BMAA and Neurodegenerative Diseases in Humans

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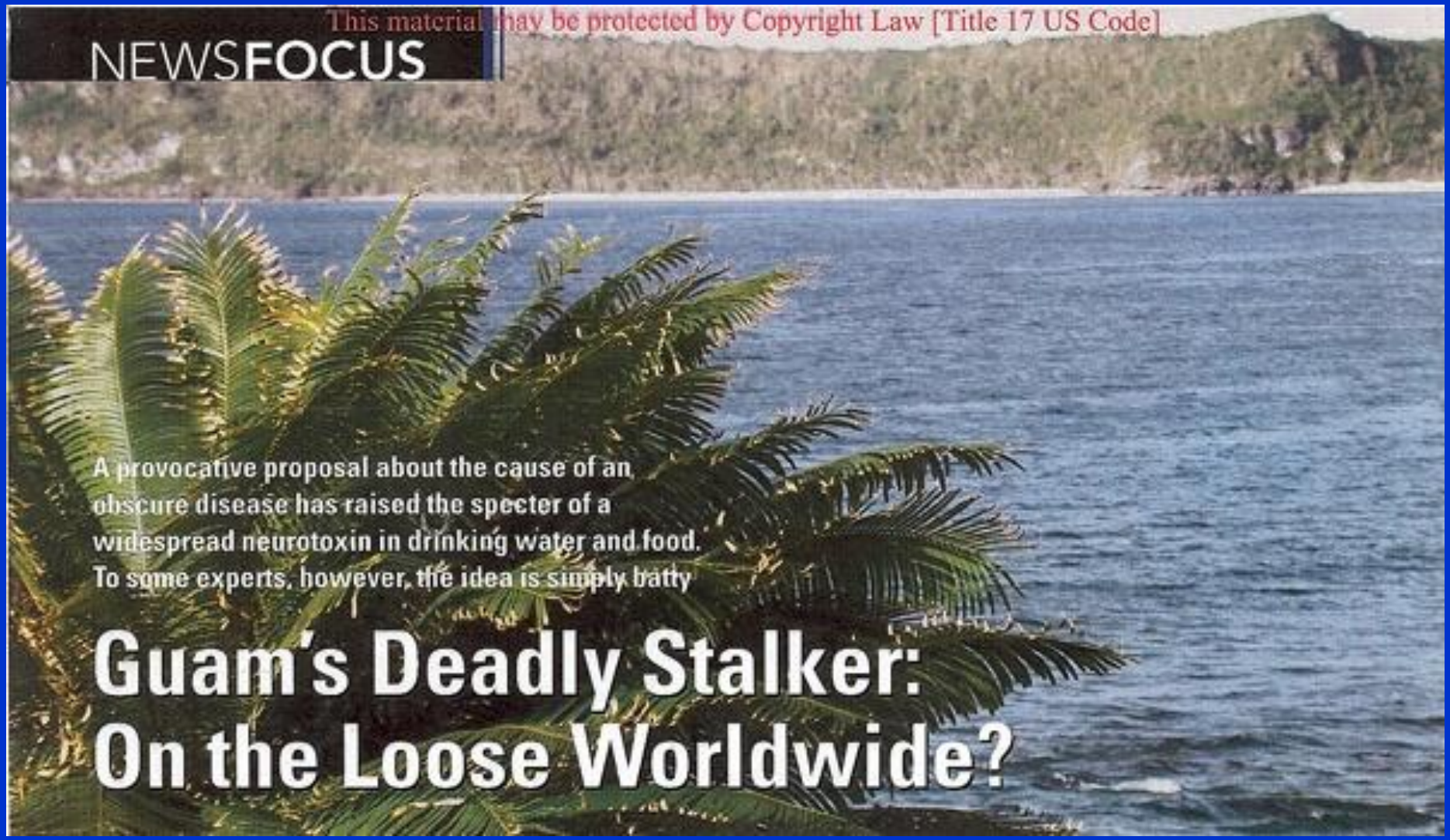

