医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2009年12月1日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	乾燥濃縮人血液凝固第Ⅷ因子		研究報告の公表状況	Biologicals 2009; AVAILABLE ONLINE 19 NOV. 2009: 1-3	公表国 日本	
販売名（企業名）	コンコエイト-HT（ベネシス）					

研究報告の概要

最近、血漿製剤を介したプリオン伝播の可能性に関する論文がいくつか報告されており、感染性プリオンの混入の可能性のある血漿製剤のリスク評価として製造工程の除去効果の評価は重要である。
我々は孔径15nmのウイルス除去膜の評価を行った。
ナノろ過直前のアンチトロンビンサンプルに2つの異なる方法で調製したプリオン物質をスパイクした。動物への感染実験による感染性プリオン除去能は≧4.72及び4.00（2回の独立したスパイク実験）であった。しかしながら、感染性は15nmろ過サンプルの超遠心後の上清および沈殿物の両方に検出され、完全な除去の困難さを示していた。
このデータは、より小さなand/or可溶性の状態（直径15nm未満）で一定量の感染性プリオンタンパク質が存在するとの結論を支持している。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1)略
1)略
2)略
3)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
血漿分画製剤の製造工程におけるウイルス除去膜（平均孔径15nm）による感染性プリオンタンパク質の除去能力を評価したところ、感染性プリオンタンパク質は15nmのウイルス除去膜を通過しうることが確認されたことについての報告である。 血漿分画製剤は理論的なvCJD伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を2003年5月から添付文書に記載している。2009年2月17日、英国健康保護庁（HPA）はvCJDに感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内でのBSEの発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは1999年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。	本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。

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コンコエイト

BENESIS2009-027
ARTICLE IN PRESS
Biologicals xxx (2009) 1–3
Contents lists available at ScienceDirect
Biologicals
journal homepage: www.elsevier.com/locate/biologicals
BIOLOGICALS
ELSEVIER

Infectious prion protein in the filtrate even after 15nm filtration

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ARTICLE INFO

Article history:
Received 20 August 2009
Received in revised form
14 October 2009
Accepted 23 October 2009

Keywords:
Prion
Removal
Infectivity
Virus removal filter
Soluble form

ABSTRACT

The evaluation of the removal efficacy during manufacturing is important for the risk assessment of plasma products with respect to possible contamination by infectious prions, as recently reported in several papers on the potential for prion transmission through plasma products. Here, we evaluated a virus removal filter which has 15 nm pores. An antithrombin sample immediately prior to nanofiltration was spiked with prion material prepared in two different ways. The removal (log reduction factor) of prion infectivity using animal bioassays was ≥4.72 and 4.00 in two independent filtrations. However, infectivity was detected in both the pellet and supernatant following ultracentrifugation of the 15 nm filtered samples, indicating difficulty in complete removal. The data supports the conclusion that a certain amount of infectious prion protein is present as a smaller and/or soluble form (less than ~15 nm in diameter).

1. Introduction

Although the risk of transmission of classical or sporadic Creutzfeldt-Jakob disease (sCJD) through blood transfusion is theoretically possible, no verifiable case of transmission has been reported. However, the risk of contracting variant CJD (vCJD) through blood transfusion has been of increasing concern, particularly since the report of a fourth possible transmission case [1,2]. In addition, two investigations of cases involving recipients of plasma products manufactured from pooled source plasma containing a vCJD-infected donor were recently reported. In the first of these reports, abnormal prion protein was detected in a patient without symptoms of vCJD, revealed vCJD abnormal prion protein at post mortem in the patient (a haemophiliac) who had been treated with a Factor VIII product derived from a source material containing plasma that included a donor who developed vCJD after the donation. The UK Health Protection Agency retained their position of 'at risk' for UK derived plasma products [3]. The FDA considers 'the estimated risk' is highly uncertain but is most likely to be extremely small in the case of US-licensed plasma products [4]. A follow-up review of the case reported that the patient was more likely to have been infected by potential subclinical vCJD donors present in normal donor plasma, than by smaller quantities of plasma derived from the donor who had developed vCJD [5,6]. In another report, vCJD abnormal prion protein was not found in a post mortem examination of a patient with common variable immunodeficiency (CVID) who had been treated with an intravenous immunoglobulin (IVIG) product derived from a source material containing plasma from a donor who later developed vCJD post mortem without symptoms of vCJD [7].

Experimental studies in animal models have demonstrated the transmission of bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD), scrapie, CJD and vCJD through transfusion [2]. Furthermore, infectivity was detected in plasma derived from vCJD-infected mice [8]. To reduce the risk of transmission through biologics derived from raw materials potentially contaminated with infectious prion protein, such as plasma, safety measures against pathogen contamination should be employed. Such measures include decreasing the potential prion load, evaluating the risk of the product and employing prion removal step(s) in the manufacturing process wherever possible [9–11].

Nano-filtration has been reported as a very effective tool for the removal of prions [12–14]. These reports suggested that the biological properties of infectious prions in the spiking material could affect

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doi:10.1016/j.biologicals.2009.10.018

evaluations of clearance. Foster [15] also reviewed the significance of the method of preparing the spiking material for clearance studies but further research is required due to a lack of consensus. Although infectious activity peaks markedly at 17–27 nm [16], our recent study reveals that even a 15 nm filter could not remove all infectious prion [14]. Our objective in this study is to clarify the infectivity of prion protein that penetrated the 15 nm filter.

