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LETTERS

Guam ALS-PDC: Possible Causes

Mention of our work in Richard Stone's Research News article (23 July, p. 424) about the possible causes of western Pacific amyotrophic lateral sclerosis–parkinsonism dementia complex (ALS-PDC) bears clarification. We and others seek to understand which agents in the neurotoxic cycad plant induce neuromuscular disease in animals and whether the neurotoxic mechanisms relate to the etiology and pathogenesis of western Pacific ALS.

Our studies began with the minor *Cycas* neurotoxin β-*N*-methylamino-L-alanine (BMAA) and progressed to cycasin (a larger component) and its aglycone methylazoxymethanol (MAM) (a genotoxin) because (i) both cycasin and BMAA are present in cycad flour consumed by the Chamorro population of Guam (*1*), (ii) both have neurotoxic properties (*2*), and (iii) cycasin and MAM induce multinucleated neurons in developing rodent cerebellum (*3*) similar to those reported in adults with Guam ALS (*4*). It is a common experimental toxicologic strategy to select a dosage of a chemical agent (BMAA) that will elicit an effect within a reasonable period of time (weeks). We also used very large doses of BMAA because previous studies with the grass pea excitotoxin β-*N*-oxalylamino-L-alanine showed that well-nourished macaques require much larger amounts than malnourished humans (the likely wartime situation in Guam) to elicit even beginning motor-system dysfunction (*5*). As stated before (*6*), the primate response to BMAA is far from a complete model of Guam ALS, and the neurotoxic properties of cycasin are of current interest.

The excitotoxic properties of BMAA are potentiated by bicarbonate and attenuated by glutamate-receptor antagonists, notably those active at non-*N*-methyl-D-aspartate (NMDA) receptors (*7*). Our macaques treated daily by gavage with more than 200 milligrams per kilogram of synthetic BMAA for 7 weeks did not display convulsions, and morphological changes in Betz cells of the motor cortex were more akin to those in chronic neuronal disease than to those in an excitotoxic neuropathology (*8*). These observations raised the possibility that low extracellular concentrations of excitotoxins perturb neurons without inducing seizures. Others have since shown that elevated glutamate (from transporter blockade) induces non-NMDA–mediated chronic motor neuron degeneration in mouse cord explants (*9*) and that cerebrospinal fluid from patients with sporadic ALS causes non-NMDA–mediated degeneration of rodent primary neuronal cultures (*10*). Thus, as we proposed in 1987 (*8*), the primate BMAA motor-system response may be broadly relevant to related non-Guam diseases, notably sporadic ALS.

While cycad or its components have the capacity to induce locomotor disorders in a variety of species (cow, goat, guinea pig, rat), these conditions are little understood. Experience with primates fed cycad flour has led to mixed results: Dastur and his colleagues (*11*) reported the induction of motor neuron degeneration and limb weakness in rhesus monkeys, but Garruto *et al.* (*12*) did not produce any clinical signs of neurological disease in two cynomolgus monkeys given aluminum and manganese plus cycad flour with unknown concentrations of cycasin and BMAA.

We and others are at an early stage investigating the neurotoxic potential of cycad chemicals and their possible relationship to western Pacific ALS-PDC. There are compelling reasons to continue this systematic study.

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References

1. G. E. Kisby, M. Ellison, P. S. Spencer, *Neurology* **42**, 1336 (1992).
2. G. E. Kisby *et al.*, *Neurodegeneration* **1**, 73 (1992).
3. M. Jones, M. Yang, O. Mickelsen, *Fed. Proc.* **31**, 1508 (1972).
4. H. Shiraki and Y. Yase, in *Handbook of Clinical Neurology*, P. J. Vinken and G. W. Bruyn, Eds. (North-Holland, Amsterdam, 1975), vol. 22, part 2, pp. 353–419.
5. P. S. Spencer *et al.*, *Lancet* ii, 1066 (1986).
6. P. S. Spencer, R. G. Allen, G. E. Kisby, A. C. Ludolph, *Science* **248**, 144 (1990).
7. J. H. Weiss and D. W. Choi, *ibid.* **241**, 973 (1988); C.

