ANNALS OF SCIENCE

THIS OBSCURE MALADY

IN late November of 1944, a physician named Harry M. Zimmerman boarded the Army troop transport Cape Cleare in San Francisco Bay and, after a layover in Pearl Harbor, completed a seven-thousand-mile journey in mid-January of 1945, when the Cape Cleare, in convoy, sailed into Guam.

Zimmerman, then forty-three, was not tall, was somewhat plump, and wore horn-rimmed glasses and smoked a pipe. An associate professor of pathology at the Yale University School of Medicine, he had been assigned to the United States Naval Medical Research Unit No. 2. The unit, composed of some two hundred corpsmen and a few dozen officer-scientists, was being assembled on the island to investigate "diseases of military importance"—malaria, infectious hepatitis, filariasis, melioidosis, hematuria, shigella, schistosomiasis, Japanese B encephalitis, and tsutsugamushi—that were threatening American troops in the Pacific theatre.

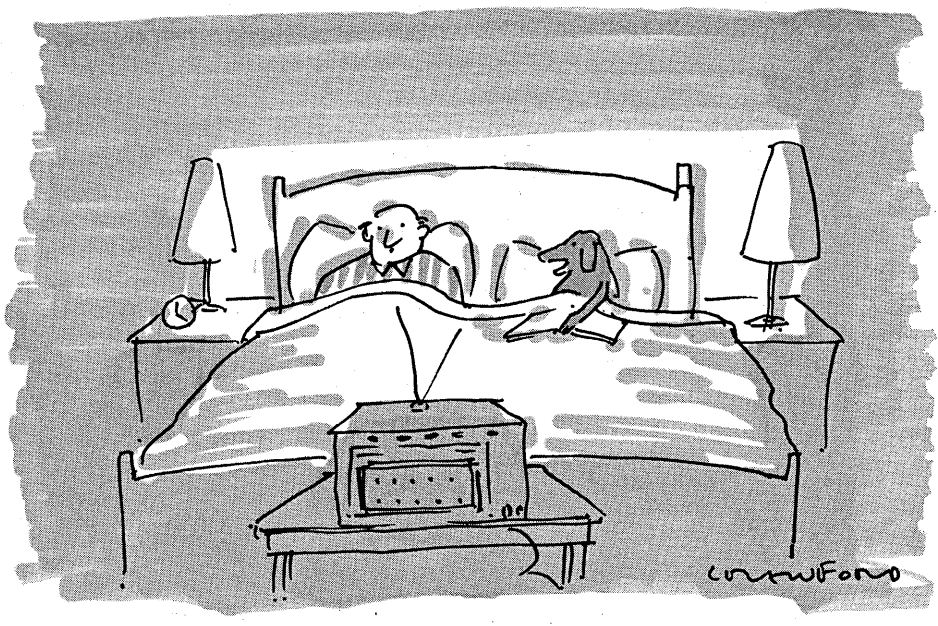
Guam, after being retaken from the Japanese the year before, served as the new headquarters of the Pacific command, and teemed with some two hundred thousand servicemen. Battleships clogged the harbors; bulldozers cleared long runways for B-29s on the forested northern plateau; half-tracks rumbled past palm trees with charred trunks and no crowns, eerie groves of giant black bristles. Agaña, the capital, on the western shore, was "as thoroughly gutted as any city could be," a newspaper report said; the "concrete, limestone and concrete-coral houses are wrecked, each and every one." While Zimmerman waited for air-conditioned Butler huts to be set up for his unit, he helped out at what remained of the civilian hospital, outside Agaña. He kept notes in a large green clothbound ledger with the word "CASH" stencilled on the cover; above that he had written "AUTOPSIES."

He performed his first autopsy on January 21st, on a twenty-year-old woman. An Army truck had run over her and fractured her skull. Zimmerman also found that she had had roundworm and tuberculosis, and had been pregnant. Later that day, he performed his second autopsy, on a sixty-five-year-old man who had died of a bacterial infection of a heart valve; the man had also suffered from hookworm. The third was performed the next day, on an eight-month-old girl; the cause of death was tubercular pneumonia, and she, too, had had hookworm. As the bodies were rolled into Zimmerman's lab, he observed, among other things, the purplish raised scars of knife and gunshot wounds and the unmistakable signs of grave vitamin deficiencies—hearts swollen by beriberi, skin inflamed by pellagra. He also saw a great many cases of parasitic worms, and the reason for the infestation, he learned, was that a lot of Guamanians had had to surrender their shoes to the Japanese, and had been going barefoot in the muck for a long time.

