

Prions

Transmissible Spongiform Encephalopathies and Dental Transmission Risk Assessment

BY JANYCE HAMILTON

AUTHOR

Janyce Hamilton is a freelance writer working out of Naperville, Ill. Her previous articles for the *Journal of the California Dental Association* are "Robots, Bionics, and Bio-engineered Replacement Parts in Dentistry," "The Link Between Periodontal Disease and Systemic Diseases: State of the Evidence 2005," "Assessing 'Real Science': Poor Studies, Industry Ties Taking Toll," and the "Dental Implications of the Human Genome Project"

ACKNOWLEDGMENTS

The author gratefully acknowledges the research assistance of Ruth Schultz at the Library of the American Dental Association in Chicago; editorial comments of Heather Larson of Phoenix and Ermias Belay, MD, of the national Centers for Disease Control and Prevention in Atlanta; and reviewer comments by James Mastrianni, MD, PhD, at the Prion Laboratory, University of Chicago.

Are instruments used on the dental patient with possible variant Creutzfeldt-Jakob disease a theoretical remote risk of little concern, or is the unknown potential transmissibility one that warrants disposal or a prion-inactivating regimen for contaminated instruments?

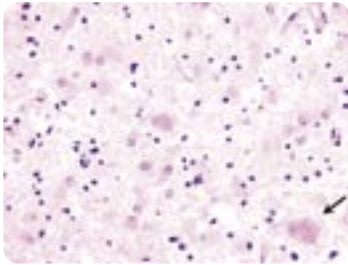
No test. No cure. No foolproof disinfection. No wonder surgeons feel uneasy about prion diseases or bristle when asked about preventing "mad cow" risk.

The national Centers for Disease Control and Prevention wants dentists and oral and maxillofacial surgeons to know that when it comes to minimizing risks of a transmissible spongiform encephalopathy (or "prion disease"), which is known in humans as Creutzfeldt-Jakob disease, there is nothing different they need to be doing in 2007 than, say, 2003. That's the year of the landmark study by Kohn and colleagues, "Guidelines for Infection Control in Dental Health-Care Settings — 2003."¹ The guidelines draw upon the World Health Organization's important report, "WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies: Report of a WHO Consultation, Geneva, Switzerland, 23-26 March 1999" for examples of sterilization.² The precautions in these documents would be pertinent for the known Creutzfeldt-Jakob disease (CJD) patient, or during major dental procedures where neurovascular tissues may be exposed, including using single-use items (needles, anesthetic cartridges); disposing of hard-to-clean equipment after one use (files, burs); avoiding flash sterilization; keeping instruments moist so tissues don't dry before cleaning and sterilization; and using

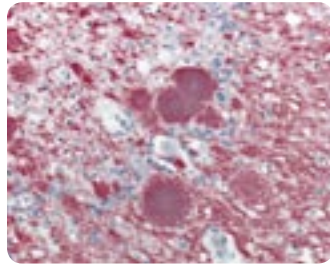
one of WHO's transmissible spongiform encephalopathy sterilization methods.²

In 2006, a new set of WHO transmissible spongiform encephalopathy guidelines on tissue infectivity was released, which confirmed the first human-to-human transmission route via blood transfusion.³ This development points to a previously unmapped way in which prion diseases have been spreading. Reportedly, the British Dental Association is going to release revised guidance based on a 2006 Spongiform Encephalopathy Advisory Committee Position Statement on variant CJD and endodontic dentistry⁴ to update the use and decontamination of dental instruments.⁵ Concerns over this issue arose well before a study of endodontic files using high magnification, postclinical use, and subsequent decontamination found 75 percent had residual adherent biomass.⁶

This article looks at the complex



Histopathologic changes in frontal cerebral cortex of the patient who died of variant Creutzfeldt-Jakob disease in the United States. Marked astroglial reaction is shown, occasionally with relatively large florid plaques surrounded by vacuoles (arrow in inset) (hematoxylin and eosin stain, original magnification x 40).



Immunohistochemical staining of cerebellar tissue of the patient who died of variant Creutzfeldt-Jakob disease in the United States. Stained amyloid plaques are shown with surrounding deposits of abnormal prion protein (immunoalkaline phosphatase stain, naphthol fast red substrate with light hematoxylin counterstain; original magnification x 158).

questions around the implications of emerging data on the abnormal prion protein (PrP^{TSE}) and infection control during hospital-based procedures as well as dental and oral and maxillofacial surgeries. Reviewed is the literature from a PubMed search of dental journals since 1999 using keywords “prion diseases.”^{1,4,6-24} The aim of the article is to summarize data for weighing potential prion transmission risks, so dentists can decide how to approach infection control.

The problem: a menacing family of diseases. On the English countryside, black cattle dot the hillsides, munching away. The story begins here, where a family of transmissible spongiform encephalopathies first showed up in these cows. Bovine spongiform encephalopathy afflicted the cattle that were fed a supplement of bone and tissue meal rendered from processing plants disposing of cattle, goat, sheep, and other carcasses. This disease, which is known as “scrapie” in sheep and goats and chronic wasting disease in deer, has several human forms, including CJD, fatal insomnia, and Gerstmann-Straussler Scheinker disease. Prion diseases have been described in the medical literature for more than 150 years, but no one understood what they were. Molecularly, neither suspicious viruses nor bacteria were found ante- or postmortem assays. All people said is that formerly gentle animals and level-headed people stared into space more, bumped into things, walked wob-

bly, lost their appetite, attacked others unprovoked, and generally acted a tad crazy.

The biological villain. American Carleton Gajdusek studied and reported on kuru, a brain wasting death in tribes who consumed human tissues as part of burial rituals. William Hadlow, a veterinary researcher, noted that the pathology of kuru was the same as scrapie in sheep. He suggested to Gajdusek that he try to transmit kuru, since Hadlow knew scrapie was transmissible. Gajdusek did this in the 1960s — kuru was transmitted to chimpanzees. Thus, Gajdusek is credited with making the connection between sheep scrapie and kuru, and was a recipient of the 1976 Nobel Prize in Medicine for this work.

In 1972, Stanley Prusiner, MD, searched for a biological commonality shared by scrapie in animals and kuru in humans. In 1982, he published a report on an unusual folded protein — termed a “prion” that was thought to be connected. Of the 30,000 or so different proteins in human blood, this one was acting independently. It

seemed this type of prion sent a signal to surrounding proteins, which “listened,” as they’d soon conform their structures and fold too. Interestingly, the manifestation of the disease didn’t seem to occur until much later, sometimes decades.

The growing numbers of PrP^{TSE} converts lurk silently, incubating before starting mass foldings within otherwise healthy-acting animals and people. Scientists are discovering bacteria communicate by releasing signaling molecules — a process known as “quorum sensing.” It is unknown if this is similar to the activity of prions.