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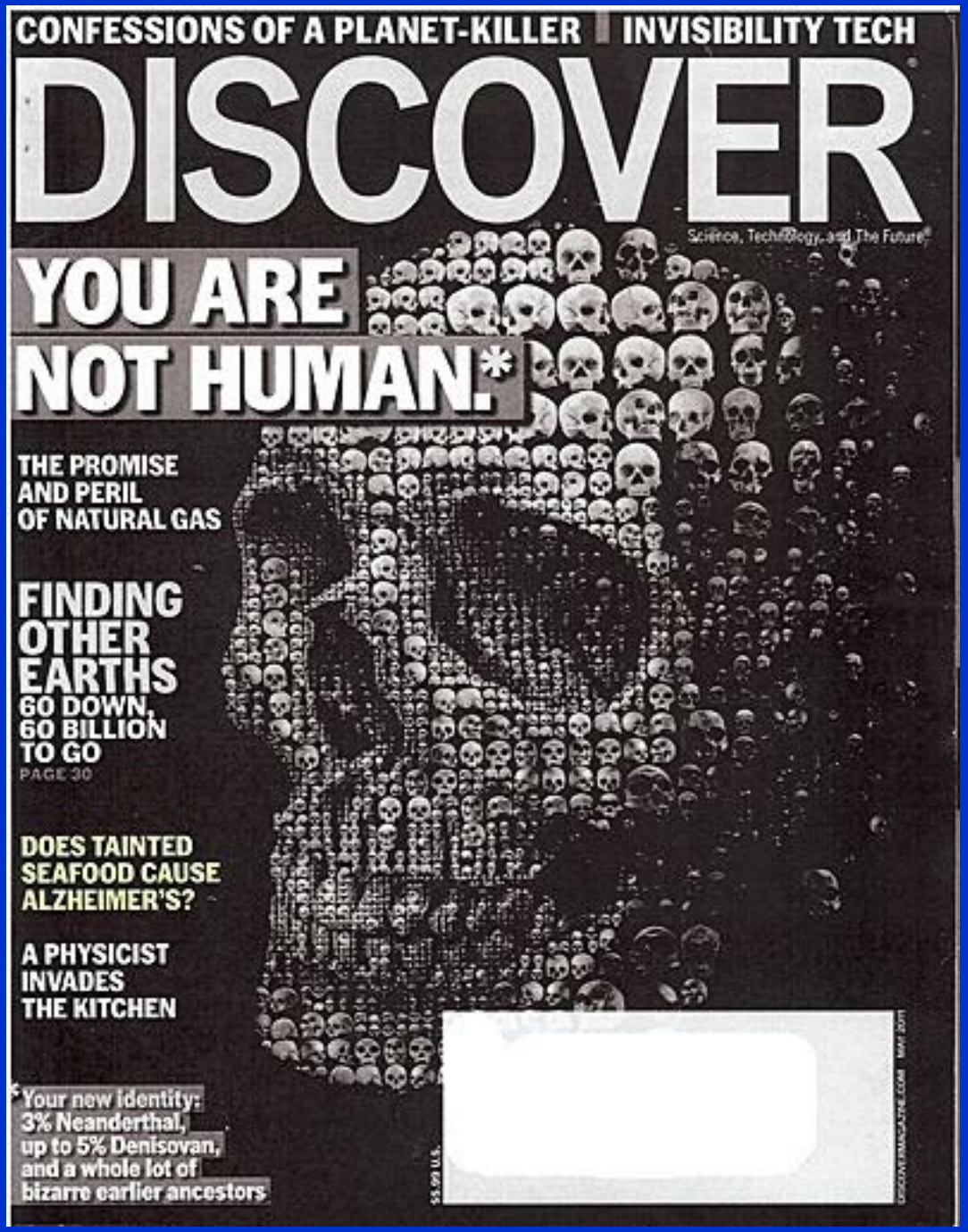

June 2011 Issue

THERE'S SOMETHING IN THE WATER

a trail of clues linking seafood to ALS, ALZHEIMER'S, and PARKINSON'S disease. toxin is called BMAA. And it's in the

