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Mad cow research to continue; 19 August 2006

One of the world's leading experts on mad cow disease tells swissinfo why the Swiss government will continue research into the disease despite its near disappearance.
Adriano Aguzzi, director of the Institute of Neuropathology at Zurich University, says research will now focus on preventing human-to-human transmission of BSE (bovine spongiform encephalitis).
Aguzzi headed research five years ago which discovered how prions – the infectious agents believed to cause BSE and its human equivalent, new variant Creutzfeldt-Jakob disease – reach the brain.
The government has decided to discontinue the BSE unit he heads in its present form at the end of the year, due to the near eradication of the disease in the country. The unit was created in 2001 to deal with the healthcare emergency.
However, the Italian scientist says research and monitoring will continue.

How do you view the decision taken by the cabinet to dissolve the "mad cow" unit?

Adriano Aguzzi: I think the decision to scale down the unit is the right one. But I'd like to

point out that the research unit will not disappear, it will simply be restructured in order to respond to other needs. We could even say that the "mad cow" unit has become a victim of its own success. In Switzerland, thanks primarily to the Federal Veterinary Office, the goal of wiping out the disease has been reached.
Mad cow disease has virtually disappeared and detailed controls, such as the one conducted up to now, have become less of a priority. However, this does not mean that we can let our guard down completely.

Can we consider the disease to have been eradicated once and for all or are we still threatened?

A:A.: There are some indicators suggesting that mad cow disease can never be overcome completely. Indeed, sporadic cases may still occasionally crop up. What counts is to be sure that the high-risk organs do not enter the human food chain. And this certainty has existed in Switzerland for over ten years.

What balance can be drawn from the work done by this unit?

A.A.: The result is very positive, also in terms of my personal experience as a scientist and researcher. I would actually like to underscore the excellent working environment at all levels. I have no doubt that if we have achieved these results it is due in part to the direct link between science, politics, administration and those called upon to take practical and specific decisions.
In all these years I have enjoyed seeing how it is possible to conduct a dialogue and cooperate at different levels. And, believe me, this is not something one can take for granted. **Thanks to these synergies, important decisions and initiatives were taken in real time**. The politicians were able to translate scientific progress into specific measures aimed at wiping out the disease.
What should be the focal point in future?
A.A.: In future, research and preventive activities will focus on the transmission of the disease not so much from cows to people **but from one person to another**. We must remember that 160 people have died from the disease. This is not a particularly high number although it was of course a tragedy for each person concerned.
Although there were no deaths in Switzerland it would be illusory to think that nobody was infected. Our efforts will now concentrate on preventing these people transmitting the disease to others.

In hindsight, do you think the concern surrounding mad cow disease was exaggerated?

A.A.: No, not at all. On the contrary, I think the level of concern helped to generate the right reaction. Because scientists and political bodies took it so seriously, we were able to take preventive action. And, let me repeat, with great success.

Do you believe that research in Switzerland is sufficiently well developed and able to deal with emergencies such as mad cow disease – and to find a response?

A.A.: In the field of research in life sciences (biology, medicine), Switzerland is certainly one of the forerunners. The number of important discoveries here in relation to the size of the population is in fact higher than in the United States.
However, it would be a serious mistake to rest on our laurels, because our future well-being

will be based precisely on the quality of research and scientific and technological progress. In this sense, I am afraid that things may develop in the wrong direction. **At the moment, in fact, Switzerland is no longer competitive in terms of investment in research.** If we think of what is currently being done in countries like China, India and Singapore which can count on high-calibre universities that concentrate on developing new technologies, Switzerland runs the risk of standing still – and suffering the consequences. Obviously, these savings are minor in the immediate future. But believe me, our children and grandchildren will not thank us at all for the decisions we take today.

Mad cow disease no longer a priority; 16 August 2006

The Federal Veterinary Office says it will reduce its BSE unit from 20 people to 12 by the end of 2006 and shift its focus to the entire food production chain.
The unit, which was created in 2001 to deal exclusively with mad cow disease, will in future concentrate on animal health and protection, humane production, food safety and hygiene.
The bovine spongiform encephalopathy (BSE) unit's budget will also be reduced by over a third, from SFr3.5 million ($2.8 million) to SFr2 million.
So far this year two cases of BSE have been reported; in 2005 the Swiss authorities reported three cases of the encephalopathy in animals that were infected in the mid-1990s.
The crisis over mad cow disease peaked in Switzerland in 1995 when 68 cases were reported across the country.
The most important signs of BSE in cows are generally slow wasting and a decline in milk yield with unchanged appetite. Other signs are excessive anxiety and nervousness, but also aggressiveness.
Affected animals often have a swaying, stiff or high-stepping gait, with buckling of the hind limbs, or in advanced disease they even remain in a recumbent position.
The infection was found to spread through the use of meat and bone meal to feed cattle. This was banned in 1990 as one of the first measures implemented by the Swiss authorities, but it took years before it completely disappeared from farms.
It was only in 2004 that no traces of banned animal products were found in feed for livestock for the first time. In 2003 0.3 per cent of tests still revealed traces.
In 1990 Switzerland became the third European country after Britain and Ireland to register cases of BSE in its cattle. The disease was first defined in Britain in November 1986. Some 83,000 cases have been detected there since then.
The human illness, Variant Creutzfeldt-Jakob Disease (vCJD), was recognised in 1996 and is thought to result from the consumption of BSE-infected meat. There have been no cases of vCJD reported in Switzerland.
In 2004, the United Nations praised Switzerland for its efforts to control mad cow disease, calling it a model for other nations.
The same year, Swiss experts were sent to the United States, following that country's first confirmed case of BSE.

Test may identify mad cow disease in humans; 7 July 2006

A test has been developed that offers the first real hope that scientists will be able to identify early those people carrying the human form of mad cow disease.

People could be infected with vCJD for more than half a century without developing the illness.

An American team today announces a blood test that can identify carriers of the disease. If the test is validated it would mark the most significant development in the understanding of the disease for many years. Discussions have already started with British authorities to use it in a screening programme.

Screening the population could energise the search for vCJD treatments, since drug companies are reluctant to carry out research on treating a disease that has caused about 150 deaths, with the numbers of cases declining from a peak in 2000.

But some influential scientists, notably Prof John Collinge of University College London, believe that the patients seen so far may be those with a genetic make-up that leads them to have shorter incubation periods. They warn that more people may be incubating the disease after eating BSE-infected meat before effective measures were enforced in 1996.

The test is also important because it will enable blood and organs to be screened for the infectious agent thought to be responsible, a version of the so-called "prion" protein.

If many people are carriers, so called secondary transmission could play a significant role in the human epidemic.

However, there could be a downside of this knowledge: insurance and mortgage -companies could insist on knowing the results of the test and it could create an underclass of people who are silently incubating the brain disease.

These extraordinary possibilities are raised by a study published today in the journal Science by Dr Paula Saá, Prof Claudio Soto and Prof Joaquin Castilla, at the University of Texas Medical Branch in Galveston.

The team describes a technique to detect infectious -prions in the blood of hamsters before signs of illness. They detected prions in as few as 20 days after the hamsters had been infected, about three months before the -animals began showing -clinical symptoms of the disease.

The experiments have been followed by tests on samples from patients and cattle.

The test picks up between 60 and 90 per cent of those infected, depending on the amount of circulating prion.

Because the amount circulating is relatively low in the hamsters compared with people, Prof Soto believes it should detect a higher proportion of human carriers. He said the tests may help estimate how many people are infected with vCJD.

Scientists find link between brain wasting, heart problems; 7 July 2006

Montana scientists have discovered that brain-wasting killers like mad cow disease can also affect the hearts of its victims, infusing heart muscle with waxy deposits making it harder for infected hearts to beat.

In a paper published today in the online edition of the journal Science, researchers at Montana's Rocky Mountain Laboratories in Hamilton, showed that special laboratory mice infected with scrapie a brain-wasting disease in sheep also had large deposits of the scrapie agent in their hearts.

Scrapie is one of a family of brain-wasting diseases, including chronic wasting disease in deer and elk, mad cow disease in cattle and Creutzfeldt-Jacob disease in people associated with twisted, malformed proteins called prions. The prions congregate in the brains of victims and are associated with Swiss-cheese like holes in brain tissue that are always fatal.

Exactly what causes the diseases, known as transmissible spongiform encephalopathies, is unclear, although one hypothesis holds the proteins themselves cause infection.

RML's Bruce Chesebro, a virologist and lead author of the paper, said the discovery is the first time prion proteins have been shown to cause heart problems and will probably prompt other researchers to start looking at the heart in future prion research.

"We don't have a clue as to why this deposited in the heart, as opposed to the liver," he said. "We don´t really understand that". The study involved special mice. Prions are misshapen proteins. But that same protein when it's not twisted up is common in the body, although researchers aren't exactly what role healthy prion proteins play.

Scientists engineered the mice in Chesebro's experiment to have a different kind of healthy prion protein. That way, when the mice are inoculated with an infectious brain-wasting disease, like scrapie, the resulting prions will behave in a certain way.

Chesebro said that at this point, it's not clear if the deposits of prion in the hearts of the mice are related to their unique make-up, or if it's common in many victims of prion diseases, but no one ever thought to look.

"We have no evidence in this paper that prions can invade human hearts, but we're interested in investigating those questions," he said.

The prion deposits formed a special kind of waxy, protein plaques called "amyloids."

Alzheimer's disease is also an amyloid disease because it is associated with waxy, protein plaques in the brain.

Amyloid heart disease is also found in people, although it is very rare.

Anthony Fauci, head of the National Institutes of Allergy and Infectious Diseases, the arm of the National Institutes of Health that oversees RML, noted that connection with prion heart disease.

"Although much work remains to be done, the diseased hearts seen in this mouse study have similarities to human amyloid heart disease, which is potentially significant," Fauci said in a statement.

The Montana scientists conducted the experiment with researchers at The Scripps Research Institute in California.

Linklater's Scotland; 25 June 2006

MAGNUS LINKLATER

TEN years ago, a new strain of human brain disease was identified, and it sparked one of the great medical scares of modern times. New variant Creuzfeldt Jakob Disease was not only a degenerative and incurable infection of the brain, it was linked to the outbreak, a decade earlier, of a similar disease in cattle - BSE. In 1996, after months of foot-dragging, John Major's government was finally forced to announce that vCJD could be caused by eating contaminated meat.

The statement led to the virtual collapse of the British beef industry, an export ban, a cost of some £3.5 billion and - since thousands of people in Britain had been exposed to the risk by eating infected beef - the possibility of a serious pandemic. Newspaper headlines spoke of hundreds of thousands of deaths from this deadly disease. Even scientists analysing likely models for the outbreak admitted that up to 80,000 people could die.

Last week I visited the website of the National CJD Surveillance Unit to check the latest figures. It showed that last year precisely three people died from vCJD. The total number of deaths since 1995 is 156, and the yearly figure has been in steady decline since 2000 - when 28 people died. Whatever happened to the great epidemic?

The headquarters of the surveillance unit is an anonymous office block at Edinburgh's Western General Hospital and is run by Dr Richard Knight, a 55-year-old clinical neurologist. His job is to monitor the progress of the disease, to plot how or whether it is changing and to inform scientists, and ultimately the public, if we are at risk. He is not only responsible for the UK's state of knowledge on the various strains of CJD, he also co-ordinates research across Europe.

Why are the figures falling? With refreshing candour, he admits, "We do not know." But the more he describes the complexities of the disease, the accepted scientific definition of its nature and the dominant theory that links it to cattle, the more I begin to question whether we might not have got the whole thing badly wrong, and to wonder whether there really is any connection between the cattle and the human disease. Could this have been the scare that never was?

This is not the way Dr Knight sees it. He believes that BSE and vCJD are the same strain of disease, and until someone comes up with a better explanation for how it is passed on, he sticks with the idea that the two are linked. "My approach is rigorously empirical," he says. "I am wedded to the principle that any scientific fact is simply a truth until the next experiment proves it to be false. When I say that BSE is the cause of vCJD, I have to be open to the idea that it may be proved false. But there is little doubt that there is a relationship between the cattle disease and the human disease, and all the facts point towards BSE as being the cause of vCJD. I know of no good evidence for any alternative."

The entire thesis rests on one of the most controversial scientific discoveries of recent times. In 1997, Stanley Prusiner, professor of neurology at the University of California, was awarded a Nobel Prize for proposing that the cause of brain diseases such as CJD, scrapie in sheep and BSE in cattle was a new type of infectious agent - not a virus or a bacterium, but a protein. He called these proteins prions, or proteinacious infectious particles.

Unlike other agents, prions have no genetic material, which makes them the only lifeform that can multiply without a gene. Prusiner says they enter the body through food, thus setting off a chain reaction, converting normal proteins into abnormal ones, creating deposits that

cause irreversible brain damage. Radical as the idea is, it has gradually been winning support, becoming today the accepted explanation for these diseases.

But there have always been doubters - maverick scientists like Professor Alan Ebringer, or the Somerset farmer Mark Purdey, who claim to have discovered other, more conventional causes of the disease. In recent years these doubts have grown, in the pages of medical journals. Researchers say they have been unable to replicate Prusiner's findings using laboratory-made prions. Experiments with sheep, given food heavily contaminated with abnormal prions, showed that the animals simply digested them, with very few of the prions surviving. It seems possible that another, unidentified agent might be responsible for the disease. Even more challenging is the suggestion that the abnormal prions might be the consequence of the disease rather than its cause.

To all of this, Dr Knight responds with measured caution. He says that there may be different reasons for the fact that so few deaths have occurred. First, the numbers, as reported in the press, were far too high. "The outlandish predictions were never likely to be realised," he says. "Even 80,000 was an upper limit, and we never seriously expected it to reach that level. Those figures should not be taken seriously."

Second, some people may have a genetic disposition to the disease while others do not, thus eliminating thousands who might otherwise have caught it. Then there is the long incubation period - as much as 40 years, which means that a victim may be infected, but is likely to die of other things long before the disease catches up with them. "Some people may have been infected, but have not yet become ill because the incubation period is so long," he says. "We are not sure about this because we have no pre-clinical tests. Then there is the possibility of the sub-clinical disease - that is, someone becomes infected, but it never develops into the full-blown disease."

But what about the possibility that the prion theory is simply wrong, that for more than a decade we have simply been pursuing the wrong trail? Dr Knight's reply is surprisingly equivocal. "The burden of proof now rests with the opposition," he says. "Someone has to come forward with an alternative. No one has done it. I'm an agnostic on the prion theory. I don't know what the cause of the prion disease is, but it is the dominant theory, and it explains an awful lot. The empirical data is difficult to explain, however. The disease occurs with high levels of infection and low levels of prion."

So could there be another cause of the disease? "It is possible for the prion theory to be false, but for the cattle disease still to be the cause [of vCJD]," he says. "It is possible that there is another agent involved, but I do not know anyone who has come up with an alternative."

