17 Amouyel P, Vidal O, Launay JM, Laplanche JL. The apolipoprotein E alleles as major susceptibility factors for Creutzfeldt-Jakob disease. *Lancet* 1994; 344: 1315–18.

18 Jackson GS, Beck JA, Navarrete C, et al. *HLA-DQ7* antigen and resistance to variant CJD. *Nature* 2001; 414: 269–70.

19 Pepys MB, Bybee A, Booth DR, et al. MHC typing in variant Creutzfeldt-Jakob disease. *Lancet* 2003; 361: 487–89.

20 Hadlow WJ. Scrapie and kuru. *Lancet* 1959; 274: 289–90.

21 Gajdusek DC, Gibbs CJ Jr, Alpers MP. Experimental transmission of a Kuru-like syndrome to chimpanzees. *Nature* 1966; 209: 794–96.

22 Gajdusek DC. Unconventional viruses and the origin and disappearance of kuru. *Science* 1977; 197: 943–60.

23 Glasse R. Cannibalism in the Kuru region of New Guinea. *Trans N Y Acad Sci* 1967; 29: 748–54.

24 Lindenbaum S. Kuru sorcery: disease and danger in the New Guinea Highlands. Palo Alto, CA, USA: Mayfield, 1979.

25 Brown P, Gajdusek DC. Survival of scrapie virus after 3 years' interment. *Lancet* 1991; 337: 269–70.

26 Klitzman RL, Alpers MP, Gajdusek DC. The natural incubation period of kuru and the episodes of transmission in three clusters of patients. *Neuroepidemiology* 1984; 3: 3–20.

27 Collinge J. Variant Creutzfeldt-Jakob disease. *Lancet* 1999; 354: 317–23.

28 Brown P, Preece M, Brandel JP, et al. Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000; 55: 1075–81.

29 Barlow RM, Middleton DJ. Dietary transmission of bovine spongiform encephalopathy to mice. *Vet Rec* 1990; 126: 111–12.

30 Wells GAH, Hawkins SAC, Green RB, et al. Preliminary observations on the pathogenesis of experimental bovine spongiform encephalopathy (BSE): an update. *Vet Rec* 1998; 142: 103–06.

31 Lloyd SE, Uphill JB, Targonski PV, Fisher EM, Collinge J. Identification of genetic loci affecting mouse-adapted bovine spongiform encephalopathy incubation time in mice. *Neurogenetics* 2002; 4: 77–81.

32 Stephenson DA, Chiotti K, Ebeling C, et al. Quantitative trait loci affecting prion incubation time in mice. *Genomics* 2000; 69: 47–53.

33 Ghani AC, Ferguson NM, Donnelly CA, Anderson RM. Predicted vCJD mortality in Great Britain. *Nature* 2000; 406: 583–84.

34 D'Aignaux JNH, Cousens SN, Smith PG. Predictability of the UK variant Creutzfeldt-Jakob disease epidemic. *Science* 2001; 294: 1729–31.

35 Collinge J, Palmer MS, Dryden AJ. Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. *Lancet* 1991; 337: 1441–42.

36 Schachter F, Faure-Delanef L, Guenot F, et al. Genetic associations with human longevity at the *APOE* and *ACE* loci. *Nat Genet* 1994; 6: 29–32.

No. 16

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2006. 7. 7	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況	Saa P, Castilla J, Soto C. Science. 2006 Jul 7;313(5783):92-4.	公表国
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社)			米国

研究報告の概要

○血中におけるプリオンの発症前検出

プリオンは伝達性海綿状脳症の病因となるタンパク様の感染性物質であると考えられている。PrP^{Sc}は、疾患の唯一の確認された代理マーカーであり、その検出は感染の拡大を最小限に抑えるために不可欠である。スクレイピーに感染したハムスターの血中から、疾患の発症前の期間の大半で、生化学的にPrP^{Sc}を検出した。潜伏期間の早期には、PrP^{Sc}はプリオンの末梢複製によって産生される傾向が強かった。一方、発症期には血液中のPrP^{Sc}は脳から漏出していた。感染したものの臨床症状を呈していない動物の血液中のプリオンの生化学的検出が可能になることで、TSEの早期の非侵襲的診断が見込まれる。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
スクレイピーに感染したハムスターの血中から、疾患の発症前の期間の大半で、生化学的にPrP^{Sc}を検出したとの報告である。	今後も引き続き、プリオン病に関する新たな知見及び情報の収集に努める。

