

Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam

Paul Alan Cox, PhD; and Oliver W. Sacks, MD

Abstract—The Chamorro people of Guam have been afflicted with a complex of neurodegenerative diseases (now known as ALS-PDC) with similarities to ALS, AD, and PD at a far higher rate than other populations throughout the world. Chamorro consumption of flying foxes may have generated sufficiently high cumulative doses of plant neurotoxins to result in ALS-PDC neuropathologies, since the flying foxes forage on neurotoxic cycad seeds.

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The high incidence of ALS-PDC in Guam has been an enigma. After World War II, the incidence of ALS, or an ALS-like condition, was more than a hundred times the incidence rate of the mainland United States.¹ A similarly high incidence of an unusual form of parkinsonism also was found in Guam. These diseases were virtually confined to the native Chamorro population. Disease incidence climaxed in the 1940s (when it constituted the main cause of death in the adult Chamorro population), but then steadily declined. Today the disease occurs only in older adults and rarely in any individual born after 1960.

Cycad consumption and ALS-PDC. In the early 1950s, Kurland and Mulder² suggested that the disease might have a genetic basis, but no clear genetic pattern could be discerned. Clinical similarities to postencephalitic parkinsonism raised the question of an infectious origin, but there was no clear evidence of any encephalitic infection having occurred on the island. Kurland and Whiting³ began ethnobotanical studies to determine if the Chamorro lifestyle and diet might be implicated. One aspect of local cuisine aroused suspicion: flour made from the seeds of a cycad, *Cycas rumphii* Miquel.⁴ The Chamorro people knew the cycad seeds to be acutely toxic⁵ and detoxified the flour made from them through multiple washings.

Kurland's⁶ hypothesis that ALS-PDC was a belated reaction to the ingestion of cycad neurotoxins aroused great interest, but despite repeated trials it was not possible to generate a comparable neurologic disease in experimental animals by feeding them cycad seeds or flour.⁷ A similar disease was found on the Kii peninsula in Japan⁸ and in Irian Jaya on the island of New

Guinea. However, apparently there was no use of cycads⁹ in these areas, so attention was focused instead on other environmental factors including possible mineral deficiencies and excesses,^{10–12} and, most recently, unusual infectious agents, including prions.¹³

Subsequently, Spencer et al.^{14,15} found that monkeys fed with large doses of the toxic amino acid from the cycad, beta-methylamino L-alanine (BMAA), had neurologic impairment: damaged motor neurons in the spinal cord produced a flaccid paralysis, and then damaged neurons in the striatum and cortex produced parkinsonian and behavioral changes. Unlike the human disease, however, the experimental condition was acute and reversible. To receive an equivalent dose of BMAA, humans would need to eat massive amounts of cycad seeds on a daily basis¹⁶ because the processed flour is low in BMAA.¹⁷

Spencer et al.¹⁸ then suggested that the glycoside cycasin, known as a carcinogen, could be present in significant concentrations even in well-washed flour, perhaps acting as a "slow-toxin"¹⁸ damaging DNA in certain vulnerable neurons so that many years later the neurons might be subject to a degenerative process—with BMAA playing an agonistic role. Such a process could lead to the deposition of the neuronal (tau) proteins present in neurofilaments and tangles in the nervous systems of those who died from ALS-PDC. In rat neuronal cultures, the aglycone of cycasin methylazoxymethanol (MAM) can damage neuronal DNA, disrupt glutamate transmission, and promote the accumulation of tau protein and neuronal degeneration.¹⁹ Moreover, evidence emerged that there was exposure to cycads in the other Western Pacific isolates.^{20,21}

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Figure 1. A flying fox of the genus *Pteropus* prepared for consumption at a Chamorro feast in Guam. After boiling in coconut milk, the animal is consumed in its entirety. Photograph by Merlin Tuttle, Bat Conservation International.

ALS-PDC and possible biomagnification of cycad toxins. We suggest that the Chamorro population of Guam ingested large quantities of cycad toxins indi-



Figure 2. A flying fox (*Pteropus mariannus*) eating the seeds of a cycad (*Cycas rumphii*) in Guam. Photograph by Merlin Tuttle, Bat Conservation International.



Figure 3. An advertisement for imported flying foxes in Guam. After the Guamanian species vanished, 18,000 were imported from Samoa during a 3-year period. Photograph by Merlin Tuttle, Bat Conservation International.

rectly by eating flying foxes (figure 1). The 950 species of bats are placed in the order Chiroptera, which is divided into two suborders: suborder Microchiroptera includes the small insectivorous bats common to North America and Western Europe, whereas the suborder Megachiroptera include the large nectar and fruit-eating flying foxes of the Old World tropics and subtropics. In Guam, flying²² foxes are eaten by the indigenous island people on ceremonial occasions and at social gatherings. Indeed, their consumption is a core part of Chamorro culture, particularly in Umatac and Inarajan villages, which had the highest incidence rate for motor neuron disease.²³

Two species of flying foxes, *Pteropus tokudae* and *P. mariannus*, once served as major pollinators and seed dispersers in Guam.²⁴ Flying foxes, which sometimes consume up to two and a half times their body weight per night in fruit and nectar,²⁵ find the seeds of *Cycas rumphii* to be highly palatable²⁶ (figure 2). They squeeze the juice from the sarcotesta and then spit out the pulp. Cycads are common in the forests, and sometimes form dense stands of vegetation beneath the forest canopy²⁷ in Guam, where they play a significant role in flying fox foraging patterns. Biomagnification in cycad-eating flying foxes could have resulted in high levels of lipophilic cycad toxins because bats are known to accumulate toxic molecules in their fat^{28,29} like other herbivorous mammals.^{30,31} Alternatively, neurotoxins could be sequestered or chemically modified in the flying fox tissues. Thus, habitual consumption of the native Guamanian bats by the Chamorro people could have resulted in significant ingestion of cycad toxins.

