CJD/PRIONS: THE BASICS AND AN UPDATE

David Jay Weber, M.D., M.P.H.
Professor of Medicine, Pediatrics & Epidemiology
Associate Chief of Staff, UNC Health Care
Medical Director, Hospital Epidemiology
University of North Carolina at Chapel Hill, USA

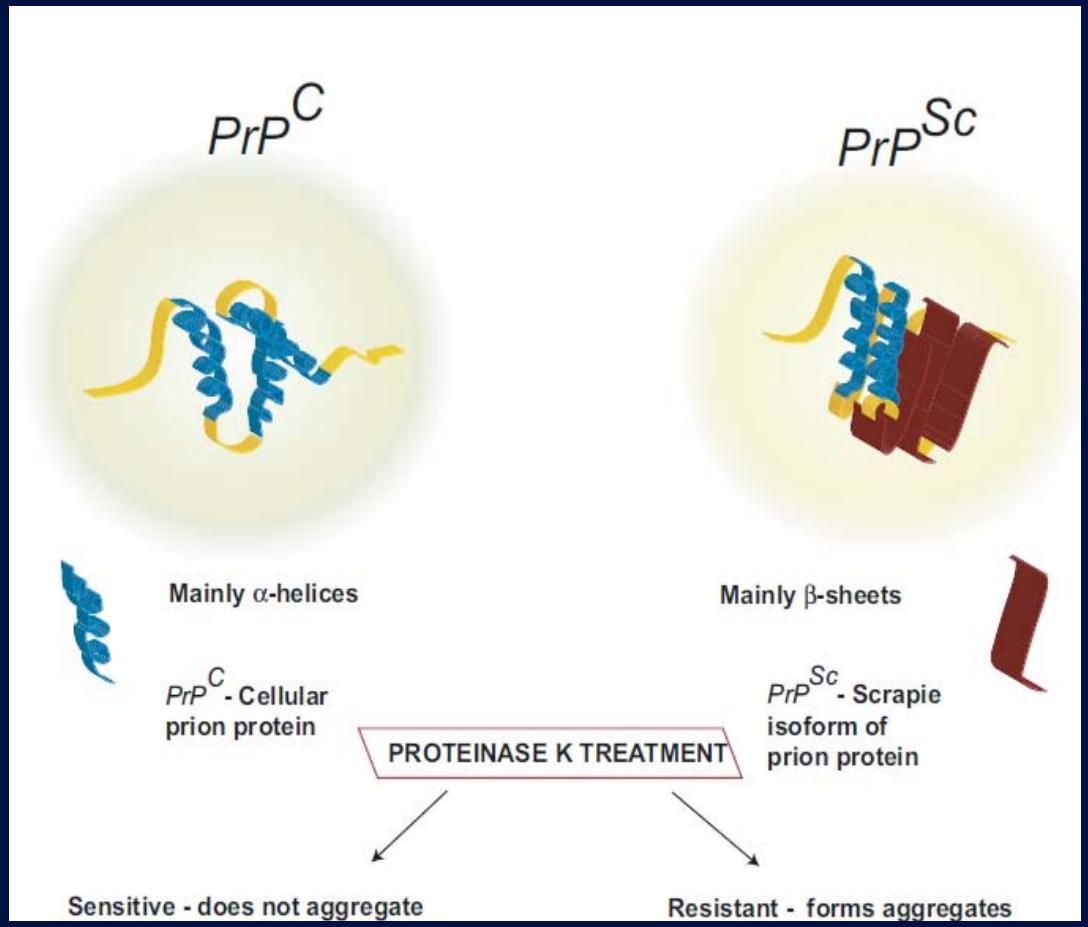
LECTURE OBJECTIVES

- Understand the pathophysiology of prion-associated diseases
- Understand the mechanisms of iatrogenic human prion-associated diseases (CJD, vCJD)
- Understand current guidelines for sterilization of prion contaminated medical instruments

CHARACTERISTICS OF MAMMALIAN PRIONS

- Prion diseases are neurodegenerative disorders of humans and animals for which there are no effective treatments or cures
- When the precursor protein is converted to a prion, it undergoes post-translational modification during which is become enriched in β-sheet structure
- β-sheet-rich conformers form oligomers that are toxic to cells
- Prion oligomers are generally rendered less toxic when they polymerize into amyloid fibrils
- Amyloid fibrils are sequestered in biologic wastebaskets such as plaques, tangles, or inclusion bodies
- Mutations in specific proteins cause familial neurodegenerative diseases by facilitating conversion of the protein into the prion state

