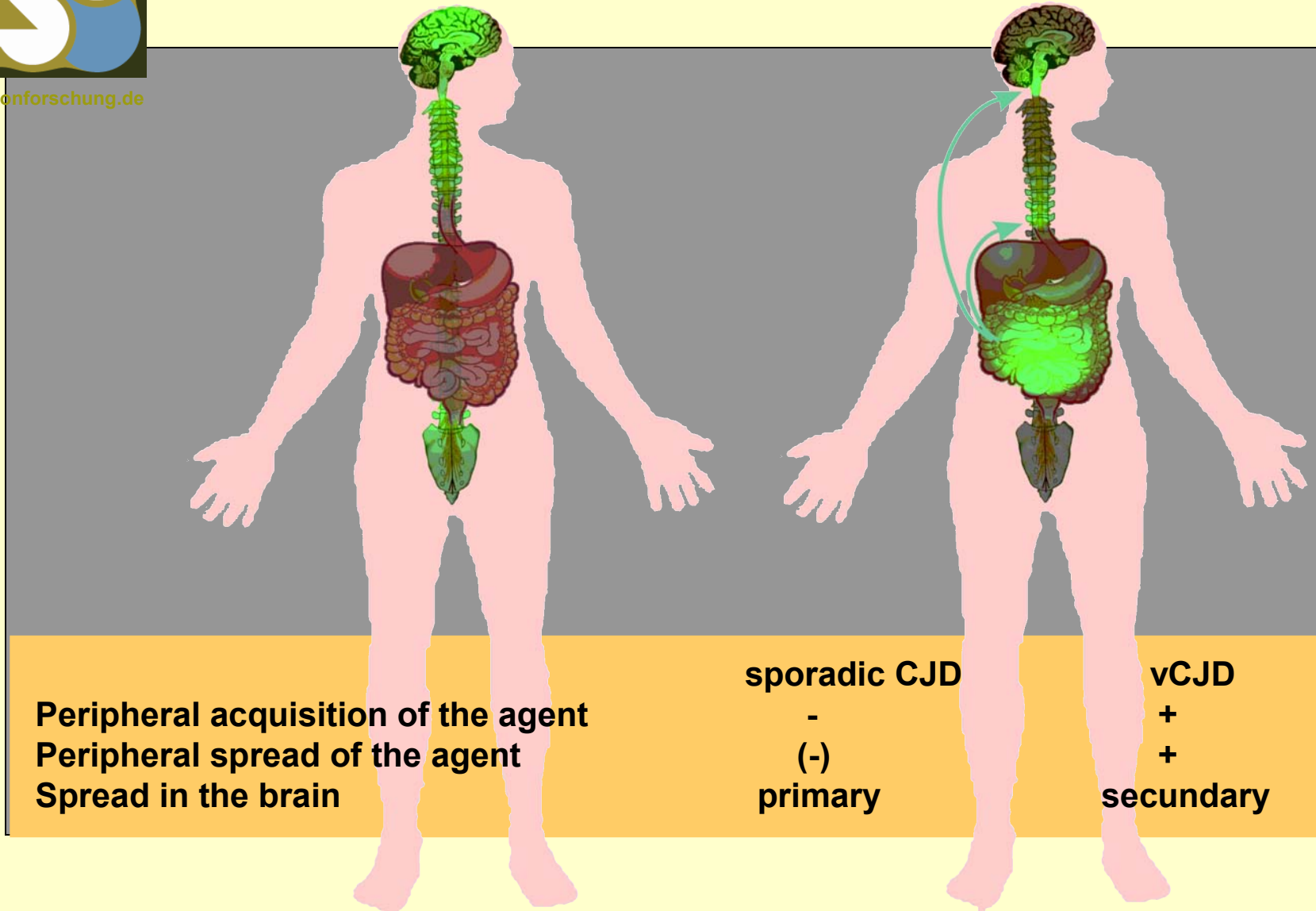


Schulz-Schaeffer et al. Arch Virol 2000



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