When masses of prions result, clumped together by their sticky surfaces, they travel throughout the body. How they are transported in the body is uncertain, but the lymphoreticular system has been suggested. The favorite stop for the traveling prions is the brain. Evidence of the occupation of the brain by prions is not stains but sponge holes, as if “eaten.” The cascading neurological impact of rapidly increasing numbers and sizes of holes makes the brain look like coral, which alters mental and physical function rapidly,



Wasting disease in deer is known as ‘scrapie’ in sheep and goats. The human forms of this disease include CJD and fatal insomnia.

driving the afflicted “mad” until death. Sometimes a patient lives a few years, but it’s not unusual for death to occur in as little as a few months or even weeks.

PrP^{TSE} diehard superpowers. The prion that causes CJD is unlike what most infection control manuals have addressed; you can’t seem to kill a prion with standard disinfecting techniques used on more fragile viruses such as HIV, hepatitis, or TB bacterium.

In late 2006, researchers meekly reported that they boiled and baked prions with exceedingly long and high temperatures, yet tests still detected the faint “signaling” of prions still active on the surface of stainless steel instruments.

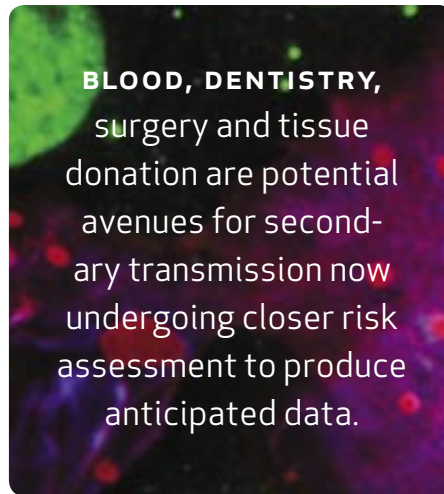
PrP^{TSE} is a cyborg — as no biological proteinase can touch it. Proteinases, which usually eat abnormal proteins, can’t seem to digest the prion, which goes about its business mechanically destroying its human host impervious to the usual macrophages and other biosoldiers of defense.

Types of human prion disease. The data for solving the mysteries of prion diseases is scanty, and most are in animal models. There are incidence statistics medical epidemiologists have collected about the three known types of transmissible spongiform encephalopathies in humans:

- Sporadic CJD (80-85 percent) (average age at death 67 worldwide³ or 68 in the United States²⁵) — spontaneous cases of unknown cause;
- Familial CJD (10-15 percent) — genetic origin;
- Variant CJD (4 percent) — least in reported numbers but not least feared is this newest form. It afflicts younger populations (average age 28²⁶). vCJD traumatized the British population, mainly transmitted from an innocuous activity: eating beef unknowingly infected with bovine spongiform encephalopa-

thy. There were more than 184,453 U.K. cases of bovine spongiform encephalopathy in cows as of Sept. 30, 2006.²⁷

While vCJD — the mad cow type — is the disease that has highest infectivity risk, all types could theoretically be transmitted through direct brain, blood, or tissue transplant/transfusion, which is why no close family relative with prion



disease should be a tissue, blood, or organ donor. The thousands of sporadic cases in the past few decades are theorized, but unproven, as a cell’s random error — a genetic triggering that mistranslates normal to warped protein. Less popular with public health scientists are the unproven theories published that a portion of sporadic cases should be investigated more carefully to look at iatrogenic or person-to-person etiology.²⁸ The United States is not the United Kingdom, but American epidemiologists do look there for clues to worst-case scenarios that could come to pass on this side of the pond. The peak number of U.K. vCJD deaths in one year was 28; in 2006, five vCJD cases were counted (as of Nov. 22).²⁶ The total number of children diagnosed with vCJD

in the United Kingdom is four definite and two probable, the youngest age 12.²⁹

vCJD British Cases Raise Questions of ‘Subclinical Carriers’ and ‘Self-Sustaining Epidemic’

Blood, dentistry, surgery, and tissue donation are potential avenues for secondary transmission now undergoing closer risk assessment to produce anticipated data.^{26,30} For example, a study of 100,000 tonsils from the National Anonymous Tonsil Archive begins in 2007 in the United Kingdom to test for abnormal prions.³¹ The U.K.’s Spongiform Encephalopathy Advisory Committee strongly recommends this testing progress with “all possible urgency.”²⁶ Imagine the epidemiological quagmire that would ensue should any of the potential 5,000 subclinical vCJD carriers donate blood or share their prion disease by infecting instruments even after a current universal sterilization regimen. These newly exposed patients themselves become vectors, and on it goes.

It’s the “what-ifs” that drive the Spongiform Encephalopathy Advisory Committee epidemiology subgroup to wonder whether instituting attributable rather than anonymous tissue testing would be a valuable public health tool so that routes of transmission could be understood, and further spread stemmed.²⁶ The proposed pragmatics are likely to be contentious in discussions, however. Studies have shown people with familial cases, such as those with a family predilection for Huntington’s disease, prefer not to know their own carrier status.

The knowledge of an increased risk of a lurking biological killer infecting the brain stem for a neurological stranglehold doesn’t sit well. Today, learning you have HIV or many cancers — which have treatments that can

TABLE 1

High, Low, or Nondetectable TSE Infectivity By Tissue**

Tissue	One or more Human TSEs Infectivity Shown	
	Yes	No
HIGH TITER INFECTIVITY TISSUES		
Brain	Yes	
Spinal cord	Yes	
Retina	Yes	
Optic nerve	Unknown‡	
Spinal ganglia	Yes	
Tigeminal ganglia	Yes	
Pituitary gland	Yes	
Dura mater	Yes	
LOW TITER INFECTIVITY TISSUES		
Peripheral nerves	Yes	
Enteric plexuses	Unknown	
Spleen	Yes	
Lymph nodes	Yes	
Tonsil	Yes	
Thymus	Unknown	
Esophagus	Unknown	
Stomach/abomasum	Unknown	
Duodenum	Unknown	
Jejunum	Unknown	
Ileum	Unknown	
Appendix	Unknown	
Large intestine	Yes	
Placenta	Unlikely (report unconfirmed)	
Lung	Yes	
Liver	Yes	
Kidney	Yes	
Adrenal		None yet, more testing needed
Pancreas	Unknown	
Bone marrow		Preliminary data, more testing needed
Skeletal muscle		Preliminary data, more testing needed
Tongue	Unknown	
Blood vessels	Unknown	
Nasal mucosa	Unknown	
Salivary gland	Unknown	
Cornea	Yes	
CSF	Yes	
Blood	Yes	

prolong and even save your life — isn't good news, but at least you can try to do *something*. For CJD exposures, should they turn into clinical manifesting disease, there is no treatment.