2. Materials and methods

2.1. Quantitative removal capacity of 15 nm filter

To evaluate the quantitative removal capacity of a 15 ± 2 nm virus removal filter virus removal filter (Pnanova 15 N, 0.001 m^2, (P-15 N), Asahi Kasei Medical Co., Ltd, Tokyo, Japan) we used a sample of the antithrombin preparation (Neuart®, Benesis Corp., Osaka, Japan) taken immediately before the P-15 N step. Briefly, the microsomal fraction as a spiking material was prepared as follows. Brain homogenates from hamster adopted scrapie 263 K strain infected hamsters in PBS (10% w/v) were centrifuged at low speed (1,000 g for 20 min, at 4 °C) and the supernatant was treated with the 0.1% detergent lysolecithin (37 °C for 30 min). Then the homogenate was centrifuged at high speed (9,100 g for 10 min at 4 °C) and the supernatant was extensively sonicated on full power (20 kHz, 550 W, Misonix XL2020, Qsonica LLC., USA) for 5 min with 2 min intervals every 1 min sonication (5 ml/tube without cymbal rod). The homogenate obtained was sequentially filtered using 0.45, 0.22 and 0.1 μm filters was used as a spiking material. The starting material was spiked (1:50 v/v) and then filtered using P-15 N. The samples, before and after the filtration of two independent runs were titrated to determine the reduction of the PrP^{res} by Western blotting (WB2 method in reference 14). An animal bioassay (BA) was also performed to determine the reduction in infectivity. For the BA, four to five-week old specific pathogen free and viral antibody-free male Syrian hamsters were inoculated i.c. with 0.05 ml/animal of the ten-fold serially diluted sample. Six animals were used for each diluted sample. The animals were monitored for general health and clinical signs, and euthanized once advanced clinical signs were evident or at the end of the assay period (383 days). A histopathological analysis was performed on all brains from animals sacrificed in the study and log reduction factors were calculated following titre determinations by the method of Kärber. This investigational TSE clearance study was performed in accordance with GLP and guidances at BioReliance, Glasgow UK and Rockville US facilities [10,17,18].

2.2. Property of P-15 N-filtered samples

To determine the characteristics of prion infectivity in the filtrate, an analysis of filtrates from additional spiked runs was performed by ultracentrifugation and qualitative (200 days) infectivity assay. Microsomal fraction as spiking material was prepared as described in 2.1 (without detergent treatment) following ultracentrifugation to purify the microsomal fraction. The microsomal fraction was then extensively sonicated at 20 kHz, 200 W (Bioruptor UCD-200 T, Cosmobio Co., Ltd., Japan), 10 min with 1 min intervals every 1 min sonication (2 ml/tube with cymbal rod) and subsequently filtered using 0.22 μm filters. This filtrate was used to spike samples. The spiked (1:20 v/v) antithrombin samples were passed through a 15 nm filter. The resultant log reduction factor by Western blotting was ≥2.8 and infectivity was detected in the filtered sample [14]. The filtered sample was ultracentrifuged at 15 0000 g for 60 min at 4 °C and the pellet was resuspended with PBS. The resuspended pellet and supernatant were inoculated i.c. to three female-specific pathogen-free Syrian Hamsters with 0.02 ml/animal of these undiluted samples. As a control, a non-ultracentrifuged filtrate sample was also inoculated. The animals were euthanized once advanced clinical signs were evident or at the end of the assay period (200 days). A histopathological analysis of the brain from all sacrificed animals was also performed described as previous study [14].

3. Results

3.1. Capacity of the 15 nm filter to remove prion

The capacity to remove prions from the antithrombin preparations during Planova 15 N filtration using either extensively sonicated lysolecithin treated prions or extensively sonicated microsomal fractions are summarized in Table 1. The log reduction factors (LRFs) using the lysolecithin spike in the animal experiments were ≥4.72 and 4.00, respectively for the duplicate runs. These results revealed that the Planova 15 N filtration is "effective but not complete" for the removal of infectious prion contamination. One of the experiments showed that a small amount of infectious prion was still detectable in the filtrate. These results demonstrate that even 15 nm filtration may not be able to completely remove infectious prion (Table 1).

3.2. Qualitative removal capacity of 15 nm filter and subsequent analysis of the filtered sample

To clarify the properties of the infectious prion, the pellet and supernatant derived from the 15 nm filtrate (using a sonicated microsomal spike material) after ultracentrifugation were investigated. PrP^{res} was not detected by Western blot assay either in the filtrate, or in the supernatant and pellet by ultracentrifugation of the filtrate. In contrast, infectivity was detected in all samples by animal bioassay, a more sensitive assay method (Table 1). This result showed that a certain amount of infectious prion was able to penetrate the 15 nm virus removal filter and was not pelleted by ultracentrifugation. Of note, one of two animals which were inoculated with the supernatant showed slightly faster disease progression than other animals after the appearance of clinical signs in the study. However, histopathological observations did not show any clear differences between the supernatant and pellet fractions after ultracentrifugation.

4. Discussion

Clarification as to the real form of infectious prion protein in infectious human and animal plasma is very important in order to

Table 1
Scrapie PrP^{Res} and infectivity in samples generated with 15 nm filtration and subsequent ultracentrifugation

Spiking material	Quantitative		Qualitative	
	WB	BA	WB	BA
	lysolecithin treated and Extensively sonicated		Extensively sonicated	
Before filtration	6.1 / 6.1	7.97 / 8.30	3.6	+ve[c]
After filtration	<2.6 / <2.6	<3.25 / 4.30	<0.8	+ve[d]
Log reduction	≥3.5 / ≥3.5	≥4.72 / 4.00	≥2.8	NA
Pellet[a]	NA	NA	<1.0	+ve[e]
Supernatant[b]	NA	NA	<1.0	+ve[f]

+ve, scrapie positive. NA, not applicable.
[a] :Pellet fraction of ultracentrifuged filtrate.
[b] Supernatant fraction of ultracentrifuged filtrate.
[c] Clinical sign was observed from 90 ~ 118 days post infection.
[d] Clinical sign was observed from 111 ~ 175 days post infection.
[e] Clinical sign was observed from 111 ~ 113 days post infection.
[f] Clinical sign was observed from 125 ~ 175 days post infection.