Zimmerman's job always began at the end; laid out on his examining table week after week were the final expressions of the brutality and deprivation of Japanese military rule, and of the scarcity in its aftermath. The island, which had been a United States possession since 1898, was so lightly defended when Japanese Imperial Forces invaded, in December of 1941, hours after the raid on Pearl Harbor, that the governor, a naval appointee, quickly surrendered. Eventually, Japanese soldiers put thousands of natives in labor camps and prison camps, where many died. Guam is forty miles from the nearest island, Rota, which was also in Japanese hands, like all the Marianas, and so there was no ready escape from Guam; a number of men and women, children and goats in tow, fled into the forest, to live in the open air and eat what they could find. The occupation lasted two and a half years.

Beginning in mid-June of 1944, American forces shelled and bombed the island for several weeks—the longest bombardment of the war. From the sky fell pamphlets telling the natives to take cover. Food became harder to find. The captors grew desperate. The New York *Times*, in a story headlined "JAPANESE CUT OFF 51 HEADS ON GUAM," reported on "one of the most bestial episodes of the war in the Pacific." In the village of Merizo, to cite another atrocity, Japanese soldiers drove men and women into caves and tossed in hand grenades, killing more than forty people. When American troops landed, in late July, islanders began staggering out of the camps and the forest. "A sadder lot I've never seen," one colonel said.

Autopsy No. 63, which Zimmerman performed on May 17, 1945, nearly a



"Joe, I want out."

year after the island's liberation, was a forty-two-year-old male. The muscles of his legs were wasted, his ribs were starkly prominent, his arms were slightly twisted, his tongue was shrunken. Zimmerman suspected that the cause of death was amyotrophic lateral sclerosis, or ALS, a disorder in which the long nerve fibres emanating from the spinal cord wither and disengage from leg muscles and, often, from chest and neck muscles, causing atrophy and paralysis. He confirmed his suspicion by microscopic analysis of spinal-cord tissue. A week and a half later, he did Autopsy No. 66. The case was an emaciated thirty-eight-year-old male with wasted legs. The cause of death was recorded as ALS.

Zimmerman, who in 1930 had opened the nation's first full-scale department of neuropathology, at Yale, knew everything there was to know about ALS. He knew that ALS was progressive, incurable, fatal, and mysterious in origin. Its cause was not known to be infectious, genetic, dietary, environmental, or toxic. The disease was idiopathic and sporadic. It just happened. In 1941, Lou Gehrig had died of ALS, at thirty-seven, five years after being named the American League's Most Valuable Player for the second time. Chiefly, ALS was remarkable for what it did not do. It did not run in families. It did not favor workers in certain occupations. It did not cluster. In no way did it advertise its origins. As far as was known, ALS occurred everywhere with the same low incidence: two new cases each year for every hundred thousand people. The native population of Guam in 1945 was less than twenty-four thousand. Statistically, the number of ALS cases that should have been seen there in a year ranged from zero to one.

In a one-and-a-half-page memorandum to his commanding officer—long lost, but found recently in a box of Navy letters in the National Archives, it was marked "Restricted" and headed "Progress Report of Work in the Laboratory of Pathology During May, 1945"—Zimmerman wrote:

> During the past few months there were admitted to the medical wards of the Civilian Hospital 7 or 8 patients with a full-blown clinical picture of amyotrophic lateral sclerosis. This was quite surprising in view of the infrequency with which this neurologic disorder is encountered in the States. Two of the patients died during the month of May and the diagnosis was confirmed at autopsy. It is now planned to investigate the hereditary background of all these patients in the effort to throw some light on the factors concerned in the etiology of this obscure malady.