For oral health clinicians, two principles should be kept in mind when reading the animal studies: 1) not every PrP^{TSE} exposure will infect you with CJD and 2) it is sensible to minimize all potential opportunities for human exposure. In animal studies, during a single time point in the incubation or clinical illness, bovine spongiform encephalopathy infectivity has been found in sternal bone marrow and palatine tonsil.³ Meanwhile, sheep blood has infectivity during the “silent portion” of the prion affliction, as does cow brain.

While a cosmetic case has not been reported, tell the Botox crowd that full, pouty lips are courtesy of injectable bovine-sourced poison and they'd frown if they could.³² The 2006 WHO report addressed such varied concerns as minimizing transmissible spongiform encephalopathy risk in vaccines, many produced with delicate animal-sourced organisms that would be destroyed by harsh purification/extraction methods; and gelatin used in food and vitamins should pose little risk after processing as long as cow skulls and vertebrae are excluded; milk is considered noninfectious if from healthy cows “fit for human consumption.”³³ Keep in mind that the oral route of administering PrP^{TSE} is inefficient — no matter the level of the food infectivity consumed; while blood transfusion, especially for those with hemophilia, is efficient even in low titer infected blood or clotting factor.³³

For tissue infectivity concerns during oral surgical procedures in the United States, William G. Kohn, DDS, from the CDC, said there has been “nothing related to dental tissues, not root canals, tooth extractions, or periodontal

TABLE 1 CONTINUED

High, Low, or Nondetectable TSE Infectivity By Tissue** (continued)

Tissue	One or more Human TSEs Infectivity Shown	
	Yes	No
NO DETECTABLE INFECTIVITY TISSUES		
Testis		Preliminary data, more testing needed
Prostate/epididymis/seminal vesicle		Preliminary data, more testing needed
Semen		Preliminary data, more testing needed
Ovary	Unknown	
Uterus (non-gravid)	Unknown	
Placenta fluids		Preliminary data, more testing needed
Fetus	Unknown	
Embryos	Unknown	
Bone	Unknown	
Heart/pericardium		Some data, more desired
Tendon	Unknown	
Gingivae		Some data, more desired
Dental pulp	Unknown	
Trachea	Unknown	
Skin	Unknown	
Adipose tissue		Preliminary data, more testing needed
Thyroid gland		Preliminary data, more testing needed
Mammary gland/udder	Untested	
Milk		Preliminary data, more testing needed
Colostrum		Preliminary data, more testing needed
Cord blood		Preliminary data, more testing needed
Saliva		Some data, more desired
Sweat		Some data, more desired
Tears		Some data, more desired
Nasal mucus		Some data, more desired
Bile	Unknown	
Urine		Some data, more desired
Feces		Some data, more desired

* Table condensed and adapted from Tables 1A-C, Annex 1, 2006 WHO Guidelines³ and 2003 WHO Guidelines.³⁴

† Noninfectivity does not mean PrP^{TSE} were not present.

‡ Unknown because not yet tested for infectivity.

bone grafting procedures.” (See **TABLE 1.**) Not in human studies, but there is hamster scrapie transmission dentally.⁹

Iatrogenic CJD (1 percent) has occurred when the disease was transmitted by transfusion with infected blood (three vCJD cases), and transplanted with infected tissues (human dura mater allografts, corneas) or organs or on surgical tools (neurosurgical) and equipment (EEG electrode). In a study by Gibbs and colleagues, electrode probes used in a middle-aged woman who had CJD that were cleaned and sterilized accidentally transmitted CJD in two younger patients.³⁵ More than two years passed, and the electrode probes were implanted in the cortex of a chimpanzee. While they had been cleaned thrice, and sterilized in ethanol and formaldehyde vapor repeatedly, the chimp got sick with CJD 18 months later.

More than 362 cases of iatrogenic CJD transmission have been counted worldwide.¹² No bone-derived graft tissues for periodontal repair or jaw buildup have transmitted CJD. Chewing (surgical bone augmentation), walking (hip replacement), and seeing (cornea implants), and extending life (bone marrow transplant) are all case-by-case risk-benefit proposition that involve demographic risk and manufacturers' safeguards.

Controversy Doesn't Die With Its Victims

Those left behind may never be satisfied with the official explanations when a family member dies of CJD. Heather Larson of Phoenix has first-hand knowledge of the familial genetic form of CJD. Her mom lived in Phoenix and worked at home. Her symptoms were classic for CJD but add nausea, hallucinations, and onset of incontinence. Heather's mom died at age 56 of familial CJD in a matter of weeks — not years — after

being diagnosed. Afterward, Heather said, the problems were far from over.

"I worked with the National Prion Disease Pathology Surveillance Center to arrange the autopsy as my mother died. It took several days of phone calls, but the [center] called me and said they had finally found someone who would do an autopsy on my mother — in New Mexico. I wanted to identify her body once it was back in Phoenix and before it was cremated. I stood alone in that room and looked at her body in a white bag marked 'biohazard.'"

Months later, her mom's dentist called to remind her it was time for a cleaning. "I had to tell them that she was deceased. They asked how she died, and I said 'CJD — the human form of mad cow disease' and they quickly got off the phone."

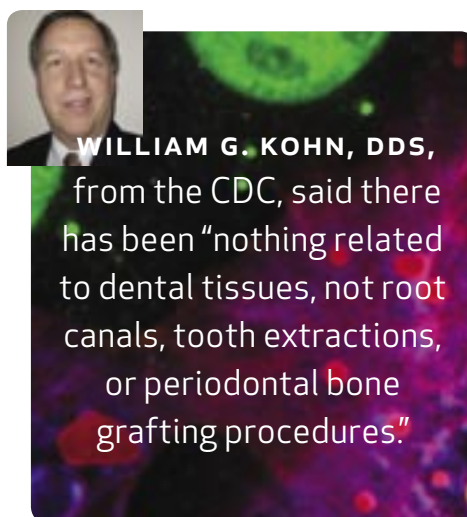
"As for myself, I don't know if it would even be something to bring up for fear of being discriminated against, however, I wouldn't want to infect anyone either. There is a 50/50 chance that I carry the gene too. I haven't gotten tested. I don't see any benefit."

The British Dental Association has urged dentists not to discriminate against suspected CJD patients. England's chief dental officer of the Department of Health mailed his dental colleagues a letter in 2005 saying nothing special need be done beyond the satisfactory standards of decontamination for all patients for the CJD symptomatic or "at-risk for CJD for public health purposes" dental patient, as long as treatment doesn't include surgery.³⁶

Blood Supply Concerns

No patient with a clotting disorder has ever been reported as contracting vCJD — including those in the United Kingdom where the risk has been highest. That is perhaps the most encouraging news of

all, which should allay some the fears over bloodborne vCJD risks. Efforts in medical product manufacturing are believed to reduce or eliminate most risk should a vCJD-infected donor unknowingly give plasma. While it's easy to let a phrase like "it is still hypothetically possible that a person getting a blood transfusion or clotting agent can be exposed to the



agent that causes vCJD if the donor(s) were incubating the disease," the lack of a single case says something. This is precisely what U.S. government public health officials want us to keep in mind.