by KATHLEEN McAULIFFE

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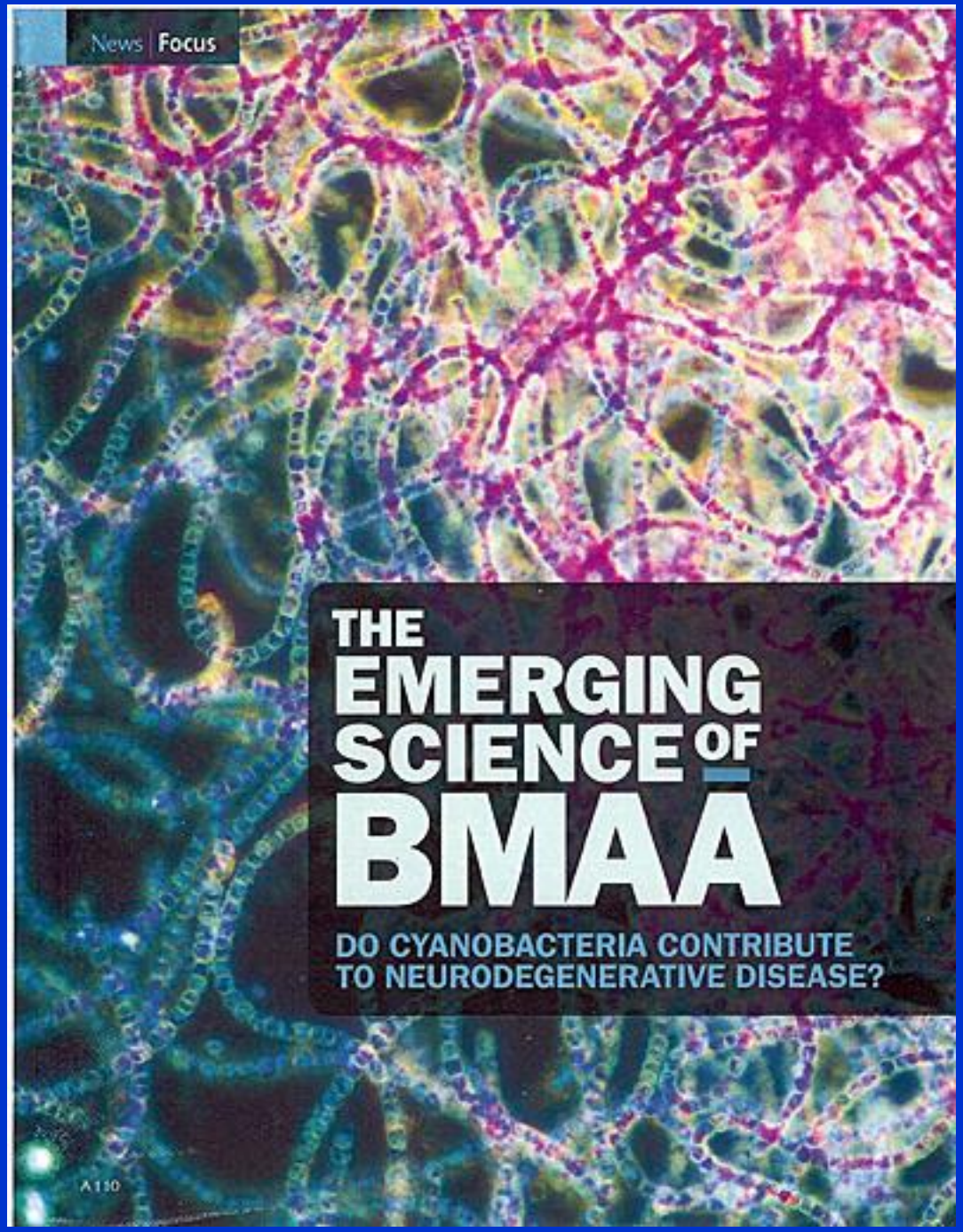
Are Toxins in Seafood Causing ALS, Alzheimer's, and Parkinson's?

06.21.2011

What started as the discovery of an unknown disease in Guam has spread to a line of ominous findings about some of our most debilitating conditions and potential toxins lurking in bodies of water around the world.

by Kathleen McAuliffe

Three fish await sale at a market in the Galápagos. Could exposure to cynobacteria and overload of BMAA make them a health threat instead of a nutritious meal?



EHP
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Topics to be covered

- ALS/PDC (lytico-bodig) (Amyotrophic Lateral Sclerosis/Parkinsonism/Dementia Complex on Guam and elsewhere)
- History of research on ALS/PDC
- The rise and fall and rise of the BMAA-neurodegenerative disease hypothesis
- Questions re: the hypothesis
- Alternate hypotheses

← Kii Peninsula, Japan

← Guam

← Irian Jaya, New Guinea

Research on Guam ALS/PDC

- 1936 – Okaya (first report of ALS/PDC)
- 1952 – Koerner (clinical aspects of ALS)
- 1954 – Kurland and Mulder (epidemiology of ALS)
- 1961 – Hirano et al. (clinical aspects of PDC)
- 1962 – Lessell (epidemiology of PDC)

Note: All of the above scientists/doctors considered ALS/PDC to be a distinct disease re: ALS,

Postulated Etiologies

- Cycasin/MAM – Kurland (1972); MAM – Spencer et al. (1991)
- Calcium deficiency – Yase (1979)
- Cycad consumption – Reed et al. (1987).
- BMAA – Spencer et al. (1987) – Cox et al. (2005)
- Trace elements – Gajdusek (1990)
- Magnesium deficiency – Durlach et al. (1997)
- Tau Gene – Poorkaj et al. (2001)
- Sterol- β -glucosides – Khabazian et al. (2002)
- BMAA-neurotoxicant synergisms – Lobner et al. (2007)

