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A Case for the Role of Copper Deficiency in "Mad-Cow" Disease and Human Creutzfeldt-Jakob Disease

Copper Applications in Health & Environment

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Background ▲

It has been recognized for centuries that copper plays a vital role in medicine. Since 1928, we have also known that copper is an essential element in human, animal and plant nutrition. ¹ Many of these findings are summarized in CDA on-line publications, *Copper in My Medicine Chest* ² and *Copper in Human Health*. ³ Copper, iron and zinc, as well as a whole host of trace elements, are essential for the activity of a number of physiologically important enzymes that function as catalysts in the body. Based on this understanding, copper supplements are routinely fed to farm animals: in cattle, to address copper deficiency in grazing fields that are high in molybdenum; in swine, as a growth stimulant; and in poultry, to prevent aortic rupture. ⁴

Research has suggested that copper also has an important role to play in the prevention or moderation of certain neurodegenerative diseases including the polyglutamine diseases (such as Friedrich ataxia and Huntington's Disease), Parkinson's Disease, Wilson's and Menkes' Diseases, amyotrophic lateral sclerosis (Lou Gehrig's Disease, also called "Motor Neuron Disease" in the UK), and Alzheimer's Disease. ⁵ It has recently been suggested that copper also affects a newly identified class of ailments known as *prion diseases*, which are described below. This is particularly the case for scrapie in sheep, bovine spongiform encephalopathy (BSE, or "mad cow disease") in cattle, chronic wasting disease (CWD) in deer and elk, feline spongiform encephalopathy (FSE) in cats, and Creutzfeldt-Jakob Disease (CJD) in humans. Collectively, these afflictions are known as transmissible spongiform encephalopathy diseases (TSEs). *Spongiform* refers to the porous nature of respective

characteristic microscopic vacuoles that form in the brains of afflicted animals or humans.⁶ The appearance of this vacuolation differs between the animal and the human disease; however, both have sponge-like aspects.

BSE, a disease in cattle similar to scrapie in sheep, was first identified in the UK in 1986. Prior to that it had never been seen anywhere in the world. CJD in humans was first identified in 1921. CJD, while traditionally a disease among the elderly, was diagnosed in a number of people in their 20s and 30s in the UK in 1996, suggesting that a new variant of the disorder, vCJD, has now crossed the species barrier from cattle to humans. It is this concern that brought the incidence of BSE in England to newspaper headlines and TV screens throughout the world in the 1990s. However, recently, issue was taken with the idea of a "new variant" CJD in which it was pointed out that 1) CJD was not necessarily a disease of the aged, since Creutzfeldt's original case died at age 28 and 2) **there is no evidence that BSE has jumped the species gap from cows into humans.**⁷

There have been two panels convened in the UK to officially examine the origin and the mechanism of transmission of BSE and vCJD: The BSE Inquiry that reported in October 2000, and a committee of academics, the Horn Committee, that reported in July 2001.^{8,9} The reports of these committees represent the official position of the British Government concerning BSE and vCJD. In these reports it was that expressed that:

1. **The actual initiating step for BSE is unknown and may never be known.** One theory considered by the BSE Inquiry and discarded but reintroduced by the Horn Committee is that BSE is a cross-species transmutation from scrapie in sheep.¹⁰
3. BSE may have been introduced into cattle by feeds containing dried meat and bone meal (MBM) and offal from scrapie-infected sheep. Another theory rejected by the BSE Inquiry but reintroduced by the Horn Committee was that a change in the rendering process used to prepare animal feed products prior to and during the time of appearance of BSE may have compounded the issue.¹¹
5. **All evidence points to the specific association of an abnormal form of the prion protein in central nervous system tissue and the development of TSEs (see discussion below).**
7. BSE-infected MBM and offal in animal feed is the vector for the spread of the disease.¹²
9. The human analog of BSE, vCJD, is caused by eating beef products contaminated with central nervous system parts infected by BSE.