evaluate the risks of prion contamination in plasma products and biopharmaceutical medicines. Some results suggesting the form of infectious prion protein in human and animal plasma have been reported. A genetically-modified animal plasma containing GPI-anchor less prion protein had some infectivity [19,20]. On the other hand, a high titer of prion remained in the supernatant of an ultracentrifuged microsomal fraction derived from scrapie-infected brain, although PrP^{res} was not detected by Western blot assay [21]. Although these results were obtained under experimental conditions, it suggests that the infectious prion protein may exist in animal plasma as a soluble or soluble-like form. Ultracentrifugation has been commonly used for the concentration of the prion protein. The ultracentrifugation and subsequent preparation of the spiking material should be done carefully in order to ensure that such preparations do not exclude such soluble-like prion protein. To avoid over estimating removal, pelleting of the spike by ultracentrifugation should not be used. However, preparation methods or employing treatment which generate small size of infectious prion such as sonication and/or detergent treatment following the ultracentrifugation (as performed in this study) should be used. Many studies to evaluate prion removal during manufacturing have been performed, however studies of the appropriateness of the spiking materials derived from prion-infected brain are limited. We reported that extensively-sonication and/or treatment with a detergent such as sarkosyl and lysolecithin were useful for the preparation of spiking material for analyzing particle size [14]. Hence, preparation methods without pelleting the prion by ultracentrifugation or with the treatment which generates soluble-like prion in the supernatant following ultracentrifugation will lead to more acceptable results for the evaluation of TSE removal, especially when an animal study is included.

In this study, we evaluated the prion removal performance of nano-filtration on a lab scale using a 15 nm Planova filter and a sample of antithrombin which was spiked with infectious prion protein. Two types of spiking material were used. Both spiking materials used in this study seemed to contain soluble-like infectious prion protein because of the preparation methods employed sonication treatment which seems to generate the soluble-like form infectious prion. Hence, the results of the filtrate sample and LRF in the studies can be considered realistic for evaluation of the filtering process with respect to prion removal.

Residual infectivity was detected in the filtered process sample of antithrombin preparations which was spiked with extensively sonicated or detergent/sonication-treated spiking material. Furthermore, the filtered sample was ultracentrifuged and subsequently the infectivity was detected in pellet and supernatant fractions after ultracentrifugation. These results showed that 15 nm filtration which is the filter of smallest pore size for virus removal removes infectious prion protein effectively but not completely under the filtration condition of antithrombin preparation. Other prion removal options such as other filter devices, column chromatography and fractionations during processing steps have also been reported [13]. One should choose a suitable spiking material for a process evaluation study, before starting the study. The combination of several different process steps for prion removal is likely to improve the removal of all forms of potential prion contamination and thus safeguard against contamination.

The results of this study also revealed that some infectious prion protein was less than 15 nm in diameter, apparently as a low molecular weight and/or soluble form. Unfortunately, the properties or presence of such a soluble-like infectious prion protein in blood have not been clarified. The properties of this form could be very important to evaluate the risk of prion contamination in biological products. Hence, further investigations are required, especially of the properties of soluble-like prion protein in blood and plasma.

Acknowledgements

This study was partially conducted based on collaborative research projects between Osaka University and Benesis Corporation, and between Rakuno Gakuen University and Benesis Corporation. The authors thank Ms. Du Anariwa, Mr. Shu-Ming Li, Osaka University and Ms. Michiko Sato, Rakuno Gakuen University, for animal rearing. The authors also thank Dr. Andy Bailey, ViruSure GmbH., Austria and Ms. Elaine Wilson, BioReliance Corp. UK. for excellent discussions and support.

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別紙様式第2-1

No. 24

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	総合機構処理欄
				2010. 1. 19	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	Kaski D, Mead S, Hyare H, Cooper S, Jampana R, Overell J, Knight R, Collinge J, Rudge P. Lancet. 2009 Dec 19;374(9707):2128.	公表国 英国	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○コドン129ヘテロ接合性の変異型CJD患者
30歳男性が、13ヶ月前から人格変化、進行性不穏、知能低下を呈し、2008年6月に入院した。患者は重度下肢痛および記憶低下を訴えた。2ヵ月後、幻視を発現し、腹部に腫瘍があるという妄想を持った。その後3ヶ月間に症状は悪化し、2008年10月の精神状態検査のスコアは26/30であった。追跡眼球運動は衝動性であり、口とがらし反射があった。腕に軽度運動失調があり、下肢には腱反射亢進と左足底伸展反応を伴う重度失調があった。歩行に2本の杖を必要とした。既往歴には、頸部リンパ節除去および扁桃摘出術(15年前)があったが、輸血歴やヒト組織の移植歴はなかった。EEGは徐波活性を示した。CSFのタンパク、ブドウ糖、血球数は正常であったが、14-3-3タンパク質が陽性であった。脳MRI所見は、視床枕徴候と一致した。評価したすべての神経放射線医が視床枕徴候を陽性と見なしたわけではないが、定量評価で尾状核と比べ視床枕核の高い対称性信号が示された。遺伝性、代謝性、自己免疫性疾患(腫瘍誘発性疾患を含む)の広範なスクリーニング検査結果は陰性であった。PRNP解析は、既知疾患に関連する突然変異を示さなかった。コドン129はヘテロ接合性だった。特徴的臨床症状、疾患の進行、他の診断の除外、ならびにMRI所見に基づき、変異型クロイツフェルトヤコブ病(vCJD)の臨床診断が下された。患者の年齢が若く、臨床症状、MRI所見、ならびにEEGでpseudoperiodic complexesが見られないことを複合的に考慮し、孤発性CJDの可能性は低いと判断した。患者の保護者はそれ以上の検査は望まなかった。患者の容態は悪化し、2009年1月に死亡した。剖検は実施されなかった。

