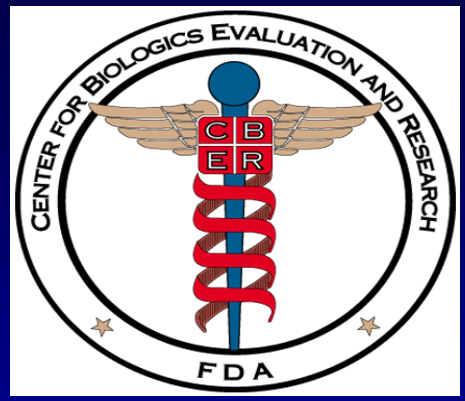

Presumptive Transfusion Transmission of Variant CJD: Implications for the Safety of Blood and Blood Products

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Presumptive Transfusion Transmission of Variant CJD: Implications for the Safety of Blood and Blood Products

- Case description
- Negative epidemiological evidence for association of CJD with blood exposure
- Evidence suggesting that blood of humans or animals with TSE may be infectious; basis for increased concern over vCJD
- Current safeguards for blood products

A Case of Presumptive Transfusion-Transmission of vCJD Reported in the UK

(from R Will and others, UK CJD Surveillance Unit, announced to UK Parliament on 17 Dec 2003)

March 1996

- A clinically healthy young blood donor donated Whole Blood to the UK National Blood Service.
- Packed RBC—not leukoreduced—were transfused into an older surgical patient (later found to be PRNP met 129-homozygous).

About March 1999 (three years post donation)

- The donor developed signs of variant CJD and later died; the diagnosis of vCJD was confirmed after autopsy.
- The UK Transfusion Medicine Epidemiology Review (TMER) enrolled recipient (with 14 other recipients of vCJD-implicated blood components) in an on-going “look-back” type of study.

December 2003 (about 6.5 years post transfusion)

- The recipient died; postmortem diagnosis was typical vCJD.
- The recipient's age-adjusted food-borne risk of vCJD was estimated by UK authorities to have been ~ 1:40,000

Presumptive Transfusion-Transmission of vCJD Reported in the UK: Evidence for Transmission

Transfusion-transmission cannot be proved in this case because the recipient is assumed to have had concurrent risk of BSE exposure from UK beef. However, transfusion–transmission is presumed because:

- -The random risk of vCJD is estimated at only 1:40,000
- -The recipient was far older than the median case of vCJD (second eldest known case) making the case less likely to be food-related
- -The incubation period post-transfusion was compatible with transfusion as the exposure event
- -The recipient had the expected Met/Met polymorphism

Epidemiological Studies of Exposure to Blood as a Risk Factor for CJD: No Evidence of Increased Risk (Adapted from Schonberger L [CDC]. Presentation to PHS AC BSA Jan 1998)

- Case reports of sporadic CJD attributable to blood: None
- National mortality surveillance:
  (CDC: 4,164 cases of CJD during 18 yr from 1979-96)
  - No increasing incidence (~$1/10^6$/yr age-adjusted)
  - No Dx hemophilia, thalassemia, sickle cell in cases
  - No CJD Dx in persons < 19 yr old
- **Hemophilia survey**
  (CDC-Hemophilia Treatment Centers)
  - No clinical Dx of CJD in >12,000 patients through 1998
  - No histopathol Dx CJD 30 autopsies (mean age 39 yr)

Epidemiological Studies of Exposure to Blood as a Risk Factor for CJD: No Evidence for Increased Risk (Adapted from Schonberger L [CDC]. Presentation to PHS AC BSA Jan 1998)

- Case-control studies: All negative for increased risk
  - 6 studies, several large size, different methods used to reduce bias, done in several countries
- **Recipients of blood components from sCJD donors**

  ARC-CDC-Nat'l Blood Donor Resource Center
  - No CJD Dx in 196 recipients of blood components from 15 CJD donors
  - 42 recipients lived > 5 yr after transfusion: no CJD

  In a similar European study, 13 recipients lived >10 yr and 8 lived > 15 yr after transfusion: no CJD

Epidemiological Studies of Exposure to Blood as a Risk Factor for CJD: No Evidence for Increased Risk (Adapted from Schonberger L [CDC]. Presentation to PHS AC BSA Jan 1998)

- Recipients of vaccines containing excipient albumin (followed through 1996):
  - >38 million children aged <5 yr received a vaccine containing excipient albumin at some time between 1967 and 1986.
  - By end of 1996 they were aged 11 to 19 yr.
  - No CJD was diagnosed in any recipient.