8. A. Dagkessamanskaia *et al.*, *Mol. Microbiol.* 51, 1071 (2004).
9. S. Peterson *et al.*, *Mol. Microbiol.* 51, 1051 (2004).
10. I. Mortier-Barrière, A. de Saizieu, J. P. Claverys, B. Martin, *Mol. Microbiol.* 27, 159 (1998).
11. E. V. Pestova, L. S. Håvarstein, D. A. Morrison, *Mol. Microbiol.* 21, 853 (1996).
12. P. Luo, D. A. Morrison, *J. Bacteriol.* 185, 349 (2003).
13. B. Martin, M. Prudhomme, G. Alloing, C. Granadel, J. P. Claverys, *Mol. Microbiol.* 38, 867 (2000).
14. To monitor antibiotic-induced competence, cells were incubated in C+Y medium with an initial pH value adjusted so that spontaneous competence induction remained a rare event (see supporting online material).
15. D. E. Grove, S. Willcox, J. D. Griffith, F. R. Bryant, *J. Biol. Chem.* 280, 11067 (2005).
16. S. C. Kowalczykowski, *Annu. Rev. Biophys. Biophys. Chem.* 20, 539 (1991).
17. J. W. Little, *Proc. Natl. Acad. Sci. U.S.A.* 81, 1375 (1984).
18. B. Martin, P. García, M. P. Castanié, J. P. Claverys, *Mol. Microbiol.* 15, 367 (1995).
19. J. W. Beaber, B. Hochhut, M. K. Waldor, *Nature* 427, 72 (2004).
20. I. Phillips, E. Culebras, F. Moreno, F. Baquero, *J. Antimicrob. Chemother.* 20, 631 (1987).
21. C. Miller *et al.*, *Science* 305, 1629 (2004).
22. C. Levine, H. Hiasa, K. J. Marians, *Biochim. Biophys. Acta* 1400, 29 (1998).
23. R. A. VanBogelen, F. C. Neidhardt, *Proc. Natl. Acad. Sci. U.S.A.* 87, 5589 (1990).
24. K. Drlica, X. Zhao, *Microbiol. Mol. Biol. Rev.* 61, 377 (1997).
25. M. Cashel, D. R. Gentry, V. J. Hernandez, D. Vinella, in *Escherichia coli and Salmonella typhimurium: Cellular and Molecular Biology*, F. C. Neidhardt, Ed. (American Society for Microbiology Press, Washington, DC, 1996), pp. 1458–1496.

26. We thank D. Lane for critical reading of the manuscript. This work was supported in part by European Union grant QLK2-CT-2000-00543.

Supporting Online Material

www.sciencemag.org/cgi/content/full/313/5783/89/DC1
Materials and Methods
Figs. S1 to S4
Tables S1 and S2
References

27 March 2006; accepted 1 June 2006
10.1126/science.1127912

Presymptomatic Detection of Prions in Blood

Paula Saá,[1,2] Joaquín Castilla,[1] Claudio Soto[1]*

Prions are thought to be the proteinaceous infectious agents responsible for transmissible spongiform encephalopathies (TSEs). PrP^{Sc}, the main component of the infectious agent, is also the only validated surrogate marker for the disease, and its sensitive detection is critical for minimizing the spread of the disease. We detected PrP^{Sc} biochemically in the blood of hamsters infected with scrapie during most of the presymptomatic phase of the disease. At early stages of the incubation period, PrP^{Sc} detected in blood was likely to be from the peripheral replication of prions, whereas at the symptomatic phase, PrP^{Sc} in blood was more likely to have leaked from the brain. The ability to detect prions biochemically in the blood of infected but not clinically sick animals offers a great promise for the noninvasive early diagnosis of TSEs.

Prion diseases, also called transmissible spongiform encephalopathies (TSEs), are a group of fatal and infectious neurodegenerative diseases, including Creutzfeldt-Jakob disease (CJD) in humans and bovine spongiform encephalopathy (BSE), scrapie, and chronic wasting disease (CWD) in animals. Prions are composed mainly or exclusively of the misfolded prion protein (PrP^{Sc}) (*1*), which replicates in the body, transforming the normal prion protein (PrP^{C}) into more of the misfolded isoform.