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使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見

プリオンタンパク遺伝子コドン129はヘテロ接合性で、臨床症状、疾患の進行、他の診断の除外、MRI所見から変異型クロイツフェルトヤコブ病と診断された患者の症例報告である。
プリオン病の原因とされる異常プリオンがコーン分画工程で効果的に除去されるとの成績と併せて、これまでの疫学研究では如何なるプリオン病も、アルブミンを介して伝播するという証拠は無い。また本製剤の使用は一時的かつ限定的であることから伝播のリスクは非常に低いものと考える。

今後の対応

日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報を収集するとともに、血漿分画製剤の製造工程における病原因子の除去・不活化技術の向上に努める。

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JRC2010T-003

Case Report

Variant CJD in an individual heterozygous for *PRNP* codon 129

Diego Kaski, Simon Mead, Harpreet Hyare, Sarah Cooper, Ravi Jampana, James Overell, Richard Knight, John Collinge, Peter Rudge

Lancet 2009; 374: 2128

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Correspondence to: Prof John Collinge, MRC Prion Unit and National Prion Clinic, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK
j.collinge@prion.ucl.ac.uk

A 30-year-old man was admitted to hospital in June, 2008, with a 13-month history of personality change, progressive unsteadiness, and intellectual decline. He complained of severe leg pain and poor memory. 2 months later he developed visual hallucinations and falsely believed he had an abdominal tumour. Symptoms worsened over the next 3 months. In October, 2008, his score on the mini mental state examination was 26/30. Pursuit eye movements were saccadic. He had a pout reflex. There was mild ataxia in the arms. His legs were severely ataxic with brisk tendon reflexes and a left extensor plantar response. He needed two crutches to walk. Medical history included tonsillectomy and removal of a cervical lymph node 15 years previously but he had never had a blood transfusion or received implantation of other human tissues.

EEG showed slow wave activity. CSF protein, glucose, and cell count were normal but the 14-3-3 protein was positive. MRI of the brain was consistent with the pulvinar sign (figure A). Although not all neuroradiologists consulted considered the pulvinar sign positive, quantitative assessment showed symmetrical higher signal in the pulvinar nuclei than the caudate nuclei (figure B). Extensive screens for genetic, metabolic, and autoimmune diseases, including those induced by neoplasia, were negative. *PRNP* analysis did not show any known disease-associated mutations; codon 129 was heterozygous. A clinical diagnosis of variant Creutzfeldt-Jakob disease (vCJD) was made on the basis of a characteristic clinical onset and progression, exclusion of other diagnoses, and MRI findings. Sporadic CJD was judged unlikely given the combination of young age, clinical features, MRI findings, and absence of pseudoperiodic complexes on EEG. His carers did not want further investigation. His condition deteriorated and he died in January, 2009. Autopsy was not done.

Human prion diseases have acquired, sporadic, and inherited aetiologies, show wide phenotypic heterogeneity, and are associated with propagation of infectious prions of many distinct strain types.[1] Since 1994, about 200 cases of vCJD, causally related to bovine spongiform encephalopathy (BSE) prions, have been identified worldwide. vCJD is generally seen in young adults, has characteristic neuropathological features and tissue distribution of infectivity, and a distinctive type 4 (London classification) molecular strain type.[2] A polymorphism at codon 129 (encoding methionine or valine) of the human prion protein gene (*PRNP*), constitutes a powerful susceptibility factor in all types of prion disease. In vCJD, every case genotyped to date has been methionine homozygous. In the other acquired prion diseases, cases have occurred in all genotypes but with different mean incubation periods,[3] which can span decades;[4] *PRNP* codon 129 heterozygotes generally have the longest incubation periods. There is a report of a recipient of a blood transfusion from a donor incubating vCJD who died of unrelated causes but showed signs of prion infection at autopsy and was *PRNP* codon 129 heterozygous.[5] Animal studies have suggested that different clinicopathological phenotypes could occur in people with various *PRNP* codon 129 genotypes.[4,5] The majority of the UK population have potentially been exposed to BSE prions but the extent of clinically silent infection remains unclear. About a third of the UK population are *PRNP* codon 129 methionine homozygous. If individuals with other genotypes are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases, which may or may not meet diagnostic criteria for vCJD, would be expected in these *PRNP* codon 129 genotypes. However, prion disease susceptibility and incubation periods are also affected by other genetic loci, and the possibility remains that cases of vCJD to date may have unusual combinations of genotypes at these loci, yet to be fully characterised.

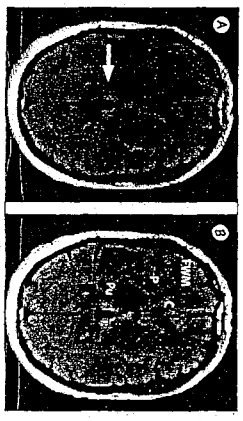

Figure: MRI
(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow). (B) ADR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (Pt), and right frontal white matter (FWM).

Contributors
All authors were involved in discussion about diagnosis, care of the patient, and preparation of the report. Written consent to publish was obtained.

Conflicts of interest
JC is a director and shareholder of D-Gen Ltd, an academic spin-out company in the field of prion disease diagnosis, decontamination, and therapy. The other authors declare that they have no conflicts of interest.