NORMAL AND DISEASE-RELATED ISOFORMS OF THE PRION PROTEIN



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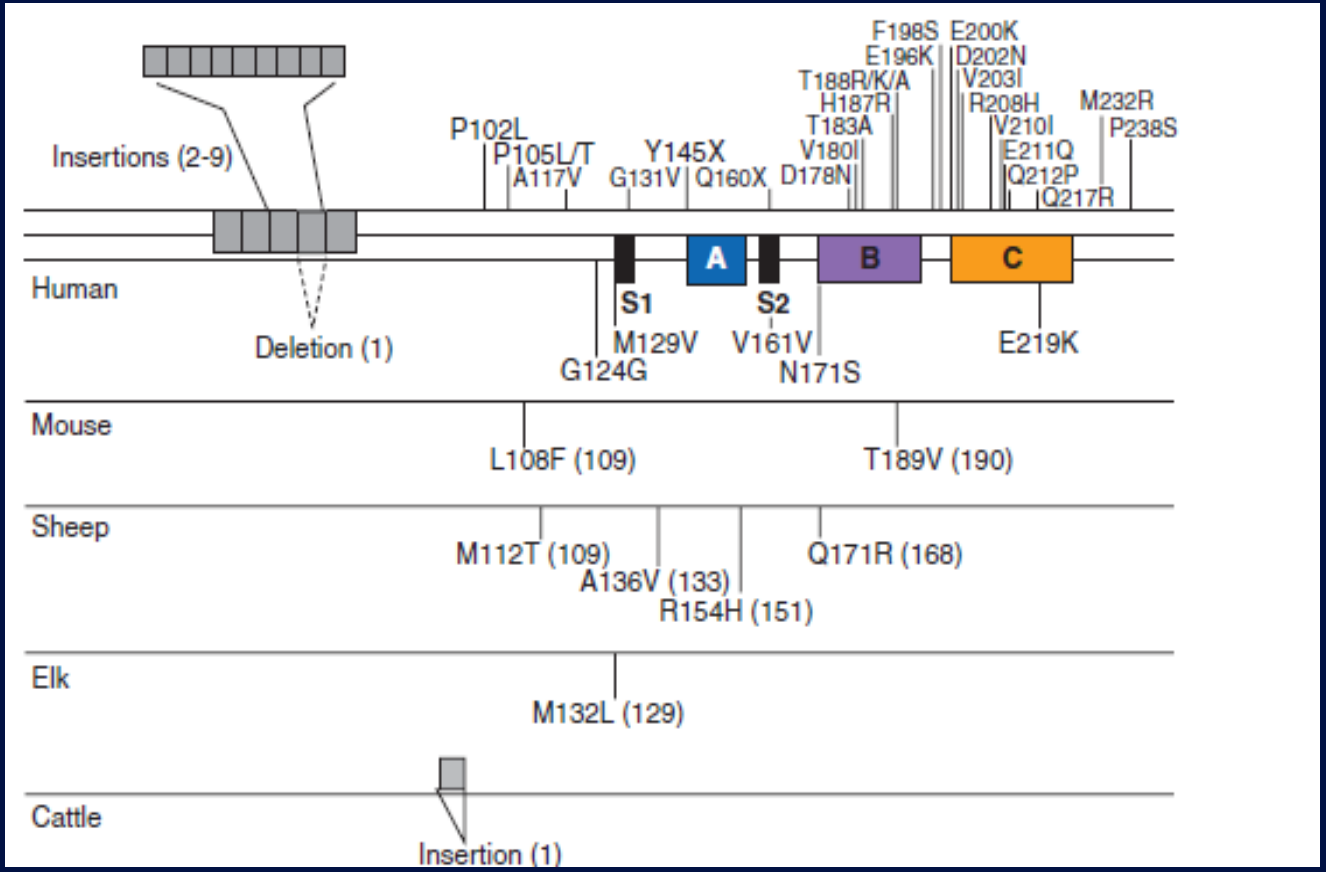
VARIATIONS IN THE PRP GENE



PRION DISEASE IN HUMANS

Year of Description	Clinical Illness	Mode of Disease
1920	Creutzfeldt-Jakob disease	Familial, sporadic, and transmitted (mainly iatrogenic)
1928	Gerstmann-Straussler-Scheinker	Familial, genetic
1941	Kuru	Transmitted
1986	Fatal familial insomnia	Familial, genetic
1995	New variant of Creutzfeldt-Jakob disease	Transmitted

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PRION DISEASES IN ANIMALS

Year of Description	Animal	Disease	Known Transmission to Humans
1732	Sheep and goats	Scrapie	No
1947	Mink	Transmissible mink encephalopathy	No
1967	Elk and deer	Chronic wasting disease	No
1986	Cattle	Bovine spongiform encephalopathy	Yes
1986	Antelopes, bison	Exotic ungulate spongiform encephalopathy	No
1990	Domestic cats and captive large cats	Feline spongiform encephalopathy	No
1996	Captive nonhuman primates	Zoo primate spongiform encephalopathy	No

CLINICAL PHENOTYPES OF PRION DISEASES

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)[a]	1–5 years	Generalized grey matter vacuolation and gliosis
GSS	Ataxia, then dementia	Typically <55 years (20s to 60s)[a]	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.