Summary of Evidence Suggesting that Blood of Humans or Animals with TSE May be Infectious

1. **Human epidemiological studies**: **most negative; however**

   one presumptive case of vCJD in RBC recipient

2. **Experimental studies**: **not all reassuring**

- **Human CJD blood**
  - into primates: all negative
  - into rodents: a few positive (±)
  - (**spleen, liver, nodes into primates: some positive**)
- **Animal TSE blood**
  - BSE cow, scrapie sheep, goat into rodents: negative
  - Mink encephalopathy into mink: negative
  - Rodent experimental CJD/scrapie/BSE into rodents:
    several models positive (low titers <100 icLD50/ml)
  - **Sheep experimental BSE blood into sheep: positive**
  - **Sheep natural scrapie blood into sheep: positive**

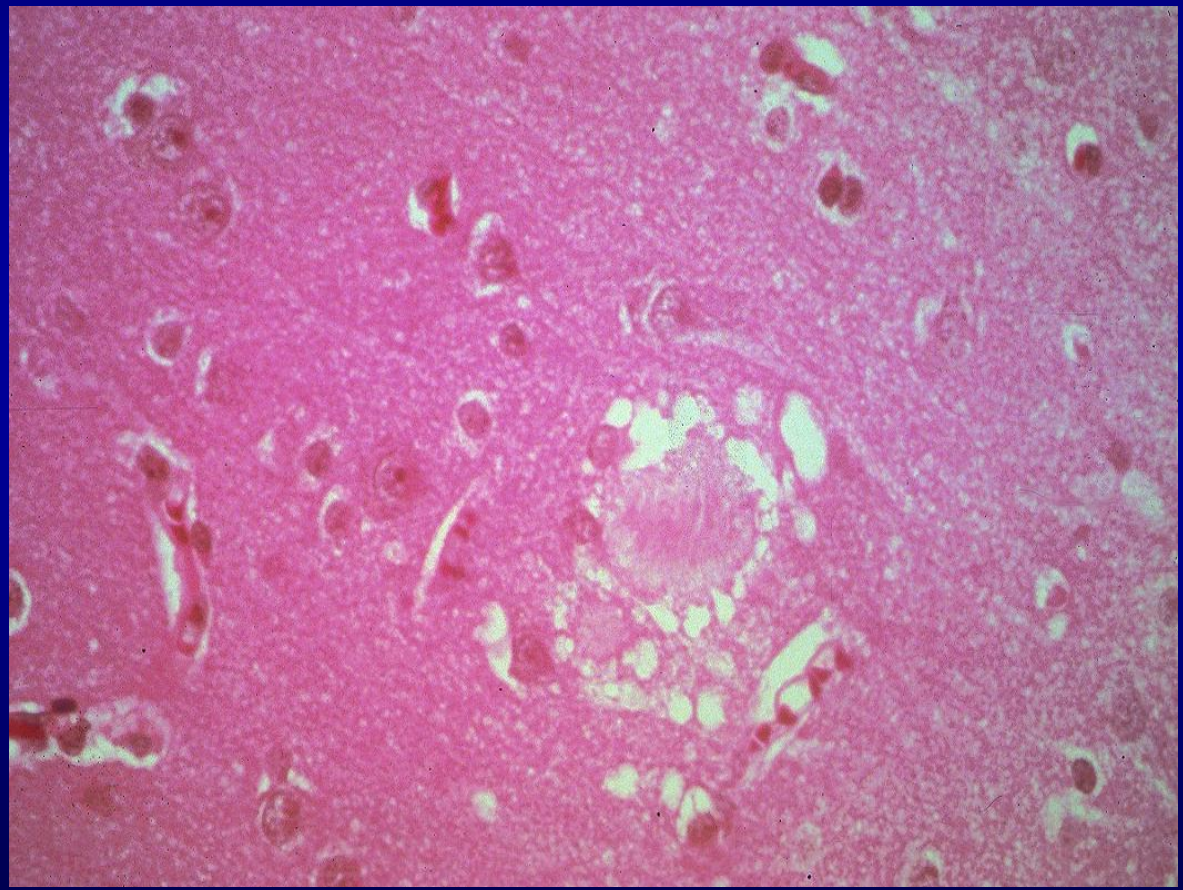
Variant CJD: Reasons for Greater FDA Concern about Potential Infectivity of Blood

- Lymphoid tissues of patients with vCJD contain much more protease-resistant prion protein than do those of patients with conventional forms of CJD. Infectivity of those tissues is not yet clear. (Note: Lymphoid tissues of some patients with conventional forms of CJD have been infectious [Brown P et al. Ann Neurol 1994;35:513].)

  Implication: Blood, containing lymphoid cells, might be more infectious in vCJD than in other forms of CJD.