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1 Collinge J. Prion diseases of humans and animals: their causes and molecular basis. *Annu Rev Neurosci* 2001; **24**: 519–50.
2 Collinge J, Whitfield J, McKintosh E, et al. Kuru in the 21st century—an acquired human prion disease with very long incubation periods. *Lancet* 2006; **367**: 2068–74.
3 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; **364**: 527–29.
4 Asante E, Linehan J, Gowland I, et al. Dissociation of pathological and molecular phenotype of variant Creutzfeldt-Jakob disease in transgenic human prion protein 129 heterozygous mice. *Proc Natl Acad Sci USA* 2006; **103**: 10759–64.
5 Wadsworth JD, Asante E, Desbruslais M, et al. Human prion protein with valine 129 prevents expression of variant CJD phenotype. *Science* 2004; **306**: 1793–96.

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	総合機構処理欄
				2010. 1. 15	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	ProMED. 20100107.0076, 2010 Jan 07. 情報源:UK: National CJD Surveillance Unit - monthly statistics as of 5 Jan 2010.	公表国	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)				英国	

研究報告の概要		使用上の注意記載状況・その他参考事項等
	○プリオン病最新情報 英国:国立CJDサーベイランスユニット、月次vCJD・CJD統計、2010年1月5日時点 英国のCJDサーベイランスユニットから公表されたvCJDを始めとするプリオン病の患者数に関する最新情報である。 vCJD確定例または可能性例総数は前月から変化なく166名のままである。生存患者は4名であるため、2009年までのvCJD症例数は合計170例である。 2009年中に新たに2症例が記録されたが、全体としては英国におけるvCJD流行は減少しつつあるとする見解に一致している。 vCJDによる死亡患者は1995年に初めて確認され、死亡患者数のピークは2000年の28名であった。その後2001年に20名、2002年に17名、2003年に18名、2004年に9名、2005年に5名、2006年に5名、2007年に5名、2008年に1名、2009年に2名となっている。 プリオン病患者全体としては、2009年の12ヶ月間に143名の照会があった。このうち、孤発性CJD:59名、家族性CJD:1名、医原性CJD:1名、GSS:3名、vCJD:2名だった。	赤十字アルブミン20 赤十字アルブミン25 赤十字アルブミン20%静注4g/20mL 赤十字アルブミン20%静注10g/50mL 赤十字アルブミン25%静注12.5g/50mL 血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
英国CJDサーベイランスユニットの統計によると、2010年1月5日の時点でvCJD死亡患者総数は170名であり、英国におけるvCJD流行は収まりつつあるとする見解に一致するとの報告である。 プリオン病の原因とされる異常プリオンがコーン分画工程で効果的に除去されるとの成績と併せて、これまでの疫学研究では如何なるプリオン病も、アルブミンを介して伝播するという証拠は無い。また本製剤の使用は一時的かつ限定的であることから伝播のリスクは非常に低いものと考える。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980〜96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報を収集するとともに、血漿分画製剤の製造工程における病原因子の除去・不活化技術の向上に努める。

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Published Date 07-JAN-2010
Subject *PRO/AH/EDR> Prion disease update 2010*

PRION DISEASE UPDATE 2010
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A ProMED-mail post
<http://www.promedmail.org>
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<http://www.isid.org>

[With the continuing decline in the number of cases in the human population of variant Creutzfeldt-Jakob disease -- abbreviated previously as vCJD or CJD (new var.) in ProMED-mail -- it has been decided to broaden the scope of the occasional ProMED-mail updates to include some other prion-related diseases. In addition to vCJD, data on other forms of CJD: sporadic, iatrogenic, familial, and GSS (Gerstmann-Straussler-Scheinker disease), are included also since they may have some relevance to the incidence and etiology of vCJD. - Mod.CP]

In this update:
[1] UK: National CJD Surveillance Unit - monthly statistics as of 5 Jan 2010
[2] France: Institut de Veille Sanitaire - monthly statistics as of 4 Jan 2010
[3] US National Prion Disease Center - not updated since 7 Nov 2009
[4] Portuguese vCJD case - pathology
[5] vCJD codon 129 heterozygote
[6] vCJD codon 129 heterozygote - Lancet paper
[7] Prion evolution & a new reagent

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[1] UK: National CJD Surveillance Unit - monthly statistics as of 5 Jan 2010
Date: Tue 5 Jan 2010
Source: UK National CJD Surveillance Unit, monthly statistics [edited]
<http://www.cjd.ed.ac.uk/figures.htm>

The number of deaths due to definite or probable vCJD cases remains 166. A total of 4 definite/probable patients are still alive, so that the total number of definite or probable vCJD cases remains 170 for the year 2009.

Although 2 new cases vCJE were recorded in 2009, the overall picture is still consistent with the view that the vCJD outbreak in the UK is in decline, albeit now with a pronounced tail. The 1st cases were observed in 1995, and the peak number of deaths was 28 in the year 2000, followed by 20 in 2001, 17 in 2002, 18 in 2003, 9 in 2004, 5 in 2005, 5 in 2006, 5 in 2007, one in 2008, and 2 in 2009.

Totals for all types of CJD cases in the UK in the year 2009

During the 12 months of 2009, there have been 143 referrals, 59 cases of sporadic CJD, one case of familial CJD, one case of iatrogenic CJD, 3 cases of GSS, and 2 cases of vCJD.

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Communicated by:
ProMED-mail <promed@promedmail.org>

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[2] France: Institut de Veille Sanitaire - monthly statistics as of 4 Jan 2010
Date: Mon 4 Jan 2010
Source: IVS - Maladie de Creutzfeldt-Jakob et maladies apparentees

[in French, trans. & summ. Mod.CP]
<http://www.invs.sante.fr/display/?doc=publications/mcj/donnees_mcj.html>

During the 12 months of 2009, there were 1486 referrals, 85 cases of sporadic CJD, 10 cases of familial CJD, 3 cases of iatrogenic CJD, and 2 confirmed cases of vCJD.

