Table S2. Characteristics of Soils Used in PrP^{Sc} Sorption Experiments

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Accession Numbers

The GenBank (http://www.ncbi.nlm.nih.gov/) accession number for PrP^{Sc} is MI4054.

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Author contributions. CJJ, DM, JMA, and JAP conceived and designed the experiments. CJJ, KEP, and PTS performed the experiments. CJJ, KEP, PTS, DM, JMA, and JAP analyzed the data. JMA and JAP contributed reagents/materials/analysis tools. CJJ, DM, JMA, and JAP wrote the paper.

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Competing interests. The authors have declared that no competing interests exist. ■

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No. 17

医薬品 研究報告 調査報告書

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販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社)					

研究報告の概要

○慢性消耗病(CWD)に感染したシカの骨格筋におけるプリオン

シカやエルクにおけるCWDの流行は広い地域に広がっており、ウシ海綿状脳症が変異型クロイツフェルト・ヤコブ病としてヒトへ種間伝播したことと同様に、CWDが人畜共通感染を起こすのではないかという懸念が起こっている。食肉の摂取が最も可能性の高い暴露の経路であるため、感染したシカ科の動物の骨格筋に感染性プリオンが含まれているかを明らかにすることが重要である。シカプリオン蛋白を発現したトランスジェニックマウスにおける動物実験で、CWDに感染したシカの骨格筋に感染性プリオンが存在することが明らかになり、CWDに感染したシカ肉を摂取あるいは取り扱う人はプリオンへの暴露のリスクがあることが示された。

報告企業の意見	今後の対応
CWDに感染したシカの骨格筋に感染性プリオンが存在することが明らかになり、CWDに感染したシカ肉を摂取あるいは取り扱う人はプリオンへの暴露のリスクがあることが示されたとの報告である。	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

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「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

(17)

Prions in Skeletal Muscles of Deer with Chronic Wasting Disease

Rachel C. Angers,[1*] Shawn R. Browning,[1*†] Tanya S. Seward,[2] Christina J. Sigurdson,[4‡] Michael W. Miller,[5] Edward A. Hoover,[4] Glenn C. Telling[1,2,3§]

Prions are transmissible proteinaceous agents of mammals that cause fatal neurodegenerative diseases of the central nervous system (CNS). The presence of infectivity in skeletal muscle of experimentally infected mice raised the possibility that dietary exposure to prions might occur through meat consumption (*1*). Chronic wasting disease (CWD), an enigmatic and contagious prion disease of North American cervids, is of particular concern. The emergence of CWD in an increasingly wide geographic area and the interspecies transmission of bovine spongiform encephalopathy (BSE) to humans as variant Creutzfeldt Jakob disease (vCJD) have raised concerns about zoonotic transmission of CWD.

To test whether skeletal muscle of diseased cervids contained prion infectivity, Tg(CerPrP) mice (*2*) expressing cervid prion protein (CerPrP) were inoculated intracerebrally with extracts prepared from the semitendinosus/semimembranosus muscle group of CWD-affected mule deer or from CWD-negative deer. The availability of CNS materials also allowed for direct comparisons of prion infectivity in skeletal muscle and brain. All skeletal muscle extracts from CWD-affected deer induced progressive neurological dysfunction in Tg(CerPrP) mice, with mean incubation times ranging between 360 and ~490 days, whereas the incubation times of prions from the CNS ranged from ~230 to 280 days (Table 1). For each inoculation group, the diagnosis of prion disease was confirmed by the presence of disease-associated, protease-resistant PrP (PrP^{Sc}) in the brains of multiple infected Tg(CerPrP) mice [see (*3*) for examples]. In contrast, skeletal muscle and brain material from CWD-negative deer failed to induce disease in Tg(CerPrP) mice (Table 1), and PrP^{Sc} was not detected in the brains of asymptomatic mice as late as 523 days after inoculation (*3*).

Our results show that skeletal muscle as well as CNS tissue of deer with CWD contains infectious prions. Similar analyses of skeletal muscle from BSE-affected cattle did not reveal high levels of prion infectivity (*4*). It will be important to assess the cellular location of PrP^{Sc} in muscle. Although PrP^{Sc} has been detected in muscles of scrapie-affected sheep (*5*), previous studies failed to detect PrP^{Sc} by immunohistochemical analysis of skeletal muscle from deer with natural or experimental CWD (*6*, *7*). Because the time of disease onset is inversely proportional to prion dose (*8*), the longer incubation times of prions from skeletal muscle extracts compared with those from matched brain samples indicated that prion titers were lower in muscle than in the CNS, where infectivity titers are known to reach high levels. Although possible effects of CWD strains or strain mixtures on these incubation times cannot be excluded, the variable 360- to ~490-day incubation times suggested a range of prion titers in skeletal muscles of CWD-affected deer. Muscle prion titers at the high end of the range produced the fastest incubation times, which were ~30% longer than the incubation times of prions from the CNS of the same animal. Because all mice in each inoculation group developed disease, prion titers in muscle samples producing the longest incubation times were higher than the end point of the bioassay, defined as the infectious dose at which half the inoculated mice develop disease. Although the risk of exposure to CWD infectivity after consumption of prions in muscle is mitigated by relatively inefficient prion transmission via the oral route (*9*), our results show that semitendinosus/semimembranosus muscle, which is likely to be consumed by humans, is a major source of prion infectivity. Humans consuming or handling meat from CWD-infected deer are therefore at risk to prion exposure.