- vCJD differs from sCJD in clinical and histopathological features; distribution of infectivity in patients with sCJD might not be predictive for vCJD.
- vCJD is a new emerging disease not found in the USA except in one long-time UK resident.
- **A presumptive transfusion-transmitted case of vCJD has been reported recently.**

vCJD: Florid Plaque in Brain (not seen in other forms of CJD)



Comparison of Sporadic and Variant CJD

(First report, modified from R Will & al. Lancet 1996;347:921)

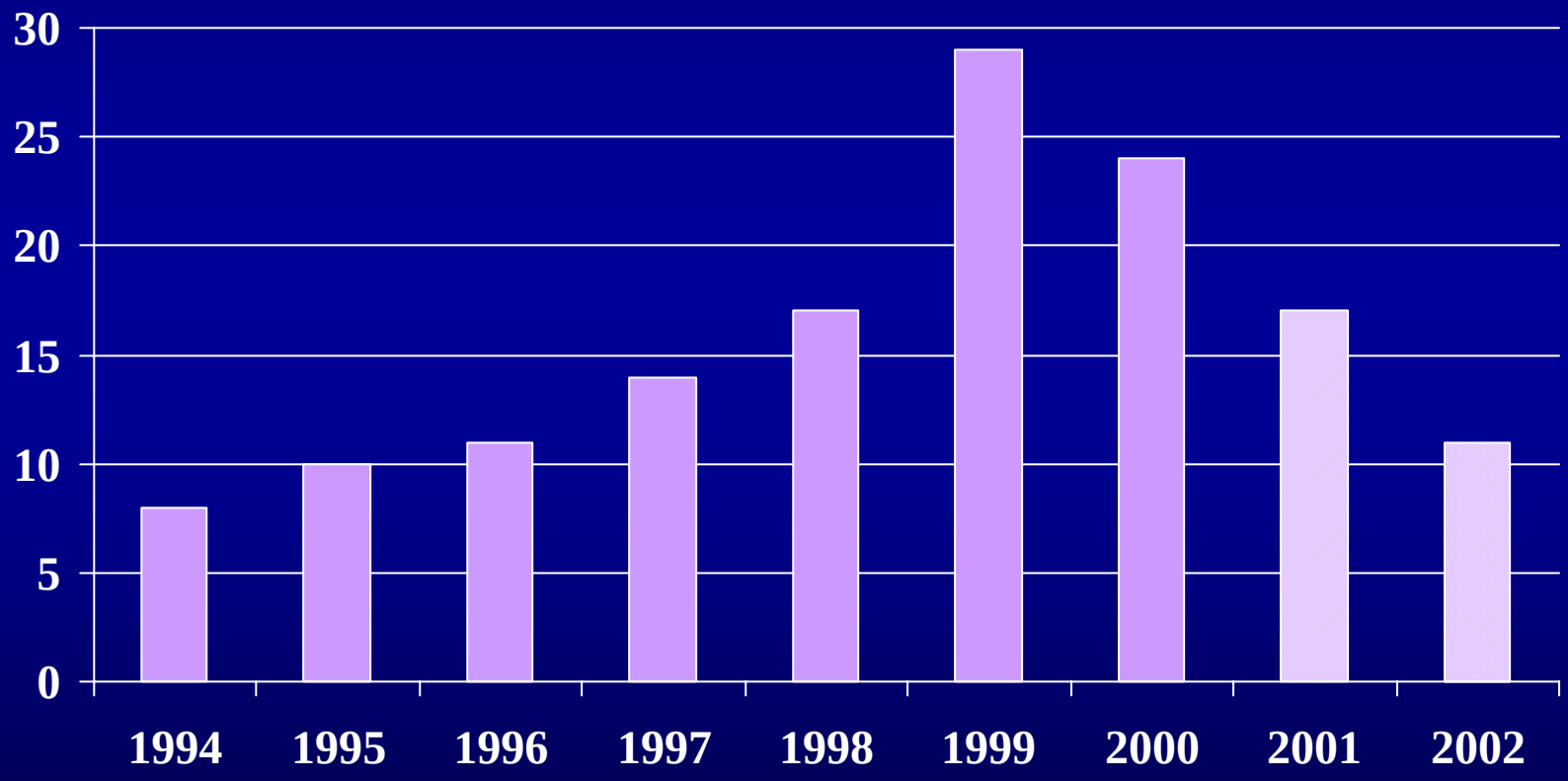
- **Sporadic CJD**
  - Mean age ~65 yr
  - Mean duration ~ 4 mo
  - Presentation: confusion, sometimes ataxia
  - EEG: periodic suppression-burst, slowing
  - *PRNP* codon 129 met/met ~80% (vs ~50% gen'l pop.)
  - Amyloid plaques ~15% (rarely "florid")
  - PrP^{sc} size, glycoform abundance: not BSE type
- **Variant CJD (1st 10 cases)**
  - Mean age ~29yr (19 to 52)
  - Mean duration ~ 12 mo
  - Presentation: abnormal behavior, dysesthesia
  - EEG: slowing without periodic suppression-burst
  - *PRNP* codon 129 met/met 100%
  - Amyloid plaques 100% ("florid")
  - PrP^{sc} size, glycoform abundance=BSE type

Cases of vCJD Worldwide
(as of Dec 2003)

UK	143
France	6
Republic of Ireland	1
Italy	1
USA	1
Canada	1

Cases of vCJD in France and Italy had no history of travel to UK. All others were current or former UK residents.