Soon after the war, doctors working on Guam discovered that ALS was far more common on the island than even Zimmerman's surprised memorandum had reported: the disease was breaking out there as it had never broken out anywhere before. Then, while studying the ALS epidemic on Guam, doctors found that a large number of Guamanians were suffering from a neurological disorder, entirely new to medicine, that impaired movement and erased memory, as if it were a dire blend of Parkinson's and Alzheimer's diseases. And quite a few patients were enduring all three diseases at once—ALS, parkinsonism, and dementia. Nothing like that had ever been documented before, either. Over the years, the epidemic on Guam, which lingers even now, has gradually shrunk in size but grown in importance. Scientists still believe that it may tell them a great deal about the origins of not only ALS but also Alzheimer's and Parkinson's—two afflictions that will probably amount to the nation's leading public-health burden in coming decades, as baby boomers grow old. One researcher, describing the broad significance of the epidemic and the often wild competition to figure it out, has gone as far as to call it "the Rosetta stone of neurology." All in all, it has been one of the most isolated, sustained, complex, intensely studied epidemics of human neurodegenerative disease in history.

A WHILE ago, I visited Zimmerman, and asked him about those first cases of ALS he had reported during the war. "I discovered that some of the patients were related," he said. "So we began to think in terms of the possibility that it was a familial, genetic type of disease. Well, we thought of it, but there was no way to prove it. What did we know about genes in 1945? We also thought of the possibility that this was an environmental thing, not an infection but maybe due to the diet. Some people still believe that that is a factor."

Zimmerman has an office at the Montefiore Medical Center and Hospital, in the Bronx, and goes to work there five days a week, sometimes six. He is eighty-nine. His hair is thick and

white, his skin as smooth as a fifty-year-old's. His hands tremble slightly; if he were a surgeon, he said, he would have fully retired by now. When I asked him what the secret of his vigor was, he replied, "Genes." He was once the chairman of pathology at Montefiore and a professor at the Albert Einstein College of Medicine. In fact, it was Zimmerman who persuaded the physicist to lend his name to the school, in 1953, and when Einstein died, two years later, at seventy-six, Zimmerman was part of the team that did the neurological post mortem. "Einstein had a normal brain for a man his age," he says. Zimmerman has participated in thirty thousand autopsies.

"Shortly after I reported the cases from Guam, I had to curtail my activities at the civilian hospital," he said as we looked through his big green ledger of the dead. "So I never got a chance to follow up on ALS while I was there."

Others picked up where he left off. Three naval-reserve physicians stationed on Guam in the late forties—Arthur Arnold, Donald C. Edgren, and Vincent S. Palladino—were impressed enough by seeing several ALS patients on the wards to go looking for more patients in the villages. They found fifty. According to their calculations, approximately one out of every hundred native Guamanians between the ages of thirty and sixty-five had ALS—an incidence about a hundred times as high as the average. In their report they said they had sought a "possible etiologic factor or factors" to account for the disorder's extraordinary prevalence, but (a sigh is almost audible) "to no avail." They sent the report to the *Journal of Nervous and Mental Disease*, but it wasn't published for four years. The journal's editors had apparently found it hard to believe.

In 1951, Donald R. Koerner, a Navy physician, began a study of the disease on Guam, the results of which were published in the *Annals of Internal Medicine* in December of 1952, beating Arnold and his colleagues into print by some months. Koerner, heading for the villages, took along a Navy-trained medical practitioner named José M. Torres, who was a Chamorro, or native Guamanian, and spoke the local language. In addition to examining thirty-five patients, Koerner and Torres checked 29,292 records of admission to the naval and civilian hospitals for the previous five years. All the ALS cases, they noted with amazement, were Chamorros.

A few months before the publication of Koerner's and Arnold's alarming reports, news of the ALS epidemic had begun drifting back to the States. Word reached Leonard T. Kurland, a researcher at the National Institute of Mental Health and a neurology resident at the Mayo Clinic, in Rochester, Minnesota, in the fall of 1952. The seed could not have fallen on more fertile soil. Kurland was a clinical neurologist, and he had just completed a doctorate in epidemiology at the Johns Hopkins University School of Hygiene and Public Health. He was interested in the patterns by which neurological diseases spread across space and time. For his doctorate he had studied the geographical distribution of multiple sclerosis in North America. Analyzing hospital and mortality records from Winnipeg and New Orleans, and taking into account economic, racial, and social differences between the two populations, he showed that MS was roughly six times as common among the Northerners as it was among the Southerners.