Although prion diseases are rare in humans, the established link between a new variant form of CJD (vCJD) and BSE (*2*–*4*) has raised concern about a potential epidemic in the human population. Over the past few years, BSE has become a substantial health problem affecting many countries (*5*), and it seems now apparent that vCJD can be iatrogenically transmitted from human to human by blood transfusion (*6*, *7*). Exacerbating this state of affairs is the lack of a reliable test to identify individuals incubating the disease during the long and silent period from the onset of infection to the appearance of clinical symptoms (*8*–*10*).

PrP^{Sc} is not only the main component of the infectious agent and the most likely cause of the disease, but it is also the only validated surrogate marker for TSEs (*9*). However, PrP^{Sc} concentration is high enough for routine biochemical detection only in the brain and some lymphoid tissues at a time close to the symptomatic stage of the disease (*9*). The development of highly sensitive presymptomatic assays for the biochemical detection of PrP^{Sc} is critical for minimizing the spread of the disease (*9*). One important aim in prion diagnosis is the noninvasive and presymptomatic biochemical detection of PrP^{Sc} in biological fluids, particularly using blood, a fluid known to contain infectivity even before the onset of clinical signs (*6*, *11*, *12*).

PrP^{Sc} has been detected in the blood of sick animals by means of the protein misfolding cyclic amplification (PMCA) technology (*13*). PMCA produces accelerated prion replication, which dramatically amplifies the quantity of PrP^{Sc} present in a sample (*14*, *15*). In a cyclical process, large quantities of PrP^{C} are converted into the misfolded form triggered by the presence of minute and otherwise undetectable amounts of PrP^{Sc}. The method is highly specific for the detection of PrP^{Sc} and leads to a several-million-fold increase in sensitivity as compared to that of standard Western blot assays (*13*).

In order to evaluate the application of PMCA for the detection of prions in blood during the presymptomatic phase, 46 hamsters were inoculated intraperitoneally with 10% brain homogenate of the 263K scrapie strain, and 38 control animals were injected with phosphate-buffered saline (PBS). At different times during the incubation period, groups of animals were killed, blood was collected, and the buffy coat fraction was separated (*13*). Samples of the buffy coat were resuspended directly on healthy hamster brain homogenate and subjected to 144 PMCA cycles. Three different aliquots were tested from each sample. To refresh the substrate, after a round of PMCA cycling, samples were diluted 10-fold into normal brain homogenate, followed by another round of 144 PMCA cycles. This procedure was repeated seven times, because according to our results, this enables the detection of 20 to 50 molecules of monomeric hamster PrP, which seems to correspond to a single unit of infectious oligomeric PrP^{Sc} (*16*).

The first group of hamsters was killed 2 weeks after intraperitoneal inoculation. None of the five infected or control animals showed any detectable quantity of PrP^{Sc} in their blood (Fig. 1 and Table 1). Thus, the PrP^{Sc} present in the inoculum disappeared to undetectable levels during the first few days after inoculation. PrP^{Sc} was, however, readily detectable in blood 1 week later (20 days after inoculation) in 50% of the animals infected but in none of the controls (Fig. 1 and Table 1). The highest percentage of positive animals during the presymptomatic phase was observed 40 days after intraperitoneal inoculation, in which the sensitivity of PrP^{Sc} detection was 60%. After 60 days, the detection of PrP^{Sc} in blood became harder. Indeed, only one out of five animals scored positive at 70 days, whereas none of the five infected hamsters had detectable PrP^{Sc} in their blood 80 days after inoculation (Table 1). At the symptomatic stage, which in this experiment was at 114.2 ± 5.6 days, 80% of animals had PrP^{Sc} in their blood (Fig. 1). We never detected a false positive result in any of the 38 control samples analyzed (Table 1).

The distribution of PrP^{Sc} detection at different times of the incubation period showed

[1]George and Cynthia Mitchell Center for Alzheimer's Disease Research, Departments of Neurology, Neuroscience and Cell Biology, and Biochemistry and Molecular Biology, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555–0646, USA. [2]Centro de Biología Molecular, Universidad Autónoma de Madrid, Madrid, Spain.