Brown K, Mastrianni JA. J Geriat Psychiat Neurol 2010;23:277-298

CLINICAL FEATURES OF SPORADIC VERSUS VARIANT CJD

Characteristic	Main Feature	sCJD	vCJD
Clinical features	Median age	68 y	28 y
	Median duration of illness	4 mo	13 mo
	Symptoms and signs	Dementia; early neurologic signs	Behavioral abnormalities, sensory symptoms and delayed neurologic signs
Clinical tests	Periodic triphasic sharp waves on electroencephalogram	Often present	Often absent
	Hyperintensity in posterior thalamus (pulvinar) in relation to the anterior putamen on brain imaging: called the "pulvinar sign"	Often absent	Present in >75% of cases
Laboratory tests	Presence of florid plaques on brain tissues including biopsy	Rare or absent	Present
	Immunohistochemistry for PrP^{Sc} in brain tissues	Variable accumulation	Marked accumulation of PrP^{Sc}
	Detectable PrP^{Sc} in lymphoid tissue including tonisllar biopsy	Not readily detected	Readily detected
	Codon 129 geneotype	Usually Met/Met	Polymorphism may be absent

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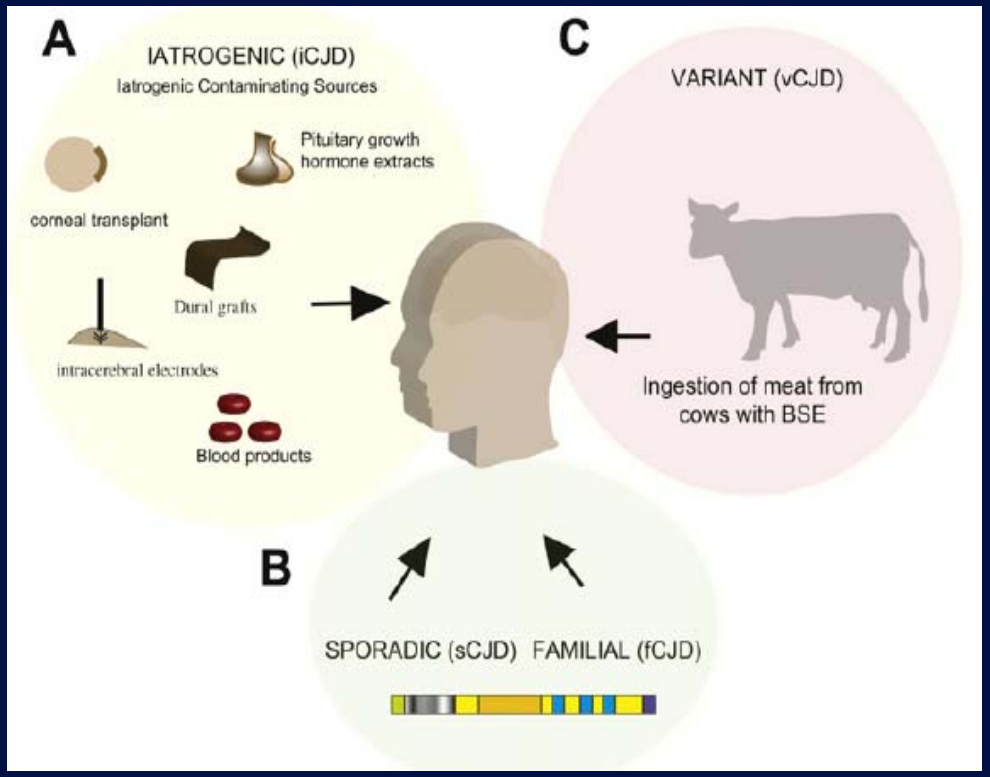
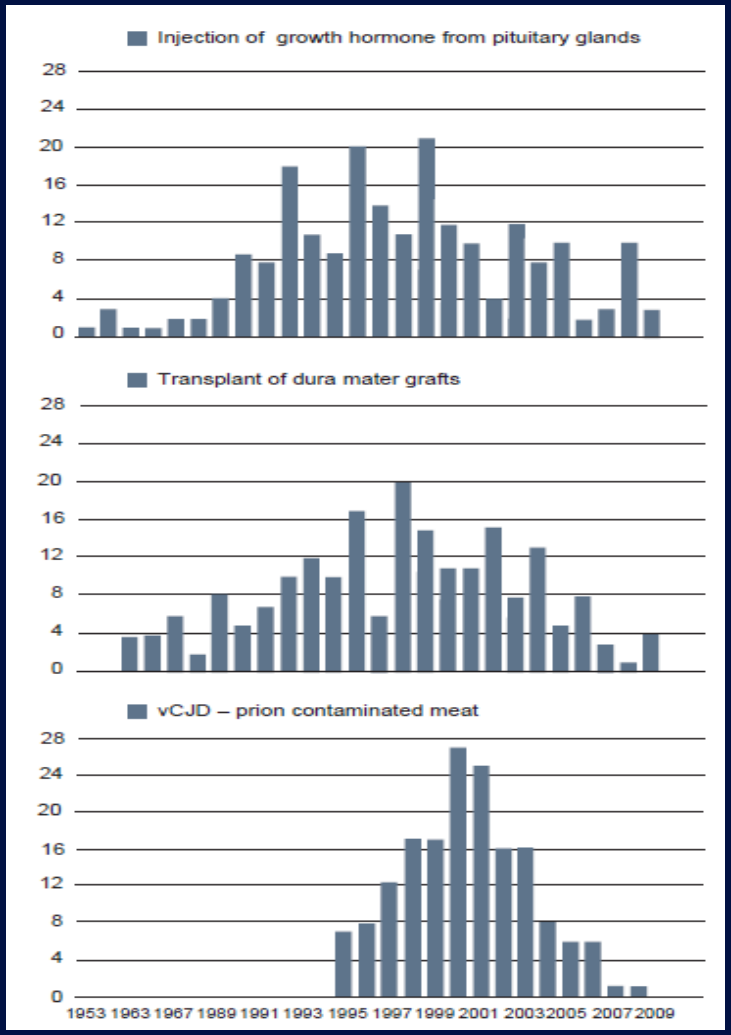
IATROGENTIC PRION DISEASES IN HUMANS