"When I first heard about Guam, my response was 'That's strange,'" Kurland told me not long ago. "I had just looked at the latest figures on the international distribution of ALS. In contrast with MS, this disease has a remarkably even distribution. I hadn't heard of any place where ALS was highly prevalent. So I wrote to the commanding officer of the naval hospital on Guam. He wrote back a rather sarcastic letter saying he didn't see the need for an epidemiologist on the island. He wasn't aware that there had been anything out of the ordinary. Besides, he said, there had been only twenty-seven cases of ALS that he knew of in the last few years. I was on my way."

The Navy arranged for Kurland and Donald Mulder, a staff neurologist from the Mayo Clinic and a lieutenant commander in the naval reserves, to do some studies on Guam. That was in 1953. "Back then, you couldn't go there without security clearance," Kurland recalled. "Our first visit was simply to establish that this was ALS

as it is defined in the textbooks. Clinically, it was. When we went door-to-door in the villages and looked intensively for it, we saw an incredible—an *incredible*—number of cases. A lot of the patients had already seen two doctors, Arnold and Koerner. And now I come along. The local people were becoming a bit concerned. Many of them asked, 'Why are you so interested in us? We have this problem, but people all over the world have it like this, too, don't they?' So we would tell them, 'No. There is something unusual here.'

"One of the great finds of our first trip was the death certificates. I went with José Torres to the office of vital statistics in Agaña. There, in a safe in the basement, we found these big red leather volumes going back to the turn of the century. Because they had been in a vault, they were not damaged when the city was levelled in the bombardment. They were practically the only documents that had survived. The earliest volumes were in Spanish. We went through all the death certificates and found numerous cases of '*paralytico*,' or '*lytico*.' It was also called 'progressive muscular atrophy' and, later on, 'amyotrophic lateral sclerosis.' The first death certificate that mentioned the disease was from 1902."

Once all the information from the surveys by Kurland and his co-workers had been gathered—after thousands of death certificates and hospital records had been checked, hundreds of doors knocked on, doctors and nurses and village leaders interviewed—the most puzzling fact of the disease's distribution surfaced: of a total of eighteen villages on Guam, one was, epidemiologically, off the charts. The disease was concentrated in Umatac, on the southwest shore. Umatac was the island's poorest community, with dirt roads and homes of thatched sword grass, and was its smallest, with six hundred and one people in 1952. It was also the most geographically and genetically isolated village, hemmed in by Umatac Bay and by steep hills, an island on an island, made up almost entirely of people from four interrelated families.

In 1954, writing in the *U. S. Armed Forces Medical Journal*, Mulder, Kurland, and Lorenzo Iriarte, another Navy-trained medical practitioner, emphasized the significance of the village as a sort of ground zero for ALS. "Umatac has been recognized in all the previous surveys as being the community with the highest prevalence of the disease. In fact," they said, moved to italics, "*one third to one fourth of all adult deaths in this village are due to amyotrophic lateral sclerosis.*"

Reflecting on that early period of discovery, Kurland told me, "Epidemiologists spend their whole career looking for a geographic isolate. If you have a focus of disease, it should be easier to explain that focus than it is to explain a relatively rare event that happens out in the general population. And here was the answer to amyotrophic lateral sclerosis. It was logical."

KURLAND is now a professor of epidemiology at the Mayo Clinic. Approaching seventy, he is compactly built, wears wire-rimmed glasses, and has white hair and longish white sideburns. When we met in Rochester one December Sunday, he wore bluejeans, a flannel shirt, a quilted vest, and a visored cap with the earflaps down. He has worked on the Guam problem longer and harder than anyone else, but the medical world knows him better as the man behind the Rochester Project. This is an archive of patient records at Mayo extending from early in the century up to the minute, and includes a tally of diagnoses made by doctors in surrounding Olmsted County—all told, records on more than four million people, a great number of them described from birth to autopsy. Drawing on this resource, Kurland and his associates have put a finger on virtually every case of every disease that has occurred in the county in the last seventy-five years. Thus central Minnesota has become a microcosm of American public health, a drop of the pond. An official who wants to know precisely how much abnormality is normal may consult one of four hundred Rochester studies that Kurland has written or collaborated on. They include, say, "The Incidence, Causes, and Secular Trends of Head Trauma in Olmsted County, 1935-1974," "Higher Risk of Seizures in Offspring of Mothers Than of Fathers with Epilepsy," and "Follow-Up Study on Amyotrophic Lateral Sclerosis in Rochester, Minnesota, 1925-1984." A National Institutes of Health internal memorandum recently described Kurland as "the gold standard" in neuroepidemiology.