The Department of Health and Human Services Administration, including the Food and Drug Administration, CDC, the National Institutes of Health, and the Office of Public Health and Science, released a joint statement Nov. 27, 2006, applicable to those with blood clotting disorders visiting dentists:

"At this time the U.S. Public Health Service does not believe there is a need for pdFVIII recipients to inform their surgeons or dentists about the recipient's potential exposure to vCJD. Also, there is no recommendation for surgeons and

dentists to take any special precautions based on such potential exposures.

"In the U.K., public health authorities notified recipients of plasma-derived products such as pdFVIII that they may have an increased risk of vCJD in addition to the risk from eating potentially contaminated beef products. The U.K. health authorities notified patients to inform their surgeons and dentists about their potential exposure as a public health precaution intended to prevent possible secondary spread of the disease from dental and surgical instruments. The PHS, including the FDA, CDC, and NIH, does not believe that such notifications are necessary in the U.S. This is based on the extremely small risk in the transmission from plasma-derived clotting factor products in the U.K. or anywhere else in the world. Given this information, the PHS believes that the potential risks of altering the standard current precautions with respect to reusable surgical and dental instruments, and instruments used for invasive procedures outweigh any potential benefits."

In the United Kingdom, from 2004 on, people with hemophilia are to tell their dentists of their possible risk of CJD from receiving pool blood clotting agent so disposable instruments can be readied as needed. The dentists are instructed not to turn them away.

U.S. Public Health Service: 'Little Cause for Worry' Here

In at least five countries as of January 2007, blood donors have gone on to develop vCJD, so unrealized spread of the disease is not out of the realm of possibility.³ The United States is not among them. Those unable to give blood in the United States due to their travels outside the country are not required to tell their dentist or oral surgeon.³⁷ In one person's circulating

blood outside the central nervous system, PrP^{TSE} titer is likely lower but it cannot be sterilized.³ It's hard enough to get the news that you are at "higher risk" for the agent causing an incurable fatal disease. That could cause significant attacks in someone with anxiety problems. People would rather not know they are at risk of something. Now the FDA would like a test to identify subclinical incubators of vCJD. This would be handy information, because then doctors would know whether you are at risk and if you would subsequently require an extraordinary approach to minimize infection risks via surgical and dental tools.

The bloodborne risk of prions is unknown but small. But until researchers produce data that shows the prion load needed to conduct infection and the corresponding risk level, the "logic" is theoretical too. Should even a single prion be left on a dental drill that is reused, we will be in the dark until there are investigations showing that one prion does or does not confer infection and the role of a host's response. In 2007, to needlessly alarm the U.S. dentist that special precautions or disposable instruments are needed is not warranted yet, and may never be.

Authorities Dispute Claim By Some That CJD Is Misdiagnosed as Alzheimer's

Because it is so rare, physicians reportedly have misdiagnosed CJD as Pick's disease, vascular degeneration, paraneoplastic syndromes, viral encephalitis, and meningitis. U.S. research teams have looked for prion gene ties with Alzheimer's and other dementias.³⁸ In England, however, there is a greater interest shown by public health officials in this area. Among the 2006 Spongiform Encephalopathy Advisory Committee recommendations is enhanced clinical

surveillance in the aged to learn if there may be any "under-ascertainment of cases in the elderly due to misdiagnosis."²⁶

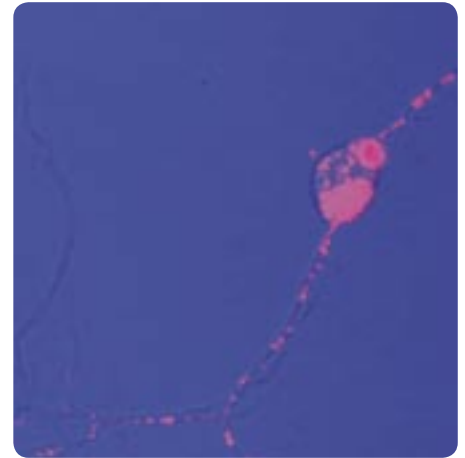
Cases of secondary transmission of vCJD, if any, may be detected in the elderly as they are more likely to have had surgeries and received blood transfusion.²⁶

Beef and Bovine Spongiform Encephalopathy in America

Is mad cow just more Y2K and the sky is falling type nonsense? To be sure, there have only been three vCJD cases in the United States, and assurances come from some public health leaders are that there's probably "few if any others in the population." Knowing this, even if current standards in dental offices do not inactivate prions on at-risk patients, will it make a difference? Why throw considerable sums of money at protections if there is no data projecting that there will be substantial new cases of other vCJD carriers in America? Also, it is unknown if some who are infected will never have the disease. So, dentists and surgeons have mostly been shrugging off theoretical risks.

Beef products may be safer in the United States today than a decade ago. Processed meats like beef hot dogs and bologna used to have the paste- and batter-like meat product produced by forcing bones, with attached meat, under high pressure through a sieve to separate the bone from the edible meat. This mechanically separated meat was banned to protect consumers against bovine spongiform encephalopathy for human food in 2004 standard changes by U.S. Department of Agriculture's Food Safety and Infection Service.

Background on animal transmissible spongiform encephalopathies. The small numbers of North American bovine spongiform encephalopathy cattle have been minor compared with the outbreaks



Prion trafficking in nerve cells. Prions branded with a fluorescent dye (pink) were added to nerve cells taken from a hamster brain. The prions initially were in the form of large clumps on the cell, but over time the clumps were broken into smaller units and transported along wire-like nerve cell projections.

in the United Kingdom and Europe. Scientists are not sure how bovine spongiform encephalopathy jumped species to humans. Luckily, the numbers of infected cattle peaked in the United Kingdom and Europe in the mid-1990s, and continues to fall.³⁹ Unfortunately, the number of countries with "mad cows" increases each year. As of fall 2006, three cows had tested positive for bovine spongiform encephalopathy in the United States; five in Canada; 83 in the United Kingdom; 189,000 worldwide. At this writing, Japan will trade U.S. cattle if 20 months or younger, and they test each of their own cows. The United States' previous wider net of testing found few in the past several years, so the decision in 2006 was to limit testing to "downers" (falling down animals) and other targeted abnormal cows because to do otherwise seemed cost-excessive. The 90 percent cutback on animals tested saves about \$35 million a year and still amounts to 40,000 animals tested per year.⁴⁰ Before the first bovine spongiform encephalopathy-positive cow was identified in America, the U.S. exports of beef product were \$3.8 billion (2003); afterward they had fallen to \$1.4 billion (2005) because of fears that the U.S. testing isn't rigorous enough.⁴¹