Severe declines in flying fox populations³² resulted from their popularity as a food item. Although flying foxes were initially so abundant in Guam "that hog raisers in outlying areas in northern Guam used to catch them and feed the cooked bats to their pigs when breadfruit and cultivated plants were scarce,"³³ within a short time their numbers decreased so sig-

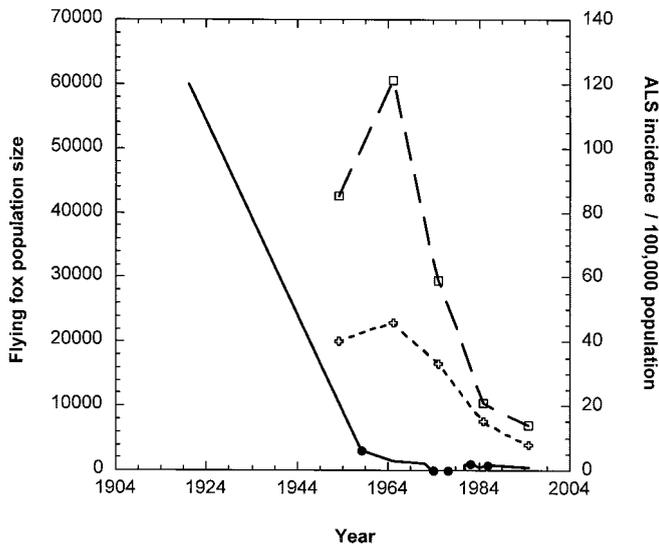


Figure 4. The decline of flying foxes in Guam plotted against incidence rates of motor neuron disease for males and females in Guam.^{2,23,24,32,34,36} Filled circle = flying fox population size; open box = ALS incidence in males per 100,000 males; open plus sign = ALS incidence in females per 100,000 females.

nificantly that they became critically endangered. Commercial hunting of the flying foxes began “in the mid to late 1960s, and peaked in the mid to late 1970s.”³⁴ *Pteropus tokudae* had been hunted into extinction by 1978, and the previous large populations of *P. mariannus* were reduced to less than 100 animals by 1974.³⁵ Massive importation soon began (figure 3): within a 3-year period 18,000 dead flying foxes were imported from Western Samoa alone, with total imports of flying foxes to Guam ranging as high as 29,000 animals annually, worth up to \$35 per carcass.³⁶ Because there are no indigenous cycads in Samoa and many other bat-exporting islands, flying foxes imported from such places would not contain any cycad toxins. Thus the Chamorro people were no longer being exposed to this putative source of cycad toxins. The decline of ALS-PDC among the Chamorro mirrors the decline of flying foxes in Guam (Figure 4).^{37,38}

Discussion. Chamorro ingestion of biomagnified cycad toxins through consumption of flying foxes is consistent with epidemiologic studies³⁹ that indicate the only variable significantly associated with an increased risk for ALS-PDC in Guam is a preference for traditional Chamorro food. Biomagnification of cycad neurotoxins by flying foxes and development of high rates of ALS-PDC in Guam fits the epidemiologic pattern of ALS-PDC in three ways: 1) high levels of flying fox consumption occur both within specific Chamorro families and villages; 2) flying fox consumption is confined to the Chamorro lifestyle (other residents of Guam do not exhibit a high incidence of ALS-PDC); (3) easy access to firearms increased hunter yields (and associated neurotoxin

ingestion), but yields declined during the 1960s and 1970s as the flying fox species were extirpated.

Preserved specimens of the Guamanian species of *Pteropus* should be examined for elevated levels of cycasin and BMAA. Cycad-fed captive individuals of *Pteropus tonganus*, a common species in other Pacific islands, also should be examined.⁴⁰ However, we do suggest an analysis of the consumption of flying foxes as well as other cycad-foraging mammals and birds by the Auyu and Jakai peoples of West New Guinea where motor neuron disease is also high. Although cycasin and BMAA are known neurotoxins, there are a variety of other complex compounds in cycads, which through biomagnification could reach toxic levels. Thus, even if elevated cycasin or BMAA concentrations are not found in cycad-fed flying foxes, other neurotoxic molecules, now biomagnified (or their metabolites), may be found in their tissues. Because there are neuroanatomic similarities between flying foxes and primates,⁴¹ characteristic pathologic lesions of ALS-PDC may be found in their nervous systems. Such lesions were observed in young Chamorros without clinical symptoms.⁴²

There have been recent reports of a high incidence of an atypical parkinsonism, progressive supernuclear palsy, and ALS-like disorders on Guadeloupe, which also have been attributed to the ingestion of phytotoxins, and perhaps biomagnification also is playing a part here.⁴³

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