Rise of BMAA hypothesis-#1

- Rao et al. (1963) – Isolated BOAA an amino acid that was linked to lathyrism (a paralytic disease in humans due to ingestion of the chickling pea).
- Vega and Bell (1967) – Identified BMAA in cycads – noted similarity to BOAA and suggested that BMAA might play a role in cycad neurotoxicity.
- Reed et al., (1987) – Food was only link to ALS/PDC on Guam.
- Spencer et al. (1987) – High dose, acute exposure in Rhesus Monkeys produced symptoms similar to ALS.

Fall of BMAA hypothesis-#1

- Duncan et al., 1990 – Cycad flour that was washed repeatedly, as is done on Guam, contains very little BMAA. The quantities that would have to be eaten to gain similar levels of BMAA as used by Spencer were so high, the idea of cycad flour BMAA causing ALS/PDC was untenable.

Epidemiology studies utilizing human brain tissues

- Murch et al. (2004) – 8 Chamorros (Guam natives) + 15 Canadians.
- Pablo et al. (2009) – 45 people from Florida: 13 ALS; 12 AD; 8 HD; 12 non-neurological disease.

Tissues were analyzed for the presence of BMAA and BMAA was identified in 32/33 ALS or AD patients vs. 4/35 without either disease when the data from the above studies are combined.

BMAA: A localized toxin becomes a potential worldwide menace

- Nostoc is a symbiont in diverse plant species and produces BMAA in 8/11 tested. BMAA was identified in 23/30 cycad species globally

- BMAA is produced by a majority of cyanobacterial species/genera:
  12/12 in England (Cox et al., 2005); 20/26 in South Africa (Esterhuizen et al., 2008); 18/18 in Portugal (Cervantes-Cianca et al., 2011).

Epidemiology studies utilizing live humans

- Caller … Stommel et al. (2009) – Cluster of ALS patients in a New Hampshire town that encompassed a lake. Authors state:
  "We suggest that the high incidence of ALS in this potential cluster could be directly related to chronic exposure to cyanobacterial neurotoxins such as BMAA."

- **Among species identified as producing BMAA in significant quantities are *Cylindrospermopsis raciborskii* and *Prochlorococcus marinus*.**

  The former is a rapidly spreading, invasive species that forms year-round single-species blooms in the U.S. and Mexico (and probably many other locations). It is also one of the highest BMAA producers in the Cox et al. study.

  The latter is a picoplanktonic marine cyanobacterium that is probably the most numerous and important species on the planet. It constitutes over 50% of the biomass in temperate oceans.

BMAA and bioaccumulation: Flying foxes are not unique

- BMAA bioaccumulates in Daphnia, often the most common zooplankton and major source of food for numerous fish species (Lurling et al, 2010).

- BMAA also bioaccumulates in marine fish and invertebrates: Baltic Sea (Jonasson et al., 2010); and Florida Bay (Brand et al., 2010). The tissue levels found in Florida waters were, in the case of blue crabs, puffer fish, and grunts, equal to or greater than those found in flying foxes, ≥ 3700ug/g.

The BMAA hypothesis: A few questions

1. **The fundamental question is whether ALS/PDC is related to ALS, P, and AD, or is it a distinct disease with symptoms of all three diseases depending on the affected parts of the brain?**

- **The rapid progression of ALS/PDC is very different than the progression of the individual diseases in all other regions of the world.**
- **The combination of diseases that is the norm in ALS/PDC is extremely rare elsewhere.**
- ***Neurofibrillary tangles are seen all regions of the brain in ALS/PDC but are generally either not seen (ALS) or seen in characteristic areas (Alzheimer's and Parkinson's).***

2. BMAA is found worldwide because a majority of cyanobacteria generate it. Or do they?

- In addition to the studies listed above that found BMAA in a variety of cyanobacterial species, there are several that did not find BMAA:
  Papageorgiou et al., 2009 (0/12)
  Kruger et al., 2010 (0/30)

3. BMAA levels have been analyzed in tissues/cells since the beginning of the research: Are the methods used accurate? Do they reflect the forms of BMAA found?

- Is there a single optimal method for analyzing BMAA – both free and “protein-associated” forms?
- Are there studies that can be invalidated because of their methodology?
- What is the nature of the protein associated BMAA? Is it “loosely” associated by chemical charge or is it incorporated into proteins as an amino acid?