W. Ron DeHaven, administrator of

the Animal and Plant Health Inspection Service for the USDA, said that he eats U.S. beef and knows there isn't a significant problem and never has been. In a 2006 editorial, DeHaven wrote that USDA's recently released surveillance data over seven years and 764,000 samples finds "the prevalence of bovine spongiform encephalopathy in the USA is less than one case per 1 million adult cattle, with the most likely range of infected animals being four to seven."⁴²

In Wisconsin, the Department of Natural Resources has spent \$27 million battling the disease since it surfaced in 2002 in that state, one of at least 14. Bovine spongiform encephalopathy jumped the species barrier to humans from cow, so who is to say chronic wasting disease won't go from deer to human?⁴³

Dental Instruments

The most recent frontier is surgical instruments, and the data are accumulating but have not yet been pooled to give any index of risk by type of tool or equipment, type of surgery, or exact questions to identify vCJD vs. probable vs. at-risk/possible vs. no/low-risk patient. Some organizations are releasing their assessment of the estimated infectivity in each human bodily tissue and fluid.

In California, one dental school admitted to tackling the potentially infected CJD patient a little differently. The University of California at San Francisco is sending patients with the potential risk of a prion disease to its medical center hospital, where gloved safety specialists pick up the contaminated waste and arrange for disposal/incineration all within one hour of its exposure. In clinics, like UCSF's Memory and Aging Center, patients are screened for prion disease risk, and if it cannot be ruled out as a possibility, should dental care be necessary, dental instruments used

are either quarantined pending diagnosis, incinerated, or cycled 10-20 times at the direction of health authorities who intend the precautions to prevent possible secondary iatrogenic spread of the disease via contaminated dental and surgical instruments.

There have been three people in the United States with vCJD, 197 elsewhere in the world. While human "mad cow" might



one year spike into an epidemic in the United Kingdom, the CDC isn't predicting an epidemic here.⁴⁴ Even if that number rose by 100 percent, that would be six people. What's the chance that one of those highly infectious "mad cow" people was sitting in your dental chair today?

Exposure Scare Over CJD-Tainted Surgical Tools Shuttters Hospital, Causing Cancellation of Surgeries, and Resulting in Patient Lawsuit

One of the first hardships of operating in a prion-potential world is how upsetting it is to patients. At Emory University Hospital in Atlanta during 2004, some 500 patients had to be telephoned with a particularly unpleasant incident report — their own.⁴⁵ The surgical instru-

ments used on their brain/spine surgeries were previously used on a patient who tested positive for sporadic CJD.

Last year, a teacher who had been among those patients informed of the potentially contaminated tools used on her surgery filed a lawsuit for monetary damages and a fund for her medical costs, should she develop the disease. Among other errors, the complainant lists not having quarantined surgical tools or using a Joint Commission on Healthcare Accreditation sterilant that "dissolves brain tissue."⁴⁶

Trying to avoid this kind of legal entanglement, hospitals are starting to gear up for these prion-risk cases. Last month, surgeries were canceled for a few days at South Ontario Hospital in Canada, as the Public Health Agency of Canada's Creutzfeldt-Jakob Disease Surveillance System was busy testing surgical instruments used on a brain surgery in a suspected CJD patient.⁴⁷ One can imagine a bank of telephones, scripts ready, hospital representatives dialing the residences of patients who may have come into contact with the instruments used in the operation. Fortunately, the more comprehensive tests of the instruments were negative as of this writing.

These hospital-based neurosurgical risk-disclosures occurred in the United States, and are educational for oral and maxillofacial surgeons and dentists performing complex protocols. All over the United Kingdom and Europe, dentistry is now a highly monitored profession because of the mad cow cases there. Patients are to inform their dentists if they have a family member with the genetic form of CJD, if they received any tissues or fluid donation, or received oral or other surgery with instruments used on someone who later was diagnosed with CJD.

If you were a dentist in Scotland

and you suspected your dental instrument accidentally abraded the tonsil (“medium” infectivity) of a patient at risk of CJD, that instrument is to be sterilized at least 10 times to minimize prions remaining on it.⁴⁸ While routine dentistry is considered low-risk, if you are an oral and maxillofacial surgeon doing procedures on the head, neck, face, or orbital regions, additional precautionary measures may be needed to reduce possible CJD transmission.³⁶

No evidence-based data and projection models have been generated to indicate whether dental transmission of vCJD has, is, or likely will occur. Indeed, the threat of transmission remains a possibility.⁴⁹

UCSF Medical and Dental Centers Adopt Highest ‘As If’ Precaution Level Infection Control Theory That Most Human Tissues and Fluids Are Infective

Few would disagree that UCSF, through the Memory and Aging Center, is on the leading edge of research into understanding prion diseases worldwide. Ermias Belay, MD, an epidemiologist with the CDC, is not alone when he points out that there are other theorems worth pursuit, “Still, there is controversy on whether prions are the only agents that cause CJD.”⁵⁰

In reading the UCSF Medical Center Infection Control Manual Guidelines on treating CJD patients, they seem to come from a different direction that overlays its own policies and procedures above the existing national and international guidelines for minimizing prion transmission.⁵¹ Because UCSF is the premier location of prion research in the United States, it is very aware of the implications of its data and protocol for infection control.

“I have read many articles from the U.K., and there are no uniform

recommendations and lots of ‘refer to your infection control coordinator for protocol,’” said Molly Newlon, DDS, MA, director of Health and Safety, UCSF School of Dentistry.

“I assume that all used items, including the metal instruments are incinerated. I do know that deactivation of prions on stainless steel is very difficult, and the



instruments must be in an autoclave for so long that it destroys the instrument. The research that is currently being done in the Prusiner lab involves testing a soaking solution that may be used prior to autoclaving that will deactivate the prion. As I understand it, this product is still being tested and is not yet available for use in the marketplace. Also, it is my understanding that conventional sterilization procedures cannot guarantee prion deactivation, which is why any instrument used on a CJD patient in dentistry is single-use only.”

Brown and colleagues conducted a 2005 instrument study that is cited in medical literature to show how corrosively damaging the WHO protocol for prion deactivation can be.⁵²

Can't Touch That

Prions on instruments are difficult to inactivate. Instead of providing a list of all the decontamination protocols that are ineffective against prions (16 minimum processes), dentists should know that when it comes to highly infectious tissues and contaminated instruments, everything you were taught in dental school can't touch it.