Another position expressed in testimony before the BSE Inquiry and in the scientific and popular literature is that of a British organic farmer, Mark Purdey, who hypothesizes that:

1. **A copper deficiency, with manganese replacement for copper in the prion protein, initially caused by the repeated application of extremely high doses of an organophosphate (OP) insecticide, phosmet, and the provision of a manganese-rich chicken manure-based feed supplement is the key to the origin of BSE in British cattle.**

2. The subsequent feeding of MBM and offal from infected cattle containing OP derivatives and/or the manganese-modified prion protein caused its spread.
3. It is copper deficiency with manganese substitution that affects humans in the BSE variant, vCJD. Mr. Purdey believes that this is caused by low copper content and high manganese content in soil and consequently in food consumed by humans. Excess manganese entered the soil by the use of sewage sludge as a soil additive and of manganese-based pesticides.

Purdey's position concerning an imbalance in the copper-to-manganese ratio has been reinforced by recent research at Cambridge University and at Case Western Reserve University (see below); however, it and the organophosphate insecticide theory have been officially rejected by both the BSE Inquiry and the Horn Committee, with certain caveats. In particular, it was admitted that the effects of copper and organophosphates on TSE susceptibility have not been tested on animals. ¹⁷

While the literature and UK government documents are unclear as to who originally came up with the idea that copper deficiency was a contributory factor in BSE, it appears to be the unspoken heart of the public dispute over the cause of the disease. Currently only 2% of all prion papers published over the last two decades pertain to the role of copper. However, since 1995 these have remarkably increased. This year alone, based on publications during the year to-date, we estimate that copper + prion papers will be 5.7% of the total.

Many of the arguments presented for BSE can be reconciled as having a copper deficiency origin. In addition to Purdey's OP hypothesis, there may be other factors contributing to copper deficiency. It may, for example, result from the high MBM-content diet, since feeds rich in protein, particularly soluble protein, decrease the efficiency of copper absorption by ruminants. ^{18, 19} McBride, at Cornell University, also pointed out the potential role of copper deficiency in BSE. ²⁰ He noted that animal protein is high in sulfur content, and that diets containing as little as 0.4% S can contribute to copper deficiency. He also pointed out that the presumed high iron content of MBM from incorporated blood also has a potential negative effect on copper availability.

Since the imposition of orders banning the use of MBM, offal and chicken manure in animal feed and the eradication of the warble fly, BSE has reached its peak and is in sharp decline in the UK. ²¹ However, as of February 2001, it continued unabated in France, Ireland, Spain and Switzerland although at much lesser levels than experienced in the UK. ²² (Note: It has been pointed out that statistics from different countries vary with the policy of the country. In Switzerland, for example, where every living animal, including pets, is sacrificed as BSE is discovered, the number is low. On the other hand, in Portugal, where the government pays a premium for sacrificing infected animals, the number is predictably high.) ²³

Thus far, what has been presumed to be vCJD has claimed the lives of 100 people in the UK and incidence of the disease increased by 20% in 2000. ²⁴ Retrospective analysis has shown the presence of CJD among people below the age of 45 in the UK and elsewhere prior to 1980;

however, these have not been at the rate seen in the UK in recent years, leading to the conclusion that vCJD is, in fact, a new disease. ^{25, 26} Conversely, Venters, suggests that vCJD is in reality the original CJD in a hitherto unrecognized population (younger people). ²⁷

Regardless of the explanation of the origins and transmission of BSE and vCJD, a growing body of evidence suggests that there may be underlying conditions based on a naturally- or artificially imposed copper deficiency that are the contributing factors in the development and transmission of BSE and vCJD. This paper discusses that evidence as it is understood at the time of publication - 4th quarter 2001.