*To whom correspondence should be addressed. E-mail: dsoto@utmb.edu

an interesting trend (Fig. 2). A first peak of PrP^{Sc} detection was observed early during the presymptomatic phase, between 20 and 60 days after inoculation. The peripheral administration of prions is known to result in an early phase of replication in lymphoid tissues and the spleen, before any infectious material reaches the brain (*17*, *18*). Indeed, little or no infectivity can be detected in the brain of animals peripherally inoculated during the first half of the incubation period (*19*). Thus, it is likely that the source of PrP^{Sc} in blood during the early presymptomatic phase is the spleen and other lymphoid organs. The quantity of PrP^{Sc} in blood goes down after this initial phase and actually disappears 80 days after inoculation (Table 1 and Fig. 2). The rise of PrP^{Sc} in blood during the early presymptomatic phase appears to coincide with the time of its exponential replication in lymphoid organs, whereas the reduction of PrP^{Sc} in blood occurs when infectivity in peripheral tissues has reached a plateau and is migrating from the periphery to the brain (*17*, *18*). Although the explanation for these results in unknown, it is possible that the proportion of circulating lymphocytes carrying PrP^{Sc} is much higher during the exponential phase of peripheral replication than during the stationary phase. At the symptomatic period, PrP^{Sc} can again be detected in the blood of most of the animals (Fig. 2). It has been reported that large quantities of PrP^{Sc} appear in the brain only a few weeks before the onset of clinical signs (*19*, *20*). Thus, PrP^{Sc} in blood samples at the symptomatic stage is likely to have come from brain leakage. It is known that at the time of symptomatic disease, TSE-affected individuals have extensive brain degeneration in the form of massive neuronal death, synaptic alterations, and brain inflammation (*21*). These abnormalities probably cause a disruption of the blood/brain barrier resulting in the leakage of cerebral proteins to the blood (*22*), in particular PrP^{Sc}, which by this time is highly abundant in the brain.

Infectivity studies have shown that the blood carries prions in both the symptomatic and presymptomatic stages of the disease in animals (*11*, *23*, *24*). Upon experimental BSE infection of sheep, infectivity can be transmitted by blood transfusion from asymptomatic infected animals (*25*), indicating that the infectious agent is present in blood during the incubation period. Recently, three cases of vCJD have been associated with blood transfusion from asymptomatic donors who subsequently died from vCJD (*6*, *7*). The alarmingly high proportion of cases transmitted by blood transfusion suggests that prions exist in relatively elevated quantities in the blood of individuals silently incubating vCJD. Based on studies with animal models, it is believed that all of the human population may be susceptible to vCJD infection (*26*), although clinical cases have so far occurred only in methionine homozygotes at codon 129 in the human prion protein gene. Because the incubation period may be several decades, it is currently unknown how many people may be in an asymptomatic phase of

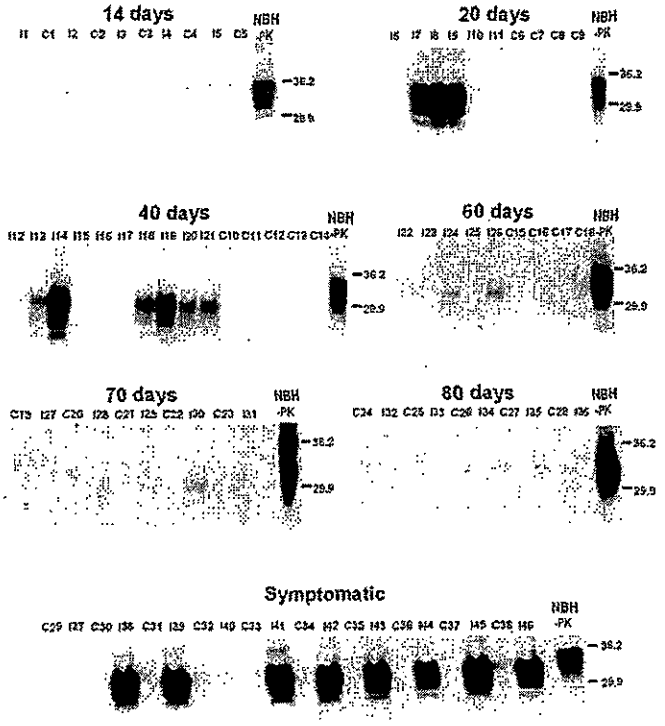


Fig. 1. PrP^{Sc} detection in the blood of scrapie-infected hamsters by PMCA. Blood samples from groups of scrapie-inoculated and control animals were taken at different times during the incubation period. Three milliliters of blood were separated in three aliquots of 1 ml each to prepare the buffy coat (*13*). Samples were subjected to 144 cycles of PMCA. Ten microliters of the sample from this first round of amplification were diluted into 90 μl of normal brain homogenate, and a new round of 144 PMCA cycles was performed. This process was repeated a total of seven times. Each panel represents the results obtained in the seventh round of PMCA with the samples from each group of animals, which are representative of the three independent aliquots taken from each animal. Ix, samples from hamsters infected with 263K scrapie; Cx, samples from control animals injected with PBS. All samples were treated with proteinase K (PK) before electrophoresis, except for the normal brain homogenate (NBH), in which no PK treatment (–PK) is indicated.