“Our studies show that the standard sterilization techniques in use are insufficient to inactivate human prions.⁵³ However, acidic sodium dodecyl sulfate combined with autoclaving can inactivate prions beyond the level of even the most sensitive detection methods,” said Kurt Giles, DPhil, assistant adjunct professor, Institute for Neurodegenerative Diseases, UCSF.

Regarding 2006 *Journal of Virology* findings of Prusiner and coauthors, Giles said, “The main findings of our paper were that human prions are 100,000 times more difficult to inactivate than hamster prions.⁵³ This is of great significance since hamster prions have historically been used as the standard for prion inactivation protocols. We also found, as have others, that prions bound to stainless steel are even more difficult to inactivate than prions in suspension (again, historically prions in tissue suspension have been used as the standard).”

U.S. Dental and Oral Craniofacial Leaders Confident While U.K. Equivalent ‘On Watch’

While American physicians and dental surgeons read relatively little about prion diseases in their journals, in England, a flurry of updated guidelines at the end of 2006 has dental practitioners sitting up. They know there will likely be word from the Department of Health that summarizes updates since the 2005 let-

ter from the chief dental officer advising that routine dentistry requires no special adaptations for infection control even on patients who may have CJD.

From the two Spongiform Encephalopathy Advisory Committee reports last year, the latest issued Nov. 30, 2006, it appears a Department of Health preliminary risk assessment recently was completed of vCJD on difficult-to-clean endodontic instruments, infectivity of dental pulp, and subclinical vCJD carrier state.^{4,26} To date, no data show that dental pulps are infectious, yet peripheral nerves and blood are both in close proximity. Said the report, "Although data are limited and indirect, it is reasonable to assume that the dental pulp of individuals subclinically infected with vCJD may be infectious although the level of infectivity is unknown."⁴

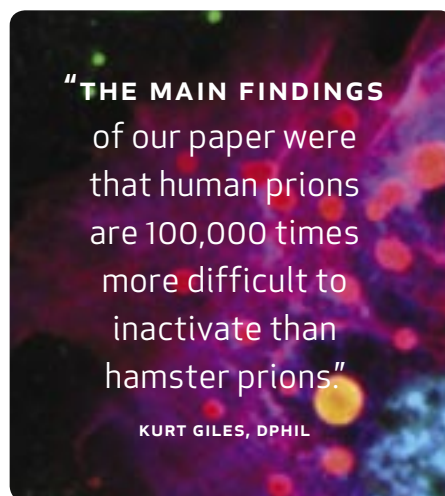
Although refinements in risk assessment and direct data from vCJD human pulps will improve predictions, the Department of Health preliminary assessment seems more concerned about endodontic equipment, which had been suggested but not required as one-use anyway: "Dental pulp is as infective as peripheral nerve tissue and if a subclinical carrier population for vCJD exists, a self-sustaining vCJD epidemic arising from endodontic surgery is plausible."⁴

William G. Kohn, DDS, associate director for Science, Division of Oral Health, CDC, said he feels at ease about the status of the information put forth for dentists. Kohn said "there is no more risks than we determined there'd be, so no updates are needed. vCJD transmission is of no greater concern for dentistry in the U.S. now than what it was in 2003."

At the time the 2003 guidelines from the CDC were printed, vCJD wasn't associated with convincing evidence of prion detection in human blood. The 2006 WHO guidelines ac-

knowledged that blood transfusions infected recipients with "mad cow."

"But you can't jump from three blood transfusions in U.K. transmitting vCJD means all blood for any dental procedure in the U.S. is now infectious with prions potentially," Kohn said. "Saying 'all blood is potentially infectious' is panic-laden statement that is invalid."



Updating Medical History Forms

In the United Kingdom, to identify patients who are about to have surgery who may be at-risk of developing CJD, individuals are questioned on family dementia before age 65; dura mater grafts; corneal transplant; pituitary hormone injection pre-1986; insulin injection pre-1989; problems concentrating, reasoning, remembering; and unsteadiness walking, jerky movements, or lacking previous coordination. If any answer "yes" to the aforementioned, they are referred to a neurologist for more careful screening of risk category.

A 2006 article written about the U.K. situation suggests that screening all patients to learn who relies on blood transfusions and clotting agents

is necessary to discern patient risks.³³

It is believed that there are lower titers of vCJD prions in lymphoid tissues of non-U.K. individuals so chances of transmission from "any" surgical procedure would be somewhat less of an issue.⁵³

Whether dentists should have any screening questions to identify patients who may be at risk of developing CJD in medical history, as done in the United Kingdom and suggested elsewhere prior to any type of surgery (patient CJD risk categories are definite, probable, possible [includes diagnosis unclear], unlikely, definitely not) remains something the CDC doesn't think is even worth going into.^{21,54}

"It's so rare in the U.S. that a dentist would likely never hear the answer 'Yes, CJD,'" Kohn said. Given the current prevalence of this disease, he added, "It doesn't make any sense to ask more specific questions to screen for it and all the other rare diseases, or you'd go on forever and screen for all kinds of conditions and it would take too long."

T. Forcht Dagi, MD, MPH, of Harvard-MIT Division of Health Sciences and Technology, agreed with the CDC's Belay on this point. Dagi explained that irrespective of diagnosis status or organism, "from a policy perspective, the American College of Surgeons has taken the route of recommending and endorsing the highest level of universal precautions for all patients."

The American Association of Oral and Maxillofacial Surgeons refers media questions to one of its members especially interested in prion diseases: oral and maxillofacial surgeon Eric R. Carlson, DMD, MD, FACS, chairman of the Department of Oral and Maxillofacial Surgery, University of Tennessee Medical Center, Knoxville. Carlson said obtaining a thorough history, particularly

related to any observations of dementia, is the starting point. Because eye tissue is contacted during facial surgeries, “I recommend that surgeons performing orbital and facial surgery follow the guidelines established by the National Institute for Health and Clinical Excellence so as to reduce the risk of transmission of Creutzfeldt-Jakob disease. This involves the adherence to steps taken to ensure that surgical instruments can be tracked,” he said. Moreover, surgeons electing to implant freeze-dried allografts, particularly dura, should obtain these from an American Association of Tissue Banks-accredited tissue bank.

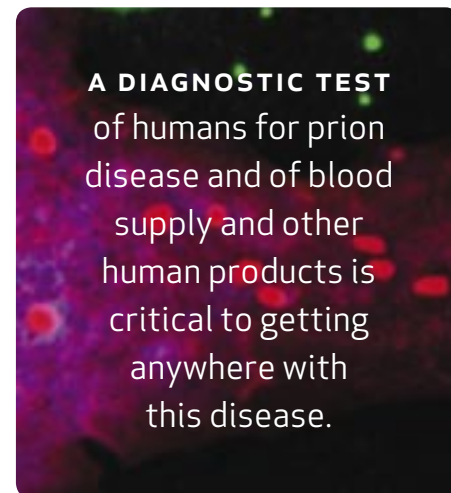
Research Frontiers

The National Institute of Dental and Craniofacial Research hasn’t conducted or funded any CJD studies, likely because there hasn’t been a single report of prion disease from dentistry. If data emerges showing surgical instrument transmission during dentistry, with solid evidence of oral tissue infectivity, it may reprioritize research funds for the good of public health. For now, the U.S. Army Medical Research and Materiel Command of the Department of Defense awarded \$42.5 million for prion disease research in fiscal year 2002. Some of those recipients began in 2003, but all will conclude their projects in 2008. We are just beginning to understand that there are prion-based diseases, so there very well may be more prion-based diseases than CJD.