Prion Proteins: A New Sort of 'Bug' ▲

Some neurodegenerative diseases — the polyglutamine diseases, Wilson's Disease and Menkes' Disease, for example - have a clear genetic basis that is expressed as an imbalance in copper in certain cells. Other neurodegenerative diseases appear to have an environmental component, *i.e.*, they are initiated or aggravated by something *external* to the victim. As will be discussed below, the evidence seems to indicate that some of these diseases are made possible, at least in part, by a deficiency of copper in a special group of cellular proteins, the prion proteins, present in the brain and central nervous system. This deficiency may be the result of a causative agent that removes or replaces copper or the result of a deficiency of copper in food intake.

Prion (pronounced 'PREE-on') proteins are natural complex amino acid molecules that were first identified in 1982 by Dr. Stanley B. Prusiner at the University of California-San Francisco (UCSF). While the scientific community was initially somewhat skeptical about Prusiner's finding, he was subsequently awarded a Nobel Prize for his discovery. Prion proteins occur in the brain and other parts of the central nervous system and, in their normal forms, are believed to act as antioxidants that protect brain cells. As an example, scientists at the University of Zürich, Case Western Reserve University and elsewhere have genetically engineered strains of mice that lack prion proteins. These "prion knock-out" mice exhibit increased levels of oxidative stress in their brains compared with normal mice. Presumably, this stress is caused by the lack of copper-containing prion protein. ^{28, 29} In other experiments, prion knock-out mice have been shown to have impaired brain function. Brown and others have proposed the prion protein as a copper transport protein for internalization of copper (II) ions. ^{30, 31}

Prions have a dark side, however, which results in their classification as "proteinaceous infectious particles":

- They are infectious agents in that they are capable of self-replication;
- They contain no nucleic acid (DNA or RNA) response;
- They invoke no immune response, and
- They can change into an abnormal form that causes "prion diseases".

The mechanism proposed for the occurrence of these conditions is that the normal prion protein (shorthand: PrP) is converted into an abnormal or "rogue" form, PrP^{Sc}, simply by changing its shape — a Dr. Jekyll and Mr. Hyde of the biological world, so to speak. Prion diseases may present as genetic, infectious, or sporadic disorders, all of which involve modification of the prion protein. Rogue proteins accumulate in the brain, disrupting or destroying neurons in large numbers, which inevitably leads to the death of the person or animal. Among the manifestations of the neurodegeneration that typifies the prion diseases are the spongiform vacuoles mentioned above and first identified in scrapie-infected sheep.

Copper Deficiency as a Cause of BSE ▲

The link between copper and prion proteins was discovered in early 1995 by Dr. Martin P. Hornshaw and his team at the MRC Neurochemical Pathology Unit, Newcastle General Hospital, in the UK. ³² After showing that synthetic peptides containing several sequences of the "octapeptide repeat" of both mammalian and chicken prions "preferably bind copper over other metals" they concluded with: *These results suggest that PrP may be a copper-binding protein in vivo.*

A Japanese group published on the subject in 1996. ³³ Working from the fact that it is a conformational change (from alpha-helix to beta-sheet) that characterizes the transformation of the normal to infective isoform of the prion, they found: *The peptide does not assume any regular structure without divalent metal ions, whereas Cu (II) binding to the HGGG segment induces formation of alpha-helical structure on the C-terminal side of the peptide chain. The N-terminal octapeptide of prion protein may be a novel structure motif that acts as a promoter of alpha-helix formation.* *In simple English, prions need copper to remain "normal" and non-infective.*

Following publication of the first Hornshaw paper, Dr. David R. Brown, working at the University of Göttingen, began work on the possible cellular function of prions and copper metabolism. His early work, published in 1997 in collaboration with Dr. David Westaway of the University of Toronto, showed that the normal cellular form of prion protein, PrP^C, has five to six sites that bind the copper (II) ion and is therefore a copper-metalloprotein. ³⁴ (Many other copper metalloproteins are known; they are largely the basis for copper's status as an essential trace nutrient. For example, ceruloplasmin, a metalloprotein, is the major vehicle of copper transport in the human body.)