- Kuru: Transmitted by ritualistic cannibalism in New Guinea
- CJD
  - Following ineffectively sterilized depth electrodes during neurosurgery (N=2)
  - Use of contaminated neurosurgical instruments (N=5?)
  - Prion-tainted human growth hormone (N=206, incubation=15 yrs)
  - Prion-tainted dura mater grafts (N=196, incubation=11 yrs)
  - Prion tainted cornea transplants (N<5)
- vCJD
  - Following ingestion of cattle with BSE (N=214, incubation=9 yrs)
  - Following blood transfusions from persons with vCJD
- Not spread by contact (direct, indirect, droplet) or the environment

IATROGENIC CJD AND vCJD





Norrby E. J Intern Med 2011;270:1-14
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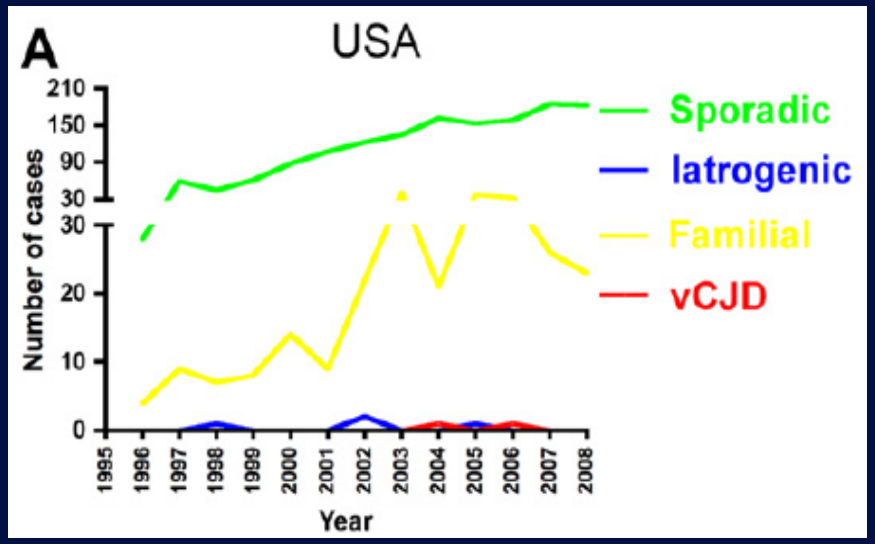
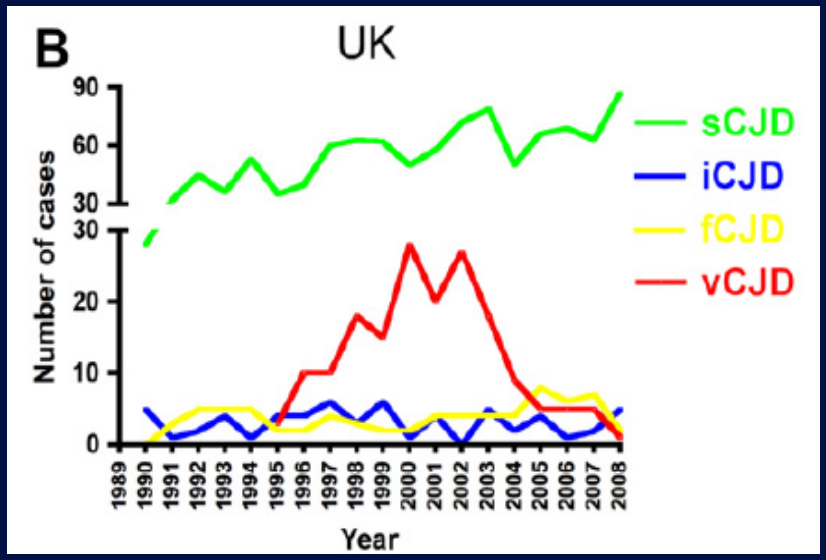
PRION DISEASES IN THE US (1996-2008) AND UK (1989-2008)





US - Green (sporadic, 85%), blue (iatrogenic, 14.7%), yellow (familial, 0.2%), red (vCJD, 0.1%)
UK – Green (sporadic, 78%), blue (iatrogenic, 4%), yellow (familial, 5%), red (vCJD, 13%)
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BSE AND vCJD OUTBREAK