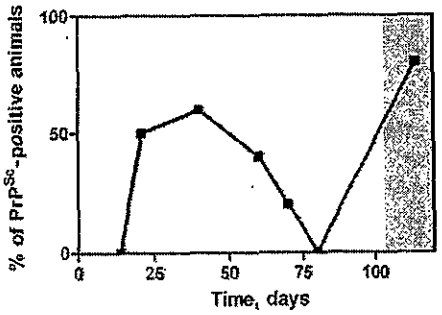


Fig. 2. Proportion of animals whose blood was PrP^{Sc} positive at different times during the incubation period. The percentage of samples scoring positive for PrP^{Sc} in blood is represented versus the time after inoculation at which samples were taken. Two phases of PrP^{Sc} detectability were observed: an early stage during the incubation period, which probably corresponds to the time during which peripheral prion replication in lymphoid tissues is occurring, and a second phase at the symptomatic stage, in which the brain contains extensive quantities of PrP^{Sc}. The vertical gray section indicates the symptomatic phase.

Table 1. Number of animals used and results obtained regarding the presymptomatic detection of PrP^{Sc} in the blood.

Time (days)	Controls (positives/total)	Infected (positives/total)	Sensitivity/ specificity
14	0/5	0/5	0%/100%
20	0/4	3/6	50%/100%
40	0/5	6/10	60%/100%
60	0/4	2/5	40%/100%
70	0/5	1/5	20%/100%
80	0/5	0/5	0%/100%
Symptomatic phase	0/10	8/10	80%/100%

vCJD infection. In addition, it is possible that some infected patients may never develop clinical symptoms but will remain asymptomatic carriers who can potentially transmit the disease to other individuals (*26*, *27*). In the absence of screening tests and effective therapies to treat this disease, a formidable worldwide public health challenge lies ahead to prevent further infections, assess infection rates, and treat infected patients. The ability to detect PrP^{Sc}, the major component of infectious prions, biochemically in the blood of infected but asymptomatic experimental animals will hopefully lead to the development of tests for human blood. Indeed, although technically more challenging, the PMCA technology has been adapted to amplify prions of human origin (*20*). The ability to accurately detect PrP^{Sc} in the presymptomatic stages of vCJD would potentially help to reduce the risk that many more people will be infected by this fatal and terrible disease.

References and Notes

1. S. B. Prusiner, *Proc. Natl. Acad. Sci. U.S.A* 95, 13363 (1998).
2. S. N. Cousens, E. Vynnycky, M. Zeidler, R. G. Will, R. G. Smith, *Nature* 385, 197 (1997).
3. J. Collinge, *Lancet* 354, 317 (1999).
4. M. E. Bruce *et al.*, *Nature* 389, 498 (1997).
5. R. Bradley, P. P. Liberski, *Folia Neuropathol.* 42 (suppl. A), 55 (2004).
6. C. A. Llewelyn *et al.*, *Lancet* 363, 417 (2004).
7. A. H. Peden, M. W. Head, D. L. Ritchie, J. E. Bell, J. W. Ironside, *Lancet* 364, 527 (2004).
8. Q. Schiermeier, *Nature* 409, 658 (2001).
9. C. Soto, *Nat. Rev. Microbiol.* 2, 809 (2004).
10. L. Ingrosso, V. Vetrugno, F. Cardone, M. Pocchiari, *Trends Mol. Med.* 8, 273 (2002).
11. P. Brown, L. Cervenakova, H. Diringer, *J. Lab. Clin. Med.* 137, 5 (2001).
12. F. Houston, J. D. Foster, A. Chong, N. Hunter, C. J. Bostock, *Lancet* 356, 999 (2000).
13. J. Castilla, P. Saa, C. Soto, *Nat. Med.* 11, 982 (2005).
14. G. P. Saborio, B. Permanne, C. Soto, *Nature* 411, 810 (2001).
15. C. Soto, G. P. Saborio, L. Anderes, *Trends Neurosci.* 25, 390 (2002).
16. J. R. Silveira *et al.*, *Nature* 437, 257 (2005).
17. R. H. Kimberlin, C. A. Walker, *J. Comp. Pathol.* 89, 551 (1979).
18. M. Glatzel, A. Aguzzi, *Microbes Infect.* 2, 613 (2000).
19. R. H. Kimberlin, C. A. Walker, *J. Gen. Virol.* 67, 255 (1986).
20. C. Soto *et al.*, *FEBS Lett.* 579, 638 (2005).
21. J. Castilla, C. Hetz, C. Soto, *Curr. Mol. Med.* 4, 397 (2004).
22. W. A. Banks, *J. Neurovirol.* 5, 538 (1999).
23. P. Brown, *Vox Sang.* 89, 63 (2005).
24. N. Hunter *et al.*, *J. Gen. Virol.* 83, 2897 (2002).
25. N. Hunter, *Br. Med. Bull.* 66, 171 (2003).
26. M. T. Bishop *et al.*, *Lancet Neurol.* 5, 393 (2006).
27. J. W. Ironside, *Haemophilia* 12, 8 (2006).

