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Thinking the unthinkable: Alzheimer's, Creutzfeldt–Jakob and Mad Cow disease: the age-related reemergence of virulent, Foodborne, bovine tuberculosis or losing your mind for the sake of a shake or burger

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Summary The possibility of the age-related reemergence of foodborne *Mycobacterium bovis* (bovine tuberculosis) as a vector for Creutzfeldt–Jakob Disease (CJD or human Mad Cow Disease) and Mad Cow disease itself is real. The CDC reported last May of an outbreak of CJD linked to the consumption of meat contaminated “with the agent causing” bovine spongiform encephalopathy (BSE) in a New Jersey racetrack between the time frame 1995–2004. In the opinion of experts, ample justification exists for considering a similar pathogenesis for Alzheimer's, Creutzfeldt–Jakob and the other spongiform encephalopathies such as Mad Cow disease. In fact, Creutzfeldt–Jakob and Alzheimer's often coexist and at this point are thought to differ merely by time-dependent physical changes. A recent study links up to 13% of all “Alzheimer's” victims as really having Creutzfeldt–Jakob disease.

Bovine tuberculosis, which includes *Mycobacterium bovis* and *M. avium* – *intracellulare* or paratuberculosis, is and has always been *the* most prevalent threat to the cattle industry, and the USDA reports that between 20% and 40% of US dairy herds are infected with paratuberculosis alone. The health risk for milk tainted with *M. bovis* has been known for decades and there was a time not so long ago when “tuberculin-tested” was printed on every milk container. Schliesser stated that meat from tuberculous animals may also constitute a significant risk of infection. At the turn of the 20th century 25% of the many US deaths from TB in adults were caused by *M. bovis*.

Dairy products aside, when past and present meat consumption are factored in, there is three times the risk of developing Alzheimer's in meat eaters as opposed to vegetarians. The investigation into the causal trail for Creutzfeldt–Jakob, indistinguishable from Alzheimer's except for its shorter, lethal course might have grown cold where it not for Roel's and others who linked mad cow in cattle with *M. bovis* and related paratuberculosis on clinical, pathologic and epidemiological grounds. The southwest of the UK, the very cradle of British BSE and CJD outbreaks, saw an exponential increase in bovine tuberculosis just prior to its spongiform outbreaks. All of this brings up the unthinkable: that Alzheimer's, Cruetzfeldt–Jackob, and Mad Cow Disease might just be caused by eating the meat or dairy in consumer products or feed. It is only appropriate therefore to explore the role of bovine TB and the atypical

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mycobacteria in Alzheimer's, JCD and Mad Cow disease and develop better serological surveillance for these pathogens.

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The unthinkable

By the early 1920s, working with Alzheimer, neuropsychiatrists Creutzfeldt and Jakob found and named the human variant of Mad Cow disease, Creutzfeldt–Jakob Disease or CJD. They identified this while actually studying the brains of patients with Alzheimer's disease variant CJD (vCJD), a strain which attacked patients under 50. Between 1994 and 1996 alone, 12 people in England came down with and died from variant Creutzfeldt–Jakob and all had eaten beef from cows suspected of Mad Cow Disease, also called bovine spongiform encephalopathy (BSE). By 1975, a new problem had arisen in the wildlife of southwest England, the cradle of BSE: virulent bovine strains of mycobacterium were isolated from the badger *Meles meles*. An entirely new development in a country where the bovine form of the disease had been supposedly eradicated since 1960, it was viewed with grave concern by public health officials. Not only was it not clear how the badgers of southwest England, in intimate contact with the cattle there, had acquired this dangerous strain of bovine tuberculosis, but it was then found that not a single badger from other areas harbored the disease [1]. The incubation period of Creutzfeldt–Jakob or human BSE (the period between infection and clinical illness) is probably at least 5 years and may be very much longer. Similarly, it could take a cow 5–8 years to have overt illness.

It is not certain when BSE infected material may have first entered the human food chain, although it is likely that this was in the early 1980s, at least 5–8 years after the badger *Meles meles* introduced its virulent *M. bovis* to the cattle of southwest England. Veterinarian David Bee, called to Stent Farm in Sussex to examine a sick cow named 131, ran across an animal with strange symptoms – its back was arched and it had lost weight. Within six weeks, cow 131 was dead, having developed head tremors and a loss of coordination. Seven months later, the UK Central Veterinary Laboratory diagnosed spongiform encephalopathy. By this time, other cows were also showing symptoms. The epidemic had begun. Cow 131 would be the first of around 1 million cattle estimated worldwide to have been infected since the onset of the BSE epidemic. England did not know it really had a Mad Cow problem until something sig-

nificant happened. Traditionally, since the early 1900s, only one out of a million people got CJD, people over age 55. A rare and sporadic brain disease, it affected up to 60 people a year in Britain. But when people under age 30 started getting it, England recognized it had a problem. In May of 1995, 19-year-old Stephenie Churchill died after an illness resembling Creutzfeldt–Jakob Disease. Two other premature deaths occurred that year, showing similar symptoms to Churchill's. James Ironside, a pathologist at the UK's National CJD Surveillance Unit, discovered that the brains of these patients showed unusual spongiform symptoms. Ironside named the condition variant CJD (vCJD).