Of the many medical scientists who have devoted themselves to the Guam

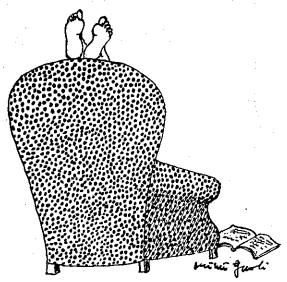
problem, he is the only one now actively working on it who was there in the beginning. In 1956, arguing that the answer to ALS was on Guam, he persuaded the National Institute of Neurological Diseases and Blindness to open a full-time clinic and laboratory on the island. The Guam Research Center was established at Guam Memorial Hospital, on a limestone rise north of Agaña.

While Mulder and Kurland were trying to come to grips with ALS—the caseload was at its peak, with one or two new cases coming to light each month—they realized that another, yet more vexing neurological disorder was also rampant on the island. It seemed at first to have nothing to do with ALS. Its course varied somewhat, from person to person. Among its symptoms were rigid muscles, a marked stoop, a stiff gait, a shuffling step, slowed speech, and an expressionless, masklike face. Several patients had hand tremors of the types aptly described as "pill rolling" and "guitar picking."

To Kurland and his colleagues this new thing looked like Parkinson's disease, with a twist. The British physician James Parkinson, in his classic treatise of 1817, said that a patient with "the shaking palsy" nonetheless possessed "senses and intellects" that were "uninjured." But many of the Guamanians with Parkinson's disease, the two doctors saw, were also demented. "They would become forgetful," Kurland recalled. "They would lose their way, not find their way home. They couldn't remember the names of their children. Had poor memory for recent events. Became disoriented. May or may not have been depressed along with this. Sort of sat around and did very little or nothing. That accounted for what some of the locals called the disease—*raput*, which means 'laziness.' It's an unfortunate name. They aren't lazy." Another Chamorro name for it is *bodig*, after an afflicted man who had run a bodega. Some islanders call it "hurryup." No such disease then appeared in the medical literature. The researchers named it "parkinsonism-dementia complex."

Now when they went to the villages, riding in a big station wagon that doubled as an ambulance and hearse, they weren't looking just for ALS. They also asked to meet anyone who was immobilized or stooped or forgetful or dazed, or whose hands trem-

bled. A person nearing the end might be in bed, fetally curled, emaciated, mute, eyes unanswering. Going door-to-door, canvassing for parkinsonism-dementia, Mulder and Kurland found it to be nearly as common as ALS, and to be concentrated in some of the same families and villages. In Umatac, the ALS focus, the epidemic was worse than had been expected, taking more than one in three adults. The astonishing truth, Kurland once reported, was that about "one-half of the adult population in this village dies either of ALS or of . . . the parkinsonism-dementia complex."



Late in 1957, Kurland shipped the formalin-fixed brains and spinal cords of two patients—one had died of ALS, the other of parkinsonism-dementia—to Nathan Malamud, a professor of psychiatry and neuropathology at Langley Porter Psychiatric Hospital, at the University of California at San Francisco. Malamud, following the standard procedure, cut portions of the tissues into vanishingly thin slices, mounted the slices on glass slides, stained them with a silver solution, and looked at the neurons through the microscope. He saw in the brain tissues, in addition to the expected shrinkage and other signs of deterioration, a great number of neurofibrillary tangles—microscopic strands of protein jumbled inside the bodies of nerve cells. Stained and magnified, neurofibrillary tangles look like hair balls. Why neurofibrillary tangles form is unknown, but the finding surprised Malamud and Kurland, because the tangles are a signature of Alzheimer's disease. Strangely, though, the other signature of Alzheimer's—plaques of protein which build up between nerve cells—was not in evidence.