Table 1. Incubation times after inoculation of Tg(CerPrP) mice with prions from skeletal muscle and brain samples of CWD-affected deer. PBS, phosphate buffered saline.

Inocula	Incubation time, mean days ± SEM (n/n_0)*	
	Skeletal muscle	Brain
	CWD-affected deer	
H92	360 ± 2 (6/6)	283 ± 7 (6/6)
33968	367 ± 9 (8/8)	278 ± 11 (6/6)
5941	427 ± 18 (7/7)	
D10	483 ± 8 (8/8)	231 ± 17 (7/7)
D08	492 ± 4 (7/7)	
Averages	426	264
	Nondiseased deer	
FPS 6.98	>523 (0/6)	
FPS 9.98	>454 (0/7)	>454 (0/6)
None	>490 (0/6)	
PBS	>589 (0/5)	

*The number of mice developing prion disease (n) divided by the original number of inoculated mice (n_0) is shown in parentheses. Mice dying of intercurrent illnesses were excluded.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/1122864/DC1
Materials and Methods
Fig. S1

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No. 19

医薬品 研究報告 調査報告書

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研究報告の概要

○CJD専門家が「ヒツジのBSE」を警告

非定型スクレイピーと呼ばれるヒツジやヤギの脳疾患は、BSEに似ており、2003年に流行が始まった。今では英国中で82,000頭ものヒツジが罹患していると見積もられており、他の欧州諸国でも症例が報告されている。

現在、生後18ヶ月を越えたヒツジ20,000頭に対しては毎年TSEの検査を行っており、今までに非定型スクレイピー108例が発見された。しかしvCJD専門家のDr. Stephen Deallerは、この疾患がどの程度まで広がっているかを把握するために、もっと若い動物に対して緊急に検査を行うよう求めている。彼は、農業への影響を懸念して大規模な検査が行えないのではないかと示唆している。Deallerは、政府が人への感染の危険があると認める6年前に、共同研究者とともにBSEに関して警告を発している。彼の調査要求は他の消費者団体からも支持されている。

現在の消費者保護規定では、BSEの感染性が高いと考えられる動物の部位(脳など)は流通工程から取り除かれる。しかし、非定型スクレイピーが他の部位から感染するかどうかは不明である。

政府に対して助言する独立科学委員会は人や動物の健康への影響について確実なリスク分析をするにはデータが不十分であると話した。海綿状脳症諮問委員会は、より多くの情報を提供するために綿密な調査が重要でありすぐに行うべきだと述べた。

食品基準庁(FSA)は今後この問題を検討する予定であり、「理論上は危険」があるとしながらも、消費者にヒツジやヤギの肉を食べないよう推奨することはしていない。

微生物学会の会長で食品基準の専門家であるHugh Penningtonは非定型スクレイピーが人に害をもたらすとは言えないと話している。「人間は200年スクレイピーのヒツジを食べてきたが、誰も感染していない」

報告企業の意見	今後の対応
非定型スクレイピーと呼ばれるヒツジやヤギの脳疾患に関して、専門家が緊急に検査を行うよう求めているとの報告である。	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

解凍赤血球濃厚液「日赤」
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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

Sunday Herald – 05 March 2006

CJD expert warns of 'BSE in sheep'

Scientist who told of threat to humans from cattle calls for urgent study to find out how many animals have new disease

By Judith Duffy, Health Correpondent

A leading vCJD expert who sounded the alarm on BSE has called for the government to "take action right now" over fears that a recently discovered brain disease in sheep and goats could pose a risk to human health.

The disease, known as atypical scrapie, is similar to BSE in cattle and first emerged in 2003. It is now estimated that as many as 82,000 sheep could be infected in the UK and cases have been reported in other European countries.

The Food Standards Agency (FSA), has admitted there is a "theoretical risk" but it is not recommending that consumers stop eating sheep or goat meat.

However, vCJD expert Dr Stephen Dealler has demanded an immediate investigation to determine the extent of the disease. Lancaster-based microbiologist Dealler and his colleague Professor Richard Lacey warned the government about the dangers of BSE in cattle six year before ministers conceded there was a risk to humans.