As of December 1, 2003, out of a total of 153 cases of vCJD reported worldwide: 143 were from the UK, all or them residing there during the key period of the UK's 1980–1996 BSE epidemic. So England was the model. And it was there, unnoticed, that an old and familiar foe, bovine tuberculosis had been busily increasing exponentially, just before the British Mad Cow and Creutzfeldt–Jakob epidemics began [2].

Overlooked

While various theories continued to swirl around the cause of the transmissible spongiform encephalopathies (TSE's), the best epidemiologic maps of the peak incidence and prevalence of one of them, bovine spongiform encephalopathy (BSE) or Mad Cow disease, done in the UK, it turns out, suggestively matched those of the highest prevalence of England's bovine tuberculosis in cattle, with a predominant distribution in the Southwest (see Figs. 1 and 2) extending to counties further north [2,3], the very area where BSE in the UK began.

An idea of the prevalence of cow tuberculosis in pre-pasteurization Great Britain can be gotten by the fact that in the early 1900s two thousand children died annually from bovine tuberculosis [4]. At that point, human tuberculosis of bovine origin was proportionately more common in the British isles than in any other industrialized country in the world [4].

It is claimed that in England, supposedly next to BSE, bovine TB is the most serious animal disease that its Ministry of Agriculture has to cope with,

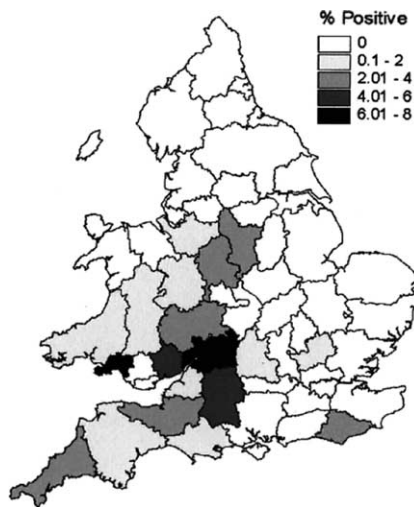


Figure 1 Bovine tuberculosis in UK 1999.

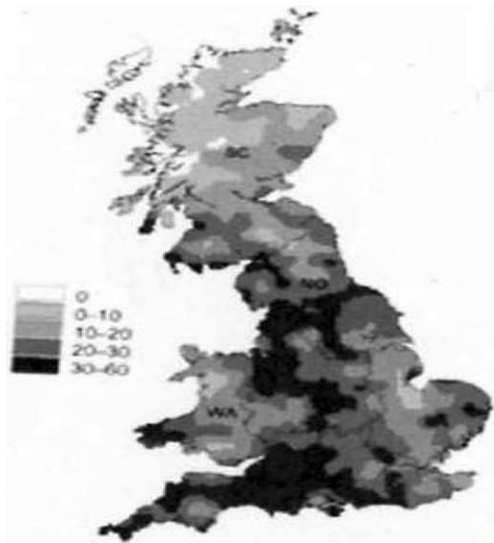


Figure 2 BSE-positive cattle in UK 1997.

and in 1934 at least 40% of British cows were infected with TB [5], accounting for 6% English deaths from tuberculosis in the 1930s and 1940s. Despite the fact that mandatory cow tuberculin skin testing was introduced in 1960, data for the year 2000 in Great Britain show a national herd incidence of 2.8%, with an exponential increase in cases in the southwest of England over the past 10 years [6].

Webb speculates that man was first introduced to tuberculosis when he began domesticating cattle around 5000 BC [7], placing human tuberculosis as having originated by transfer of *M. bovis*, which has the potential to infect the human body, where it adapted as the tubercle bacillus [7]. Garnier though, using deletion analysis, recently questioned this, placing human *M. tuberculosis* as having come first, and, having infected cows at the

time of cattle domestication 10,000–15,000 years ago [6]. At any rate, prior to that, the tuberculous bacilli, always soil born, first infested and then infected an assortment of mammals, both ruminants and primates. Modern genetics has verified that DNA between human (*M. tuberculosis*) and cow (*M. bovis*) tuberculosis are almost identical, indicating they are virtually the same species [8]. Even in culture plates their appearance is similar.