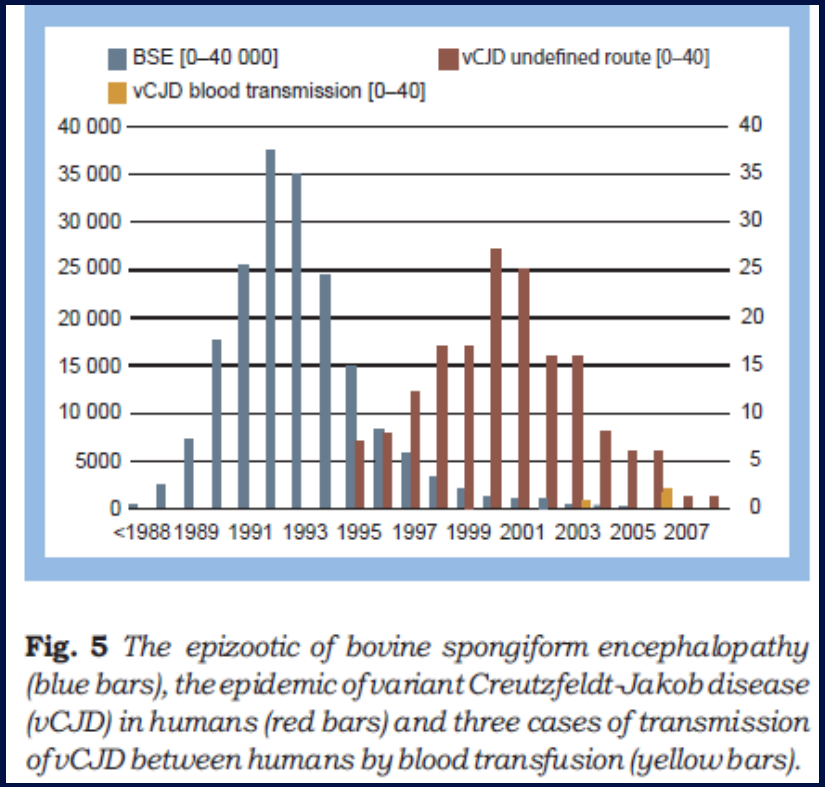
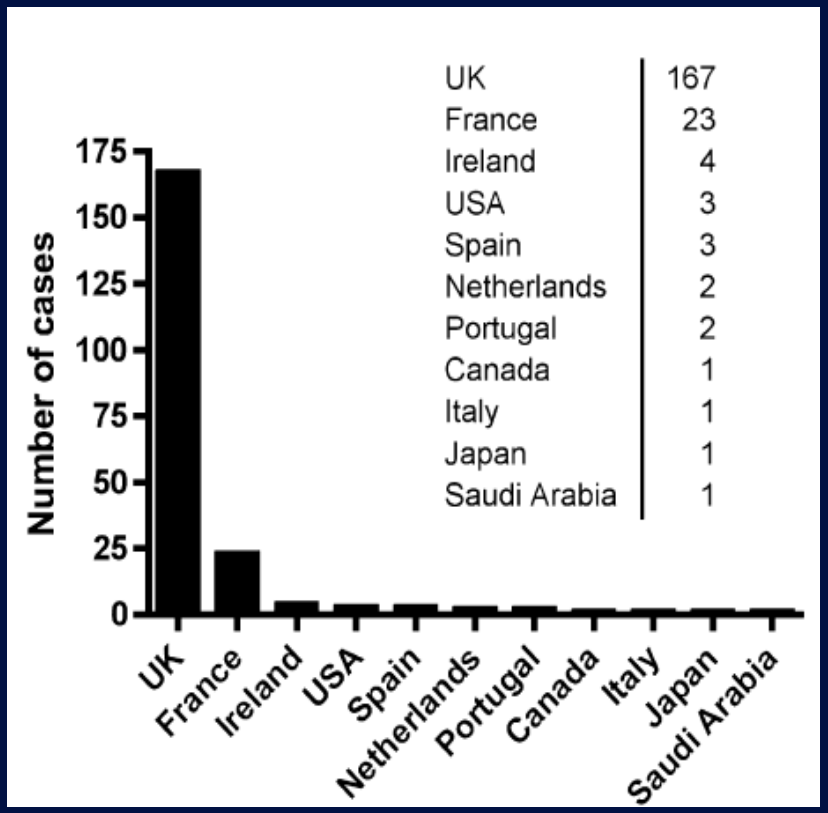


Fig. 5 *The epizootic of bovine spongiform encephalopathy (blue bars), the epidemic of variant Creutzfeldt-Jakob disease (vCJD) in humans (red bars) and three cases of transmission of vCJD between humans by blood transfusion (yellow bars).*

Norrby E. J Intern Med 2011;270:1-14



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CASES OF vCJD CAUSED BY BLOOD TRANSFUSIONS