A CJD test. Available tests for prion diseases are mostly postmortem, invasive, nonsensitive, and nonquantitative. A diagnostic test of humans for prion disease and of blood supply and other human products is critical to getting anywhere with this disease. In animal models, an in vitro “asymptomatic prionemia” blood test in development

is encouraging, with at least one team publishing promising results in 2006.⁵⁵ Human vCJD prion-laden blood has yet to be rigorously investigated. A PrP^{TSE} test for the sporadic form of CJD in the nasal olfactory mucosae is also being studied.³

Respected University of Chicago neurologist James A. Mastrianni, MD, PhD, at the Prion Laboratory, is try-



ing to make infectious prions. If he and his team can learn the mechanism behind the folding machine, identifying novel therapies for treating prion diseases would be a next step. He said he’d like to define sites on the PrP^{TSE} to target with a “designer peptide” to bind and block interaction that causes nearby normal prions to go abnormal.

Vaccine. More cases of vCJD in the United States would have to occur before enough human agent is supplied to work on developing a vaccine. The few, precious vCJD blood samples for researchers aren’t enough to go around for the world community of scientists, and this is a major hurdle for any potential developer.

Therapeutic directions. With prion discovery relatively new — compared

to fungi, parasites, bacteria, and viruses — drugs or gene therapy could involve inactivating prion formation and eradicating existing clumping prions. Again, there is the idea to “unfold” them to make them vulnerable to destruction.⁵⁶

Effective infection control method for prions. Paul Brown, MD, leading epidemiology bovine spongiform encephalopathy expert, has researched and published on various decontamination regimens. He suggested to dentists that a regimen of immersion in NaOH/bleach for at least an hour, washed, then autoclaved at 132 C for at least 20 minutes isn’t perfect but better than what many are now doing.

FDA and CDC Monitoring Disease Etiology and Incidence Patterns for Clusters Around Healthcare Workers and Pathologists

The CDC’s Belay is not alone in the reassurance that he hasn’t seen any cluster of CJD among dentists or any other profession.⁶ “The group who we would think to be maximally at risk of CJD infection because of professional exposure would be neuropathologists, and no cluster of cases among neuropathologists has been reported. We don’t expect to see it in dentists either.”

The CDC’s Kohn assures that if the rate of incidence changes and more vCJD patients are sitting in dental chairs, or any new data emerges of dental mechanisms that spread PrP^{TSE} that put patients or providers at risk, they will act. “But three cases of vCJD transfusion in the U.K. doesn’t warrant any changes at this time in the U.S.”

In 10 to 20 years, we’ll know “the last chapter.”

Until then, any measures introduced for infection control in American dentistry in response to the three “mad cow” cases will need to be evidence-based and proportionate to the risks. ■■■■