In the United States, from 1979 through 1998, 4751 deaths from Creutzfeldt–Jakob Disease were reported, yet Mad Cow was not [9]. Supposedly rare in America, Mad Cow, again, could take five to eight years for a cow, once infected to develop. Most of the cows in America are under that age. By the time they are three or four years old, they are sent to a slaughterhouse so it is rare that America sees it. Tellingly, the age of recently *M. bovis* tuberculin positive cattle sent to slaughter at the Kankan and Bissau abattoirs in Africa was also approximately 5–8 years old [10].

Nor was beef-eating implicated alone. A case of probable transmission of vCJD through transfusion from an asymptomatic donor who subsequently developed the disease was reported. And to this day, blood donors for the American Red Cross or any other US blood bank are asked if they have ever lived in England longer than three months. If they have, they do not let them donate blood. The American Red Cross therefore recognizes that blood can transmit Mad Cow disease.

The health risk for milk tainted with *M. bovis* has been known for decades and there was a time when “tuberculin-tested” was printed on each milk container sold in the United States. Because fresh milk normally contains a phosphatase slightly less sensitive than the *M. bovis* bacilli, pasteurized milk that gives a negative phosphatase test is considered adequately pasteurized in practice [11]. But no matter what the method used, milk is in no way sterilized [11]. A typical dairy cow filters 10,000 quarts of blood through her udder. And the average quart of milk sold in the US in 2003 contained 322 million dead white blood cells. The power of oral consumption of virulent mycobacteria into the alimentary tract was unfortunately shown in the German Lubeck tragedy, in which inadvertent mycobacterial contamination of otherwise simple oral immunization by watered-down bovine tuberculosis killed seventy-two out of 251 newborns [12].

Common ground

In the opinion of experts, ample justification exists for considering a similar pathogenesis for Alzhei-

mer's, Creutzfeldt–Jakob and the other spongiform encephalopathies such as Mad Cow disease [13,14]. In fact, Creutzfeldt–Jakob and Alzheimer's often coexist and at this point are thought to differ merely by time-dependent physical changes [14]. Dairy products aside, when past and present meat consumption are factored in, there is three times the risk of developing Alzheimer's in meat eaters as opposed to vegetarians [15]. This brings up the unthinkable: that Alzheimer's and Creutzfeldt–Jakob disease might be caused by the meat or dairy products that we eat.

In one study Alzheimer's was misdiagnosed in up to 13% of autopsied patients actually suffering from this Creutzfeldt–Jakob (CJD) disease [16]. But the full number of US CJD patients will never be known until it is proclaimed a reportable disease.

Other supporting evidence

That tuberculosis and *M. Bovis* can cause the progressive ataxia found in Mad Cow 'downers' has been adequately cited, in both man and cattle [17–19]. Moreover, that *M. bovis* or cow tuberculosis, can cause "Mad Cow Disease" in cattle is also a matter of record [20]. A known virulent, predominantly food-borne pathogen to man, so close are *M. bovis* and *M. tuberculosis* that at one time *M. bovis* was referred to as "*M. tuberculosis* variety *bovis*". Koch had insisted that Bovine TB was not pathogenic to man and it took many years before it was realized that *M. bovis* could cause all the forms of TB that the human type of bacillus could [4].

Carnivores may acquire *M. bovis* through the alimentary tract by eating infected meat [21,22]. Man is no exception [23,24]. Schliesser (1985) states that meat from tuberculous animals may constitute a significant risk of infection if available for consumption [25]. The neurotoxic potential for cow tuberculosis was shown in pre-1960 England, where one quarter of all tuberculous meningoencephalitis victims suffered from *M. bovis* infection [26]. Worldwide, usually food-borne, bovine tuberculosis was a relatively common cause of TB meningitis in pre-pasteurization times, causing meningitis and encephalitis in humans [27–29] and cattle alike [30]. At the turn of the 20th century it was estimated that 25% of the many US deaths from TB in adults were caused by *M. bovis* [31]. The US Department of Agriculture clearly warns that in diagnosing bovine TB, like BSE, lesions must be looked for in the nervous system of cattle [32].

Of course bovine tuberculosis also includes fowl tuberculosis in cattle, or paratuberculosis, classified under the mycobacterium avium complex (MAC). Paratuberculosis (*M. paratuberculosis*), extremely slow growing, causes Johne's disease, a problem known and neglected in cattle and sheep for almost a century. The USDA reports that between 20% and 40% of US dairy herds are infected [33]. The evidence to support *M. paratuberculosis* infection as a cause of Crohn's disease is mounting rapidly [34]. Since paratuberculosis is not classified as a human pathogen, the beef from cattle infected with it is not prevented from entering the food chain [35]. To complicate the situation further, when pathology is found, *M. bovis* produces lesions almost identical to paratuberculosis [36]. The combined economic losses from tuberculosis-like *M. bovis* and *M. paratuberculosis* (a species of fowl tuberculosis) in the cattle industry remains unmatched [32,37]. Rossiter found paratuberculosis in up to 34% of dairy cows [38], the very same cattle frequently used for the production of the ground beef that enters the food chain [39]. Paratuberculosis is extremely heat resistant and central neurologic manifestations in Crohn's are not unknown [40,41].