28. This research was supported in part by NIH grants AG0224642 and NS049173.

Supporting Online Material

www.sciencemag.org/cgi/content/full/313/5783/92/DC1
Materials and Methods
References

21 April 2006; accepted 5 June 2006
10.1126/science.1129051

Prion-Induced Amyloid Heart Disease with High Blood Infectivity in Transgenic Mice

Matthew J. Trifilo,[1] Toshitaka Yajima,[2] Yusu Gu,[2] Nancy Dalton,[2] Kirk L. Peterson,[2] Richard E. Race,[3] Kimberly Meade-White,[3] John L. Portis,[3] Eliezer Masliah,[4] Kirk U. Knowlton,[2]* Bruce Chesebro,[3]* Michael B. A. Oldstone[1]*

We investigated extraneural manifestations in scrapie-infected transgenic mice expressing prion protein lacking the glycophosphatydylinositol membrane anchor. In the brain, blood, and heart, both abnormal protease-resistant prion protein (PrPres) and prion infectivity were readily detected by immunoblot and by inoculation into nontransgenic recipients. The titer of infectious scrapie in blood plasma exceeded 10^7 50% infectious doses per milliliter. The hearts of these transgenic mice contained PrPres-positive amyloid deposits that led to myocardial stiffness and cardiac disease.

In humans and animals, transmissible spongiform encephalopathies (TSEs), or prion diseases, cause neurodegeneration and death following ingestion or experimental inoculation of infected material. Prion diseases are characterized by the conversion of the normal protease-sensitive host prion protein (PrPsen) to a disease-associated protease-resistant form (PrPres). Although prion disease damages the central nervous system (CNS), infectivity and PrPres can be detected within peripheral tissues, including lymphoid organs in humans, sheep, and deer (*1*, *2*), as well as skeletal muscle (*3*), kidney, and pancreas (*4*) of some transgenic rodent models. Despite the toxic effect on the CNS, few if any histopathological changes have been observed at peripheral sites.

Transmission of TSE disease to humans has resulted from cannibalism, contaminated surgical instrumentation, and tainted growth hormone (*5*–*7*). A human disease termed variant Creutzfeldt-Jakob disease (vCJD) has occurred more recently, apparently through the ingestion of bovine spongiform encephalopathy (BSE)–infected cattle products (*8*). Recent evidence suggests that transmission of vCJD between humans may occur through blood transfusion (*9*, *10*), and this conclusion is supported by experimental transmission of BSE between sheep via blood transfusion (*11*). TSE infectivity has been demonstrated in blood by intracerebral-inoculation in mouse, mink, hamster, and goat models (*7*, *12*–*20*). However, infectivity in such cases is low, $\leq 10^2$ 50% infectious doses (ID_{50}) per ml of blood compared to 10^6 to 10^{10} ID_{50}/g in the brain.

Normal prion protein, PrPsen, is expressed primarily as a membrane-bound, glycophosphatydylinositol (GPI)–anchored protein. The role of cellular PrP membrane anchoring in prion disease has been studied in transgenic mice expressing GPI-negative anchorless PrP, which is secreted from cells (*21*). Intracerebral inoculation of these GPI-negative anchorless PrP transgenic (tg) mice with murine scrapie results in scrapie replication and deposition of PrPres within the brain. Although wild-type (WT) mice infected with scrapie usually develop a nonamyloid form of PrPres, in these tg mice the PrPres is primarily in the form of amyloid plaques (*21*). At the same time, these mice do not manifest the clinical and pathologic alterations normally associated with prion disease, thus demonstrating a separation between PrPres amyloid accumulation and clinical CNS disease (*21*). In the brain of these infected tg mice, PrPres was located primarily within and around endothelial cells (*21*) (Fig. 1A), leading to the hypothesis that anchorless PrPres may be secreted in the blood. Here we examined this possibility.