Kurland needed a neuropathologist on the spot to see if other brains had tangles, and he consulted the obvious expert, Harry Zimmerman. Zimmerman sent a collaborator and former student, Asao Hirano, who, with his new bride, went to Guam in 1959—the island's first postwar Japanese honeymooners. Hirano is now the head of neuropathology at Montefiore Hospital, and has an office across the street from Zimmerman's. Tall and elegant, he manages to be precise and jolly at the same time. When I asked how Guamanians treated him then, only fourteen years after the war, Hirano said, "They were polite." Did he feel awkward? "I was thinking about science! I wasn't thinking about war!"

Hirano performed dozens of careful post mortems on Guam. Donning gloves and mask, using an electric saw to cut the skulls along the hatline, snipping through the glistening dura membranes, severing the blood vessels and the olfactory, optic, and other cranial nerves, and removing the brains to sterile trays, he could see that they weren't merely a little shrivelled; they were practically hollow, like seeded cantaloupes. One brain, from a thirty-five-year-old woman, was three-quarters of its former mass; typically, from ten to twenty per cent of a brain had disappeared, and the shrinkage was from a loss not of water but of gray matter, of countless nerve cells. Looking through the microscope at a slice of brain tissue that should have been dotted with nerve cells, Hirano sometimes saw none at all, only neurofibrillary tangles embedded there, like the fossil remains of a mass extinction.

Tangles were everywhere. Analyzing the brains of parkinsonism-dementia patients, Hirano found neurofibrillary tangles in the cortex, where higher thoughts are processed, and in the hippocampus, where memories are laid down; destruction of these areas, which is typical of Alzheimer's disease, accounted for the dementia. He found tangles in and around the substantia nigra, a midbrain structure named for its blackish pigmentation, where fine movements are regulated by the flow of the neurotransmitter dopamine; destruction of the substantia nigra causes Parkinson's disease. And tangles, this clear-cut sign of dementia, showed up in the spinal cords from some ALS patients, a finding as out of place as footprints on the ceiling.

The neurofibrillary tangles, even more than the "paucity of neurons," as the technical publications nicely put it, would become the outstanding pathological feature of the disease on Guam. From then on, there could be little doubt, given this shared pathology, that ALS and parkinsonism-dementia were different reactions to the same destructive agent, the same insult. Any attempt to explain the origins of the

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disease had to account for the tangles, and any effort to model the disease in animals could not be deemed successful unless the animals developed those tangles along with outward neurological symptoms.

With the discovery of parkinsonism-dementia and of the tangles that tied this oddity to ALS on Guam, the epidemic suddenly became more crucial than anyone had imagined it to be. It spoke now to a wider audience. ALS is fairly rare, afflicting around seven thousand people in the United States each year, but Alzheimer's is the most common neurodegenerative disease, afflicting two in ten people over the age of seventy, and a total of four million people in the United States, and Parkinson's is the second most common, striking one in forty people over seventy, or around half a million people in the United States. If Guam offered the key to solving all three diseases at once, then this was a monumental opportunity. The answer to a variety of neurodegenerative diseases associated with aging, perhaps even the key to the nature of aging itself, was, as one doctor said, "somewhere on that damn island." And so "the Guam riddle," as Kurland calls it, acquired such a legendary allure that one eminent scientist after another has made the journey there to try to pull the sword from the stone.

FROM the mid-fifties through the seventies, epidemiological and clinical and pathological studies on the Guam patients and various inquiries into the origins of the disease were all going on simultaneously. A measure of the intensity of the work is that in those years researchers published in the medical literature more than two hundred and fifty papers on all facets of the problem. The foremost concern remained the cause. When it seemed that microbes might be involved, researchers sought microbes. Screening the blood of Guamanians for nervous-system pathogens, they found nothing pertinent. They scoured brain tissues for infectious agents. On the N.I.H. campus, in Bethesda, Maryland, the esteemed microbiologist Clarence J. Gibbs minced and extracted brain tissues removed at autopsy from diseased Guamanians, and injected the extracts into a variety of lab primates in an effort to transmit the disease. After fifteen years of such experiments, Gibbs stated—and no one disagrees—that the disease is not of infectious origin. When the researchers wondered if the disease might be inherited, as is one rare form of ALS, they sought signs of an errant gene. In one remarkable search, the geneticist Chris Plato, of the N.I.H., worked out the overlapping family histories of nearly the entire community of Umatac, covering a wall-size chart with circles and squares and interconnecting lines. But this village diagram turned up no definitive pattern typical of a disease genetically passed down the generations. Quite conclusively, then, by the mid-seventies the experts had ruled out microbes and genes as causes of the disease on Guam.