He concedes that because prions have no genetic code it is hard, if not impossible, to codify different strains of the disease in cattle and humans. "The prion theory has not yet been fully proved," he says. "It might be proved wrong. It is simply a theory about the nature of the infectious agent, but it does not have an adequate explanation of strain behaviour. The prion protein theory explains an enormous amount, but it fails to explain certain things adequately. There is an important piece missing."

The scientists who finds that piece could well be on the way to winning another Nobel Prize. In the meantime, though, we can simply give thanks that a killer disease is on the wane and that we can continue to eat beef and mutton without a qualm.

This is the last of Linklater's Scotland. From next month Magnus Linklater will be writing for the Review section.

Human mad cow infection could hide for 50 years; 24 June 2006

INFECTION with the lethal prions that cause the human form of "mad cow" disease could last more than 50 years before symptoms appear, research based on an old cannibal disease from Papua New Guinea shows.
During that time, victims with silent infection could pass on the prions via blood transfusions, organ or tissue donations or insufficiently sterilised metal surgical instruments.
In a unique piece of research which continues the meticulous records that have tracked the epidemic of kuru - the "shivering" disease - since 1957, Australian, British and PNG researchers tracked a group of 11 former cannibals dying from the always fatal prion disease between 1996 and 2004.
Forming the tail-end of the epidemic, they were all born before 1950 and took part in endocannibalism, a ritual in which the whole body of deceased relatives was consumed as a sign of love and respect. The ritual was eradicated by Australian authorities by 1960.
The data gathered on these victims and published today in *The Lancet* have provided a model using actual cases instead of the usual mathematical modelling for future predictions for those infected after eating beef products contaminated with bovine spongiform encephalopathy (BSE). The human equivalent of BSE is variant Creutzfeldt-Jakob disease (vCJD).
Apart from the emerging epidemic of vCJD, in which 192 people have died since 1995 - mainly in Britain, but also in France, Ireland, Canada, the US, Saudi Arabia, Japan, Italy, Hong Kong and the Netherlands - kuru is the only other major human epidemic of prion disease with an oral transmission route.
British prion experts, including Professor John Collinge from University College London, and Professor Michael Alpers from Curtin University - the Australian kuru expert who has followed the disease since arriving in PNG in 1962 - calculated the minimum incubation period for kuru starting at 1960 to the birth year of the last recorded patient.
That minimum incubation time ranged from 34 to 41 years but in men it was calculated to be between 39 and 56 years - and possibly up to seven years longer.
For vCJD it might be even longer, because the infection was transmitted between species, from cows to humans, which usually takes longer than infection within the same species.
Australian prion experts have closely monitored the decade-old vCJD epidemic, and have long recognised from continuing kuru cases that incubation periods could top 50 years.
A professor of pathology and a CJD expert at the University of Melbourne, Colin Masters, commented yesterday: "These new data reinforce our need to maintain vigilance over potential risks to the safety of Australia's blood supply, since it has now been demonstrated that vCJD can be transmitted by blood transfusions."
In an accompanying editorial, *The Lancet* stated: "Any belief that vCJD incidence has peaked and that we are through the worst of this sinister disease must now be treated with extreme scepticism."

Human mad cow epidemic may be underestimated; 24 June 2006

London, June 24: People could be infected with the human form of mad cow disease for more than 50 years without developing the illness, which means the size of a potential epidemic may be underestimated, UK scientists said on Friday.

So far about 160 people have been diagnosed with variant Creutzfeldt-Jakob disease (vCJD). Cases of the fatal disease have also been reported in France, Italy, Ireland, the Netherlands,

Canada, Japan and the United States.

Estimates have varied widely of how many people are likely to develop the brain illness caused by eating meat products contaminated with Bovine Spongiform Encephalopathy (BSE).

It has been difficult to predict due to the long incubation period, which scientists had thought could be up to 20 years.

But Professor John Collinge and researchers at University College, London believe it could be longer and that an eventual epidemic could be bigger.

"Recent estimates of the size of the vCJD epidemic ... could be substantial underestimations," he said in a report in The Lancet medical journal.

The scientists' findings are based on a study of another human disease called kuru, which like vCJD is caused by a mutated prion brain protein.

Kuru reached epidemic proportions in some parts of Papua New Guinea where cannibalism had been practised up to the 1950s in a ritual where natives ate dead relatives as a mark of respect.

Researchers Say Incubation Period for Mad Cow Disease May Be Longer Than Thought; 23 June 2006

June 23, 2006 -- Symptoms of mad cow disease (bovine spongiform encephalopathy, BSE) may emerge more than 50 years after infection in humans, according to a new study.

Researchers say the findings show that the size of a potential mad cow disease epidemic may be much bigger than previously thought.

John Collinge of University College London and colleagues studied the only other known BSE disease outbreak in Papua New Guinea and found those infected in the initial outbreak in the 1950s were still developing the disease 50 years later.

Researchers say large segments of the U.K. population have been exposed to BSE prions by eating infected meat. So far about 160 cases of the human variant of mad cow disease (variant Creutzfeldt-Jakob disease, vCJD) have been identified in the U.K., with cases also reported in other countries. Prions are unconventional proteins that are behind mad cow disease, vCJD, and other types of degenerative diseases.

Recent estimates on the eventual size of a BSE outbreak are based on current numbers of vCJD patients. But researchers say determining the incubation period for the disease is critical to predicting the true extent of an epidemic and has been unknown until now.

Mad Cow May Wait to Emerge

In the study, published in *The Lancet*, researchers studied the only example of a human prion disease epidemic, a disease called kuru. Kuru is caused by cannibalism and reached epidemic proportions in the parts of Papua New Guinea where the consumption of dead relatives -- as a mark of respect and mourning -- occurred through the 1950s.

Between 1957 and 2004, the total number of kuru cases was more than 2,700. The average time before symptoms emerged was 12 years but was more than 50 years in some cases.

The last year of birth recorded for a patient with the disease was 1959, and researchers assumed that transmission of the disease by cannibalism stopped when the practice ceased by 1960.

However, they identified 11 people in the region who were diagnosed with new symptoms of kuru from 1996 to 2004, which meant that incubation periods for the disease ranged from 34 to 56 years and may have been even longer.

Genetic analysis showed that people recently diagnosed with kuru had a particular gene variation that is associated with extended periods of incubation and resistance to the disease.

They say the results suggest that the incubation time for kuru and other BSE diseases, including mad cow disease and variant Creutzfeldt-Jakob disease, may be much longer than previously thought.

As a result, Collinge says current predictions of the size of a human BSE epidemic may be substantially underestimated.

Mad cow disease could remain hidden in humans for decades; future death waves possible; 23 June 2006

A new study of members of New Guinea's Fore tribe suggest that more people may die from past mad cow disease outbreaks. The study shows that tribe members who contracted a similar disease to mad cow through cannibalism may have lived for decades before finally succumbing. This leads some scientists to question if additional mad cow deaths could show up long after intial reports of the disease were made.

Until the 1960s, the Fore tribe practiced ritualistic cannibalism and many contracted kuru, a disease caused by misfolded prion proteins in the brain. Creutzfeldt-Jakob disease occurs when people consume brain tissue from cows infected with mad cow disease, and works in much the same way.

In the study, authors recorded the age of death and genetic makeup of 11 members of the Fore tribe who died of kuru between 1996 and 2004. All eleven members were born prior to the 1950s when the Australian government outlawed the tribe's practice of honoring their dead by eating them at mortuary feasts.

Researchers noted that some infected members of the tribe were able to live for years without any symptoms of kuru, and found that the disease can incubate for up to 56 years before causing a rapid descent into dementia and death. The study authors theorize that some people infected with mad cow disease may also be able to live long lives before succumbing to the disease.

However, many experts disagree with this assumption. As a human disease, kuru is more likely to infect people than mad cow disease. Also, cannibals in the Fore tribe had direct contact with infected brain tissue, while most people who eat beef do not consume brain matter.

Mad cow risk still present as cattle feed in nine states found to contain banned cow remains; 23 June 2006

Livestock feed manufacturer H.J. Baker & Bro. has issued a recall for supplements sold in nine states that may have been contaminated with cattle remains, a violation of a 1997 ban meant to protect against the spread of mad cow disease.

Samples of two supplements added to dairy cattle feed tested positive for cattle meat and bone meal in a test by the U.S. Food and Drug Administration, according to the Connecticut company's president, Mark Hohnbaum. He said he did not know how much of the infected feed was sold.

"This is very concerning to us," said Hohnbaum. "We are very serious about food safety."

Mad cow disease is spread when cattle eat feed containing the nerve or brain tissue of cows infected with the disease. Prior to the ban, cattle were routinely fed parts of other cows to speed growth. Some critics say this practice still regularly occurs.

Hohnbaum says his company is notifying customers in the nine states affected by the voluntary recall, which include Alabama, California, Florida, Georgia, Kentucky, Louisiana, Michigan, Mississippi and Tennessee.

Human Mad Cow Disease May Be Lethal 50 Years After; 23 June 2006

Infections caused by lethal prions can be very difficult to detect since the human form of "mad cow" disease has a long incubation period, according to a new research.

The symptoms can take as long as 50 years to appear and victims of this "silent killer" could unknowingly pass on the infection to others through blood transfusions and organ or tissue donations.

Variant Creutzfeldt-Jakob disease, or vCJD (the human "mad cow" disease) thus has the potential to cause an epidemic, the researchers add in the report appearing in the June 24 issue of the Lancet. They arrived at this conclusion after analyzing a brain-wasting disease in

cannibals.

The disease in cannibals is called kuru. This is also caused by abnormal prions and is characterized by brain wasting. Kuru like vCJD is caused by prions, which are mutated proteins. In the early 1920s kuru took on epidemic proportions in the New Guinea cannibals.

The disease was though to result from the Fore practice of honoring their dead by butchering them with bamboo knives at mortuary feasts and eating them. In some cases the Fore members were known to smear themselves with brain tissue, which would drive infection into cuts and scratches.

Researchers at University College London tracked patients suffering from kuru in Papua New Guinea society. The disease was common there due to the practice of cannibalism, which incidentally was banned in 1960.

The researchers analyzed the incubation period for kuru by collecting the birth year data of eleven participants. All participants were born between 1933 and 1949. These members belonged to the Fore tribe and died from 1996 to 2004 of kuru. The disease can lie dormant for a long period of time before presenting as dementia and finally death.

The researchers calculated that the 11 patients had minimum incubation periods of between 34 and 41 years. More accurately in men it was between 39 and 56 years. The researchers said that a genetic variant in the participants protected them from kuru for a long period of time.

Researchers feel that the incubation period for BSE (bovine spongiform encephalopathy) could be even longer. This is because infection between different species typically takes longer to develop than one passed within the same species.

Professor John Collinge, who is the lead researcher of the Lancet study says that CJD patients identified so far "could represent a distinct genetic subpopulation with unusually short incubation periods for BSE". He added that a human BSE epidemic might have a number of phases.

"For the first time we can see the extraordinary incubation period in human prion disease," Collinge said. "It's sobering that half a century on, this disease has not disappeared."

"Recent estimates of the size of the vCJD epidemic based on uniform genetic susceptibility could be substantial underestimations," Collinge said. "A human BSE epidemic may be multiphasic, and recent estimates of the size of the vCJD epidemic based on uniform genetic susceptibility could be substantial underestimations."

While experts were impressed with the tenacity shown by researchers in tracking the incubation period of kuru, they said that with the mad cow disease, the researchers had perhaps jumped to conclusions. Dr. David Westaway, a prion expert at the University of Toronto told The New York Times, "That's a provocative conclusion, but I'm not sure it's totally plausible."

But Collinge urged caution, "Most people seem to be thinking that we're over the worst of it," he said. "We have to be cautious about assuming this disease is going away."

Till date, vCJD or mad cow disease has claimed 160 victims mostly in Britain. The disease spreads through cows by contaminated feed and is transferred to humans by eating contaminated beef.

variant Creutzfeldt-Jakob Disease
* BSE (bovine spongiform encephalopathy) is a progressive neurological disorder of cattle that is caused by an agent called as prion. It is not properly understood how this prion transmits itself among cattle.

* The disease is characterized disorientation in the affected animals, clumsiness and aggressive behavior towards humans and other animals. BSE is usually a fatal disease.

* In humans BSE takes the form of a variant CJD (Creutzfeldt-Jakob Disease). This disease is characterized by psychiatric/behavioral symptoms; painful dyesthesiasis and delayed neurological signs.

* The CDC says that the median age of death in the variant form is 28 years and death usually occurs within a year of contacting the infection.

* The onset of illness in the first case of vCJD occurred in early 1994, nearly a decade after the first case of BSE was recognized in cattle.

* Although averaging only 10-15 cases a year since its first appearance in 1994, its future magnitude and geographic distribution cannot yet be predicted.

* The incubation period of the disease remains unknown.

Human 'Mad Cow' Could Cause Eventual Epidemic; 22 June 2006

(HealthDay News) -- Variant Creutzfeldt-Jakob disease, or vCJD, the human form of "mad cow disease," has a long incubation period and could cause an eventual epidemic, researchers report.

Reporting in the June 24 issue of the *Lancet*, they looked at a similar disease -- linked to cannibalism -- to better understand the impact such an epidemic might have.

Mad cow disease, or bovine spongiform encephalopathy (BSE), is caused by misfolded brain proteins called prions, which cows contract through contaminated feed. Humans can catch the human form the disease, vCJD, by eating contaminated beef. So far, the fatal degenerative illness has infected about 160 people in the United Kingdom. More cases have been confirmed in six other countries, including the United States.

Now, researchers at University College London have determined, through the study of a similar disease, that BSE has an incubation period of more than 50 years before it actively becomes vCJD.

Patients in Papua New Guinea with a disease called kuru -- the only currently epidemic human prion disease -- were studied to determine how long the disease was dormant before symptoms appeared.

Kuru occurs in Papua New Guinea society because the disease was transmitted through cannibalism -- a common cultural practice up until 1960. By comparing the birth year in relation to the cessation of cannibalism in the community, the researchers were able to assess incubation periods of the disease.

Eleven participants in the kuru study had minimum incubation periods of between 34 and 41 years, the researchers calculated. They could more accurately calculate the date of infection for men, and estimated an incubation period of between 39 and 56 years, with the potential for even seven years longer.

The researchers also noted a genetic variation in some kuru patients that has been known to promote long incubation periods.

John Collinge, one of the researchers, wrote in a prepared statement that the current small cohort of vCJD patients "could represent a distinct genetic subpopulation with unusually short incubation periods for BSE," suggesting that many more vCJD patients who caught the disease via contaminated beef could emerge in the coming decades.

"A human BSE epidemic may be multiphasic, and recent estimates of the size of the vCJD epidemic based on uniform genetic susceptibility could be substantial underestimations," Collinge said.

New warning on mutton as brain disease hits sheep; 14 June 2006

Food experts say that BSE-style illness might affect humans

MEAT-EATERS have been told that avoiding mutton, goat and some sausages is the only way to reduce the risks from a new animal brain disease.

Britain’s food watchdog admitted yesterday that it could not rule out a risk to human health from the brain disease atypical scrapie, which is similar to BSE.