A total of 25 cases of confirmed or probable vCJD has now been recorded in France since 1997. The 25 confirmed cases comprise 13 females and 12 males. All 25 are now deceased. Their median age is 37 (between 19 and 58). Seven were resident in the Ile-de-France and 18 in the provinces. All the identified cases have been Met-Met homozygotes. No risk factor has been identified. One of the 25 had made frequent visits to the United Kingdom.

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[3] US National Prion Disease Center - not updated since 7 Nov 2009
Date: Sat 7 Nov 2009
Source: US National Prion Disease Pathology Surveillance Center [edited]
<http://www.cjdsurveillance.com/pdf/case-table.pdf>

(Report not updated since 7 Dec 2009): During the period 1 Jan 2009 to 7 Nov 2009, there were 341 referrals, of which 198 were classified as Prion disease, comprising 133 cases of sporadic CJD, 33 of familial CJD, and no cases of iatrogenic CJD or vCJD.

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[4] Portuguese vCJD case - pathology
Date: Fri 1 Jan 2010
Source: J Neurol Neurosurg Psychiatry 2010 Jan;81(1):112-4. [edited]
<http://jnnp.bmj.com/content/81/1/112.abstract>

Title: Variant Creutzfeldt-Jakob disease: the first confirmed case from Portugal shows early onset, long duration and unusual pathology.

Authors: Barbot C, Castro L, Oliveira C, Carpenter S.
At: Department of Neuropaediatrics, Hospital Maria Pia, Porto, Portugal.

Summary:
We present clinical and autopsy findings in the 1st case of variant Creutzfeldt-Jakob disease diagnosed and confirmed in Portugal. Onset was at 11 years, the earliest onset reported, and the course (32 months) relatively long. Western blot showed protease resistant prion protein, mainly of type 4 (2B) isoform. The cerebral cortex revealed severe spongiform change with numerous amyloid plaques, which did not fit the definition of florid plaques. In the striatum, spongiform change was limited, but the extracellular space was dilated. Other reports have found marked spongiform change in the striatum and little in the cortex. Massive neuronal loss, in excess of what has been described, was found in the thalamus and pontine grey. The cerebellum showed, as expected, severe loss of granule cells, moderate loss of Purkinje cells and marked immunopositivity for the prion protein. Differences between our findings and previous ones probably result from the patient's long survival.

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Communicated by:
Terry S. Singeltary Sr. <flounder9@verizon.net>

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[5] vCJD codon 129 heterozygote
Date: Fri 19 Dec 2009
Source: BBC News, Health [edited]
<http://news.bbc.co.uk/1/hi/health/8419459.stm>

A 30-year-old man thought to have died in January [2009] from vCJD belonged to a genetic group that had not shown any signs of the disease, scientists say. In the UK, 166 people have died of vCJD, linked to eating BSE [bovine spongiform encephalopathy] infected beef, and all were thought to have shared a certain gene.

Writing in the Lancet, scientists say that the victim, a resident of, Lanarkshire [Scotland], had a different version of the gene. They estimate that up to 350 people in this group could get vCJD. Scientists have always thought that a 2nd wave of vCJD cases would emerge some time after the 1st. This is the 1st indication that this theory is being born out, with the identification of the 1st probable vCJD patient outside of the initial genetic group, BBC science correspondent Pallab Ghosh reports.

The father believes his son was incubating the disease for much of his life. It is probable because the diagnosis is based on observations of the progression of the disease rather than post-mortem tests which would have provided absolute confirmation of the disease, he adds.

The case report written by Professor John Collinge of the National Prion Clinic and colleagues is a reminder that the disease has not gone away. Many thousands of people may be carrying the infection, and although they will never show any symptoms, they have the potential to infect others.

vCJD is caused by infectious agents called prions. Prion diseases affect the structure of the brain or other neural tissue and are currently untreatable. Disease-causing prions are thought to consist of abnormally folded proteins, which spread by encouraging the normal healthy prion protein found on the surface of most cells in the body to change shape. Tests showed that the patient had a heterozygous version of the gene which codes for the human prion amino acids valine (V) or methionine (M). People can be V V (homozygous), M M (homozygous) or M V (heterozygous). Since 1994, around 200 cases of vCJD have been identified worldwide, and all those tested have been M M homozygous. [However, genetic analysis of 2 out of 3 prion-positive appendix samples in the tissue-based prevalence study in 2001-2004 showed that both were valine homozygous (VV) at codon 129 in the prion protein gene (Ironside et al, Brit Med J 2006). - Mod.CP]. However, this most recent victim was M/V heterozygous. It is thought that 47 percent of the population have this version of the gene. Professor Collinge said: "The majority of the UK population have potentially been exposed to BSE prions, but the extent of clinically silent infection remains unclear. About 1/3rd of the UK population are M/M homozygous. If individuals with other genotypes [M/V and V/V] are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases would be expected."

The scientists have previously looked at another prion disease in New Guinea called "kuru" [which was induced by eating infected human brain tissue. - Mod.CP]. The original cases were all M/M, but more recently, M/V cases have appeared. They say this indicates that M/V people can get prion diseases like kuru but have a much longer incubation period.

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[The abstract of the Lancet paper upon which the above report is based is reproduced below. - Mod.CP]

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[6] vCJD codon 129 heterozygote - Lancet paper
Date: Thu 18 Dec 2009
Source: Lancet 2009; 374: 2128 [edited]
<http://press.thelancet.com/vcjd.pdf>

[A Case Report published in the 18 Dec 2009 issue of the Lancet by Professor John Collinge, MRC Prion Unit and National Prion Clinic,

UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London]

A 30-year-old man was admitted to hospital in June 2008 with a 13-month history of personality change, progressive unsteadiness, and intellectual decline. He complained of severe leg pain and poor memory. Two months later, he developed visual hallucinations and falsely believed he had an abdominal tumour. Symptoms worsened over the next 3 months. In October 2008, his score on the mini mental state examination was 26/30. Pursuit eye movements were saccadic [a rapid movement of the eye between fixation points]. He had a pout reflex. There was mild ataxia in the arms. His legs were severely ataxic with brisk tendon reflexes and a left extensor plantar response. He needed 2 crutches to walk. Medical history included tonsillectomy and removal of a cervical lymph node 15 years previously, but he had never had a blood transfusion or received implantation of other human tissues.