Another possibility was a nerve poison, and right away researchers turned up something that fitted into the picture almost exactly. In times of hardship and scarcity, Chamorros traditionally relied on the starch of the cycad seed, which they ate after painstakingly washing the seed of its poison and then grinding it into a coarse flour known as *fadang;* also, Chamorros had long used cycad-seed juices and raw pulp as a topical medicine for abrasions and infections of the skin. During the war, with countless families scavenging the forest, Guamanians ate more cycad seeds than at any other period in this century and, being on the run, were more likely to detoxify the seeds incompletely. Significantly, this sudden surge in the consumption and probably also the medicinal uses of cycad seeds coincided with Zimmerman's report of the ALS cases. In fact, when Marjorie Grant Whiting, the first researcher to advance the cycad hypothesis, asked Guamanians after the war what they considered to be the cause of the disease, many of them told her "*Fadang*."

Whiting, a nutritionist, had spent two years on Ponape, in the Caroline Islands, writing a Ponapean dictionary with her husband, an anthropologist, and in 1954, as she was passing through Guam, Kurland persuaded her to stick around and look into traditional Chamorro folkways and diet. She stayed for a month in Umatac, with a family who lived next to the bay; village women who came by the house to cook and gossip found a woman with a handsome face, a strong nose, and light hair, who customarily dressed in a bright smock and sandals. Whiting would be sitting on a stump taking notes, and on Saturdays she would stay up with the women all night cooking for the fiesta after Mass. "I became an avid collector of recipes for native dishes," she recalled some years later of her approach. In 1962, she told a scientific gathering:

> I used such leading questions as "What do you use as a substitute when you have no store flour (or bread, or rice, or soya, or salt)?" "What would people around here eat if they had no money?" and "How did you manage to survive during World War Two?" . . .
>
> I checked reports of sudden illness and of a few deaths which reputedly followed consumption of a particular food item. Although many of these occurred years ago, survivors readily recalled the details. Some incidents followed consumption of bitter cassava, others of cycad starch. . . .
>
> In other ways also, [cycad starch] seemed to fulfill my requirements for a toxic food warranting further study. People like to eat it and although they know of its toxicity go to considerable lengths to obtain and process it. Because of its peculiar mucilaginous property it is highly desirable for making tortillas and as a thickening for other dishes. . . .
>
> On the other hand, "everyone" knows of the toxic properties of the plant. Dogs and chickens reputedly die if they drink the wash water. Preparation is laborious. Directions vary but soaking [the freshly picked seeds] is required for "several" days with "frequent" changes of water. During the process of [opening the seeds and cutting them up] some persons become dizzy and have to leave their work for a time to recover. Children are not allowed to participate in this stage of the processing. Only small amounts are given to children because many become ill when they first eat a dish made with cycad starch.

For Kurland, the potency of cycad seeds revealed itself one day when he and Whiting were visiting a Chamorro woman at home. He saw on the kitchen counter an open pot of halved cycad seeds soaking in water. He wondered why the woman would leave valuable food out and uncovered in the tropical heat. "Won't the bugs spoil it?" he asked.

"Bugs don't go near it," the woman said.

Undoubtedly, the cycad seed's chemical defense is one of the reasons for the success of the species. The cycad is one of the most ancient seed-bearing plants on earth. Its woody stem and sexual means of reproduction—cones and motile spermatozoids—rank among the high achievements of the Mesozoic Era. Cycads grew while dinosaurs roamed. In an illustration of a tyrannosaurus standing knee-deep in swamp you can usually find a cycad in the picture; it looks like a palm, only more primitive. Cycads generally have short trunks, under twenty feet, topped by long, stiff, waxy, bipinnate fronds growing in rosette formation. They are sometimes called fern trees. They bear large seeds, naked of fruit. There are about a hundred species, all tropical or subtropical, in the family *Cycadaceae*. The smallish *Cycas revoluta*, native to southern Japan, is a common ornamental; it has dark-green feather-shaped fronds, which keep fresh for a long time and are therefore used in funeral arrangements. Cycads grow all over Guam. The species that grows most abundantly on Guam, and is the most wide-ranging of all cycads, is *Cycas circinalis*. Its trunk reaches a height of ten or twelve feet. The ripe seeds are lemon-size, and cluster around the base of the fronds. Its Spanish name is *federico*. It resists fire, pests, drought. A typhoon will flatten corn crops, and even banana trees and coconut palms, but not *federico*.