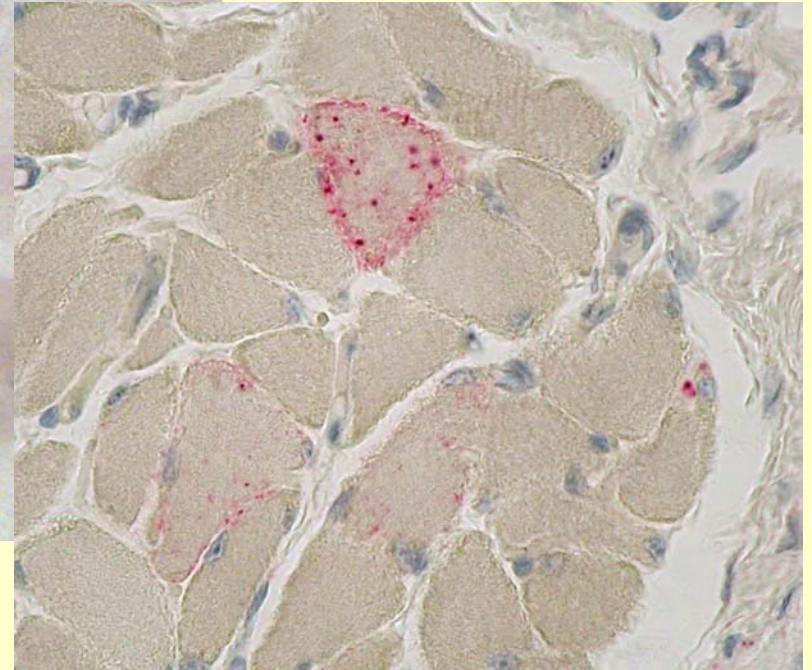
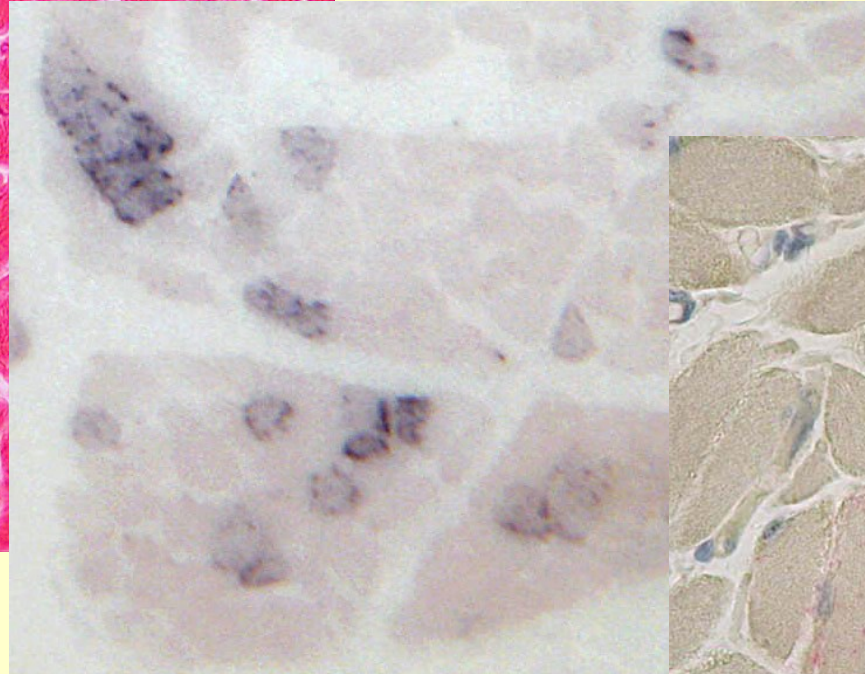
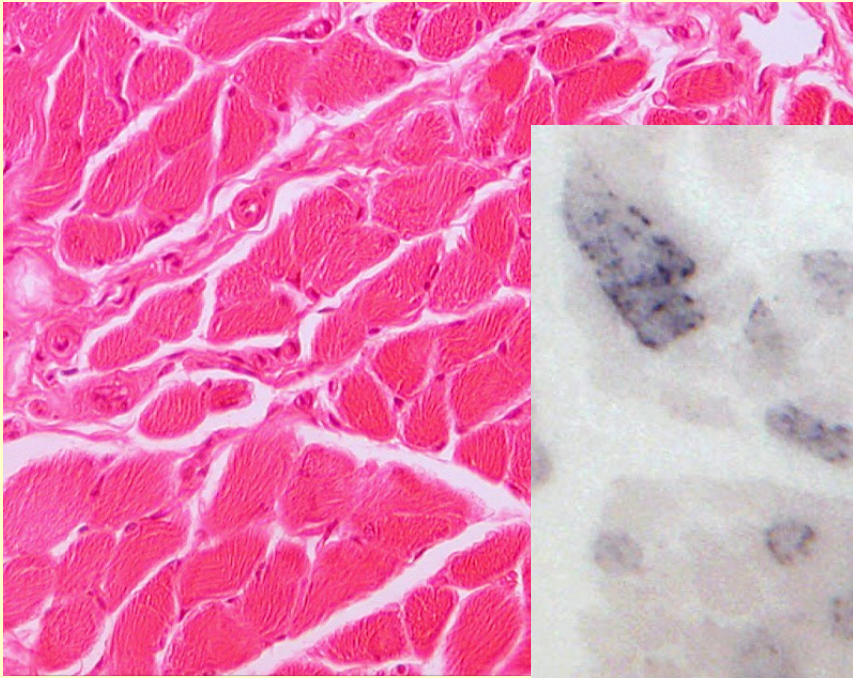
Spread of agent in different human CJD