"The worry is, of course, that atypical scrapie will be infectious to humans, but we don't know," Dealler said.

"All I can say at the moment is that with atypical scrapie, let's wait and see - but should we, in this wait-and-see period, be taking more aggressive action?

"Lots of people are saying we shouldn't just stand here and wait, lots of people are saying take action right now."

Under current regulations, 20,000 sheep in the UK over 18 months old are tested annually for brain diseases known as transmissible spongiform encephalopathies (TSE). These include atypical scrapie as well as the more common form of scrapie and BSE.

To date, a total of 108 cases of atypical scrapie have been detected via this testing programme. But Dealler called for further testing to be urgently carried out, particularly in younger animals, to determine exactly how widespread it is.

"At the moment, without the data on how much disease is out there, it is difficult to know what to do and how fast to act," he said. "That is why I say we need a survey right now.

"What they could certainly do is to do surveys and take so many sheep, test them when they are being slaughtered, and then see what proportion of those is atypical form.

"You can find BSE in the brains of cows long, long before they showed any symptoms at all and this will almost certainly be true with scrapie as well."

He suggested that concerns about the impact on farming were likely to be hindering an expansion in testing.

Current controls to protect consumers mean that parts of animals most likely to carry BSE infectivity - such as brains - are removed from sheep and cattle before entering the food chain. But it is uncertain if atypical scrapie could be carried in other tissue.

Dealler's calls for an investigation have been backed by consumer groups.

Sue Davies, Which? chief policy adviser, said: "We need urgent answers as to the many uncertainties surrounding this finding as quickly as possible so that there is a better understanding of whether there are any human health implications and, if so, whether existing control measures are adequate."

An independent scientific committee that advises the government said last week there is "insufficient data, as yet, to make reliable risk assessments for human health or animal health and welfare". In a statement, the Spongiform Encephalopathy Advisory Committee (Seac) also concluded that rigorous studies are "critical and urgent" to provide more information.

The FSA is due to initially examine the issue at a board meeting on Thursday . Possible options for precautionary risk reduction measures will be then discussed next month. An FSA spokeswoman said she could not pre-empt discussions by suggesting what - if any - measures might be taken.

"We can't rule out any theoretical risk, but we won't be changing our advice at this stage ," she said. "Based on the information we have, we are not recommending people change their eating habits on sheep or goats."

Professor Hugh Pennington, president of the Society for General Microbiology and an expert on food standards, said current evidence did not suggest atypical scrapie was a threat to humans.

He added: "The big question is: what implications does it have for human health? As far as we know, there are none basically, but of course we have to keep on doing research on this.

"One certain thing is that we have been eating scrapied sheep for 200 years and nobody has come to any harm."

Back to previous page

別紙様式第２－１

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
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研究報告の概要

英国政府は 1990 年代に輸出した英国製汚染血漿分画製剤により、患者が vCJD を発症するリスクにさらされていると 14 ヵ国（ブラジル、トルコ、ブルネイ、アラブ首長国連邦、インド、ヨルダン、オマーン、シンガポール、ベルギー、モロッコ、エジプト、フランス、オランダおよびイスラエル）に警告した。
問題は血漿分画製剤が数千人の血液から製造されいていることであり、科学者は未発症の感染者の供血によって引き起こされる「第二波」の災害を懸念している。
血液を介した感染リスクは 2003 年 12 月までは仮説に過ぎなかったが、その後輸血を介して感染した英国人患者が出現し、さらに 2 例が見いだされていることから、保健当局は国立企業の Bio Products Laboratory（BPL）により国外に輸出された血液製剤を再調査しなければならなくなった。
保健保護局は、輸出量や危険性を勘案し、最も危険性の高いブラジルとトルコ、それより危険性は低いが予防措置を講じる必要がある 6 ヵ国（ブルネイ、アラブ首長国連邦、インド、ヨルダン、オマーンおよびシンガポール）へは、予防措置（患者を追跡し、血液や臓器を提供しないよう通知すること、治療を必要とする場合は医師や歯科医に知らせるよう通知すること）を講じるように保健省に勧告した。危険性の低いベルギー、モロッコ、エジプトと、血液製剤を製造できるフランス、オランダおよびイスラエルについては自ら評価するよう勧告した。
BPL を管理する NHS 血液・移植当局は「現在のところ血漿分画製剤と関連づけられた vCJD 症例はない。」としている。

報告企業の意見	今後の対応
vCJD 多発国である英国が 14 ヵ国に血漿分画製剤を輸出していたので、該当国に対し警告を発したとの報告である。報告中で NHS は「現在のところ血漿分画製剤と関連づけられた vCJD 症例はない。」と述べている。 なお、当社では英国より血漿分画製剤又はその原料血漿を輸入したことはない。	今後とも vCJD に関する安全性情報、規制情報等に留意していく。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
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。

theguardian

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.