N. Allen, P. S. Spencer, D. O. Carpenter, *Neuroscience* **54**, 5677 (1993).
8. P. S. Spencer *et al.*, *Science* **237**, 517 (1987).
9. J. D. Rothstein, L. Jin, M. Dykes-Hoberg, R. W. Kuncl, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
10. P. Couratier, J. Hugon, P. Sindou, J. M. Vallat, M. Dumas, *Lancet* **341**, 265 (1993).
11. D. K. Dastur, *Fed. Proc.* **23**, 1368 (1964); ———, R. S. Palkar, D. K. Manghani, in *ALS: New Advances in Toxicology and Epidemiology*, F. C. Ross and F. H. Norris, Eds. (Smith-Gordon, London, 1990), pp. 129–144.
12. R. M. Garruto, R. Yanagihara, D. C. Gajdusek, *Lancet* **II**, 1079 (1988); R. M. Garruto, M. J. Strong, R. Yanagihara, *Adv. Neurol.* **56**, 327 (1991).

There has been a long-standing but unsuccessful search for an environmental cause of ALS-PDC not only on Guam but also in two other places with a high incidence of ALS-PDC, the Hobara and Kozagawa regions of the Kii Peninsula on Honshu Island in Japan and the Auyu and Jakai villages of West Irian in New Guinea. ALS-PDC appeared in these culturally different and relatively isolated regions at about the same time as it did in Guam, and its incidence then steadily declined. The pathology of ALS-PDC shows that it is distinctly different from classical ALS and Alzheimer's disease. Neurofibrillary tangles are not present in ALS, and while they are present in Alzheimer's disease, their distribution is different from that in ALS-PDC (*1*). Senile plaques, sparing of the globus pallidus, and clinical differences (*2*) also distinguish Alzheimer's disease from ALS-PDC. However, the clinical features and pathology of ALS-PDC strongly resemble postencephalitic parkinsonism–ALS, a sequel of encephalitis lethargica first described by Constantin von Economo in 1917 (*3*).

Encephalitis lethargica accompanied the swine influenza pandemic in the 1920s, peaking in 1920 and 1924, and disappeared at the end of the decade. Because of their coincidence they were believed to be related, but this remained unproved. However, postencephalitic parkinsonism–ALS continued to appear over the next three decades. Guamanian ALS-PDC was first recognized in 1947 and was initially thought to be a late sequel of encephalitis lethargica, but attention soon focused on environmental toxins. It is probable that small epidemics of encephalitis lethargica have recurred for centuries, each having been referred to with different names, such as "febrilis comatosa" and "La Nona" (*4*). We may now be observing the decline of a postinfective illness that has finally run its course on Guam, West Irian, and the Kii Peninsula. The genetic isolation of island, valley, and tribal peoples may have produced a marked susceptibility to disease that has far more genetic importance than we realize.

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References

1. A. J. Hudson and G. P. A. Rice, *Can. J. Neurol. Sci.* **17**, 427 (1990).
2. A. J. Hudson, *ibid.* **18**, 387 (1991).
3. C. von Economo, *Encephalitis: Its Sequelae and Treatment* (Oxford Univ. Press, London, 1931).
4. *Brit. Med. J.* 1, 748 (29 March 1890).

Stone's article on Guam disease concentrates on the search for a toxic agent or agents as a cause for ALS-PDC, but there is suggestive evidence—epidemiological, pathological, and clinical—that Guam disease may be due to a transmissible agent, probably a virus. There are many affinities between Guam disease and postencephalitic syndromes. Encephalitis lethargica, after raging for some years, also vanished and apparently died out completely around 1927. It too could produce neurological syndromes many years or decades after the original infection—the longest such interval in my experience was 45 years. And these syndromes could be extremely variable—some patients presented ALS-like syndromes, some amnesia, and a great many parkinsonism, all of which are common in Guam disease. Moreover, as I saw myself during a recent visit to Guam, ALS-PDC can also present as catatonia, ticcing, or arousal syndromes intensely sensitive to the "awakening" effects of L-dopa, precisely as in postencephalitic patients.

It is difficult to imagine a toxin having effects so varied, so unpredictable, so delayed; it is much more plausible to conceive of an infectious agent, with perhaps an animal reservoir or vector that was destroyed or altered around the time of World War II.

It is crucially important, as Stone points out, that this unique disease be cracked before it disappears, for even if its etiology is different, it could cast a flood of light on every sort of neurodegenerative disease and process. And it is especially important that the current research on Guam itself be properly funded and encouraged, for this is where we will find the answer.

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Quantum Mechanics: Not Mysterious

I write to disagree fundamentally with the 12 March article by David H. Freedman (Research News, p. 1542). Leaving aside the discomfort I feel with language like "mysterious," "queerness," and "somehow [collaps-