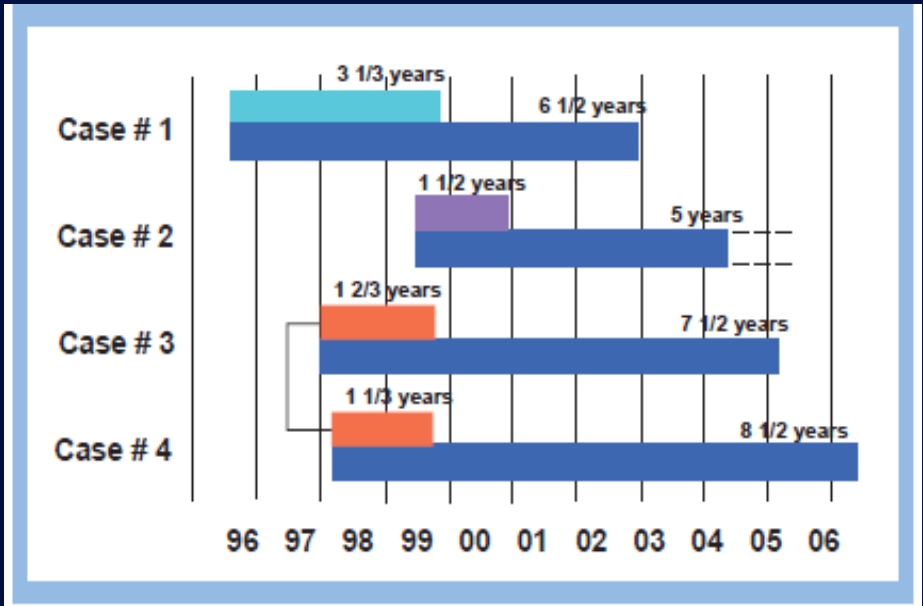

Fig. 6 *Four cases of variant Creutzfeldt-Jakob disease (vCJD) prion infection caused by blood transfusion. Cases 3 and 4 were infected by transfusion of blood from the same donor. In each case, the upper bar shows the time until the donor developed disease and the lower bar the time until disease appeared in the recipient or, as in case 2, vCJD prions were demonstrated in the tissues. Figure kindly provided by Paul Brown.*

Decreasing Order of Resistance of Microorganisms to Disinfectants/Sterilants

Most Resistant

Most Susceptible

Prions (CJD)

Spores (*C. difficile*)

Mycobacteria (TB)

Non-Enveloped Viruses (norovirus)

Fungi (*Aspergillus*)

Bacteria (MRSA, VRE, *Acinetobacter*)

Enveloped Viruses (HIV)

GENERAL INFECTION PREVENTION PRECAUTIONS

- Standard Precautions should be used for patients with CJD; Gloves worn for handling blood and body fluids
- Masks, gowns, and eyewear if exposure is anticipated
- No additional precautions for laundry or handling food utensils
- Patients with prion diseases should not serve as organ donors
- No special precautions for disposal of body fluids or regulated medical waste
- No excess precautions needed for burial

GUIDELINE FOR DISINFECTION AND STERILIZATION OF PRION-CONTAMINATED MEDICAL INSTRUMENTS

Rutala WA, Weber DJ.

Infect Control Hosp Epidemiol 2010;31:107-117

Applies only to CJD (not vCJD)

COMPARATIVE FREQUENCY OF INFECTIVITY IN ORGANS, TISSUE, AND BODY FLUIDS OF HUMANS WITH PRIONS (CJD)

Infectious risk[a]	Tissue
High	Brain (including dura mater), spinal cord, posterior eye, pituitary tissue
Low	Cerebrospinal fluid, liver, lymph node, kidney, lung, spleen, placenta, olfactory epithelium
No risk	Peripheral nerve, intestine, bone marrow, whole blood, leukocytes, serum, thyroid gland, adrenal gland, heart, skeletal muscle, adipose tissue, gingiva, prostate, testis, tears, saliva, sputum, urine, feces, semen, vaginal secretions, milk, sweat

NOTE. Modified from Brown[14] and Brown et al,[15] with information from other studies.[16-20]

[a] High risk indicates a rate of transmission to inoculated animals of >50%; low risk indicates a rate of transmission to inoculated animals of ⩾10%–20% (except for lung tissue, for which transmission is 50%); no risk indicates a rate of transmission to inoculated animals of 0% (several tissues in this category had few tested specimens).

EFFICACY OF STERILIZATION PROCESSES IN INACTIVATING PRIONS

Ineffective ($\leqslant 3$ $\log_{10}$ reduction within 1 hour)	Effective (>3 $\log_{10}$ reduction from 18 minutes to 3 hours)
Autoclave at standard exposure conditions (121°C for 15 minutes)	Autoclave at 121°C–132°C for 1 hour (gravity displacement sterilizer) or 121°C for 30 minutes (prevacuum sterilizer)
Boiling	Autoclave at 134°C for 18 minutes (prevacuum sterilizer)
Dry heat	Autoclave at 134°C for 18 minutes immersed in water
Ethylene oxide	Hydrogen peroxide gas plasma (Sterrad NX)
Formaldehyde	Radiofrequency gas plasma
Hydrogen peroxide gas plasma, Sterrad 100S (ASP)	Sodium dodecyl sulfate, 2%, plus acetic acid, 1%, plus autoclave at 121°C for 15–30 minutes
Ionizing radiation	Sodium hydroxide (NaOH), 0.09 N or 0.9 N, for 2 hours plus autoclave at 121°C for 1 hour (gravity displacement sterilizer)
Microwave	Vaporized hydrogen peroxide, 1.5–2 mg/L
UV light	

NOTE. The same process may be listed as both effective and ineffective because of differences in sterilant concentration, exposure time, temperature, etc, or differences in testing methods. All of these experiments were performed without cleaning. Modified from Rutala and Weber,[16] with information from other studies.[27-52]