Brown continued his copper and prion studies in Germany and after relocating to the UK, first to Cambridge and then, this year, to the University of Bath. *Following up on his work on copper binding by prions, Brown has shown that copper-containing prion proteins have antioxidant activity and that that activity enhances the survival of neurons in culture.* ^{35, 36, 37} These results suggest that prion disease may involve disturbance of brain-copper homeostasis, *i.e.*, the ability to maintain proper tissue levels of the metal. Brown and his team have demonstrated not only that that PrP^C protects cells against oxidative stress, but that its antioxidant activity is like that of *superoxide dismutase and is in proportion to the amount of copper it binds.* ^{38, 39}

Prusiner and his colleagues demonstrated that prion protein selectively binds copper (II) ions. ⁴⁰ They observed that PrP^{Sc}, the infectious isoform, is derived from PrP^C in a conversion reaction that involves a dramatic structural reorganization of the protein. The binding of copper (II) ions promotes a shift, described above, from a beta-sheet structure (PrP^{Sc}) to a predominantly alpha-helical structure (PrP^C). The stoichiometry of the reaction was at that time suggested to be approximately two copper atoms per PrP molecule. *Thus, Prusiner identified the fact that it is copper that is the controlling factor in forming and maintaining the normal (non-infective) form of PrP.*

Brown's laboratory tested the ability of PrP to bind other cations and found that only manganese and nickel could substitute for copper. ⁴¹ The manganese-PrP had the PrP^{Sc} (infective) structure and chemical characteristics. Interestingly, they found that manganese-PrP was partially resistant to protease (one of a series of enzymes that degrade proteins such as normal copper-PrP in normal body function) *so that in the presence of excess manganese, manganese-PrP eventually predominates.* This finding shows that it is possible to generate protease-resistant PrP from normal cells through an external agent (manganese, in this case) and, more to the point, *it suggests a possible mechanism for the formation of the scrapie isoform, PrP^{Sc}, known to be present in prion diseases.*

Following up on this work, Wong and his team at the National Prion Disease Pathology Surveillance Center, Case Western Reserve University School of Medicine, in Cleveland, Ohio, working with Brown, has also studied metal binding by prion proteins. He found that copper binding to prions from CJD cases was significantly reduced (by 70 to 90%) compared with control (normal form) prions. Prions from diseased tissue bound significant amounts of manganese or zinc; whereas, control prions carried neither of these metals. *He found that the brain tissue of patients with CJD contain up to half as much copper and 10 times as much manganese as those with normal brain cells.* ⁴² *He suggests that manganese, which is detectable by MRI, might be used as a diagnostic marker for the progress of the disease.*

(Note: Like copper, manganese (Mn) is an essential trace element. Manganese is an important cofactor for essential enzymes, notably Mn-superoxide dismutase, which carries out important antioxidant functions. *Dietary manganese deficiency is probably rare in humans. But manganese has its dark side too; if present in excess it can be toxic. Manganese toxicity is often called "Mn-induced Parkinsonism", as the name suggests, a condition resembling Parkinson's disease.* Toxic accumulation of excess Mn in brains is associated with progressive neurodegeneration with symptoms include bradykinesia, tremor, impaired postural reflexes and dystonia. ⁴³ According to the US Department of Health and Human services, because higher organisms including humans have complex mechanisms to maintain manganese homeostasis, the potential risk of receiving excess manganese through food is low. One exception may be from a vegetarian diet, which may contain excess levels of Mn. Environmental sources of excess manganese, particularly in the form of dust, may cause acute toxicity. *It should be noted that Mn-induced Parkinsonism, while also a neurodegenerative disease is not the same as the prion diseases.*)

Jackson and his colleagues at the Imperial College School of Medicine and elsewhere examined the location and properties of metal-binding sites on the human prion protein. ⁴⁴ They found that copper (II) ions are strongly bound to human prion protein with Ni^{+2} , Zn^{+2} , and Mn^{+2} more weakly bound by 6, 7 and 10 orders of magnitude, respectively. Human PrP is capable of binding up to five copper (II) ions per molecule. *They concluded that: A role for prion protein (PrP) in copper metabolism or transport seems likely and disturbance of this function may be involved in prion-related neurotoxicity.*