The advice from the Food Standards Agency raises the most serious concern about the safety of the meat since the discovery of “mad cow” disease in cattle. The new disease is similar to classic scrapie, a brain-wasting disease that has been known in sheep for more than 100 years, but which has never posed health concerns in human beings.

Mutton accounts for a quarter of sheep meat sold in Britain and is commonly used in many meat pies, pasties, curries and some ready meals. The risk from sausages comes from haggis and some upmarket brands that use casings made from sheep’s intestines.

The agency said that it was updating guidance to shoppers because it did not know whether atypical scrapie could affect health.

While it is not advising people to stop eating sheep or goat meat, or their dairy products, it makes clear that consumers can reduce the risk of a new disease.

However, shoppers will find it difficult to identify mutton products because there is no requirement to label it, except for pre-packed sausages. There is also no legal definition of what comprises mutton.

The agency is to ask the European Commission for the urgent introduction of new labelling rules that would mean manufacturers would have to identify products containing mutton.

Proposed new advice, to be discussed by the Food Standards Agency tomorrow, says: “While the agency is not advising anyone to stop eating sheep or goat meat or products, any possible risk could be reduced further by not eating meat from older animals.”

It adds: “In addition, some sausages are contained in natural sheep casings made from sheep intestines which are more likely to carry the disease agent and therefore could present a greater risk.”

Atypical scrapie is now identified in the national flock — there could be as many as 82,000 cases — and it has been found in sheep throughout Europe.

The move threatens to derail a new offensive from the Prince of Wales to bring about a renaissance in mutton eating. Peter Morris, chief executive of the National Sheep Association, said last night that the agency advice would trigger a new food scare.

“It runs the risk of people not eating mutton and sends out negative messages about mutton, when there is no proven risk.

“The Prince of Wales is such a keen supporter for the revival in mutton I am sure he will be among the first to put out the message that people should keep potential risks in proportion and keep eating mutton.”

Peter Ainsworth, the Conservative rural affairs spokesman, said: “We need to be cautious about any threat to human health. But there is a real danger that a message of this kind will create serious difficulties for sheep farmers at a time when they least need further problems from government agencies

“It’s incredibly important that the FSA behaves in a measured and appropriate manner.”

The 8,000 tonnes of British mutton eaten each year in Britain is worth about £400 million a year.

Safety-first policy raises public fears; 14 June 2006

SINCE “mad cow” disease (BSE) appeared in 1986, far closer surveillance has been put in place — both for cattle and for sheep, which can suffer from a closely related disease, scrapie.

An unusual form of this disease was detected in 2004 by the Veterinary Laboratories Agency as part of a survey of samples from abbatoirs and stock that died in the fields.

Atypical scrapie, as it is called, is neither traditional scrapie — which has been present in British flocks for 250 years — nor BSE.

One of its characteristics is that it appears in sheep whose genetic make-up makes them especially resistant to classic scrapie.

The unanswered question is whether atypical scrapie is a health hazard to humans. The chances are it has been around for a long time, but has been detected now because methods have become more sensitive.

Classic scrapie has never infected humans, so far as we know. So why worry that atypical scrapie might?

In the background is the awareness that ministers gave falsely reassuring advice about BSE when it emerged. They asserted, wrongly, that it could not transmit to humans. As we now know, in a few cases it can.

So scientists, Defra and the Food Standards Agency are bending over backwards not to make the same mistake again.

The trouble is that once the agency starts advising consumers to avoid products — mutton and sausage cases made from sheep intestines, in this instance — they raise the suspicion there is something to worry about.

Key stress protein implicated in Parkinson´s and Alzheimer´s; **2 June 2006**

Researchers have discovered a mechanistic link between cellular stress caused by free radicals and accumulation of misfolded proteins that lead to nerve cell injury and death in neurodegenerative disorders such as Alzheimer's and Parkinson's Disease.

The link is Protein Disulphide Isomerase (PDI), a chaperone protein that is necessary for proper protein folding in times of cellular stress. Published in the current issue of Nature, these findings from workers at the Burnham Institute for Medical Research revealed that in patients with Alzheimer's and Parkinson's Disease, overproduction of free radicals, specifically nitric oxide (NO), causes inhibition of PDI by a reaction called S-nitrosylation, thereby reducing PDI's neuroprotective benefits. This data provides the first molecular link between NO free radicals and protein misfolding, which is currently thought to be a common pathway in the pathogenesis of virtually all neurodegenerative conditions. Such conditions also include ALS (or Lou Gehrig's disease), Huntington's disease, and many others. Understanding the PDI pathway may lead to the development of new therapeutic approaches for these neurodegenerative diseases and other disorders associated with abnormal protein accumulations due to cellular stress.

"To our knowledge, this is the first published evidence of a link between protein misfolding due to enzymatic machinery malfunction found in a number of degenerative diseases and free radical stress in nerve cells," said Stuart A. Lipton, Professor and Director of the Del E. Webb Center for Neurosciences and Aging at the Burnham Institute and senior author of the study.

"Our data demonstrate a previously unrecognized relationship between NO and protein misfolding in degenerative disorders, showing that PDI can be a target of NO in cellular models of Parkinson's disease and human neurodegenerative disease."

A protein's structure determines its function. Genetic defects as well as exposure to free radicals or possibly other types of cellular stress can cause small structural defects that lead to protein misfolding. If the misfolded proteins cannot be refolded properly or degraded, they may build up in the cell to cause dysfunction. Defects in either the protein folding or degradation pathways can lead to accumulation of misfolded proteins. The accumulation of misfolded proteins is a common pathogenic mechanism in many diseases, including neurodegenerative disorders.

Can this really kill you?; 30 May 2006

The Nobel prize-winning hypothesis that infectious proteins can cause CJD and 'mad cow disease' is still being challenged. Roger Highfield reports

A decade or so ago, the Nobel prize for medicine was awarded to a scientist who had an idea so radical that it was condemned as heresy by his peers. Rather than blame conventional agents such as viruses and bacteria for a series of baffling "spongiform" brain disorders like Creutzfeldt-Jakob Disease (CJD), scrapie and BSE, Stan Prusiner proposed that a novel type of infectious agent was responsible.

Prusiner began his long journey to this breakthrough in 1972 after one of his patients died of dementia resulting from CJD. Now a professor at the University of California in San Francisco, he named the culprit the "prion" - "proteinaceous infectious particle".

Unlike viruses, bacteria or parasites, a prion is an infectious protein that contains no genetic material. When he suggested the idea, it was greeted with disbelief since it marked the only lifeform that could multiply without a gene. Scientific ridicule was heaped on Prusiner's head, but in 1997 his dogged persistence paid off and his Nobel prize citation described how "an unwavering Prusiner continued the arduous task to define the precise nature of this novel infectious agent".

Abnormal prions are thought to enter the body through food or cuts to set off a chain reaction: the infectious, abnormally shaped prion causes a domino effect, converting normal forms of the protein into abnormal proteins, creating deposits that cause irreversible brain damage. Because these prion diseases have such long incubation times, it has taken an age to study them in detail and there is still a lot we don't understand.

But even today, and almost a decade after Prusiner's Nobel prize, findings still challenge his hypothesis so that, at best, it seems incomplete and, at worst, it may even be wrong.

One recent example came from Dr Martin Jeffrey at the Veterinary Laboratories Agency. His team studied 50 sheep to see what happened when they ate food contaminated with the spongiform disease scrapie. The team monitored the passage of half a gram of liquified brain containing millions of abnormal prions. They were thought to pass undigested through the gut wall into specialised lymphoid tissue called Peyer's patches, where they multiplied before spreading to the central nervous system and on to the brain.

But his team reports in the Journal of Pathology how the prions did not go to Peyer's patches as expected, but were digested or vanished into the lymph nodes. Separate experiments show that abnormal prions can easily be digested by sheep stomach juices, so even if an animal ingested large quantities of infected feed, hardly any abnormal prions would survive.

In the three sheep that did develop scrapie after being injected with diseased tissue, abnormal prions began accumulating in the Peyer's patches 30 days later, even though all the prions from the original gut injections had long gone. When Dr Jeffrey looked into this, he found that the prions were being formed afresh in the patches.

Because the disease was triggered by liquefied sheep brain, the study raises the possibility that an unidentified agent caused the infection which, a month later, triggered the Peyer's patches to make the abnormal prions. This will remain only conjecture until the infectious agent is identified, but the work shows that the prion hypothesis "is not completely satisfactory", says Dr Jeffrey.

To further undermine the link between prions and spongiform disease, his team has shown that the prions do not seem to build up into clumps of sufficient size and in the right place in animals to link with the symptoms of spongiform disease. Working with Dr Bruce Chesebro of the Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, Dr Jeffrey found damaged areas in scrapie brains where there were no prions.

Dr Chesebro's own experiments have raised questions. He exposed two groups of six-week-old mice to different strains of scrapie. Within 150 days of being inoculated with the natural form of scrapie prion protein, all 70 mice in the control group showed signs of infection: twitching, emaciation and poor co-ordination. But in GM mice that made a prion protein that does not anchor to cells, he found clumps of abnormal protein in the brain, brain damage, but no disease. "The mice didn't get sick. That's very significant. The dense accumulations of scrapie plaque in the brain resembled the plaque seen in Alzheimer's, but
it wasn't toxic."

These findings once again raise the possibility that the abnormal proteins are a consequence of the disease process, rather than a cause. (Interestingly, a similar argument is raging over the protein deposits linked with Alzheimer's disease.)

The most fundamental issue of all was raised by the Nobel prizewinner Prof Kurt Wuthrich of the Swiss Federal Institute of Technology, Zurich: he pointed out that researchers have failed to produce spongiform disease using laboratory-made prions, the only real way to eliminate the possibility that another agent might be responsible.

That challenge seemed to have been met last year in the journal Cell, in an experiment by Prof Claudio Soto at the University of Texas Medical Branch at Galveston. His team took prions from infected hamsters and placed them in test tubes containing healthy brain proteins. When the healthy proteins had been largely transformed into prions, the samples were diluted over and over again and the process repeated, until the only remaining prions were presumably those that had been newly generated in the test tubes. These were then injected into the brains of healthy hamsters, which died less than six months after inoculation.

But, say the critics, extraordinary claims need extraordinary evidence. The infectivity was tiny and there are questions over how Prof Soto purified the prions and whether a non-prion disease agent could have remained after dilution.

Prof Soto has confirmed his results in other species, and using more stringent conditions. "Indeed, we have a couple of papers currently under review showing that we can generate infectious prions starting from what is estimated to be one single molecule of infectious

prion," he says. But although he believes the evidence for prions is overwhelming, he admits that it is "a minor possibility" that "there might be another component necessary for infectivity, including a possible nucleic acid (DNA or RNA genetic material)".

Dr Surachai Supattapone, from Darmouth University in New Hampshire, has repeated the same study using purified protein in which, presumably, no nucleic acids are present and presented his results in March at a conference in Saint Moritz. "I can't give too much detail at this point, but I think that our studies with purified protein cannot rule out a second component," says Dr Supattapone.

Another central tenet of the Prusiner hypothesis is that a single prion protein can give rise to different strains of disease with varying infectivity and other properties, each reflecting different shapes of the prion protein. This seemed to be confirmed in work on yeast by a team led by Dr Jonathan Weissman at the University of California, San Francisco, and Dr Chih-Yen King at Florida State University.

But yeast prions "are quite distinct from mammalian prions in spite of the similar names", commented Dr Chesebro, who remains unconvinced. And when his British collaborator, Dr Jeffrey, looked at the effects of prion shape in sheep, he found that the shape can vary, depending on which sort of cell it inhabits, even though it produces the same strain of disease in mice.

Similar observations that prion shape changes do not alter the strain of the disease have also been reported by Prof Laura Manuelidis of Yale Medical School, who concluded that many facts "are discordant with the prion hypothesis" in a review in the journal Viral Immunology.

Prusiner's idea does not fulfil the classic criteria formulated by Robert Koch in 1884 to link an agent to a disease, says Prof Manuelidis. "Not a single one of Koch's proven postulates of infection are fulfilled by prion proteins."

Such is the hold of the prion hypothesis over the scientific establishment, she says, that "this evidence (or lack of evidence) led one dominant prion proponent to question the use of Koch's postulates".

There is even evidence for viral particles, although she says this has been ignored. "It has also been obvious for a long time that abnormal prion protein is the consequence of infection, but not the causal agent," she says. "You might say that abnormal prion protein lacks the dynamite for weapons of mass destruction, though it certainly has a lot of rhetoric inside it. Those natural truths are not defined by popular vote or cabal."

She is also disturbed by the hostility faced by those who question the prion idea and says she has seen the good work of others trashed by the traditional weapon of choice in scientific disputes - anonymous peer review. "At issue, unfortunately, is public health."

• Roger Highfield will judge the FameLab final at the Cheltenham Science Festival, celebrating its fifth and most successful year, from June 7-11. To mark the occasion, Lord Robert Winston will chair debates on the big science issues: cloning, human genetics and energy. Once again the festival is joined by high-profile names, including environmentalist James Lovelock, humanitarian Terry Waite, director of the Royal Institution Susan

Greenfield, neuroscientist Steven Rose, presenter Adam Hart-Davis, physicist Frank Close, architect Charles Jencks and chairman of the Arts Council Sir Christopher Frayling…

The two people have a different genetic make-up from all known victims; 27 May 2006

Could a whole new section of the population be at risk of developing the human form of mad cow disease? That is the big question following the discovery of the agent responsible for variant Creutzfeldt-Jakob disease (vCJD) **in the appendixes of two people who have a different genetic make-up** from all other known victims of the disease.

So far, the **UK has recorded 161 cases of vCJD, and all the patients** have had the same gene variant for the prion protein that is implicated in the disease: **the MM genotype, which is found in 40 per cent of the population**. The **two infected appendixes**, found by a team led by James Ironside of the UK's National CJD Surveillance Unit in Edinburgh, **were the first from people with the VV form of prion gene, found in 10 per cent of the population.**

The infected organs were identified during a screening programme the team undertook on 11,109 appendixes and 1565 tonsils removed in operations in the UK between 1995 and 2000 (*BMJ*, vol 332, p 1186). Neither patient is traceable, but no vCJD cases in VV individuals have yet been found, suggesting they remain healthy for now. **The vulnerability of the remainder of the population, who have the MV form of the prion, is not known.**

The fear is that individuals with this genotype may be at risk of developing the condition, **possibly with longer incubation periods, say the authors**. Alternatively, these people may be asymptomatic carriers who might transmit the condition to other susceptible individuals by blood transfusion or surgery.

Though they warn against over-interpreting data from only two positive cases, they conclude that these uncertainties further underline the need for continued surveillance of vCJD in the UK.