EFFICACY OF CHEMICALS IN INACTIVATING PRIONS

Ineffective ($\leqslant 3$ $\log_{10}$ reduction within 1 hour)	Effective (>3 $\log_{10}$ reduction within 1 hour at temperatures of 20°C–55°C)
Acetone	Alkaline detergent (specific formulations)
Alcohol, 50%–100%	Chlorine, >1,000 ppm
Alkaline detergent (specific formulations)	Copper, 0.5 mmol/L, and hydrogen peroxide, 100 mmol/L
Ammonia, 1.0 M	Enzymatic detergent (specific formulations)
Chlorine dioxide, 50 ppm	Guanidine thiocyanate, >3 M
Enzymatic detergent (specific formulations)	Hydrogen peroxide, 59%
Formaldehyde, 3.7%	Peracetic acid, 0.2%
Glutaraldehyde, 5%	Phenolic disinfectant (specific formulation), >0.9%
Hydrochloric acid, 1.0 N	Quaternary ammonium compound (specific formulation)
Hydrogen peroxide, 0.2%, 3%, 6%, 30%, 60%	Sodium dodecyl sulfate, 2%, and acetic acid, 1%
Iodine, 2%	Sodium hydroxide, $\geqslant 1$ N
Ortho-phthalaldehyde, 0.55%	Sodium metaperiodate, 0.01 M
Peracetic acid, 0.2%–19%	
Phenol/phenolics (concentration variable)	
Potassium permanganate, 0.1%–0.8%	
Quaternary ammonium compound (specific formulation)	
Sodium dodecyl sulfate, 1%–5%	
Sodium deoxycholate 5%	
Tego (dodecyl-di[aminoethyl]-glycine), 5%	
Triton X-100, 1%	
Urea, 4–8 M	

NOTE. The same process may be listed as both effective and ineffective because of differences in chemical concentration, exposure time, temperature, pH, etc, or differences in testing methods. All of these experiments were done without cleaning. Modified from Rutala and Weber,[16] with information from other studies.[27-30,32-35,37-39,42,44-49,60,61,64,66,78-88]

CJD: DISINFECTION AND STERILIZATION

- Cleaning
  - Cleaning results in a 4- to 6 -og$_{10}$ reduction of microbes and ~2-log$_{10}$ reduction in protein contamination (prions ?)
  - Some alkaline detergents reduce 5-log$_{10}$ prions; some enzymatic detergents reduce 5-log$_{10}$ prions
- Sterilization
  - Steam sterilization (121^{o} or 132^{o}C) results in a 4- to 7-log$_{10}$ reduction

CATEGORIZATION OF RECOMMENDATIONS

Category	Definition
Category IA	Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies.
Category IB	Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies, and a strong theoretical rationale.
Category II	Suggested for implementation and supported by suggestive clinical or epidemiologic studies or by a theoretical rationale.
No recommendation	Unresolved issue. Practices for which insufficient evidence or no consensus exists regarding efficacy.

CAVEATS ON INTERPRETING PRION STERLIZATION DATA

- In general, studies have not incorporated a cleaning procedure prior to sterilization (cleaning reduces protein contamination by 4-6 $\log_{10}$)
- Prion studies have been performed with tissue homogenates, and the protective effect of tissue may explain, in part, why the CJD agent is difficult to inactivate
- Results of inactivation studies of prions have been variable because of the use of differing methods, which may have varied according to prion strain, prion concentration, prion detection, tissue or composition of the brain material tested, animals tested, surfaces tested, testing method, duration of follow-up of inoculated animals, exposure container, method of calculating log10 reductions in infectivity, concentration of the disinfectant at the beginning and end of the experiment, cycle parameters of the sterilizer, type of sterilizer, and exposure conditions.

RECOMMENDATIONS FOR PROCESSING CJD-CONTAMINATED PATIENT-CARE EQUIPMENT

- Do NOT allow instruments to become dry after use. Keep instruments moist (either wet by immersion in water or a detergent with prionicidal activity or, in not possible, by use of a wet cloth draped over the instruments) after use and during storage or transport prior to decontamination. Instruments should be decontaminated as soon as possible after use. Decontaminate instruments in a mechanical washer with detergent (preferably one that has prionicidal activity), and after decontamination, sterilize by one of the methods shown to be effective {IA}
- Use one of the recommended procedures to reprocess critical or semicritical items that have been contaminated with high-risk tissue from high-risk patients {IB}
- Clean devices that have been constructed so that cleaning procedures that result in effective tissue removal and then sterilize these devices by one of the methods listed on the next slide {IB}

STERILIZATION OPTIONS FOR PROCESSING CJD CONTAMINATED PATIENT-CARE EQUIPMENT

Listed in Order of Preference (High Risk Tissue)

1. Autoclave at 134 ^{o}C for $\geq$18 minutes in a prevacuum sterilizer
2. Autoclave at 132 ^{o}C for 1 hour in a gravity displacement sterilizer
3. Immerse in 1 N NaOH for 1 hour; remove and rinse in water, then transfer to an open pan and autoclave (121 ^{o}C for 1 hour in a gravity displacement sterilizer or 134 ^{o}C in a porous or prevacuum sterilizer) for 1 hour
4. Immerse in 1 N NaOH for 1 hour and heat in a gravity displacement sterilizer 121 ^{o}C for 30 minutes (to minimize autoclave and operator exposure to gaseous NaOH when immersing instruments and autoclaving in NaOH, the use of containers with a rim and lid designed for condensation to collect and drip back into the an is recommended); then rinse and subject to routine sterilization