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Spread of PrP^{Sc} to muscles



**PET blot and immunohistochemistry:
Antibody 3F4**

Schulz-Schaeffer et al. JCI 2004

Risk stratification of patients

Group I. High risk of having/developing CJD:

- Patients with definite CJD
- Patients with clinical suspicious CJD (probable or possible CJD)
- Carriers of pathogenic mutations in the prion protein gene
- Members of a family with familial CJD
- Patients suffering from a neurological disease of unknown etiology where the diagnosis of CJD is being actively considered (UK)

Group II. Heightened risk of having/developing CJD:

- Patient with unclarified, rapidly progressing CNS-disease with/without dementia
- Members of families in which those diseases having often occurred
- Recipients of human pituitary gland hormones (growth hormone, gonadotropines)
- Recipients of dura mater implants in the years 1972-1987 (UK: before 1992)

Group III. Low risk of having/developing CJD:

- All other people



Tissue handling and safety precautions

Figure 6.1 Distribution of infectivity in the human body*

Infectivity category	Tissues, secretions, and excretions	
High infectivity	Brain Spinal cord Eye	
Low infectivity	CSF Kidney Liver Lung Lymph nodes/spleen Placenta	
No detectable infectivity	Adipose tissue Adrenal gland Gingival tissue Heart muscle Intestine Peripheral nerve Prostate Skeletal muscle Testis Thyroid gland Blood*	Tears Nasal mucus Saliva Sweat Serous exudate Milk Semen Urine Faeces

Tissue handling and safety precautions

Tissue	Presence of abnormal Prion Protein and level of infectivity			
	CJD other than vCJD		vCJD	
	PrP-res detected	Assumed level of Infectivity	PrP-res detected	Assumed level of infectivity
Brain	+ve	High P	+ve	High P
Spinal cord	+ve	High P	+ve	High
Spinal ganglia	+ve	High	+ve	High
<i>Dura mater</i>	NT	High	NT	High
Cranial nerves	+ve	High	+ve	High
Cranial ganglia	+ve	High	+ve	High
Posterior eye	+ve	High P	+ve	High
Anterior eye and cornea	-ve	Medium	-ve	Medium
Olfactory epithelium	+ve	Medium	NT	Medium
Tonsil	-ve	Low	+ve	Medium P
Appendix	-ve	Low	+ve	Medium
Spleen and thymus	-ve	Low P *	+ve	Medium P
Other lymphoid tissues	-ve	Low P *	NT	Medium P
Peripheral nerve	-ve	Low	-ve	Low
Dental Pulp	-ve	Low	NT	Low
Gingival Tissue	NT	Low	NT	Low
Blood and bone marrow	NT	Low	NT	Low
CSF	-ve **	Low P **	-ve**	Low
Placenta	NT	Low	-ve	Low
Urine	NT	Low	NT	Low
Other tissues	NT	Low P *	NT	Low



Tissue handling and safety precautions

1. Route of exposure:

- Cutaneous exposure of intact skin or mucous membranes except those of eyes poses negligible risk – it is highly recommended to avoid exposure when working with high infectivity tissues.
- Transcutaneous exposures pose a greater potential risk.