REFERENCES

1. Kohn WG, Collins AS, et al, Guidelines for infection control in dental health-care settings. *MMWR* 2003 52:(RR17):1-61, 2003. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5217a1.htm. Accessed Dec. 13, 2006.
2. World Health Organization. WHO infection control guidelines for transmissible spongiform encephalopathies: Report of a WHO consultation, Geneva, Switzerland, March 23-26, 1999. Geneva, Switzerland: WHO communicable disease surveillance and control, 2000.
3. World Health Organization. WHO guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies. Geneva, Switzerland: WHO quality and safety of plasma derivatives and related substances, Department of Medicines Policy and Standards, Health Technology and Pharmaceuticals Cluster, May/June 2006.
4. SEAC Position Statement. Position Statement vCJD and Endodontic Dentistry. London: Spongiform Encephalopathy Advisory Committee; May 2006.
5. Dr. Peter Bennett, U.K. Department of Health, personal communication, Nov. 27, 2006.
6. Azarpazhooh A, Leake JL, Prions in dentistry — What are they, should we be concerned, and what can we do? *J Can Dent Assoc* 72(1):53-60, 2006.
7. Scully C, Smith AJ, Bagg J, Prions and the human transmissible spongiform encephalopathies. In: Glick M, ed. *Infectious, Infectious Diseases and Dentistry, Part I. Dent Clin N Am* 47(3):493-516, 2003.
8. Head MW, Ritchie D, et al, Levels of abnormal prion protein in dental tissue. *Br Dent J* 195(6):339-43, 2003.
9. Ingrassio L, Pisani F, Pocciani M, Transmission of the 263K scrapie strain by the dental route. *J Gen Virol* 80(Pt 11):3043-7, 1999.
10. Smith A, Dickson M, et al, Contaminated dental instruments. *J Hosp Infect* 51(3):233-5, 2002.
11. Porter S, Scully C, et al, The human transmissible spongiform encephalopathies (TSEs): implications for dental practitioners. *Br Dent J* 188(8):432-6, 2000.
12. Chan SW, Collins S, et al, Classical and variant Creutzfeldt-Jakob diseases and their potential impact on the practice of clinical dentistry in Australia. *Aust Dent J* 46:4, 2001.
13. Gill DS, Tredwin CJ, Gill SK, The transmissible spongiform encephalopathies (prion diseases): A review for dental surgeons. *Int Dent J* 51(6):439-46, 2001.
14. Whitworth CL, Variant Creutzfeldt-Jakob Disease — A problem for general dental practitioners? *Primary Dent Care* 9(3):95-9, 2002.
15. Bebermeyer RD, Powell JF, et al, Dental practice implications of prion diseases. *Quintessence* 34:38-44, 2003.
16. Prions and dental practice. *Biological Therapies Dent* 18(6), April/May 2003.
17. Smith A, Bagg J, CJD and the dentist. *Dent Update* 30(4):180-6, 2003.
18. Porter SR, Prion disease: Possible implications for oral health care. *J Am Dent Assoc* 134:1486-91, 2003.
19. Smith AJ, Bagg J, et al, Prions and the oral cavity. *J Dent Res* 82(10):769-75, 2003.
20. Smith AJ, Sweeney MP, Bagg J, Prion disease and dental treatment: principles and practice of patients with/suspected or at-risk of CJD: Case reports. *Br Dent J* 195(6):319-21, 2003.
21. Transmissible spongiform encephalopathies: Implications for the practice of dentistry. FDI Statement. *J Can Dent Assoc* 68(1):18, 2003.
22. Cuny E, Prion diseases and infection control precautions. *Dent Today* 24(4):106-7, 2005.
23. Keogh PV, Flint SR, Transmissible spongiform encephalopathies and dentistry. *J Ir Dent Assoc* 50(4):160-2, 2004.
24. Smith AJ, Russell DI, et al, Presentation of a case of variant CJD in general dental practice. *Br Dent J* 197(2):75-6, 2004.
25. Belay ED, Schonberger LB, The public health impact of prion diseases. *Annu Rev Public Health* 26:191-212, 2005.
26. SEAC Epidemiology subgroup position statement on the vCJD epidemic. London: spongiform encephalopathy advisory committee, SEAC Epidemiology Subgroup; Nov. 30, 2006.
27. Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom. Paris: World organisation for animal health. Available at: www.oie.int/eng/info/en_esbru.htm. Accessed Dec. 13, 2006.
28. CJD Scare — Ask the BDA, http://news.bbc.co.uk/1/hi/talking_point/forum/862986.stm. Accessed Dec. 13, 2006.
29. Fourteenth Annual Report 2005: Creutzfeldt-Jakob Disease surveillance in the U.K. Edinburgh, England: The National CJD Surveillance Unit, Western General Hospital; 2005. Available at <http://www.cjd.ed.ac.uk/report14.pdf>. Accessed Dec. 13, 2006.
29. Hilton DA, Sutak J, et al, Specificity of lymphoreticular accumulation of prion protein for variant Creutzfeldt-Jakob disease. *J Clin Pathol* 57:300-2, 2004.
30. Garske T, Ward HJ, et al, Factors determining the potential for onward transmission of variant Creutzfeldt-Jakob disease via surgical instruments. *J R Soc Interface* Aug. 1, 2006.
31. Ironside JW, Bishop MT, et al, Variant Creutzfeldt-Jakob disease: Prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study. *BMJ* 332:1164-5, 2006.
32. Carruthers J, Carruthers A, Mad cows, prions, and wrinkles. *Arch Dermatol* 138(5):667-70, 2002.
33. Ironside JW, Variant Creutzfeldt-Jakob disease: Risk of transmission by blood transfusion and blood therapies. *Haemophilia* 12(s1):8-15, 2006.
34. WHO Guidelines on Transmissible spongiform encephalopathies in relation to biological and pharmaceutical Products, 2003. Geneva, Switzerland: World Health Organization, 2003. Available at: www.who.int/bloodproducts/publications/en/WHO_TSE_2003.pdf. Accessed Dec. 13, 2006.
35. Gibbs CJ Jr., Asher DM, et al, Transmission of Creutzfeldt-Jakob disease to a chimpanzee by electrodes contaminated during neurosurgery. *J Neuro Neurosurg Psychiatry* 57(6):757-8, 1994.
36. Bedi R, Information for dentists about the management of patients with, or "at risk" of, Creutzfeldt-Jakob Disease (CJD) including variant CJD (vCJD) [letter]. London: Department of Health, Feb. 4, 2005.
37. In-depth discussion of variant Creutzfeldt-Jacob disease and blood donation, Washington, D.C.: American Red Cross. March 21, 2005. Available at: www.redcross.org/services/biomed/blood/supply/CJDv.html. Accessed Dec. 13, 2006.
38. Li X, Rowland LP, Mitsumoto H, Prion protein codon 129 genotype prevalence is altered in primary progressive aphasia. *Ann Neurol* 58(6):858-64, 2005.
39. Brown P, Will RG, et al, Bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease: Background, evolution, and current concerns. *Emerg Infect Dis* 7(1), January-February 2001.
40. USDA announces new BSE surveillance program. USDA News Release. Washington, DC.: USDA; July 20, 2006.
41. Mad cow watch goes blind. *USA Today* Aug. 3, 2006.
42. DeHaven WR, Our safeguards are working. *USA Today* Aug. 3, 2006.
43. Belay ED, Maddow RA, et al, Chronic wasting disease and potential transmission to humans. *Emerg Infect Dis* 10(6), June 2004.
44. Human "mad cow" could cause eventual epidemic. *HealthDay News* June 22, 2006. Available at: www.forbes.com/forbeslife/health/feeds/hscout/2006/06/22/hscout533415.html. Accessed Dec. 13, 2006.
45. Brain disease exposure scare. Atlanta, *Associated Press* October 2004.
46. Megeerian C, Woman sues hospital after infection scare. *The Emory Wheel* April 4, 2006.
47. London surgeries still on hold amid CJD fears. CTV.ca; Dec. 6, 2006. Available at: www.ctv.ca/servlet/ArticleNews/story/CTVNews/20061205/cjd_london_061206/20061206?hub=Canada. Accessed Dec. 13, 2006.
48. Creutzfeldt-Jakob disease (CJD) and surgery: Information for medical staff. Glasgow, Scotland: Health Protection Scotland, October 2006.
49. Sutton JM, Dickinson J, et al, Methods to minimize the risks of Creutzfeldt-Jakob disease transmission by surgical procedures: Where to set the standard? *Clin Infect Dis* 43:757-64, 2006.
50. Arjona A, Simarro L, et al, Two Creutzfeldt-Jakob disease agents reproduce prion protein-independent identities in cell cultures. *Proc Natl Acad Sci (USA)* 101(23):8768-73, 2004.
51. UCSF Medical Center Infection Control Manual. Infection control policies and procedures for patients with suspected or confirmed human prion disease (e.g., Creutzfeldt-Jakob Disease [CJD]). San Francisco: UCSF; Reviewed 2005:1-21.
52. Brown SA, Merritt K, et al, Effects on instruments of the World Health Organisation recommended protocols for decontamination after possible exposure to transmissible spongiform encephalopathy-contaminated tissue. *J Biomed Mater Res B Appl Biomater* 72:186-90, 2005.
53. Peretz D, Supattapone S, et al, Inactivation of prions by acidic sodium dodecyl sulfate. *J Virol* 81(1):322-31, 2006.
54. Section 21. Guidelines for the management of transmissible spongiform encephalopathy (TSE) including Creutzfeldt-Jakob disease (CJD). Canterbury, Kent, England. East Kent Hospitals, NHS Trust, September 2004.
55. Chang B, Cheng X, et al, A blood test for prion: Disease associated prion aggregate is detected in the blood of infected but asymptomatic animals. *Clin Vaccine Immunol* Nov. 1, 2006.
56. Caughey B, Baron GS, Prions and their partners in crime. *Nature* 443(7113):803-10, 2006.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE

CONTACT Janyce Hamilton, 110 Townsend Circle, Naperville, Ill., 60565-3065.