Researchers at the Washington University School of Medicine, St. Louis, Missouri, found that copper ions play a role in the biology of both normal cellular prion protein (PrP^{C}) and pathologic (PrP^{Sc}) prion protein. ⁴⁵ Specifically, copper-treated PrP was found to be structurally and chemically distinct from PrP^{Sc} , which is consistent with the fact that the metal ion alters the biochemical properties of PrP when it directly binds with it. The St. Louis researchers say that their results suggest potential roles for copper in prion diseases as well as in non-pathological physiological functions of PrP^{C} . However, they found that brain copper content was independent of brain PrP levels and, in contrast to Brown's findings, they found that manganese had no effect on PrP.

McBride, at Cornell University, has provided some insight into the apparently different effects of manganese on prion proteins reported in the literature. ⁴⁶ This may have to do with the oxidation state. Mn(II) behaves very much like Ca(II) and should bind weakly to the prion, hardly competing at all with Cu(II) . However, cellular enzymes tend to oxidize Mn(II) to Mn(III) , and this cation is a notoriously strong complexer as well as a powerful oxidant. Thus, experimenters must be sure of the oxidation state of the manganese they are investigating.

The consequences of copper deficiency were implied many years ago in a series of experiments in which it was found that the laboratory reagent, cuprizone, caused spongiform encephalopathy in rats, mice, hamsters and guinea pigs when added to their feed. ^{47, 48, 49} Cuprizone is a powerful chelator of copper used to study the effects of copper deficiency in the central nervous system. ⁵⁰ It is also used as an analytical reagent for the detection of trace amounts of copper in wastewater.

Aftermath: The (potential) Good News ▲

If further investigations prove the "copper deficiency-TSE" hypothesis to be accurate, *i.e.*, if the laboratory work being conducted by Brown and many other researchers shows that a deficiency of copper and an overabundance of manganese is the root cause of BSE and vCJD, or at least a necessary precursor, it will have profound influence on how BSE and vCJD are treated, and, hopefully, cured. Proof would also eliminate public fear that contaminated meat produces vCJD in humans. The economic implications for the British dairy and cattle industries defy calculation.

Purdey's hypothesis, if proven to be correct, would mark BSE as the tragic result of environmental circumstances, in this case triggered by the mandated use of a particular insecticide. The hypothesis may also indicate that experiments should be conducted into the use of copper supplements in cattle feed as a preventative measure for BSE and scrapie.

Confirmation of the hypothesis presumably would indicate that immediate attention should be paid to the mineral content of animal feeds and correct copper nurture of farm animals in all countries that are not BSE-free in order to prevent the spontaneous eruption of the disease there.

Definitive scientific work will be required to prove or disprove the currently accepted explanation for the anomalous occurrence and transmission of BSE and presumably to the human analog, vCJD, or the hypothesis advanced by Mark Purdey. Fortunately, the enormous importance of the subject has drawn dozens of researchers throughout the world to investigate the role of copper deficiency in these diseases. Sooner more so than later, the true circumstances behind the initiation and propagation of BSE and vCJD will be understood and corrective measures can be developed.

There is currently no question that copper may have a vital role to play in the prevention of these diseases, and indeed, there is already evidence that copper is essential for the *prevention* of the formation of the life-threatening prion, PrP^{Sc}. The emerging insight into the beneficial effect of copper may lead to a better understanding of the cause of BSE and vCJD, and with that insight, the hope that preventative measures and a cure will be found.

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- ▲ 11. Note: A solvent extraction step using trichloroethylene or perchloroethylene was omitted during the period 1981-1982. The purpose of solvent extraction was to remove fats from the recycled cow/sheep waste meat and bone meal fed to cattle as MBM.
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