RECOMMENDATIONS FOR PROCESSING CJD-CONTAMINATED PATIENT-CARE EQUIPMENT

- Discard devices that are impossible to clean {II}
- Do not use flash sterilization for reprocessing instruments {IB}
- Discard items that permit only low-temperature sterilization (e.g., ethylene oxide) {IB}
- No recommendation can be made regarding the use of low-temperature technologies that have shown prionicidal activity, such as specific type of hydrogen gas plasma, and vaporized hydrogen peroxide as data are limited and require corroboration {unresolved}
- Recall contaminated items (e.g., medical devices used for brain biopsy before diagnosis) that have not been processed according to there recommendations and appropriately reprocess them {II}

RECOMMENDATIONS FOR PROCESSING CJD-CONTAMINATED PATIENT-CARE EQUIPMENT

- To minimize patient exposure to neurosurgical instruments later determined to have been used on a patient with CJD, use the sterilization guidelines above for neurosurgical instruments used on patients undergoing brain biopsy when a specific lesion (e.g., a suspected tumor or abscess) has not been demonstrated by CT or MRI. Alternatively use disposable neurosurgical instruments on such patients {IB}

RECOMMENDATIONS FOR CLEANING ENVIRONMENTAL SURFACES AND NONCRITICAL DEVICES

- Clean noncritical environmental surfaces contaminated with high-risk tissues (e.g., a lab surface in contact with brain of a CJD-infected person) with a detergent and then spot decontaminate these surfaces with 1:5 to 1:10 dilution of sodium hypochlorite (i.e., bleach; a 1:5 dilution of 5.25-6.15% sodium hypochlorite provides 10,500-12,300 ppm chlorine), ideally for a contact time of at least 15 minutes. To minimize environmental contamination, use disposable plastic-backed cover sheets on work surfaces {IB}
- Clean and then disinfect noncritical equipment that has been decontaminated with high-risk tissue using a 1:5 to 1:10 dilution of sodium hypochlorite or 1 N NaOH, depending on material compatibility. Ensure that all contaminated surfaces are exposed to the disinfectant {IB}

RECOMMENDATIONS FOR REPROCESSING DEVICES OR SURFACES CONTAMINATED WITH LOW-RISK TISSUES

- No recommendation can be made regarding the use of the procedures listed for reprocessing of critical or semicritical medical devices that that been contaminated with low-risk tissues {unsolved}
- Use only standard disinfection to process environmental surfaces contaminated with low-risk tissues {IB}

RECOMMENDATIONS FOR REPROCESSING DEVICES OR SURFACES CONTAMINATED WITH NO-RISK TISSUES

- Use the following recommended procedures to reprocess critical or semicritical medical devices that have been contaminated with no-risk tissue:
- Clean and either disinfect or sterilize these devices using conventional protocols of heat or chemical sterilization or high-level disinfection {IB}
- Use standard cleaning and high-level disinfection protocols for reprocessing endoscopes (except neurosurgical endoscopes with central nervous system contact) because these devices can become contaminated only with no-risk tissues {IB}
- Use standard disinfection to process noncritical equipment and noncritical environmental surfaces that have been contaminated with no-risk tissues or fluids {use disinfectants recommended by OSHA for decontaminating blood-contaminated surfaces){IB}

OTHER RECOMMENDATIONS

- If the operating surgeon believes that the patient is at risk for a TSE such as CJD, he or she should communicate that information to the operating room charge nurse, the anesthesiology staff, the neuropathology or clinical pathology laboratory staff, the risk manager, and the infection preventionist. Train clinicians and reprocessing technicians on how to properly tag the equipment and train them in the special prion reprocessing protocols. Because standard decontamination of tissue sample (e.g., with formalin) or specimens may not inactivate CJD, all tissue samples should be handled with the use of standard precautions (i.e., gloves). Tag equipment that requires special prion reprocessing after use. The tissue samples and specimens should be labeled as a "biohazard" and as "suspected CJD" before being sent to the laboratory {IB}

OTHER RECOMMENDATIONS

- A quality control program should be established and maintained that enhances healthcare personnel performance (orientation, continuing education, and documented competency) and monitors disinfection and sterilization efficacy (e.g., sterilizer maintenance and repair history; sterilization process monitoring by means of physical, chemical, and biological monitors; and disinfectant concentration) {Ib}

vCJD: Disinfection and Sterilization

- To date no reports of human-to-human transmission of vCJD by tissue but 4 cases by blood transfusion
- Unlike CJD, vCJD detectable in lymphoid tissues (e.g., spleen, tonsils, thymus, appendix) and prior to onset of clinical illness
- Special prion reprocessing (or single use instruments) proposed in the UK in dental, eye, or tonsillar surgery on high risk patients for CJD or vCJD
- If epidemiological and infectivity data show these tissues represent a transmission risk then special prion reprocessing could be extended to these procedures

THANK YOU!!