It is important to **be cautious in interpreting the results of this study, warn experts from Canada in an accompanying editorial.** The study shows the existence of the prion protein in two tissue samples**, not clinical evidence of vCJD in two patients**. The study also provides no evidence to suggest that tissue from these two people could transmit vCJD to others.
"Studies such as this are essential to the continuing effort to control the extent of the epidemic and highlight the urgent need for ongoing surveillance for vCJD," they add. "**They also pose challenges to health officials who have to formulate policies comprising difficult trade-offs based on uncertain evidence.**"

Enigmatic prion disease continues to baffle; 27May 2006

Our picture of prion disease is tantalisingly incomplete, but much rests on getting to the bottom of it

Until 1982, brain diseases such as scrapie and Creutzfeldt-Jakob disease (CJD) were biological enigmas. In that year, Stanley Prusiner suggested a simple explanation for

their cause: a misshapen prion protein that could convert any normal prion it met into its own aberrant form. The abnormal protein resists degradation by enzymes, so it accumulates in the brain, causing damage and death.

Controversy followed. The idea of an infectious agent that could replicate without genetic material was too much for some biologists. Prusiner's explanation is still the best we have, and it earned him a Nobel prize in 1997, but though it offers a skeleton for the story of infection, putting flesh on the bones is proving frustrating.

How do abnormal prions - if not in food - spread between unrelated individuals, for example? It seems they can move from the brain along facial nerves to the tongue…

Human risk of vCJD revised; 27 May 2006

Could a whole new section of the population be at risk of developing the human form of mad cow disease? That is the big question following the discovery of the agent responsible for variant Creutzfeldt-Jakob disease (vCJD) **in the appendixes of two people who have a different genetic make-up** from all other known victims of the disease.

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Study Suggests New Human Genotype May Be Prone To VCJD; 20 May 2006

A small study in this week's BMJ **suggests a new human genotype may be prone to variant Creutzfeldt-Jakob disease (vCJD).**

Although this new evidence may rekindle fears of a larger epidemic, others warn that it is important to be cautious in interpreting these results.

Since the initial discovery of vCJD in the United Kingdom a decade ago, there has been concern **about the ultimate extent of the epidemic**. Fortunately the magnitude of the epidemic at present seems to match the lower limit of the early estimates, with 161 definite or probable cases in the UK.

Researchers at the University of Edinburgh analysed DNA from two tissue samples that harboured prion proteins (a marker for vCJD infection) **to identify the genetic make-up (genotype) of the patients.**

So far, **all clinical cases of vCJD have occurred in individuals with the homozygous methionine (MM) genotype**, and it was hoped that this was the only susceptible population group**. But both these samples carried the homozygous valine (VV) genotype**, suggesting that individuals with the VV genotype may also be **susceptible to vCJD infection.**

The fear is that individuals with this genotype may be at risk of developing the condition, **possibly with longer incubation periods, say the authors**. Alternatively, these people may be asymptomatic carriers who might transmit the condition to other susceptible individuals by blood transfusion or surgery.

Though they warn against over-interpreting data from only two positive cases, they conclude that these uncertainties further underline the need for continued surveillance of vCJD in the UK.

It is important to **be cautious in interpreting the results of this study, warn experts from Canada in an accompanying editorial.** The study shows the existence of the prion protein in two tissue samples**, not clinical evidence of vCJD in two patients**. The study also provides no evidence to suggest that tissue from these two people could transmit vCJD to others.
"Studies such as this are essential to the continuing effort to control the extent of the epidemic and highlight the urgent need for ongoing surveillance for vCJD," they add. "**They also pose challenges to health officials who have to formulate policies comprising difficult trade-offs based on uncertain evidence."**

Court clears government of BSE failures; 8 May 2006

The Federal Court has thrown out a call for financial compensation by more than 2,000 Swiss farmers for losses incurred during the crisis over mad cow disease.
After nine years of legal wrangling, judges said the authorities could not be held liable for the losses, but the farmers said they might take their case to a European court.
The ruling, published on Monday, said the Federal Veterinary Office and the Agriculture Office could not be blamed for failing to implement a ban on meat and bone meal in cattle feed before 1990.
The first case of Bovine Spongiform Encephalopathy (BSE) in Switzerland was reported in 1990 – the first to be discovered on the European continent. However, BSE initially appeared in Britain in 1986.
The court also cleared the authorities of failing to impose a ban on importing such meal from Britain or other European Union countries.
The demands by a group of 2,206 farmers for a total of SFr300 million ($245.4 million) in damages for lost income also included a complaint about the government waiting until 2001 to outlaw meat and bone meal in chicken and pig feed.
The government introduced various measures to prevent the spread of the disease to humans and the infection of other animals, but a complete ban on animal products was only introduced in 2001.
At the time, meat sales in Switzerland dropped by about ten per cent because of low demand for beef.
BSE peaked in 1995 when nearly 70 cases were reported across the country.
Monday's ruling comes after nine years of legal debate. In 1999 the finance ministry

rejected the demand by farmers saying it was handed in too late.
One year later the Federal Court overturned the decision by the finance ministry, which in turn ruled in 2002 that the federal administration had no blame in its handling of the mad cow crisis.
But then a federal commission in 2004 found that the administration at the time had acted illegally in favour of feed producers rather than the public interest.
However, this decision has now been declared null and void by the country's highest court.
In response to Monday's ruling a farmers' group announced it was considering whether to take their case to the European Court of Human Rights in Strasbourg.

Variant Creutzfeldt-Jakob disease and the risks from blood transfusion; May 2006

Whilst the incidence of clinical cases of variant Creutzfeldt-Jakob disease (vCJD) has declined in recent years, concern has increased over the possibility of an epidemic arising through blood transmission. **Here we review important aspects of the disease and its epidemiology and consider their implications for the risks from blood transfusion.**

Epidemiology

vCJD was first identified in the UK in 1996 and was distinguished from classical CJD by its different clinical presentation and neuropathology. Through March 2006 there have been 154 deaths from vCJD in the UK with a further six probable cases remaining alive. Elsewhere cases have been reported in Ireland, France, Italy, United States, Canada, Saudi Arabia, Portugal and Japan.

The incidence of deaths in the UK peaked in 2000 with 28 deaths and has declined thereafter with only 5 deaths in 2005. The median age at death has remained stable at approximately 28 years, with a significant excess of cases in those aged 10 to 40 years. This excess is most likely to be due to increased susceptibility in the young, but could also be due to greater exposure. Host genetics also influence susceptibility, with all clinical cases to date having a genetic characteristic shared by approximately 40% of the population (methionine homozygous at codon 129 of the prion protein gene). Recent findings have shown that other genetic groups are also susceptible to infection but to date no clinical cases have been observed.

Transfusion

The primary route of transmission of vCJD **from cattle to humans is believed to occur through consumption of BSE-infected beef and beef products.** Over the course of the BSE epidemic in Great Britain it is **estimated that up to two million infected animals** were slaughtered for **human consumption**. Whilst the majority of the population was therefore likely to have been exposed to the infectious agent, it is still uncertain to what extent the population is infected. **Studies in mice and hamsters** have demonstrated a substantial species barrier for these types of disease **and hence it is likely that transmission from cattle-to-cattle is much more effective than from cattle-to human.**

Recently, concern has arisen over the **possibility of onward human-to-human transmission**. High levels of the infectious prion agent are believed to aggregate in regions of the body including the brain, the central nervous system and lymphoreticular tissues. **One theoretically possible source of transmission is via surgical instruments** used on multiple patients which permit transmission because prions are able to withstand high temperatures and sterilisation methods. A **second potential transmission route is via blood transfusion, which was demonstrated to be feasible in sheep studies**. More

recently, **three vCJD infections have been identified in UK patients who received red blood** cell transfusions using blood donated from individuals who later went on to develop vCJD. The first transmission occurred through blood donated from the index patient 3·5 years before onset of disease and resulted in the onset of clinical vCJD in the recipient 6·5 years after receiving the blood transfusion. The second transmission occurred through blood donated by the index patient 18 months before onset of disease. In this case, the recipient died from unrelated causes five years after receiving the blood transfusion, but at autopsy was found to have signs of vCJD infection in her spleen.

Risks from blood transfusion

The risk of acquiring any infection from a blood transfusion will depend on the prevalence of that infection in the population (and hence in the blood supply). The prevalence of vCJD infection in the UK population remains highly uncertain. To date, our best estimate comes from a large-scale retrospective survey of tonsil and appendix tissues removed during routine operations between 1995 and 2000. This survey, designed to focus on the 10–30 age group, found three appendix tissues that were positive for infection in a sample of 12,674 tissues, giving a prevalence estimate of 237 per million (95% confidence interval 49–692 per million) if the test is assumed to detect all infections. Translated into numbers of people, this suggests approximately 3,800 infected individuals among those aged 10–30 years. In contrast, a smaller prospective study of tonsil tissues did not detect any positives. These results are consistent with the retrospective study: the sample size was smaller, and around half of this sample were tissues removed from those aged under nine, who were less likely to have been exposed to BSE infection. There are, however, a number of uncertainties to consider when interpreting these results. On the one hand, it is likely that the ability of the tests to detect infection will increase over the course of the incubation period but will never be perfect, meaning there are more people infected than suggested by these results. On the other hand, it is possible that one or more of the three positives may be 'false-positives' which would suggest that the true prevalence is lower. In addition, it is not possible to say whether those infected in this way are themselves infectious to others, or even whether they will go on to develop clinical disease within their normal lifespan.

The risk of acquiring infection will also depend on the risk of receiving infected blood via transfusion. In a study in North-East England, the mean age of those receiving a transfusion was 63 years. As those in the 10-50 age-group are most likely to have acquired vCJD infection through infected beef, they will have donated infected blood and thus led to the first generation of blood-related infections. However, the eventual size of the epidemic will be limited by the age characteristics of the second, and subsequent, generations of infections, who tend to be transfusion recipients (mean age 60-plus) and who donate relatively small amounts of blood. Conversely, blood donors are normally aged 18 to 65 with most in the 40–50 age-group. As it is the 10–50 age-group who were most affected by vCJD, this suggests that the first generation transmission could be effective, but that susequent generations from these transfusion recipients (aged 60-plus) may be less effective since this group donate relatively little blood. Modelling work is required to assess whether a self-sustaining epidemic (i.e. several generations of transmission) is possible before measures to eliminate onward transmission are introduced (see below).

A study co-ordinated by the National CJD Surveillance Unit in Edinburgh has traced and followed up all individuals known to have received blood components donated by vCJD patients. As of 30 January 2006, 18 of the vCJD cases were known blood donors and could be traced to donation centres. Sixty-six components of blood were transfused from these patients to 66 named recipients, 26 of whom are currently alive.

Measures to reduce the risks from blood transfusion

Several measures have been put in place in the UK to reduce the risks from blood

transfusion. From 1997 onwards, all probable vCJD cases have been reported to the National Blood Service and any remaining blood donated by the cases is destroyed. Between July 1998 and October 1999, leucodepletion was phased in; recent research has suggested that approximately 40% of infectivity is removed through this process, but the effect of lower infectivity on the risk of infection is unclear. From April 2004, recipients of blood transfusions received since 1980 in the UK have been excluded from donating blood. In August 2004, this was extended to exclude apheresis donors who were unsure about whether they have had a blood transfusion.

Other blood products

Blood, or its derivatives, are used in a number of other products including clotting factors for haemophilia patients. Whilst transmission via these other products has not yet been observed, the potential risks of acquiring infection similarly depend on the prevalence of infection in the population. One particular concern is that such products are derived from large 'pooled' donations and, as such, the potential for receiving infected blood could be much greater. To reduce these risks, between November 1998 and December 1999, UK-sourced plasma was phased out in the manufacture of blood products.

Summary

The incidence of vCJD has continued to decline from its peak in 2000. **However, there remains substantial uncertainty about the number of people harbouring infection, with recent survey results suggesting approximately 3,800 infected individuals in the 10–30 age-group.** The risks of transmission via blood transfusion depend on this underlying prevalence of infection and on the age-dependent patterns of blood donation and transfusion. Measures are currently in place to reduce this risk including leucodepletion and a ban on donating blood for those who have previously received a blood transfusion.

Mad cow protein found to have a sane side; 27 April 2006

It's a devastating disease, changing behavior, causing uncontrolled movements, blindness, coma, and, finally, death. And we all have the makings of it in our heads.

When it topples cows, it's known as mad cow disease. The human form is called Creutzfeldt-Jakob disease. In sheep, it's scrapie. It's a rare malady caused by a misshapen protein known as prion protein, or PrP. The big mystery is why people, cows, sheep, and other mammals have so much of the protein in their bodies, particularly in the brain.

"It's intriguing to find that PrP, which, when 'misfolded,' subjects people and animals to these ravaging diseases, is so abundant in our brains," notes Jeffrey Macklis, an associate professor of surgery at Harvard Medical School and Massachusetts General Hospital. "Why is it kept in the system if it has the ability to wreak so much havoc? It must have an important function."

In proteins, form determines function. The strings of amino acids of which proteins are made can twist in one way and be beneficial to a body, but if they fold in another way they can be disastrous to the same body. When a small amount of PrP misfolds, it influences normal PrPs near it, causing them to assume the same shape, a wrecking ball that breaks the brain from the inside out.

Macklis, along with Harvard postdoctoral fellows Jason Emsley and Hande Ozdinler, teamed up with Susan Lindquist and her student Andrew Steele at the Whitehead Institute for Biomedical Research to try to find out what value the Jekyll and Hyde protein might offer.

They studied mice in which the gene that makes PrP was knocked out, and compared it to another group in which the protein was overproduced. Their investigation revealed that PrP is present where nerve cells form in the developing brain of embryonic mice. They also located PrP in a few spots in the adult brain. In both places, PrP increases the number of precursor

cells that develop into brain and other nerve cells. In the knockout mice, this new cell production was delayed. But when additional PrP was available, new cells formed at a much faster rate.
"The more PrP a cell has, the faster it becomes a mature nerve cell," notes Steele.
The good side of PrP was discovered. "We found that the normal prion protein is a key player in the fascinating and important process of creating nerve cells. We now want to think of ways to interfere with the misfolding of PrP. There's a very active prion-disease community studying how to block its spread in the brain," says Macklis, who also heads the Nervous System Diseases Program at the Harvard Stem Cell Institute.

Prions win a prize

Only 25 years ago, prions were completely unknown. Then, in the early 1980s, Stanley Prusiner at the University of California, San Francisco, was puzzling over how one of his patients died of dementia caused by Creutzfeldt-Jakob disease. He noted that it resembles another human malady known as kuru, which can be transmitted through cannibalism, specifically consuming human brain or nervous tissue. By 1982, Prusiner produced a speck of infectious protein taken from the brain of a diseased hamster - the first prion had been found.
However, discovery of the rogue protein was greeted with great doubt. Many scientists refused to believe that such a small bit of protein could cause that much damage. But further research proved Prusiner right. He was awarded a Nobel Prize in 1997 for discovering "a new biological principle of infection."