Variant CJD: UK Cases with Onset by Year
(R Will, unpublished Oct 2003)



FDA Recommended Safeguards for Minimizing Risk of vCJD from Blood Products: Deferral of donors based on risk of BSE exposure

- Guidance to Industry 1999
  - Donor deferrals undertaken concurrent with a commitment to monitor the blood supply (estimated loss 2%)
  - Donor deferrals recommended for:
    - travel/residence in U.K. for ≥six months between 1980- 1996
    - Receipt of bovine insulin sourced in the U.K. after 1980
  - Product retrieval recommended if donor later discovered to have vCJD

FDA Recommended Safeguards for Minimizing Risk of vCJD from Blood Products: Deferral of donors based on risk of BSE exposure

- Guidance to Industry 2002
  - Added donor deferrals for risk of BSE exposure in Europe
  - Tightened U.K. donor deferral
  - Called for implementation in two phases by 5/02 and 10/02
  - Estimated 90% reduction in risk with cumulative loss of 7% of donor base

FDA Recommended Safeguards for Minimizing Risk of vCJD from Blood Products: Deferral of donors based on risk of BSE exposure

- Donor currently are deferred based on the following criteria:
  - ≥ 3 months residence/travel in U.K. 1980 - 1996
  - ≥ 5 years residence/travel in Europe
    - ➢For donors of Source Plasma this criterion applies only to France (5-10% consumption of UK beef)
  - ≥ 6 months on certain US military bases in Europe between 1980-1990 or 1980-1996 (up to 35% UK beef consumed)
  - Transfusion in the U.K. 1980 – present
  - Receipt of bovine insulin sourced in the U.K. after 1980

FDA Recommended Safeguards for Minimizing Risk of vCJD from Blood Products: Validation of TSE Clearance for Plasma Derivatives

- Several plasma derivative manufacturers have demonstrated significant clearance of model TSE agents at a number of steps used in manufacturing different products
- Questions remain how to assess the significance of these data, e.g.
  - How should clearance be assayed (in vitro vs. in vivo?)
  - How much reduction of infectivity (or prion protein) is “enough” to assure safe products?
  - Which clearance steps are additive and which are not?
  - How many “orthogonal” clearance steps are necessary?

Methodological Challenges in Studies of Clearance of TSE Agents

- What source of infectivity should be used?
  - Animal model (characterized; not known to be have different properties from human infectious agent- evidence of similarities; precedent for models (HCV)
  - Human
- What "form" of infectious agent is most relevant to blood transmission?
  - Brain
  - Subcellular membrane fractions
  - Acellular material (fibrils)
  - Blood (very low infectivity)
- Limits of assay sensitivity

FDA Recommended CJD Risk Labeling for Plasma Derivatives

Current recommended labeling (See Guidance 01/09/02; http://www.fda.gov/cber/gdlns/cjdvcjd.htm)

> "**Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease agent."**

In February 2003, TSEAC endorsed FDA consideration of labeling claims for TSE clearance in plasma derivatives based upon specific demonstration of TSE removal during manufacturing

Cautionary Notes about vCJD Risk Reduction in Blood Products

- Deferral of all donors who have potentially been exposed to BSE would make blood and plasma supplies unsustainable
- People with coagulation disorders and primary immune deficiencies have lifelong exposure to products
- While the vCJD epidemic is diminishing, it is still not known whether
  - Additional presumptive transfusion cases will arise
  - Whether people with Met/val or val/val at prion protein codon 129 will manifest vCJD with a longer incubation period and/or different clinical/pathological presentation

Additional FDA Actions to Address Product Risks from BSE

- Maintains updated lists of bovine materials used to make medical products
- Encourages manufacturers to eliminate use of bovine-derived materials where possible
- Conducts research on methods to remove and/or inactivate TSE's on surfaces
  - TSEAC review of facility cleaning methods 7/18/03
- Will examine its current policies with TSEAC in light of the recent presumptive case of transfusion transmission of vCJD, and the first U.S. case of BSE (February 12-13, 2004)

TSEAC February 12-13, 2004

http://www.fda.gov/cber/advisory/tse/tse0204.htm

- Informational presentations on risk of transfusion-transmission of vCJD
- Update on BSE in the U.S.
- Models for risk-based sourcing of bovine materials in FDA-regulated medical products
- Discussion of current methods to minimize risks of TSE agents in FDA regulated medical products