2. Blood, CSF:

- Blood specimen from patients with CJD are considered to be not infectious. No special precautions were needed for its handling in clinical laboratories.
- CSF may be infectious. It is recommended that analyses not be performed in automated equipment, and any materials coming in contact with the CSF must either be incinerated or decontaminated (Appendix 4.1)



Tissue handling and safety precautions:

- **Decontamination of instruments**

Dependent upon:

- probability, that an individual has or will develop TSE
 - level of infectivity in tissues or fluids of the individual
 - the expectation of how the instrument will be reused
-
- Adopt the highest decontamination method feasible;
 - Surgical instruments for reuse may be mechanically cleaned in advance of subjecting them to decontamination (cleaning material must be treated as infectious waste, cleaning station must be decontaminated by methods of Annex 4.1);
 - Treat instruments by one of the recommended decontamination methods (Annex 4.1);
 - Reintroduce instruments into the general instrument sterilization process



Tissue handling and safety precautions:

• Decontamination of instruments

Complex and expensive instruments that cannot be decontaminated according to Annex 4.1:

- Instruments should be protected from surface contamination by wrapping or bagging with disposable material;
- Those parts that come into contact with patient tissues should be subjected to the most effective decontamination procedure tolerated by the instrument;
- If can be done safely, adherent particles should be removed through mechanical cleaning;
- Removable parts should be dismantled and decontaminated with the most effective procedure tolerated;
- Decontamination procedures should be applied even if the instrument has been reused before discovery of ist potential contamination;
- Contaminated instruments should not be cleaned in automated washers without first having been decontaminated using a method recommended in Annex 4.1.



Tissue handling and safety precautions:

- **Decontamination methods (Annex 4.1)**

1. Incineration

- use for all disposable instruments, materials and waste
- preferred method for all instruments exposed to high-infectivity tissues



Tissue handling and safety precautions:

• Decontamination methods (Annex 4.1)

2. Autoclave/chemical methods for heat-resistant instruments

- a) Immerse in 1N NaOH and heat in a gravity displacement autoclave at 121°C for 30 min, (clean, rinse in water and subject to routine sterilization);
- d) Immerse in NaOH or NaOCl (20.000 ppm available chlorine) for 1 h, afterwards autoclave at 121°C for 1 h in water in a gravity displacement autoclave (+ routine sterilization) or
- c) Autoclave after NaOH or NaOCl immersion without water bath 121°C in a gravity displacement or 134°C in a porous load autoclave for 1 h (+ routine steril.)
- d) Immerse in NaOH and boil for 10 min (clean, rinse in water, subject to routine sterilization)
- e) Immerse in NaOCl (or NaOH) at ambient temperature for 1 h (clean, rinse...)
- k) Autoclave at 134°C for 18 min

a -> f: decreasing effectivity of the decontamination method



Tissue handling and safety precautions:

• Decontamination methods (Annex 4.1)

Chemical methods for surfaces and heat sensitive instruments

- Immerse in 2N NaOH or undiluted sodium hypochlorite for 1 h
- Whereas surfaces cannot tolerate NaOH or hypochlorite, thorough cleaning will remove most infectivity by dilution and some additional benefit may be derived from the use of one or other of the partially effective methods:

Variably or partially effective

chlorine dioxide

glutaraldehyde

guanidinium thiocyanate (4 mol/litre)

iodophores

sodium dichloro-isocyanurate

sodium metaperiodate

urea (6 mol/litre)

Variably or partially effective

autoclaving at 121 °C

for 15 minutes

boiling in 3% sodium

dodecyl sulfate (SDS)

General procedure for processing of medical devices

French and Swiss recommendations:

- Sterilization of all reusable thermostable surgical instruments at 134°C for 18 min in a porous load steam sterilizer

German recommendations:

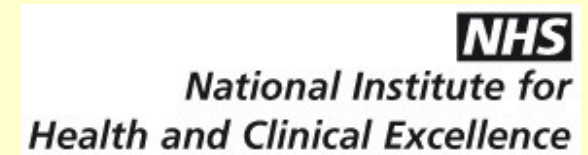
- Not protein-fixating precleaning/pretreatment



Processing by combining two methods suitable for (partial) decontamination/inactivation of TSE-agents:

- Cleaning under alkaline conditions (NaOH or KOH, tensides, elevated, not protein-denaturing temperature expected to be effective within 10 min)
- Steam sterilization at 134°C according to European standards
(Steam sterilization at 134°C for 18 min in case that alkaline cleaning is not feasible or not used)

Prevention of transmission of prion diseases



General recommendations:

- All surgical instruments contaminated with CNS, eye, olfactory epithelium or lymphatic tissue from patients presenting a recognizable risk for CJD (group I+II) should be disposed of by incineration or
- Quarantined in a sealed container until diagnosis has been established
- All other instruments in contact with less infective tissues may be reprocessed according to the best currently available practice. Disposable instruments should be used whenever possible.
- It is the duty to explore the risk status for every patient undergoing an operation or invasive medical intervention.

Prevention of transmission of prion diseases

CJD other than vCJD

Tissue Infectivity	Status of patient			
	Definite/probable	Possible	At risk	
			Genetic	Iatrogenic
High: <ul style="list-style-type: none"> Brain Spinal cord Posterior eye 	D	Q	D	D
Medium: <ul style="list-style-type: none"> Anterior eye* Olfactory epithelium 	D	Q	D	D
Low/none detectable	NSP	NSP	NSP	NSP

*Although tests for PrP-res in anterior eye tissue have been negative, transmission has been documented via corneal grafts. There are insufficient data to justify moving away from the precautionary principle for anterior eye tissue at this stage.

NHS

*National Institute for
Health and Clinical Excellence*

vCJD

Tissue Infectivity	Status of patient			
	Definite/probable	Possible	At risk	
				Iatrogenic
High: <ul style="list-style-type: none"> Brain Spinal cord Posterior eye 	D	Q		D**
Medium: <ul style="list-style-type: none"> Lymphoid tissue* Anterior eye Olfactory epithelium 	D	Q		D**
Low/none detectable	NSP	NSP		NSP

* PrP-res has been detected in tonsil, appendix, lymph-node, spleen, thymus, adrenal gland and rectum of vCJD patients.

Decontamination of instruments



Thermostabile instruments		Thermolabile instruments	
No CJD suspicion	CJD suspicious	No CJD suspicion	CJD suspicious
reprocess according to regular practice	a)disposable instruments b)decontamin. with 2M NaOH or 2,5-5% NaOCl or 4M GdnSCN 2 x 30 min + cleaning followed by steam sterilization at 134°C for 1 h	reprocess according to regular practice	a)disposable instruments b)decontamin. with 2M NaOH or 2,5-5% NaOCl or 4M GdnSCN 2 x 30 min + cleaning followed by disinfection and sterilization

Decontamination of endoscopes

Recipients of plasma products made from donors later developing vCJD having a relevant risk of developing vCJD themselves and defined „at risk of vCJD for public health purposes“. Their number is in the order of 6500. Predominantly haemophiliacs and immunodeficiency patients are involved – diseases that require frequently endoscopic procedures. Four centers serving for ¼ of „at risk“ patients reported over 15% of their scopes were used for invasive GI endoscope procedures for these patients during 12 months

Although there is no evidence of vCJD transmission via endoscopes the risk of endoscope contamination needs to be minimized:

- Biopsy tissue only when necessary, using disposable biopsy forceps;
- Disposing of the biopsy rubber cap after use on all patients;
- Instruments used for procedures not expected to result in potential contamination with lymphoid tissues can be decontaminated in the normal way and reused
- Blood and bodily secretions do not pose a threat – blood is considered low-infectivity tissue
- Endoscope procedures are defined whether deemed to be invasive or not

Decontamination of endoscopes

sCJD patients:

Omit use of neurological endoscopes in definite, probable, possible or „at risk“ CJD;

If necessary, endoscope should be single use instruments or quarantined if diagnosis is pending

If there is a risk that an endoscope used in the nasal cavity could become contaminated with olfactory epithelium, a single use endoscope should be used otherwise the endoscope should be removed from use or quarantined.