Adults get new brain cells

Despite a hundred years of belief to the contrary, new cells do form in adult human brains, but only in two places. One lies in a tiny subsection of the hippocampus, a structure deep in the brain that deals with memory. The other is in the olfactory bulb, the part of the brain that recognizes odors.
Late last year, Macklis and his colleagues found out what new smell cells do for adult mice. "They respond to odors that are novel," he says. Even if the animal only detects it for a short time, the odor becomes linked to new cells and circuits in the brain. Many scientists are also investigating whether such links occur in a similar fashion in the hippocampus, perhaps to create memories.
The primary place where brain cells form, of course, is in the embryo of a developing mouse or human. That's where PrP is most needed to help create nerve cells.
Macklis' expertise on the birth of nerve cells led to a collaboration with Lindquist. An expert on prion protein, she had been working with Whitehead Institute colleague Harvey Lodish on the role of PrP in the genesis of blood cells. Along with graduate student Steele, they had discovered that stem cells with PrP developed into mature blood cells much faster than those without the protein.
About that time, Steele attended a lecture by Macklis on development of early nervous system cells, and he wondered whether PrP also contributed to their maturity into brain and nerve cells. Macklis enlisted the help of Emsley and Ozdinler to find out. In February, they published a report in the Proceedings of the National Academy of Sciences presenting evidence that normal PrP increases the speed and number of nerve cells that are made both in embryos and in adult brains.

Playgrounds for mice

Could PrP be manipulated to increase the capabilities of human brains? There's no answer to that question yet; a lot more knowledge is needed about what happens to new brain cells once they come into being and what other proteins are required for the process.
When adult mice get extra PrP, their brain cells grow faster, but, strangely, they end up with the same number of cells as mice who didn't get such a boost. "We think that not all of these cells get included in functional brain circuits," Macklis notes. "And cells that do become part of a circuit die in weeks if not used." If a new odor isn't smelled for a long while, the brain forgets it.
To encourage growth and survival of new adult brains cells, Emsley and Steele are setting up playgrounds for mice with and without extra PrP. Usually the rodents live in small, sparse cages. Those in the experiments will enjoy spacious cages, have small balls to play with, wheels to exercise on, tunnels to explore, and cotton to build nests. There will even be hidden granola treats. These rodents will be more like natural mice who search fields and dumpsters for food, explore ways to get into your house, and chase each other around. What will extra jolts of PrP do for them?
Even such insight into mouse life isn't going to tell the whole story, however. As Macklis emphasizes, PrP does not work alone in making nerve cells. "The birth of new cells is too important and complex to rely on a single protein," he says. "We identified PrP as one central and crucial building block, but we're sure other proteins are involved, some of which are known and probably many that are not known."

Suspected Mad Cow Disease In Japan, 20 Month Old Holstein; 17 April 2006

Japanese authorities say they have found a suspected case of Mad Cow Disease (BSE) in Fukushima Prefecture, north-east Japan. The animal was a 20-months-old Holstein. If confirmed, it will be the youngest head of cattle to test positive in Japan. This new development could have an effect on beef imports from North America. At the end of last year Japan started importing beef from the USA as long as the animal was no older than 20 months. Following a shipment of US veal containing body parts that might carry BSE, an import ban was imposed again.

There have been three confirmed cases of BSE in Japan this year.

What is BSE?

Bovine Spongiform Encephalopathy (BSE) is a disease that affects adult cattle **(it is unusual for a 20-month-old to show symptoms**). It attacks the nervous system of the animal (including brain) and eventually kills it.

BSE has a long incubation period. An infected animal may not show BSE type symptoms for 4 to 6 years.

Scrapie, a disease that affects sheep and goats, is another Prion Disease. Scrapie is common in many parts of the world. No link has been found between scrapie and human illness.

How easily BSE infected animals can make humans ill is really unknown. Many experts argue there is no (or virtually no) risk, while others say it is too early to tell,

as we do not know what the incubation period for CJD is (the human version of BSE).

Are prions the real cause of BSE and vCJD?;15 April 2006

Abnormal prions - misshapen versions of normal brain proteins - may not be infectious agents, but a consequence of "prion diseases"

It is a finding that could turn the conventional wisdom of what causes diseases such as BSE and variant Creutzfeld-Jakob disease on its head. **Experiments in sheep suggest that abnormal prions - misshapen versions of normal brain proteins - may not be infectious agents,** *but a consequence of "prion diseases".*

Abnormal prions were thought to trigger disease by getting into the body through food or cuts and setting off a chain reaction that transforms native prions into harmful ones. These multiply and clog up the brain, and can be fatal. **Prions eaten in contaminated food were thought to pass undigested through the gut wall into specialised lymphoid tissue called Peyer's patches, where they multiplied up before spreading to the central nervous system.**

This is what **Martin Jeffrey at the UK Veterinary Laboratories** Agency in Penicuik, Midlothian, expected to find when they examined 50 sheep to see what happens to the ...

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New evidence questions the simple link between prion proteins and vCJD; 30 March 2006

> While newly published research confirms that under laboratory circumstances prion-protein can be absorbed across the gut, it also shows that this is unlikely to occur in real life. In addition, the results show that the places in the gut that do take up these disease-associated proteins are different from the locations where infectivity is known to be amplified. The findings will be published in the Journal of Pathology.
>
> Since the outbreak of BSE in cattle and vCJD in humans, scientists have struggled to make sense of how an abnormal variation of a normal protein can trigger an infectious disease. Some are questioning whether this simple relationship exists at all. This paper adds new evidence that can inform the

debate.

Firstly, it is known that individual people and animals have different levels of genetic susceptibility to this group of diseases, but no one knows how this resistance is achieved. One option is that resistant people do not absorb the disease-associated prion protein (PrP) from their guts.

To test this, the researchers worked with 50 sheep, with different degrees of genetic resistance to scrapie – the sheep form of the disease. When they injected material containing abnormal prion protein (PrP) into the sheep's gut, it was equally absorbed by all sheep.

"This clearly shows that resistance is not achieved by blocking uptake of abnormal proteins from the gut – it must be achieved by some other mechanism," says lead author Dr Martin Jeffrey.

Secondly, they looked in more detail at the route of absorption in the gut. Using surgically modified sheep, they loaded a small area of the gut with a fluid mixture containing 0.5 grams of scrapie infected brain containing a large amount of the disease specific variant of the PrP protein and watched how it was taken up. They saw the abnormal PrP was rapidly taken up by finger-like projections called villi and passed in to the lymph. It was not, however, taken up by structures called Peyer's nodules, that are believed to be the places where animals amplify the infective agent.

"The fact the PrP isn't taken up by the Peyer's nodules questions whether PrP is really infectious, or whether PrP is really just a secondary marker of the presence of the scrapie agent," says Jeffrey.

His belief in this need to reappraise the fundamental understanding of prion diseases is enhanced by one more observation published in this same paper. The team pre-digested a mixture containing disease specific PrP with standard stomach contents, and then injected the resulting mixture into the gut. No PrP transferred into the villi. When they used a highly sensitive version of Western Blot analysis to examine the contents of this pre-digested mixture, they found only the faintest suggestion that some of the PrP had survived. This was despite the fact that the original mixture had a contained a high level of PrP.

"Think about it – a sheep grazing in a field is not naturally exposed to highly infected brain and could only pick up a tiny amount of PrP from other tissues. This will then be exposed to 48 hours or more digestion before it arrives in the gut, and our experiments show that after this, the chance of there being more than an unmeasurably small amount of PrP left to absorb is very small," says Jeffrey.

"As sheep can become infected, the theoretical probability of this being due to an invisible sub-fraction of digestion resistant PrP molecules is unlikely. The possibility of there being infectious molecules other than PrP must therefore be seriously considered," says Jeffrey.

"A lot of people are completely wedded to the prion hypothesis of diseases like vCJD, but the more you deal with whole animals as opposed to relying purely on in vitro studies, the more cautious you are about saying that prion proteins alone cause the disease," says Martin Jeffrey.

In a commentary published in the same edition of the journal Dr Nicole Sales of the Department of Infectology, at the Scripps Research Institute Jupiter, Florida, suggests that one possible explanation that keeps with the prion hypothesis is that infection occurs as PrPs are absorbed in the mouth, rather than in the gut.

Dr Jeffrey, however, is not convinced by this argument. "Were infection to be acquired from the mouth then the first tissues to accumulate infectivity would be lymph nodes in the throat or the tonsils. But we don't tend to see this in animals, and have no reason to believe it would be different in humans,"

Insight: Mad cows and the UK's beef industry;18 March 2006

British beef is back on European tables following a devastating 10-year ban, but BSE could just as easily have appeared in a different country first

British beef is back on European dinner tables. Last week, the European Union lifted the ban it imposed on UK beef exports in 1996 to protect consumers against meat infected with mad cow disease (BSE).

The ban had a devastating effect on the British beef industry, and when it was imposed the UK government's handling of the BSE epidemic in cattle was widely portrayed as a national scandal. Yet it has become clear that early government action may have helped to save thousands of lives, not to mention the global beef trade.

Though BSE was detected first in British cattle, this was just the UK's bad luck. **The Phillips report, a 4000-page review of the BSE crisis** commissioned by the UK government and published in 2000, **concluded that the abnormal prion protein that causes BSE emerged spontaneously. It could have appeared in any cattle herd anywhere in the world** …

Atypical scrapie in sheep and goats update: 13 March 2006

The Food Standards Agency is keeping consumers informed about the situation relating to the emerging evidence on atypical scrapie in sheep and goats following its open Board meeting of 9 March 2006.

FSA Board discussion: 9 March 2006
The FSA Board had an initial discussion about the significance of the Spongiform Encephalopathy Advisory Committee's (SEAC) statement, released on 28 February 2006. SEAC is an independent expert scientific committee that advises Government.

Following this discussion, the Agency's advice on the risk of eating sheep and goats remains unchanged. The FSA is not advising people to stop eating sheep or goat meat or products.

The FSA Board is expected to discuss this issue again in April 2006 and will consider the practicality of possible precautionary measures, initial stakeholder responses and any

emerging information.

SEAC statement

Prior to the 9 March open Board meeting, the Agency's previous update on atypical scrapie in sheep and goats was on 28 February 2006. The update followed the SEAC statement.

SEAC has been considering the significance of atypical scrapie, a brain disease of the type known as transmissible spongiform encephalopathies (TSEs) that affects sheep and goats.

The most well known TSE is one that affects cattle: BSE.

Sheep are known to get another TSE known as classical scrapie. Unlike BSE, classical scrapie is not known to be linked to any human disease. To date, BSE has not been found in the current UK sheep flock, although surveillance is ongoing.

In 2003 the FSA Board first discussed emerging evidence of the possible existence of atypical scrapie (then referred to as anomalous or unconfirmed scrapie) and acknowledged uncertainties about the significance of these findings.

Since then, scientists in the UK and internationally, including SEAC members, have been working to better understand the significance of these findings.

The SEAC statement, published following its meeting on 24 February 2006, looked at the potential impact of atypical scrapie on human and animal health.

SEAC concluded that 'atypical scrapie could reliably be distinguished both from classical scrapie and from experimental BSE in sheep'.

The SEAC statement also concludes: 'There is no evidence to date that atypical scrapie can infect humans, although a theoretical risk cannot be excluded.'

The FSA Board had an initial discussion of the significance of these findings at the open Board meeting on 9 March 2006.

Dr Alison Gleadle, Head of the FSA’s TSE Division, said:

'The Food Standards Agency has always been open about the uncertainty surrounding the possible risk of BSE and other brain diseases in sheep. Emerging evidence and expert opinion is pointing to more uncertainty. Much more work is needed before we can form a clearer picture of what, if any, risk there might be to people.

'While FSA advice remains that are not advising people to stop eating sheep or goat meat or products, this issue will be discussed thoroughly by our Board and kept under review as evidence emerges.'

Controls

Due to controls to protect consumers from BSE, all parts most likely to carry BSE infectivity are removed from cattle and sheep before entering the food chain.

These parts are referred to as Specified Risk Material (SRM).

However, BSE-infected sheep are thought to have similar tissue distribution of infectivity to

scrapie-infected sheep.

This means that the existing SRM controls would be insufficient to eliminate all the risk of exposure to BSE infectivity.

Nevertheless, these SRM controls offer further protection to consumers should research reveal atypical scrapie poses a risk to human health.

In addition, SEAC refers to SRM controls in its statement, saying: 'The available evidence suggests that, unlike experimental BSE in sheep, atypical scrapie may be absent from the lympho reticular system (LRS). Thus, assuming SRM regulations remain in place, if atypical scrapie can be transmitted to human, it may pose a relatively lower health risk than BSE if it ever enters the sheep flock. However, one study using oral delivery to a VRQ sheep suggests that PrP^{res} may be present in the LRS. It is urgent to clarify this issue.'

CJD expert warns of 'BSE in sheep'; 5 March 2006

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

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 years 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.”*

Mad Cow Protein Might Be Necessary For Healthy Brain Function As It Aids Creation Of Brain Cells; 18 February 2006

Few conditions are more detrimental to human brains than the one popularly referred to as mad cow disease. *But now there's reason to suspect that the protein* which, when malformed, causes bovine spongiform encephalopathy in cows and Creutzfeldt-Jakob disease in people, *might also be necessary for healthy brain function*. Researchers from Whitehead Institute for Biomedical Research and Harvard Medical School/Massachusetts General Hospital have discovered that the normal form of this detrimental protein may actually help the brain create neurons, those electricity-conducting cells that make cognition possible**.**

"It's been difficult to understand why this prion protein, which when malformed subjects us to this horrible disease, is so abundant in our brains in the first place," **says Whitehead Member Susan Lindquist, who is also a professor of biology at MIT. Along with Jeffrey Macklis of Harvard Medical School and Massachusetts General Hospital, she is co-senior author on this Proceedings of the National Academy of Sciences paper, scheduled to be published the week of February 13.** "We've known for years what happens when this protein goes wrong. Now we're starting to see what its normal form does right**."**

For over ten years, researchers have known that a protein called PrP causes mad cow disease and its human equivalent, Creutzfeld-Jakob disease, when it forms incorrectly. PrP is a prion, a class of proteins that has the unusual ability to recruit other proteins to change their shape. (PrP is shorthand for "prion protein".) This is significant, because a protein's form determines its function. When a prion changes shape, or "misfolds," it creates a cascade where neighboring proteins all assume that particular conformation. In some organisms, such as yeast cells, this process can be harmless or even beneficial. But in mammals, it can lead to the fatal brain lesions that characterize diseases such as Creutzfeld-Jakob.