To determine whether PrPres and/or scrapie infectivity was present in blood, four infected tg mice were bled between 450 and 512 days postinfection (dpi) with the RML strain of scrapie. Inoculation of a 1:500 dilution of blood from all four mice induced scrapie in WT (C57BL/6) recipients in ~145 days. In addition, blood of two mice analyzed by serial dilution titration gave titers of $\geq 1.6 \times 10^7$ and $\geq 1.6 \times 10^5$ ID_{50}/ml blood (Table 1).

[1]Viral-Immunobiology Laboratory, Departments of Molecular and Integrative Neurosciences and Infectology, Scripps Research Institute, La Jolla, CA 92037, USA. [2]Department of Medicine, University of California, San Diego, La Jolla, CA 92093, USA. [3]Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, Hamilton, MT 59840, USA. [4]Departments of Neurosciences and Pathology, University of California, San Diego, CA 92093, USA.

*To whom correspondence should be addressed. E-mail: mbaobo@scripps.edu (M.B.A.O.), bchesebro@niaid.nih.gov (B.C.), kknowlton@ucsd.edu (K.U.K.)

別紙様式第2-1

No. 15

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2006. 5. 11	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況	Guardian Unlimited, The Guardian. 2006 May 2.	公表国
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社)			英国

研究報告の概要

○英国の血漿分画製剤が14カ国でvCJDのリスクを引き起こす可能性
英国政府は、1990年代に輸出された英国産の血漿分画製剤によって患者にvCJDのリスクがあると14カ国に警告した。
2003年12月に輸血によるvCJD感染が英国で発生し、血液製剤による感染伝播に対する安全対策が実施された。当局は、国営企業Bio Products Laboratory(BPL)から海外に輸出された製剤を再調査する必要に迫られた。
当局は、vCJDの潜在的リスクは「非常に不確実」であるとしながらも、ブラジルとトルコの保健省に対して予防措置を取るよう勧告した。この措置には患者の追跡調査、供血や臓器・組織提供をしないよう求めることが含まれる。また、患者は医師や歯科医師に治療を受ける際に申し出るよう求められる。
英国内では、危険のある人は最大で6000人と考えられる。問題は、血漿分画製剤が何千もの供血血液を処理して製造されることである。vCJDを発症した9人の供血者のたった23供血から懸念が生じた。
BPLを所管するNHSの血液・移植部門は「これまで血漿分画製剤が関係したvCJD症例はない。英国の血漿由来の製剤の使用は1999年に終了した。しかし、供血経験のある人がvCJDと診断されたため、終了以前に製剤を投与された患者にリスクがある可能性が出てきた。2004年以降、1980年以降に輸血を受けた人は供血不可としている」と話している。
ブルネイ、UAE、インド、ヨルダン、オマーン、シンガポールはブラジルやトルコに比べて危険性は低いものの、予防措置をとる必要がある。ベルギー、モロッコ、エジプト、フランス、オランダ、イスラエルには危険性の少ない製剤が輸出されており、製造の最終工程はこれらの国で行われたため、各国での分析を続けるよう勧告された。フランス政府は、同国から他の10カ国に再輸出された製剤には危険はないとしている。

報告企業の意見	今後の対応
英国政府は、英国産の汚染された血漿分画製剤によって患者にvCJDのリスクがあると14カ国に警告したとの報告である。	今後も引き続き、プリオン病に関する新たな知見及び情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

British blood products may pose vCJD risk in 14 countries

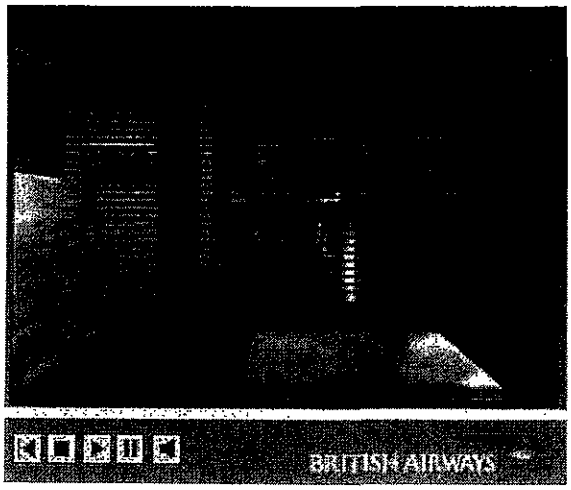
- UK issues warning on 'mad cow disease'
- Documents show Brazil and Turkey are high on list

James Meikle and Rob Evans
Tuesday May 2, 2006
The Guardian

The government has been forced to warn 14 countries that patients are in danger of developing the human form of mad cow disease as a result of contaminated British blood products sold abroad.