EEG showed slow wave activity. CSF protein, glucose, and cell count were normal, but the 14-3-3 protein was positive. MRI [magnetic resonance imaging] of the brain was consistent with the pulvinar sign (illustrated in the original text). Although not all neuroradiologists consulted considered the pulvinar sign positive, quantitative assessment showed symmetrical higher signal in the pulvinar nuclei than the caudate nuclei (illustrated in the original text). Extensive screens for genetic, metabolic, and autoimmune diseases, including those induced by neoplasia, were negative. PRNP analysis did not show any known disease-associated mutations; codon 129 was heterozygous. A clinical diagnosis of variant Creutzfeldt-Jakob disease (vCJD) was made on the basis of a characteristic clinical onset and progression, exclusion of other diagnoses, and MRI findings. Sporadic CJD was judged unlikely given the combination of young age, clinical features, MRI findings, and absence of pseudoperiodic complexes on EEG. His care givers did not want further investigation. His condition deteriorated, and he died in January 2009. Autopsy was not done.

Human prion diseases have acquired, sporadic, and inherited aetiologies, show wide phenotypic heterogeneity, and are associated with propagation of infectious prions of many distinct strain types (1). Since 1994, about 200 cases of vCJD, causally related to exposure to bovine spongiform encephalopathy (BSE) prions, have been identified world-wide. vCJD is generally seen in young adults, has characteristic neuropathological features and tissue distribution of infectivity, and a distinctive type 4 (London classification) molecular strain type (1). A polymorphism at codon 129 (encoding methionine or valine) of the human prion protein gene (PRNP) constitutes a powerful susceptibility factor in all types of prion disease. In vCJD, every case genotyped to date has been methionine homozygous. In the other acquired prion diseases, cases have occurred in all genotypes but with different mean incubation periods (1), which can span decades (2); PRNP codon 129 heterozygotes generally have the longest incubation periods. There is a report of a recipient of a blood transfusion from a donor incubating vCJD who died of unrelated causes but showed signs of prion infection at autopsy and was PRNP codon 129 heterozygous (3). Animal studies have suggested that different clinicopathological phenotypes could occur in people with various PRNP codon 129 genotypes (4,5). The majority of the UK population have potentially been exposed to BSE prions but the extent of clinically silent infection remains unclear. About 1/3rd of the UK population are PRNP codon 129 methionine homozygous. If individuals with other genotypes [V/V or V/M] are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases, which may or may not meet diagnostic criteria for vCJD, would be expected in these PRNP codon 129 genotypes. However, prion disease susceptibility and incubation periods are also affected by other genetic loci, and the possibility remains that cases of vCJD to date may have unusual combinations of genotypes at these loci, yet to be fully characterised.

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(1) Collinge J. Prion diseases of humans and animals: their causes and molecular basis. Annu Rev Neurosci 2001; 24: 519-50.

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(3) Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 2004; 364: 527-29.

(4) Asante E, Linehan J, Gowland I, et al. Dissociation of pathological and molecular phenotype of variant Creutzfeldt-Jakob disease in transgenic human prion protein 129 heterozygous mice. Proc Natl Acad Sci USA 2006; 103: 10759-64.

(5) Wadsworth JD, Asante E, Desbruslais M, et al. Human prion protein with valine 129 prevents expression of variant CJD phenotype. Science 2004; 306: 1793-96.

[Acknowledgment: MRC Prion Unit and National Prion Clinic, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK (D Kaski MRCP, S Mead PhD, H Hyare FRCR, Prof J Collinge FRS, P Rudge FRCP); Institute of Neurological Sciences, Glasgow University, Glasgow, UK (S Cooper MRCP, R Jampana FRCR, J Overell FRCP); and National CJD Surveillance Unit, Western General Hospital, Edinburgh, UK (Prof R Knight FRCP)]

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[To put this work in perspective, parts of a British Medical Journal editorial by Maurizio Pocchiari are reproduced below. - Mod.CP.

Date: 21 May 2009
Source: BMJ 2009;338:b435 [edited]
<http://www.bmj.com/cgi/content/full/338/may21_2/b435>

"Prevalence of variant CJD in the UK

The number of cases of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom has decreased since 2000, but controversy remains about how many people carry the infectious agent and will eventually develop disease. Clewley and colleagues in a limited study add to the debate by assessing 63 007 pairs of tonsils for the only available marker of prion disease, the pathological, partially protease resistant, prion protein. Although more than half of the samples came from people born between 1961 and 1995, when the risk of exposure to bovine spongiform encephalopathy (BSE) infection was high, no convincingly positive tonsil specimens were detected. This study estimated that the prevalence of vCJD in the British population is zero, but with a large confidence interval of 0 to 113 per million.

This result agrees with one UK survey of 2000 tonsil specimens, but it differs from another survey of 1427 tonsils and 11 247 appendices, which found that more than 10 000 people might be incubating the disease. However, despite the discrepancy, the 95 percent confidence intervals of the 2 studies overlap, indicating that the results do not differ significantly and that many people in the UK may be carriers.

The chance that no one in the UK is incubating the disease, as suggested by the lower confidence limit of Clewley and colleagues' study, is unlikely because backup calculations predict up to 100 new cases of vCJD in the next 50 years. This prediction seems reasonable unless most cases of vCJD were missed by surveillance in the past years.