Curiously, however, PrP can be found throughout healthy human bodies, particularly in the brain**. In fact, it's found in many mammalian species, and only on the rarest occasions does it misfold and cause disease. Clearly, scientists have reasoned, such a widely conserved protein also must play a beneficial role.**

In 1993, scientists created a line of mice in which the gene that codes for PrP was knocked out, preventing the mice from expressing the prion in any tissues**. Surprisingly, the mice showed no sign of any ill effect.** The only difference between these mice and the control mice was that the knock-out animals were incapable of contracting prion-related neurodegenerative disease when infected. **Researchers knew then that PrP was necessary for mad-cow type diseases; any other kind of normal function remained unknown….**

In addition, the researchers discovered that in adult mouse brains, PrP is only expressed in neurons, but not in the glial cells, **cells that form the brain's connective tissue. They also found that while the amount of PrP does affect the speed with which neurons were produced in the adult brain, ultimately the different mice ended up with the same number of neurons. In order to further investigate these findings, the researchers are currently placing these different groups of mice in stimulation-rich environments that will require the quick production of new neurons. The idea is to observe the mice and see if there are any significant differences in how they perform and behave.**

"We now see that the normal form of this prion protein is one of many key players in the

fascinating and important process of neurogenesis**," says Macklis, who is also a member of the Harvard Stem Cell Institute.**

When prions are 'good for the brain';18 February 2006

Prion proteins that play a key role in diseases such as BSE in cattle and vCJD in humans might have a benign alter ego

Prion proteins that play a key role in diseases such as BSE in cattle and vCJD in humans might have a benign alter ego. In their normal form they may help the development of a healthy nervous system.

No one quite knows what function normal prions serve in healthy tissue. Now Andrew Steele at the Whitehead Institute in Cambridge, Massachusetts, and Jason Emsley at Massachusetts General Hospital have **found that prions act as a type of molecular "gas pedal" for the rudimentary stem cells that turn into the different types of neurons in the brain.**

Mice genetically engineered to produce no prions take longer to develop new neurons, while those hyperloaded with normal prions develop new neurons at a much faster rate than their normal counterparts. All the mice ultimately develop the same number of new neurons however, suggesting that other systems might also govern the speed of neural cell ...

Mad Cow Protein Might Be Necessary For Healthy Brain Function As It Aids Creation Of Brain Cells; 18 February 2006

Few conditions are more detrimental to human brains than the one popularly referred to as mad cow disease. *But now there's reason to suspect that the protein* which, when malformed, causes bovine spongiform encephalopathy in cows and Creutzfeldt-Jakob disease in people, *might also be necessary for healthy brain function.* Researchers from Whitehead Institute for Biomedical Research and Harvard Medical School/Massachusetts General Hospital have **discovered that the normal form of this detrimental protein may actually help the brain create neurons, those electricity-conducting cells that make cognition possible**.

"**It's been difficult to understand why this prion protein, which when malformed subjects us to this horrible disease, is so abundant in our brains in the first place,**" says Whitehead Member Susan Lindquist, who is also a professor of biology at MIT. Along with Jeffrey Macklis of Harvard Medical School and Massachusetts General Hospital, she is co-senior author on this Proceedings of the National Academy of Sciences paper, scheduled to be published the week of February 13. "**We've known for years what happens when this protein goes wrong. Now we're starting to see what its normal form does right**."

In addition, the **researchers discovered that in adult mouse brains, PrP is only expressed in neurons, but not in the glial cells,** cells that form the brain's connective tissue. They also found that while the amount of PrP does affect the speed with which neurons were produced in the adult brain, ultimately the different mice ended up with the same number of neurons. In order to further investigate these findings, the researchers are currently placing these different groups of mice in stimulation-rich environments that will require the quick production of new neurons. The idea is to observe the mice and see if there are any significant differences in how they perform and behave.

"**We now see that the normal form of this prion protein is one of many key players in the fascinating and important process of neurogenesis**," says Macklis, who is also a member of the Harvard Stem Cell Institute.

New case of variant CJD associated with blood transfusion; 9 February 2006

A new case of variant-CJD associated with a blood transfusion has recently been diagnosed. The patient developed symptoms of vCJD about 8 years after receiving a blood transfusion from a donor who developed symptoms of vCJD about 20 months after donating this blood. The patient is still alive and is under the care of doctors at the National Prion Clinic.

This third occurrence of vCJD infection associated with blood transfusion is further evidence that vCJD can be transmitted between humans by blood transfusion. All three cases to date relate to the transfusion of blood components and not treatment with plasma products.

The patient is one of a small number (less than 30) of living individuals who are known to have received a blood transfusion in the UK from a donor who later developed vCJD. All these individuals have previously been informed of their potential exposure to vCJD and asked to take certain precautions to reduce the chance of passing on vCJD on to other people via healthcare procedures, such as surgery.

Professor Peter Borriello, Director of the HPA's Centre for Infections said, “The occurrence of a third case of vCJD infection in a small group of patients like this suggests that blood transfusion from an infected donor may be a relatively efficient mechanism for the transmission of vCJD, although much still remains unknown. This underlines the importance of the existing precautions that have been introduced to reduce the risk of transmitting vCJD infection through blood transfusion.

“We have been in contact with the doctors caring for the other patients who have been exposed to blood transfusion from donors who later developed vCJD. This is to ensure that these patients are informed of this new development and have access to the latest information and to specialist advice about their situation.”

Dr Angela Robinson, Medical Director of NHS Blood and Transplant said, “Our thoughts go out to the patient and their family. Our prime concern is always the safety of patients through maintaining the quality of blood and we have introduced a range of precautionary measures against the risk of vCJD. Blood transfusion is often a life saving treatment and the benefit of receiving a blood transfusion when needed far outweighs any possible risks”

vCJD is a rare disease, and only less than 2% of the 160 vCJD cases to date in the UK have been associated with blood transfusion.

Notes to Editors

1. 'Blood Transfusion' means transfusion with labile blood components (e.g. red cells, platelets, fresh frozen plasma). This latest case (and the previous two referred to) relate to transfusion of blood components and not treatment with plasma products (i.e. products that are manufactured from plasma). **To date, no case of vCJD has been associated with treatment with plasma-products (e.g. clotting factors used to treat individuals with bleeding disorders such as haemophilia).**

2. **This third case has been classified** by the National CJD Surveillance Unit **as a 'probable' case of vCJD**. Of the 154 vCJD cases that have died, **all 110 that have undergone post-mortem (44 have not) have been 'confirmed' by neuropathological examination (examination of brain tissue).**

3. The first clinical case of vCJD associated **with transfusion was identified in December 2003.** A case vCJD 'infection' associated with transfusion was identified a few months later. **(the patient had no symptoms but evidence of infection (abnormal prion proteins) was identified in a post mortem investigation.** The individual died from causes unrelated to vCJD…

Concerns rise over deer with chronic wasting disease; 04 February 2006

It's not good news for North American deer, and it's not good news for anyone who hunts them for food.

Deer infected with chronic wasting disease, which is similar to BSE, carry a significant amount of the abnormal prion protein in their muscle. While no one knows if CWD can jump from deer and elk to people as BSE did, if it does, anyone eating infected meat from the two provinces of Canada and 13 states of the US where CWD has been recorded might be at risk.

Glenn Telling of the University of Kentucky at Lexington and colleagues infected the brains of mice engineered to be susceptible to CWD with tissue from the thigh muscle of an infected deer. Twelve to 18 months later, the mice developed neural symptoms typical of the disease (*Science*: DOI: 10.1126/science.1122864).

The prions were found in the muscle of deer already ill with CWD, and North American hunters have been warned not to eat obviously sick animals. But we don't yet know, Telling warns, whether the infection already lurks in muscle from animals still incubating the disease. "If I were a hunter, I would be cautious about eating deer in areas affected," he says.

Prions may hold key to stem cell function; 30 January 2006

The curative properties of stem cells may rely on prions, a new study suggests, the type of protein made infamous by mad cow disease.

Prions are a special class of protein that can change the shape and function of other proteins around them. While these are found throughout any mammal's body, the understanding of their biological role is limited. What is known is that prions that become misshapen, through some unknown process, can result in BSE (bovine spongiform encephalopathy) – mad cow disease – and its equivalents in other animals.

Researchers at the Whitehead Institute in Cambridge, Massachusetts, US, have now found that adult stem cells in bone marrow gradually lose their ability to regenerate without their normal complement of membrane-bound prions. Stem cells are primitive cells which have the potential to divide endlessly, and the ability to differentiate into any cell type in the body – offering hope for future therapies.

First answers

Andrew Steele, Cheng Cheng Zhang and colleagues used radiation to deplete the bone marrow of mice genetically engineered to not produce the prion proteins. The animals' marrow regenerated quickly at first, but eventually slowed to a stop. The marrow also lost its regenerative abilities when transplanted into normal mice.

"**For years we've wondered why evolution has preserved this protein, what positive role it could possibly be playing," says Susan Lindquist, one of the team. "With these findings we have our first answer."**

The question of how prions sustain stem cell activity remains unanswered, but the finding is a first step to understanding the destructive streak of misshapen prion proteins, Steele says. **Similar tests on neural and lung stem cells are underway.**

Journal reference: *Proceedings of the National Academy of Sciences* (DOI: 10.1073/pnas.0510577103)

Mad cow protein found in deer meat; 30 January 2006

Scientists have found that North American deer with an infection similar to mad cow disease carry the rogue prion protein in their muscles, a finding that serves a warning to hunters and deer farmers in parts of Canada and the United States.

The condition, chronic wasting disease (CWD), is spreading among deer and elk in North America and now affects captive and wild herds in two Canadian provinces and 13 US states.

CWD is similar to bovine spongiform encephalopathy (BSE), as mad cow disease is commonly known, a disease in sheep called scrapie, and variant Creutzfeldt-Jakob disease (vCJD), which is linked to eating BSE-tainted beef.

In each of these conditions, a form of prion protein proliferates in the brain, turning it spongy, and eventually causing death.

It is unknown whether CWD can be transmitted to humans, although health officials in afflicted states have advised hunters not to eat animals that obviously have CWD, and also to discard brain and spinal cord, the tissues that are most affected by the prion.

But in a study published online on Friday by the US journal Science, researchers say that the prion can also lurk in deer thigh muscle — a meat that hunters are far likelier to eat than brain and nerve tissue.

The team used lab mice that had been genetically engineered to be vulnerable to CWD.

One group of mice was injected in the brain with either brain or leg muscle that came from deer with CWD. The other group received similar tissues, but from healthy deer.

Those injected with tissues from CWD deer all fell sick, in a timescale ranging from 230 to 490 days. The longest period of incubation was for those injected with leg muscle, which showed it had fewer prions.

In contrast, the mice injected with tissues from healthy deer remained unaffected.

"Skeletal muscle as well as CNS [central nervous system] tissue of deer with CWD contains infectious prions," say the authors.

They worry that hunters and farmers in CWD-hit areas, and those who eat or handle infected meat, could be at risk.

The study only addresses the case of infected animals.

It does not address some big questions, such as how many prions hole up in deer muscle and the extent of the prion's spread among deer that have not fallen sick.

Also unknown is whether CWD can infect other animal species; whether it can can be passed on to humans who eat venison; and how it is transmitted among deer themselves.

A 2003 study on CWD, published in the British journal Nature, suggested that the protein could be handed on through faeces that are deposited on grazing land, or perhaps through saliva.

Eating wild deer unsafe; 27 January 2006

Previous studies found that mice injected with brain tissue from infected deer get brain wasting disease, indicating that nervous systems are the risky material. The current finding shows that eating infected deer muscles can also be a way for the disease to spread to humans.

In the study, mice injected with extracts from leg muscles of deer infected with chronic wasting disease were found to suffer the same disease, proving that the infectious prions are present in leg muscles, not just nervous tissues.

Glenn Telling, the lead researcher from the University of Kentucky, said that these findings may prove venison can carry chronic wasting disease to humans.

"We don't know how the infectious prion goes from the central nervous system into the muscle," Telling was quoted as saying by Newsday.

"But it raises the possibility that hunters could be exposed to prions by consuming or handling (deer) meat."

Chronic wasting disease is a serious disease that has affected deer and elk throughout North America. It has already been found in both wild and captive deer and elk in many states including Colorado, Illinois, Kansas, Minnesota, Montana, Nebraska, New Mexico, Oklahoma, South Dakota, Utah, Wisconsin, New York, Wyoming, and West Virginia.

The finding will raise much concern about meatpackers and hunters that continually deal with venison meat. In addition, the muscle part of the deer is commonly used in food meals and dishes.

"Anybody who may be handling or eating infected deer may be inadvertently exposed," Telling was quoted as saying to the Milwaukee Journal Sentinel.

Last year, chronic wasting disease was found in captive deer in New York. The state officials said that no evidence indicates humans get brain wasting disease by eating infected deer meat. The current study is expected to affect the government's advisories on deer meat consumption.

State officials, namely Wisconsin Department of Health's epidemiologist James Kazmierczak, are stating that nothing new has to be done to avoid the spread of the chronic wasting disease. They now call for the destruction of any animal carrying the disease, whether the infection is in the brain or leg muscle although these special precautions might not be taken seriously by everyone, according to Kazmierczak.

It is known that people who consume beef from cattle infected with bovine spongiform encephalopathy (BSE) can get the human form ma d c ow disease called variant Creutzfeldt-Jakob disease or vCJD, which have victimized more than 100 people worldwide.

The new evidence suggests the transmission may not be necessary because the meat is tainted with the risky material such as brain tissue, but because the meat may contain infectious agents.

However, that turns out not to be true. One of the alarming characteristics of m ad cow disease is that prions are not found in the leg muscle.

So far, it has not been unclear where the deer chronic wasting disease comes from. It may be a result of spontaneity or transmitted from other animals. If the latter holds true, the prion may be changing when it makes the jump from animal-to-animal

The Associated Press reported that Judd Aiken, a prion researcher at the University of Wisconsin, believes that no one should eat venison from areas that are suspected of infection. He believes that this precaution should be practiced even in areas where negative tests have come about.

However, the real risk may not be as it appears to be. Chronic wasting disease does not transmit into mice with human prions, indicating that humans may be more resistant to the disease, the New York Times cited Dr. Telling as saying. Also oral transmission of the prion protein is less efficient than injecting prions into the brain.

The transmissible spongiform encephalopathy (TSE) agents or prions are extremely resistant to heat, ultraviolet light, ionizing radiation, normal sterilization processes, and common

disinfectants that normally inactivate viruses and bacteria, according to United States Department of Agriculture. No one should expect that ordinary cooking methods kill the agents.

Did prior infection save British from vCJD?; 29 October 2005

The low death toll in the UK from the human form of mad cow disease is one of the great puzzles of recent years, but it may now be explained

The unexpectedly low death toll in the UK from variant CreutzfeldtJakob disease is one of the great puzzles of recent years. There might now be an explanation.

Though 151 people have died so far, epidemiologists had predicted many more deaths because of the large quantity of infected beef consumed in the UK.

Now experiments on mouse brain cells have hinted at a tantalising explanation: most people were protected through prior infection with an as yet unidentified milder strain of agent similar to the one that causes vCJD in humans and BSE in cows.

Laura Manuelidis of Yale University School of Medicine infected mouse brain cells in sequence with four variants of the infectious agent - two that cause sporadic CJD in humans and two that cause scrapie in sheep. She found that cells infected with one of the human strains, dubbed SY, could not then be infected by any of ...

New form of scrapie discovered; 22 October 2005

A previously unknown form of the prion disease that affects sheep could derail EU plans to breed scrapie out of Europe's flocks

A new form of scrapie, the prion disease that affects sheep, could derail European Union plans to breed scrapie out of Europe's flock.