Documents released under the Freedom of Information Act show that patients in Brazil and Turkey are most at risk from the products, although it is too early to know how many, if any, foreign patients may develop the incurable variant CJD, as it takes many years to appear. The Turkish authorities said they had traced patients at risk and were closely monitoring them, while Brazil would not comment.

Article continues



The contaminated blood products were exported in the 1990s by the British government to treat conditions such as haemophilia, severe burns and immune deficiency. At the time the government considered there was no risk.

Twenty-eight people abroad have already developed vCJD by eating cattle meat from Britain infected with BSE. However, the

dangers of another route of transmission are now becoming more evident. Scientists are worried about a "second wave" of casualties caused by blood donated by people infected but not yet displaying symptoms of the disease.

The risk of passing on the disease in this way was considered only theoretical until December 2003, when it emerged that a patient in Britain had been infected through a blood transfusion, leading to new safety measures. Another two cases have since been identified. Health authorities then had to re-examine blood products sent abroad by the state-owned company Bio Products Laboratory (BPL).

The documents show that, following the rethink, the Health Protection Agency was concerned "about the potential infectivity of blood". Believing the potential risk of vCJD to be "very uncertain", the agency advised the Brazilian and Turkish health ministries to take precautions to reduce the possibility of spreading vCJD as "sufficient quantities" of the "at-risk" products had been exported.

These measures included tracking down patients and telling them not to donate blood, organs or tissues. Patients are also told to inform doctors and dentists if they need any treatment.

In Britain, up to 6,000 people were considered to be at risk. The problems stem from the way blood products are made, from processing thousands of separate donations. The concerns arise from just 23 donations made by nine people who went on to develop vCJD, showing how minute amounts may be infectious.

The NHS Blood and Transplant Authority, which is responsible for BPL, said: "So far no vCJD cases have been linked to plasma products ... The use of products derived from British blood plasma was ended in 1999 as a precautionary safety measure because of what were then regarded as only theoretical risks. But cases where patients might have been put at risk before that date have since come to light as further cases of vCJD have been diagnosed in people who were blood donors. Since 2004, no one who received a blood transfusion after 1980 has been allowed to donate blood themselves."

The Health Protection Agency decided that patients in six countries - Brunei, UAE , India, Jordan, Oman and Singapore - had been put in less jeopardy than those in Brazil and Turkey, but might need to take precautions. Less dangerous batches were imported by Belgium, Morocco and Egypt. France, Holland and Israel were advised to carry out their own assessments, as manufacture of the blood products was completed in their countries. The French government concluded that there was no danger from the products, which were re-exported to 10 unnamed countries.

The Guardian has previously reported that patients worldwide may have been exposed to vCJD, but the documents detail for the first time the countries, the amounts and the risk assessments. British authorities cannot say how many patients abroad may now be in danger.

There have been 161 cases of vCJD in Britain. There are 15 cases in France, four in Ireland, two in the US, and one each in Canada, Italy, Japan, the Netherlands, Portugal, Saudi Arabia and Spain.

Some of these victims are known to have caught vCJD by eating infected beef in Britain. Most others live in countries that

have also had outbreaks of BSE that may well have originated from Britain.

Graham Steel, whose brother Richard died from vCJD, drew parallels to the spread of BSE. "[It is] eerily reminiscent of the 1980s when 'theoretically' infectious meat and bonemeal was exported by the UK around Europe and beyond despite the fact that the risks of spreading diseases were known about in 1972-73. A total recall was deemed too expensive."

Special reports
BSE and CJD
What's wrong with our food?

Explained
The threat to humans from BSE

Cartoon
Steve Bell on the BSE report

Useful links
Official BSE inquiry
Human BSE Foundation
CJD Support Network
British Medical Journal CJD page
Department of Health CJD/BSE page
Department for Environment, Food and Rural Affairs BSE page
The UK CJD disease surveillance unit
Food Standards Agency BSE page

Printable version | Send it to a friend | Save story

Daily sections

Weekly sections