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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

医薬品 研究報告 調査報告書

識別番号・報告回数		1	報告日	第一報入手日 2006 年 4 月 10 日	新医薬品等の区分	厚生労働省処理欄
一 般 的 名 称	別紙のとおり		研究報告の公表状況	Identification of a Novel Single-Stranded DNA Fragment Associated with Human Hepatitis J. Inf,,Dis. 15;193(8):1089-97. 2006	公表国 日本	
販 売 名（企 業 名）	別紙のとおり					

研究報告の概要

（問題点：原因不明の急性肝炎発症患者の血液から、A型からE型ではない未知のDNA配列を持つ「NV－F」感染症が確認された。）

原因不明の急性肝炎を発症した患者の血液から、未知のDNA配列「NV-F」を発見。A型からE型までの肝炎ウイルスが検出されない、原因不明の肝炎患者 69 人中の 17 人（24.6%）で、NV-F が検出された。

17 人のうち 1 人は劇症肝炎で、NV-F は発症から約 10 日間、血中に現れ、症状の回復につれて消えた。この患者の肝細胞からは、NV-F が作り出した抗原が検出され、NV-F が肝臓で増殖したことをうかがわせた。

NV-F は、B 型や C 型と同じ経路で感染しやすいウイルスの DNA と推測される。

使用上の注意記載状況・その他参考事項等

記載なし

報告企業の意見	今後の対応
別紙のとおり	現時点においては、特段の対応は不要と考えるが、今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

MAJOR ARTICLE

Identification of a Novel Single-Stranded DNA Fragment Associated with Human Hepatitis

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By performing nonspecific polymerase chain reaction followed by elimination of chromosome-derived sequences, foreign DNA fragments were obtained from the serum of a patient with non–A–E hepatitis. One of the sequences, named NV-F, contained a partial open reading frame and was detected in 17 (24.6%) of 69 patients with non–A–E hepatitis, including 1 with fulminant hepatitis (vs. in 5 [2.8%] of 180 healthy individuals). A peptide was synthesized accordingly, to detect serum anti–NV-F antibody, which was found in 49 (75.4%) of 65 patients positive for NV-F. This DNA fragment was sensitive to S1 nuclease digestion. Cesium chloride gradient analysis revealed that the NV-F–associated particles had buoyant densities of 1.33–1.39 and 1.22–1.25 g/mL. Immunofluorescence analysis revealed that the novel antigen was present in the hepatocytes of patients infected with NV-F. In conclusion, we have identified a novel single-stranded DNA fragment derived from a virus-like agent associated with human hepatitis.

Previously, when diagnostic tests for the detection of hepatitis A and B viruses (HAV and HBV) were globally available, it had been recognized that a significant proportion of patients with acute and chronic hepatitis were not infected with either virus, and the diseases were referred to as "non-A, non-B hepatitis" [1]. Owing to technological advances in molecular biology, hepatitis C and hepatitis E viruses (HCV and HEV) were subsequently discovered to be the major causes of parenteral and enteric non-A, non-B hepatitis, respectively [2]. Despite this significant progress, the etiology of acute and chronic hepatitis in a substantial number of patients remains unknown. In our previous studies, we found that 15.9% of hospital inpatients with acute hepatitis had non–A–E hepatitis [3]. Additionally, 9.7% of patients with fulminant hepatitis had non–A–E hepatitis [4]. Another study indicated that no definite etiology could be found in 4.9% of patients with chronic hepatitis or cirrhosis; these cases were termed "cryptogenic" [5]. Approximately half of these patients had received transfusions, which supported a virological etiology. Furthermore, enhanced HLA expression in liver samples from patients with chronic non–A–C hepatitis has been reported, which also supports a virological etiology [6]. Therapeutic trials using interferon-α to treat chronic non–A–C hepatitis have consistently resulted in an ~50% response rate, indicating a viral pathogen [7]. Inspired by these observations, scientists struggled to unearth the theoretically existing hepatitis viruses. As a result, several new viruses, including GB virus type C (GBV-C) [8], TTV [9], and SEN virus [10], were discovered. However, epidemiological data failed to confirm a causative role for these viruses in hepatitis. In addition, a high percentage of individuals infected by these viruses were found to be healthy carriers. Furthermore, in some studies, it was argued that GBV-C was not, in fact, a hepatotropic virus [8].

In the present article, we describe a novel agent associated with human hepatitis. Epidemiological data suggest that it is highly associated with non–A–E hepatitis. Biochemical evidence indicates that it is hepatotropic. Additionally, it was detected in a patient with fulminant non–A–E hepatitis.

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