Conclusion

Since species identification is not carried out routinely, it is difficult to estimate the present contribution of *M. bovis* [42] to the 3 million deaths tuberculosis causes each year. In the meantime, Rich believed that there was no greater susceptibility in humans towards *M. tuberculosis* than there is to *M. bovis* [4].

Whether the unthinkable: that Alzheimer's disease and Creutzfeldt–Jakob might be caused by the mycobacterial load in the meat or dairy products of animals with *M. bovis* caused Mad Cow Disease will require further investigation, a task made only more difficult by the fact that studies such as Hartley's show pathology identical to "Mad Cow" from *M. bovis* in cattle, causing a tuberculous spongiform necrotizing encephalitis, without recovery from the central nervous system of classical forms of bovine TB [43]. In Alzheimer's, CJD and Mad Cow, clinical symptoms appear only after much destructive damage to the brain has already occurred [43], a situation in which the mycobacteria have a long track record of suddenly disappearing from.

Yet the trail of evidence remains intact. At least four autopsy studies have uncovered that anywhere from five to 30% of the 4.5 million US Alzheimer's

victims and an untold number of those with dementia are apparently misdiagnosed [44] and many could actually have Creutzfeldt–Jakob disease (CJD), the “variant” form of which has in the past been called Mad Cow in humans [44,45], and whose plaques and cortical preference simulate Alzheimer's [46].

Today, despite the media and scientific hush, the two leading cattle diseases being pursued in grants assigned by the US Dept of Agriculture (USDA) are bovine tuberculosis and Bovine Spongiform Encephalopathy or Mad Cow disease, both seen as “emerging” diseases, both shared between livestock and wildlife, and both targeted for “control and eradication”, a certain sign of their potential human health risk [36,47].

The investigation into the trail of the cause of Creutzfeldt–Jakob, indistinguishable clinically from Alzheimer's except for its shorter lethal course, might have grown cold where it not for Roel's and others thru which one is able to link Mad Cow in cattle with *M. bovis* and related strains on clinical, pathologic [20], and epidemiologic grounds [48,49]. To mirror reality, the agent behind the TSE's (Transmissible Spongiform Encephalopathies), including Creutzfeldt and Mad Cow, would have to attack a wide variety of different mammalian species [46], including domestic pets. The first hint that humans could be affected by BSE came in 1990, when a Siamese cat called Max fell ill with the feline version of it. That same year, scientists showed that the disease could be orally transmitted to mice. Bovine tuberculosis has one of the broadest host ranges of all pathogens [50].

Although Alzheimer's disease occurred long before Alzheimer labeled it, Whaley relates that it did not become a common term or even of major concern until the explosion of neurological research that occurred in the late 1970s [51]. In the 1960s there was a skyrocketing overdiagnosis of “atherosclerotic dementia”. Today residents and physicians alike automatically link memory loss in the aging to Alzheimer's [44]. Boller, in an autopsy-founded 1989 dementia study, warned that physicians would be better advised to acknowledge that the cause of a mentally demented patient cannot be accurately predicted in life [44].

The social importance of both TB and Alzheimer's are just going to increase as life expectancy in our population increases. Tuberculosis, traditionally the leading infectious cause of destructive degenerative amyloid, and wrongly assumed to be under control [52], continues to proliferate, in man, cattle and wildlife. And hospitals once crowded with frank tuberculous patients and psychotics are now admitting aging people with men-

tal deterioration with increasing frequency. Solid clinico-pathologic studies show tuberculous-like organisms as both the underlying cause of Alzheimer's [53,54], and Parkinson's [55,56], whose amyloid plaque, neurofibrillary tangles, and dementia, oddly enough, often simulate Alzheimer's [57–59].

Marchand questioned whether the same degenerative amyloid disease, attacking at the time and place of its choosing, did not only cause Pick's Disease, Alzheimer's disease, Parkinson's and the senile dementias without cholesterol [60], an issue which weighed on his mind since an earlier study of dementia that simulated the psychosis of Pick's and Alzheimer's in a patient with tuberculous encephalitis [61].

Be this as it may, Alzheimer's, Parkinson's, and to a lesser extent Creutzfeldt–Jakob or the other types of senile or presenile mental deterioration ought to be recognized as one of the most urgent problems of public health and welfare today. It is only human nature when confronted with diseases as terrible as Creutzfeldt–Jakob and progressive Alzheimer's that something new or unknown and terrible must be involved and many scientists feed into such expectations, but sometimes the answer is as simple as yesteryears' epidemics and, you might just say, losing one's mind for the sake of a shake or a burger.

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