Quarantined endoscopes may be-reused exclusively in the same individual patient if required

For all other types of endoscopy, normal decontamination procedures (MDA DB2002(05)) should be followed.

Decontamination of endoscopes

vCJD patients:

The same procedures as in sCJD patients for neurological endoscopes and endoscopy of the nasal cavity are recommended

But

For all other types of endoscopy the use of the instrument for inspection in the absence of invasive techniques is deemed to be a low risk procedure.

If biopsy or other invasive procedure is carried out, the possibility of the contamination of the instrument channel with lymphoid tissue means the endoscope should be quarantined pending assessment of likely contact with potentially infective tissue. If this is considered possible and an alternative diagnosis is not obtained (possible or at risk vCJD) the endoscope should be removed from use.

Decontamination of endoscopes

Table F1. CJD other than vCJD

Tissue Infectivity	Status of patient		
	Symptomatic		Asymptomatic
	Definite/probable	Possible/diagnosis unclear ¹	At risk ² iatrogenic/familial
High: • Brain • Spinal cord	single use OR destroy ³ after use	single use OR quarantine ⁴ pending diagnosis	single use OR quarantine ⁴ pending exclusion of CJD
Medium: • Olfactory epithelium*	single use OR destroy ³ after use	single use OR quarantine ⁴ pending diagnosis	single use ⁵ OR quarantine ⁴ pending exclusion of CJD
Low/none detectable: • All other tissues	no special precautions ⁶	no special precautions ⁶	no special precautions ⁶

Decontamination of endoscopes

Table F2a vCJD

Tissue Infectivity	Status of patient		
	Symptomatic		Asymptomatic
	Definite/probable	Possible/diagnosis unclear ¹	At risk ² iatrogenic
High: <ul style="list-style-type: none"> • Brain • Spinal cord 	single use OR destroy ³ after use	single use OR quarantine ⁴ pending diagnosis	single use OR quarantine ⁴ pending exclusion of CJD
Medium⁸: <ul style="list-style-type: none"> • Olfactory epithelium* • Lymphoid tissue** 	single use OR use dedicated endoscope ⁷ OR destroy ³ after use	single use OR quarantine ⁴ pending diagnosis	single use ⁵ OR quarantine ⁴ pending exclusion of CJD
Low/none detectable⁸: <ul style="list-style-type: none"> • All other tissues 	no special precautions ⁶	no special precautions ⁶	no special precautions ⁶

** spleen, thymus, tonsils, adenoids, lymph nodes, appendix, GI-tract submucosa

Decontamination of endoscopes

Decontamination procedure for endoscopes used for PEG or potential contact with low risk tissues:

France:

- double clean the endoscopes:
use two complete cleaning processes with intermediate water rinse.
- peracetic acid is favored as disinfectant as the highest rated of the listed chemical decontamination procedures because of its reliably good antibacterial, antiviral and antifungal effects.
Meanwhile its insufficient prion inactivation is known.



Decontamination of endoscopes

Decontamination procedure for endoscopes used for PEG or potential contact with low risk tissues:

- Avoid precleaning with alcohol or aldehydes;
- Incubate in 4-molar Guanidinium thiocyanate (GdnSCN) solution for 1 h;
- GdnSCN solution needs to reach all internal and external surfaces.
Use a syringe to aspirate the solution into each channel separately;
- After 30 min immersion, clean channels mechanically with single use brushes and immerse for further 30 min;
- Remove GdnSCN solution carefully with rinsing water;
- Process the instrument with the regular program in a washer/disinfector.

Currently no reuse of endoscopes after contact with high risk tissues is recommended.

Optionally: use instruments from regional CJD-endoscope pools.