Since 1998, Norway has been finding scrapie-positive sheep with prions and brain changes unlike normal scrapie. **Meanwhile, an EU monitoring programme that started in 2002 has found that 20 per cent of the sheep and goats that tested positive for scrapie also have unusual prions.**

Annick Le Dur and colleagues at the French National Institute for Agronomic Research (INRA) lab at Jouy-en-Josas have **injected brain tissue from animals with scrapie into the brains of mice genetically modified to have the same prion protein as sheep. Both the Norwegian and the European tissue caused the same unusual brain changes, suggesting that the animals it came from all had the same, previously unrecognised, form of scrapie** (*Proceedings of the National Academy of Sciences,* DOI: 10.1073/pnas.0502296102).

Protein involved in 'mad cow' disease; 19 October 2005

The PrPC is a normal physiological protein, especially present in the central nervous system, including that of the human, with functions that are little known as yet. Altered prionic proteins, pathogens, infectants, i.e. prions, are responsible for spongiform encephalopathies, amongst these being bovine spongiform encephalopathy (BSE or mad cow disease). In order to operate, prions require the presence of the PrPC. Thus, the importance of this investigation for the location of

the PrPC in the central nervous system.

Knowing where in the central nervous system the prions operate

Locating the PrPC meant being able to identify which places in the central nervous system the prions operate. **The findings enabled the research team to establish that the PrPC is a protein involved in the neuronal metabolism of calcium**. Moreover, the existence of neurones without PrPC and surrounded by perineuronal nests breaks with the hypothesis, to date, that the disappearance of such nests - a special form of extracellular matrix - is a primary event in the course of spongiform encephalopathies; rather it is secondary event.

According to the researchers' observations, the loss of these nests and consequent neuronal death are due to the damage produced after the appearance of the prions in the brain, where they act upon such perineuronal nests, amongst other structures.

According to the researchers' comments, **extrapolating these results from the rat to the human is valid**, given that similar results had been obtained after carrying out the study on human brains. Moreover, this work and others carried out on the brains of the autochthonous Pyrenees breed of cow will help to explain the operating mechanisms of the prions in bovine spongiform encephalopathy.

This study, published in Brain Research, is an addition to the work of the Department of Pathological Histology and Anatomy at the University of Navarra regarding the manner in which prions enter the digestive tube of bovine animals, from which organ they enter the central nervous system, causing the mad cow disease or bovine spongiform encephalopathy.

The authors are José Luis Velayos and Francisco José Moleres, research scientists at the Department of Anatomy at the University of Navarra.

Hypothesis that BSE originated from a human TSE; 19 October 2005

….Summary of SEAC's Discussion :

SEAC considered it unlikely that the origins of BSE would ever be determined conclusively.

It is not possible to determine, from current knowledge of the characteristics of prion strains, whether BSE originated from CJD or other animal prion strains.

There was evidence to suggest that human remains may have been included in animal feed derived from the Indian subcontinent in the past, and the **hypothesis presented by Professor Colchester was therefore considered plausible, but ultimately untestable**...

Mad cow disease could spread through urine, Swiss study; 14 October 2005

Researchers from the University Hospital of Zurich have found that prions can be spread through urine. Prions are proteins that cause mad cow disease, CJD and scrapie.

You can read about this study **in the journal Science**.

Lead researcher, Adriano Aguzzi, **said that prions could be found in the urine of scrapie infected mice with kidney inflammation. Mice without kidney inflammation (infected with scrapie) had no prions in their urine.**

Hence, they concluded that prions could be transmitted through urine….

BSE may have come from dead people; 10 September 2005

British cattle could have caught mad cow disease after eating the remains of people who died of the human equivalent, CJD, a new study suggests. The search for the original cause of mad cow disease just took a gruesome turn. Rather than originating in British cattle in the 1980s, or in an exotic animal ground up and fed to them, the prion disease may have come from dead people. **Alan Colchester and Nancy Colchester at the universities of Kent and Edinburgh in the UK suggest that British cattle could have caught BSE after eating the remains of people who died of the related human prion disease CJD.** The team has discovered that the UK imported hundreds of thousands of tonnes of carcass scraps in the 1960s and 1970s for use in feed and fertiliser. **Nearly half came from India, where many incompletely cremated human bodies end up in rivers.** From there they may be retrieved by bone collectors who supply the carcass exporters. These shipments - which continue, although no longer to Europe - were ...

BSE may have originated from a human form of the disease, new theory; 4 September 2005

Animal feed contaminated with human remains may have caused the first cases of bovine spongiform encephalopathy, suggests a hypothesis published in this week's issue of THE LANCET.

The cause of the original case or cases of BSE is currently unknown. Sheep scrapie or a previously undetected bovine transmissible spongiform encephalopathy (TSE) that arose spontaneously have long been considered as candidates. However, no convincing evidence to support these proposals has been found.

Alan Colchester (University of Kent, UK) and Nancy Colchester (University of Edinburgh, UK) propose a new theory consisting of three hypotheses, that human TSE-contaminated material was the cause of BSE; that this was transmitted orally via animal feed; and the infective material originated from the Indian subcontinent. The authors present substantial circumstantial evidence to show that human material was imported into the UK from India with other animal remains for the production of animal feed over a long period. They also argue that human TSE and BSE strain characteristics have sufficient similarities to be consistent with their hypothesis.

Professor Colchester concludes: "Further investigations are needed into the sources of animal by-products used in animal feed manufacture, and into the transmissibility of human TSEs to cattle… Within as well as between countries, it will be particularly important to establish

cooperation between public health, agricultural, and industry organisations, as well as researchers, to try to ensure that further investigations are sufficiently thorough. WHO might be the best international body to coordinate this collaboration."

In an accompanying comment Susarla Shankar (National Institute of Mental Health and Neurosciences, Bangalore, India) states: "So far not a single case of BSE or scrapie had been reported from India, except for one case of scrapie from the Himalayan foothills in a sheep, which was probably imported…Scientists must proceed cautiously when hypothesising about a disease that has such wide geographic, cultural and religious implications. We agree that the idea proposed by the Colchesters needs to be probed further. Facts to support or refute their hypothesis now need to be gathered with urgency and great care."

New Theory on How Mad Cow Disease Strated; 4 September 2005

A new theory on the origins of mad cow disease is sparking debate in *The Lancet*.The theory traces the seeds of mad cow disease back to humans. But it doesn't have solid evidence behind it. No one knows how bovine spongiform encephalopathy (BSE, or "mad cow" disease) got started.

The husband-and-wife scientists who propose the theory admit that. They don't claim to have solved the mystery. They are Alan Colchester, FRCP, of Kent Institute of Medicine and Health Sciences at the University of Kent in Canterbury, England, and Nancy Colchester, MBChB, of the University of Edinburgh College of Medicine and Veterinary Medicine in Scotland.

Human Origins?

First, the Colchesters shoot down the notion that the disease may have started with scrapie, a usually fatal nervous system disease in sheep. There's "no convincing evidence" of that theory, write the Colchesters.

Next, they outline another possibility: Maybe mad cow started in the Indian subcontinent when ground-up bones of sick people wound up in animal feed that was shipped to the U.K., where the disease eventually became BSE.

The human illness must have been a "prion" disease, write the Colchesters. Prion is a protein that has been tied to mad cow disease. In humans, mad cow disease is called variant Creutzfeld-Jakob disease.

Bone Beginnings

How do the Colchesters explain how human bone might have gotten into British animal feed? They write that Indian and Pakistani peasants sometimes gather large bones from land and rivers to sell, and that "Hindus believe that it is essential for their remains after death to be disposed of in a river, preferably the Ganges."

"The ideal is for the body to be burned, but most people cannot afford enough wood for full cremation," the Colchesters continue. During the 1960s and 1970s, the U.K. got a lot

of raw material for fertilizers from Bangladesh, Pakistan, and India, write the Colchesters. Some of that raw material could have included human bones and may have been mixed into animal feed, despite rules to the contrary, they theorize.

In other words, the Colchesters suggest that humans already had variant Creutzfeld-Jakob disease, passed it on to cows through ground-up bones in animal feed, and then the cows gave it back to people.

Jumping to Conclusions?

An editorial in *The Lancet* punches holes in the Colchesters' theory. The editorial comes from Susarla Shankar, MD, and colleagues from the National Institute of Mental Health and Neurosciences in Bangalore, India. "So far, not a single case of BSE or scrapie has been reported from India, except for one case of scrapie from the Himalayan foothills in a sheep, which was probably imported," they write.

The editorialists also dispute the bodies-in-the-river theory.

"By the Colchester's extrapolation, 150 deaths in India are related to Creutzfeld-Jakob disease. In most of the hospital-related deaths, the bodies are not taken to Varanasi, the holy city on the banks of the Ganges in North India, but [are] cremated or buried in community burial grounds," they write. "Even in Varanasi, most Hindus do not put half-burnt bodies into the river. The Colchesters have drawn heavily from pictures on the Internet and other sources," the editorialists continue.

There's also no proof that cattle could get the disease from ground-up human bones, they write. The Colchesters agree with that point, and they call for tests to see if it's possible.

Proceed With Caution

"Scientists must proceed cautiously when hypothesizing about a disease that has such wide geographic, cultural, and religious implications," write Shankar and colleagues.

"We agree that the idea proposed by the Colchesters needs to be probed further. Facts to support or refute their hypothesis now need to be gathered with urgency and great care," they conclude.

Sheep can pass BSE to their lambs; 17 August 2005

BSE has been shown to spread naturally between sheep for the first time. It passed from mother to lamb, before or during birth, in an experimentally infected flock. But if the study shows the infection spreads more generally within the flock, that means BSE could still be lurking in Europe’s sheep, possibly posing a greater health risk to people than that from “mad” cows.

Scientists found in 1996 that sheep develop a disease similar to BSE if they eat infected cattle tissue. **But feeding cattle remains to sheep was banned in Britain in 1988, and in the EU in 1994**. All the sheep infected before then should be gone by now.

So there should be no more BSE sheep – unless they can transmit BSE to each other. Cattle cannot do this, **but sheep transmit a related disease called scrapie between themselves, apparently when they eat placentas and other birthing remains in the field.** If BSE also spreads "horizontally" in this way – between other members of the flock – it might have kept spreading in sheep even after the feed ban.

And because the symptoms of BSE in sheep resemble scrapie, "mad" sheep might not have been noticed. Nearly 2700 sheep with apparent scrapie have now been tested for BSE in the UK. None so far had clear BSE, though two are being tested further. **BSE-infected goats, which are biologically similar to sheep, were found in France and possibly the UK in 2005.**

BSE-infected sheep are potentially more dangerous to human consumers than BSE-infected cows, as they carry the infection in more of the tissues people eat.

Mother to lamb

Sue Bellworthy and colleagues at the UK's Veterinary Laboratories Agency (VLA) report that two ewes experimentally infected with BSE in a flock in Warwickshire in 2000 gave birth to lambs in 2003 that died of BSE this year. This is the first confirmation of "vertical" transmission of BSE from mother to offspring. It has been suspected but never proved in cattle.
In sheep, given how scrapie spreads, "this was expected," Danny Matthews, a BSE expert at the VLA, told "But vertical transmission alone would not be enough to keep BSE going in the sheep population after the feed ban." Transmission would be limited to one family line, which would die out as animals die of BSE or are eaten.
The experimental herd is now being watched to see if adults can transmit BSE horizontally to other ewe's lambs now being born and raised within the flock. So far none has, and no uninfected adult sheep have caught the disease from experimentally infected sheep. But it's still "too early to say", cautions Matthews.
Journal reference: *Veterinary Record* (Aug 13, p 206)

Prion diseases - is the worst to come? 2 August 2005

Early predictions of an epidemic have not proved true. But what if vCJD occurs in people of the same age as most CJD patients? Then the true epidemic will explode 20 years from now. The latest Biochemist takes a look at the prion family and how they work.

A field on fire
By David R. Brown
It is now ten years since the panic created by the first cases of variant CJD were identified. Has work in this field really advanced?

Copper and the prion protein
By John H Viles
The normal function of the prion protein is yet to be established, but its affinity for copper ions also suggest a role in copper homeostasis.

Fungal prions
By Laurent Malato and Sven Saupe
Fungal prions represent valuable model systems because they are safe to handle and

incomparably easier to study than mammalian prions.

Prion protein genetics
By Wilfred Goldmann
By far the most important host gene in TSEs is the PrP (prion) protein gene. It modulates TSE susceptibility at many levels and is the crucial element in the treatment and eradication of these diseases.

The search for a cure
By Lee J. Byrne and Mick F. Tuite
There is increasing activity, but as yet limited success, in the search for therapeutic compounds that can be used to treat these diseases. This is in part because a number of significant problems exist hampering the route to rational drug screening strategies.

Making blood safe
By S. O. Sowemimo-Coker (Pall Corporation)
A new filtration technology that removes prions from red cell concentrates has been developed and it will be available commercially in Europe this summer.

From pabulum to prions (via DNA): a tale of two Griffiths
By John R Lagnado

All this plus Helen Wallace, of GeneWatch UK, on genetic testing and insurance, book reviews and exhibition reports.

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US „rediscoveres“ its second mad cow;13 June 2005

The US has found its second case of mad cow disease in a cow suspected, but cleared, of having BSE in November 2004. Although meat from the cow did not enter the food chain, the finding calls into question the accuracy of the country's BSE surveillance programme. The cow might also be the first case born in the US.

The first US case was in a cow imported from Canada in 2003. In 2004 the country started testing "high-risk" cattle - those that show neurological symptoms, are found dead or are "downers" (unable to stand).

Since then it has tested 375,000 cattle. None were declared positive. **In contrast, Canada has tested 30,000 cattle and found three positives**. The rate at which the tests uncover positive cattle depends on the sample size, stresses Marcus Doherr of the University of Bern in Switzerland, who helped develop Swiss BSE surveillance.

This means either that BSE is less evenly distributed in North America than thought, or that the US is missing cases. Unlike Canada, which uses the rapid "western blot" test, the US uses a test called ELISA, which is more prone to false positives.

Prion diffusion

In 2004 the ELISA test detected three BSE positive cattle in the US. When these brains were re-tested, the ELISA was negative. Then they were subjected to immunohistochemistry (IHC) testing - a thin slice of brain is stained with antibodies for the prion protein that causes BSE. All were negative, and the cattle were declared BSE-free. "But if the prion is diffuse enough in the brain tissue, you can get a weak signal with the ELISA, and a negative with IHC," says Doherr. Another test is needed to be certain, he says.
It was revealed on 10 June that the US Department of Agriculture's own Inspector General asked the USDA to carry out western blot tests on the three conflicting samples from 2004. One sample - a downer from November - came back positive.
The animal was reportedly nine years old - born just before the US banned the use of cattle remains in cattle feed, which can spread BSE. USDA would not confirm this or the origin of the animal, though John Clifford, the USDA's chief veterinary officer, notes that "we have no information that it was an imported animal".
But the animal is still not officially BSE positive. Because of the conflicting results, says Clifford, the sample will be re-tested at the USDA lab in Iowa, and the international BSE reference lab at Weybridge, UK.