4. The relationship between BMAA and ALS/PDC has been predicated on the consumption of flying foxes, and data showing the population of these animals dropping has been used to explain the reduced incidence of ALS/PDC on Guam.

- Humans are not the only species to have consumed flying foxes on Guam. Another species invaded Guam (around 1950) and devastated the endemic fauna – birds, mammals and reptiles. How much did this invader affect the flying fox populations as compared to humans?

5. The BMAA hypothesis is highlighted, in part, by the Stommel epidemiology study, as well as well as Cox et al. (2009) who postulated a link between BMAA in desert air & increased ALS in Gulf War veterans.

- The Stommel paper suggests a causal relationship between BMAA from a lake, and ALS. Where is the evidence of that occurring in any other similar environments?
- Why was almost no BMAA found in normal human tissues if BMAA is ubiquitous? Were the techniques improper, the sensitivity too low, or some other reason for this discrepancy?

- If the Cox desert air inhalation hypothesis is correct, one might expect ALS to be far more common than it is, given the global occurrence of BMAA in food, water and air.
- Why were Montine et al (2005) unable to find BMAA in brains of Pacific Northwest and Guam people who had ALS or Alzheimer's?
- The ALS/PDC seen on the Kii peninsula and in Irian Jaya has been attributed to the use of cycads in folk medicine - as poultices for cuts and abrasions in Irian Jaya, and ingestion of seeds for a variety of ailments in Japan. What has not been addressed is the question of whether these uses are unique to these limited localities where ALS/PDC is seen.

6. Are there validated animal models for neurotoxicological effects induced by BMAA?

- It is universally agreed that a validated animal model for BMAA effects would be a tremendous asset – both providing compelling evidence of the validity of the central hypothesis, and enabling researchers to ask questions that cannot be asked with human populations. The problem is that there is little agreement between published studies using animals.

Postulated Etiologies - Current

- **MAM – Spencer et al. (1991)**
- Cycad consumption – Reed et al. (1987).
- **BMAA – Cox et al. (2005)**
- **Sterol- β -glucosides – Khabazian et al. (2002)**
- BMAA-neurotoxicant synergisms – Lobner et al. (2007)

Methylazoxymethanol (MAM)

MAM is a metabolite of cycasin, a neurotoxic and carcinogenic glucoside produced by cycads. It is suspected of inducing a neurological disease in cattle that eat cycads – the "Zamia staggers".

The basic theory advanced by Spencer and Kisby is that MAM exposure early in life produces molecular damage that results in altered gene expression systems. This damage will manifest itself as carcinogenicity in dividing cells and long-term neurodegeneration in central nervous systems cells that do not divide. The long latency between exposure and disease occurrence is the result of a slow build-up of damage to a system that has significant redundancy. Currently, this hypothesis remains largely untested, especially using in vivo systems.

Sterol- β -glucosides

Shaw, Wilson and Khabazian et al. have strongly disagreed with the BMAA hypothesis and have, instead, focused on a group of putative toxins that are not removed from flour with washing. These toxins are sterol β-D-glucosides (BSSG); chemicals derived from glucose.

Glucosides are common in plants, and some are known to be toxic. These workers theorize that the toxicity seen in mice fed washed cycad flour is due to these insoluble chemicals that exert a neurotoxicity basically due to glutamate excitotoxicity. They have noted several types of toxicity in both in vivo and in vitro systems and measured high levels of BSSG but have not been able to relate BSSG exposure in mice to glutamate excitotoxicity that might be responsible for the observed neuronal loss. The research on these glucosides is interesting but not yet at a point where we can conclude that they play a definitive role in ALS/PDC.

Summary and Conclusions

- There are three major current theories concerning the Guam ALS/PDC. Two of these – the Spencer/Kisby and the Shaw/Wilson research groups – appear to have focused on the Guam experience and toxins present in cycads that are not removed from flour with washing; while the third (Cox et al.) still considers BMAA as a potential causal factor in neurodegenerative diseases worldwide.

  There is not currently sufficient evidence to conclusively validate any of these hypotheses in terms of causing ALS/PDC or the separate diseases. There have been three thorough government-sponsored reviews of the BMAA hypothesis [Sundh et al. (2007) TemmaNord (Scandinavia); Rumsby et al., (2008) DEFRA/DWI (England); Papageorgiou et al. (2009) WQRA (Australia)]. All of these reviews as well as Faison et al. E.P.A. (U.S.) agreed that there is not sufficient evidence to link BMAA with neurological diseases; many critical data gaps exist; and there is no current need for regulatory action.