Until December 2008, all 210 people reported to have vCJD (164 in the UK, 46 in other countries) were homozygous for methionine at the polymorphic codon 129 of the prion protein gene (PRNP), suggesting that genetic factors strongly influence the development of disease. Whether people who are heterozygous for methionine and valine or homozygous for valine at this codon (about 60 percent of the population) will develop vCJD in the future is still unknown. However, data from gene targeted transgenic mice indicate that these people are also susceptible to BSE and vCJD, although incubation periods are longer than in those who are homozygous for methionine."

Interested readers should consult the original article for further information and references. - Mod.CP]

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[7] Prion evolution & a new reagent
Date: 1 Jan 2010
Source: BBC Health News [edited]
<http://news.bbc.co.uk/1/hi/health/8425320.stm>

Abnormal prion proteins cause at least 20 fatal diseases. Scientists have shown for the 1st time that "lifeless" prion proteins, devoid of all genetic material, can evolve just like higher forms of life. The Scripps Research Institute in the US says the prions can change to suit their environment and go on to develop drug resistance.

Prions are associated with 20 different brain diseases in humans and animals. The scientists say their work suggests new approaches might be necessary to develop therapies for these diseases. In the study, published in the journal Science [see below], the scientists transferred prion populations from brain cells to other cells in culture and observed the prions that adapted to the new cellular environment out-competed their brain-adapted counterparts. When returned to the brain cells, the brain-adapted prions again took over the population.

Charles Weissmann, head of Scripps Florida's department of infectology who led the study, said: "On the face of it, you have exactly the same process of mutation and adaptive change in prions as you see in viruses. This is a timely reminder that prion concerns are not going away and that controls to stop abnormal prions being transmitted to humans through the food system or through blood transfusions must be vigorously maintained."

Professor John Collinge, Medical Research Council Prion Unit stated that: "This means that this pattern of Darwinian evolution appears to be universally active. In viruses, mutation is linked to changes in nucleic acid sequence that leads to resistance. Now, this adaptability has moved one level down -- to prions and protein folding -- and it's clear that you do not need nucleic acid (DNA or RNA) for the process of evolution."

Mammalian cells normally produce cellular prion protein or PrPC. During infections, such as the human form of mad cow disease, known as vCJD, abnormal or mis-folded proteins convert the normal host prion protein into its toxic form by changing its conformation or shape. "It was generally thought that once cellular prion protein was converted into the abnormal form, there was no further change," Prof. Weissmann said. "But there have been hints that something was happening. When you transmit prions from sheep to mice, they become more virulent over time. Now we know that the abnormal prions replicate and create variants, perhaps at a low level initially. But once they are transferred to a new host, natural selection will eventually choose the more virulent and aggressive variants."

Professor John Collinge, of the Medical Research Council's (MRC) Prion Unit, described the research as exciting confirmation of a hypothesis that he had proposed 2 years ago, that there could be a "cloud" or whole array of prion proteins in the body. He called it the cloud hypothesis: "The prion protein is not a clone, it is a quasi-species that can create different protein strains even in the same animal. The abnormal prion proteins multiply by converting normal prion proteins. The implication of Charles Weissmann's work is that it would be better to cut off that supply of normal prion proteins rather than risk the abnormal prion adapting to a drug and evolving into a new more virulent form. You would do this by trying to block the sites on the normal prion protein that the abnormal form locks on to to do its conversion. We know there is an antibody that can do this in mice, and the Medical Research Council's Prion Unit have managed to engineer a human antibody to do this. It is currently undergoing safety tests, and we hope to move to clinical trials by the end of 2011."

Professor Collinge said the MRC was also trying to find more conventional chemical compounds to do this and has been collaborating

with the chemical company GlaxoSmithKline (GSK). He said: "They have given us access to their chemical libraries, which contain millions of compounds, and we have already identified some that may work well. This is a timely reminder that prion concerns are not going away and that controls to stop abnormal prions being transmitted to humans through the food system or through blood transfusions must be vigorously maintained."

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[The abstract and the reference for the Science paper descried above are the following: Science DOI: 10.1126/science.1183218, Published Online 31 Dec 2009.
<http://www.sciencemag.org/cgi/content/abstract/science.1183218>.
Darwinian Evolution of Prions in Cell Culture. By Jiali Li, Shawn Browning, Sukhvir P. Mahal, Anja M. Oelschlegel, Charles Weissmann
At: Department of Infectology, Scripps Florida, 130 Scripps Way, Jupiter, FL 33458, USA.

Abstract: "Prions are infectious proteins consisting mainly of PrPSc, a sheet-rich conformer of the normal host protein PrPC, and occur in different strains. Strain identity is thought to be encoded by PrPSc conformation. We found that biologically cloned prion populations gradually became heterogeneous by accumulating "mutants," and selective pressures resulted in the emergence of different mutants as major constituents of the evolving population. Thus, when transferred from brain to cultured cells, "cell-adapted" prions out competed their "brain-adapted" counterparts, and the opposite occurred when prions were returned from cells to brain. Similarly, the inhibitor swainsonine selected for a resistant substrain, whereas in its absence, the susceptible substrain outgrew its resistant counterpart. Prions, albeit devoid of a nucleic acid genome, are thus subject to mutation and selective amplification."

From a theoretical standpoint, this work has great significance. Nonetheless, the immediate interest of the BBC News report is the information that Professor John Collinge's MRC group has succeeded in engineering a humanised monoclonal antibody that interacts with the sites on the normal prion protein that the abnormal form locks onto to achieve its conversion and that it is hoped eventually to move to clinical trials of this reagent. - Mod.CP]

[see also:
2009

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CJD (new var.) - UK: update 2004 (14) 20041206.3242
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