Prion antibodies open way for vCJD vaccine; 26 March 2005

It might be possible to create vaccines to prevent prion diseases - even after people have been infected with the prions that lead to vCJD

It might be possible to create vaccines to prevent prion diseases such as mad cow disease and its human equivalent vCJD.

Prion diseases are caused by a misshapen form of an ordinary cell-surface protein called PrP. Immunising against the abnormal PrP should in theory prevent animals or people from developing vCJD if they eat BSE-contaminated meat. In theory, a vaccine might even be used to prevent prions reaching the brain after people have been infected, though detecting infection at this early stage is difficult.

But because PrP is one of the body's own proteins, no one has managed to persuade the immune system to attack the normal or even the abnormal form. **Now a team at the Paul Ehrlich Institute in Langen, Germany, has taken the first step. They have managed to get mice to produce antibodies to the normal protein.** They did this by injecting them with virus-like particles ...

BSE 'may have entered baby food in 70s'; 4 March 2005

Scientists are to test a hypothesis that young people who have died from the human form of BSE were infected by contaminated baby foods as far back as 1970. The controversial idea supposes that some meat products were harmful to people 16 years before BSE in cows was even recognised, and 25 years before young adults began dying from its dreadful human equivalent. Should this prove true, it will mean rethinking the likely future course of the disease, which is predominantly British, although cases have occurred in other countries.

Variant CJD here appears to be on the wane. Only nine people died in 2004, the fewest since 1995, its first recorded year, giving rise to the hope that no more than a few hundred

may eventually succumb to it. Since 1995, 154 Britons have been identified with the disease, a handful of whom are still alive. **But the hypothesis advanced by Stephen Dealler**, a microbiologist at Lancaster Royal infirmary, suggests that only the "first wave" is declining. He argues that there were further infections in the mid- to late-1980s, when teenagers and others ate contaminated meat, including burgers. By then hundreds of thousands of cattle were carrying BSE and the tissues most likely to contain infection were not banned in food until 1989….

Dr Dealler put his ideas to the Spongiform Encephalopathy Advisory Committee, a government advisory body, **which greeted them with scepticism.**

But even doubters are concerned that the average age of victims at death is still in the late 20s, an average which ought to be getting higher as more years pass since the food controls introduced in the late 1980s.

Extrapolation from studies of otherwise healthy appendixes have suggested that as many as 3,800 people may be carrying the infection.

Moreover, all those who have died from the disease so far have been from one genetic group, but evidence of vCJD infection in the spleen has been found in a patient who died from another cause and had a different genetic make-up.

This raised the fear that far more people may yet go down with the disease while displaying different symptoms.

Dr Dealler claims that his hypothesis fits the evidence from animals with similar diseases, and from cannibals in Papua New Guinea acciden tally infected with a brain disease.

"**It has been shown that neonatal animals are more easily infected, and with lower doses of disease, than older animals,**" he said. "The real epidemic of BSE in humans has not actually started. What we are just seeing is the beginning with young children."

Proving his ideas will be difficult, and food manufacturers have refused to give him data from the 1970s and 1980s.

The possible drawbacks to his hypothesis include the fact that many of the 15 people infected with vCJD recorded abroad had never been to Britain, and only one, from the US, was a baby in Britain.

Other scientists question his assumptions about the incubation periods in animals and humans.

Professor James Ironside, of the CJD surveillance unit in Edinburgh, was cautious, but admitted: *"Exposure to baby food is indeed a possibility*."

Professor Chris Higgins of Imperial College London, who chairs Seac, was blunter: ***"There is a lot of anecdote there, rather than hard and fast data.***

"We really need to go away and assess that before anyone jumps to any conclusions. I think we would all accept there is some age range during which infection probably occurs. But I

am not at all convinced at the moment, until we have looked at all the details, that the idea that it is first the very young, and secondly pre-the main epidemic is likely to be right at all."…

British goat may have harboured BSE; 8 February 2005

A British goat which died in 1990 may have had BSE, UK government officials revealed on Tuesday. The discovery means the infection may have circulated in goats in the past, and may even be circulating at low levels today.

This follows the recent disclosure of the first natural case of BSE to be found in a goat - a French animal that died in 2002. New Scientist has learned that the British goat was discovered as a result of the French case, as UK government scientists prepared for the increased testing of goats after the discovery.

It has long been assumed that sheep and goats may have been exposed to BSE in feed made from infected cattle. But unlike cattle, both creatures can transmit such infections between individuals, which might have kept the disease circulating after infected feed was banned.

BSE in sheep and goats would also be hard to spot, as both can naturally develop a similar disease called scrapie which has the same symptoms, although it is not thought to pose a risk to human consumers. And, unlike cattle, sheep experimentally infected with BSE carry the infectious prion in muscle meat, so the infection in sheep and goats could pose more of a risk to consumers.

For these reasons European Union countries have been testing sheep and goats for BSE since 2002. These tests discovered the infected French goat.

Telling the difference

"We were involved in helping evaluate the French data in December," says Danny Matthews of the UK's Veterinary Laboratories Agency, the EU reference lab for BSE. It was clear that the EU would probably ask for increased testing in goats as a result, he says.
In fact, from February, 80% of healthy slaughtered goats over the age of 18 months, plus "high risk" goats such as those found dead or unable to stand, should be tested, officials have just agreed. Three different test methods - called western blot, ELISA and immunohistochemistry (IHC) - will be used to distinguish scrapie from BSE.
"We haven't had to test many goats in the UK," says Matthews. "We thought we should test our current IHC on goat brain to make sure it distinguishes BSE." Besides goats and sheep experimentally infected with scrapie or BSE, they tested two brain samples at random from within a selection of goats thought to have died of scrapie.
One of them gave an IHC result that looked like BSE. "We can't do the other two tests as we processed all the tissue we had from that animal for IHC," says Matthews. But the team will nevertheless attempt to extract enough tissue from the IHC test material to do the definitive BSE test. This involves injecting tissue into mouse brain to see if BSE develops. But that will not yield results for two years.
"What is important now is not what happened back in 1990, but whether the infection is still circulating in goats," notes Matthews.

Infectious agent linked to mad cow disease found in organs other than the brain; 5 February 2005

Prions, infectious proteins associated with bovine spongiform encephalopathy (BSE) or Mad Cow Disease, were previously thought to accumulate mainly in the brain, but Yale and University of Zurich researchers report in Science that other organs can also become infected.

Past research had shown that the brain and spinal cord bear the highest infection risk for BSE, followed by organs such as the spleen, lymph nodes and tonsils. All other organs were thought to be devoid of prions.

Ruddle and co-authors analyzed three organ systems that are typically free of prions: liver, pancreas and kidney, in five different mouse models of chronic inflammation. After the mice were infected with prions, the team detected prion accumulation in the inflamed organs. They concluded that the spectrum of organs containing prions might be considerably increased in situations of chronic inflammation.

"The study suggests that the current prion risk-classification of farm animal organs may need to be reassessed in animals suffering from inflammation due to microbial infection or autoimmune disease," said Nancy H. Ruddle, the John Rodman Paul Professor and Director of Graduate Studies in the Department of Epidemiology and Public Health at the Yale School of Medicine.

Previous research in Adriano Aguzzi's group at the Institute of Neuropathology at University of Zurich showed that B cells are essential for the spread of prions to organs other than the brain. B cells are found in lymphoid organs in healthy humans and animals, but they can migrate into non-lymphoid organs under inflammatory circumstances.

Other researchers on the study include first author Mathias Heikenwalder, Nicolas Zeller, Harald Seeger, Marco Prinz, Peter-Christian Klohn, Petra Schwarz, Charles Weissman and the director of the study, Adriano Aguzzi.

Goat found infected with BSE; 5 February 2005

A French goat has been confirmed as the first food animal other than a cow to catch BSE. The finding deepens fears that the disease is lurking undetected in European sheep, which are farmed in a similar way.

The goat may have developed the disease before the European Union banned potentially infected feed in 2001. Unlike cattle, sheep and goats are thought to be able to transmit BSE to each other, and this would keep the disease circulating despite the feed ban. Also unlike cattle, both species carry the infection in muscle, making their meat potentially more dangerous.

There are further fears that scrapie, a BSE-like disease widespread in Europe, might have masked the presence of BSE in sheep and goats. So animals that appear to have scrapie are

now being randomly tested for BSE. The European Commission aims to quadruple the number of tests to assess the extent of any infection.

Before cattle remains were banned in animal feed, French goats might have run a higher risk of acquiring BSE than sheep or goats elsewhere in Europe. The remains were used as a protein supplement, which is needed mainly by animals that are heavily milked. Goat's cheese is a huge industry in France. Sheep and goats might have been less likely to be affected in the UK, where they are rarely kept for their milk.

Inflamed organs could act as prion incubators; 29 January 2005

Experiments in mice find that prions can collect in organs previously thought to be safe - there could be repercussions for mad cow testing

Inflamed organs in cattle could act as incubators for prion diseases such as BSE. It could mean that organs we thought were safe are a source of infection.

So far the effect has only been seen in laboratory tests on mice, but if the results hold true for cattle this could have significant implications for countries such as the US and Switzerland, which have opted for limited BSE testing programmes.

Until now, the abnormal prion proteins that cause BSE have been found only in specific organs in cattle, such as the brain and intestines. "So the assumption has been that other parts are safe to eat," says Adriano Aguzzi, of the University Hospital of Zurich, Switzerland, who led the new research.

The findings add to growing evidence that prion infection can be found in other parts of the cow. "It now seems that countries which decided not to go for ...

Illness can make BSE prions appear in more organs than originally thought; 23 January 2005

Prions that transmit BSE (mad cow disease) can appear in more organs than were originally thought if the infected animal has an inflammatory disease. Scientists have thought that prions would only appear in the brain, spinal cord, spleen and lymph tissue of an infected animal - meaning, even if you eat some other part of that animal you will never develop the human vCJD.

However, tests have shown that mice infected with the prion which also had an inflammatory disease had the prions in other organs. If what seems to be the case with mice is also the case with livestock animals, one wonders whether the current measures to stop the spread of BSE are appropriate.

You can read about this study in the journal Science.

In this latest study, scientists administered prions to mice with five inflammatory diseases of the kidney, pancreas or liver. In all cases, chronic lymphocytic inflammation enabled prion accumulation in otherwise prion-free organs.

Inflamation lets prions invade „safe“ tissue; 20 January 2005

Inflammation can cause the deformed proteins that cause prion diseases, such as BSE, to invade organs that normally resist infection. **If the new research in mice holds true for cattle, it could mean that some organs previously thought to be safe to eat are not - with significant implications for BSE testing programmes.**

Previous screening tests have shown the prions that cause BSE are found only in specific organs, such as the brain and intestines. "So the assumption has been that other parts are safe to eat," says Adriano Aguzzi, at the University Hospital of Zurich, Switzerland, who led the new research.

"People in countries with BSE still eat steak because the authorities say if you stay away from the brain and lymphoid tissue, you should be safe," he told . However, the experiments to find out where BSE prions lurk in cattle incubating the disease have been done in otherwise healthy animals, he says: "If you have a sick cow, these rules may no longer apply."

The US and UK agencies responsible for BSE testing say the findings do not warrant any immediate changes to existing regulations, but say they plan to review the new research in depth.

Infectivity can vary between species, says Danny Matthews, at the UK Department for Environment, Food and Rural Affairs, so the results need to be replicated in cattle. The officials also claim that inflamed tissue can be identified and removed from carcasses along with specified risk organs.

Prion bioreactor

However, if the findings of Aguzzi's team translate to cattle, changes may be needed. Current European surveillance programs test the central nervous system of slaughtered cattle for signs of infection, on the assumption that even animals incubating the disease poses no risk to consumers until prions show up in the brain.
But if inflamed organs are infected with prions earlier than brain tissue - as preliminary results from Aguzzi's lab suggest - animals whose brains test negative for BSE could still be carrying dangerous levels of prions in other organs, and those could end up in food.
In their new study, the researchers tested mice with five different inflammatory diseases of the kidney, pancreas and liver. They found that in all cases, chronic inflammation caused a build up of prion proteins in organs that are normally prion-free.
"The organ transforms itself into a bioreactor for prions," says Aguzzi. For example, diabetic mice injected with prions end up with a pancreas full of the misfolded protein, while the organ is unaffected in healthy mice.

Immune reaction

While inflammation does affect where prions accumulate, it does not make animals more susceptible to brain infection or affect how quickly the disease makes the animals sick. The team now plans to carry out similar experiments with farm animals.

The scientists are not sure why inflamed organs become more vulnerable to prions, but suspect it may be connected to the immune reaction. When an organ is inflamed, the immune system produces blood cells called lymphocytes to help battle the disease.
These cells produce a substance called lymphotoxin, which Aguzzi says may trigger a reaction that turns a normal cell into one capable of replicating prions. His lab has found that mice lacking the lymphotoxin receptor lack prion disease in inflamed organs.
Journal reference: *Science* (DOI: 10.1126/science.1106460)

Likelihood of a large vCJD epidemic remains small claim researchers; 12 January 2005

The likelihood of a large number of future cases of vCJD remains small claim researchers from Imperial College London.

According to research published today in Journal of the Royal Society Interface, the team believe there will be around 70 future cases of vCJD arising from the consumption of BSE-infected beef. At most this could rise to a total of around 600 deaths, although the researchers feel this is unlikely.

This work follows on from a study in 2003 at Derriford Hospital, Plymouth, which looked at tissue from appendectomies. The researchers found a higher prevalence of vCJD than expected from clinical data alone, indicating that around 3,800 individuals in the UK could test positive.

The team at Derriford found three positive samples among 12,764 tonsil and appendix samples and from this concluded that around 3,800 individuals could be at risk across the UK. Despite this, only one of the three samples positively matched tissues taken from those with clinical disease. The interpretation of the other two samples was less certain, and could indicate individuals infected with vCJD that do not go on to develop clinical symptoms - so called sub-clinical infections.

Dr Azra Ghani, from Imperial College London, and based at St Mary's Hospital, comments: "Since 2000 there has been a decline in the number of clinical cases reported. One reason for the discrepancy between the high estimated number of positive tests and low number of actual recorded clinical cases could be that many infected individuals do not go on to develop clinical disease in their lifetime."

Using computer modelling the team ran a number of different scenarios. The first scenario in which 90 per cent of infections are sub-clinical suggested that relatively few future cases would arise through primary transmission, such as eating BSE infected beef. The other 'worst case' scenario, where all genetic groups were susceptible, suggested that a five fold rise could be possible, although this was felt to be unlikely, due to the low number of clinical cases currently recorded in these other genetic groups.

Dr Ghani adds: "Although our results indicate there is little chance of large numbers of vCJD infections from primary transmission, we have not taken into account the possibility of additional cases infected by blood transfusion. This could result in more clinical cases emerging at a later date."