Having broadened the scope of her research on cycads, Whiting reported in 1963 in the journal *Economic Botany* that parts of various cycads had been eaten or used as a medicine by native peoples of the Pacific Islands, Indonesia, Indo-China, Japan, India, Australia, East Africa, South Africa, Central America, and Florida. Nearly all cultures that consumed the plant had learned (presumably the hard way) that not only its seeds but its roots, buds, shoots, and leaves could be poisonous. To detoxify cycad stems, a native South African group, according to an eighteenth-century report, used to wrap the pith in an animal skin for two months; thus fermented, it was made into cakes. The Karawa of Australia once buried cycad seeds in grass-lined trenches for two or three months; the fermented seeds were then dug up and

pulverized into flour for baking. The Seminoles of Florida peeled, boiled, and mashed the roots of the local cycad (genus *Zamia*), known as coontie, and added the gruel to meat stew. The pharmacopoeia of many traditional cultures, Whiting went on to say, included chews, extracts, and poultices prepared from raw or processed cycad parts—treatments for skin ulcers, wounds, boils, "diseased hair," colic, diarrhea, constipation, snakebites, insect bites, swelling, headache, neuralgia, and sexual apathy.

Whiting also compiled documentary evidence of the ill effects of cycads on livestock and human beings. Around the turn of the century, on ranches in New South Wales, Australia, thousands of cattle were plagued by acute gastrointestinal illness and, more significant, by hind-limb paralysis, probably as a result of grazing on cycad shoots and leaves. In 1929, in the same region, more than two thousand sheep were fatally poisoned after grazing on cycads. Livestock in the Caribbean have also been intoxicated by the plant. In Australia, Whiting related, cattle were said to have become "addicted" to cycad shoots, going far out of their way for them, and these addicts had been observed showing others in the herd where to get the stuff.

It is not impossible for people to become addicted to cycad seeds, but, historically, the main problem caused by the seeds has been acute poisoning. Upon arriving in Australia in 1770, a landing party of Captain Cook's found empty cycad husks near a campfire, concluded that the plant was edible, and feasted on cycad seeds; the men became violently ill. A group of Union soldiers wandering in Florida during the Civil War ate some bread made of ill-prepared coontie; several died. On Celebes, in Indonesia, juice from *C. circinalis* seeds was once used to commit infanticide. In Honduras, *Zamia* root was reserved for executing criminals. In Western Australia, in 1894, a local newspaper said that a few days after eating *Zamia* seeds a child became paralyzed from the waist down—the only reported case (and the details are sketchy) of acute cycad-induced human paralysis. In the Ryukyu Islands, south of Japan, "following World War II, several persons are reported to have died and others to have become acutely ill from eating improperly prepared cycad starch," Whiting wrote. "A physician describing his own experience said he broke into perspiration, vomited, and lost consciousness." Another incident in that region, in 1956: "Five persons died, one recovered, following use of inadequately washed and dried starch."

On Guam, cycad meal was apparently not eaten until the seventeen-hundreds, when, according to an 1819 account by a member of a French expedition, the Spanish taught the Chamorros how to detoxify and cook the material. By the early eighteen-hundreds, cycad seed was Guam's leading crop. Men and boys gathered cycad seeds in the forest, sometimes overnight, and back home the women husked and sliced the seeds, and rinsed them in numerous changes of water over days or weeks. "A bird, goat, sheep, hog or cat that drinks from the first water in which the *federico* has been soaked is apt to die," Governor Luis de Ybáñez y García observed in 1871. "This does not happen with the second; much less the third, which can be consumed without danger." How long the soaking continued and how often the rinse was changed depended on family custom—and, presumably, hunger. The washed cycad slices, after being dried in the sun, were ground into the gritty *fadang* flour. This went into dumplings or, as a thickener, into soups and stews. Most often *fadang* was mixed with water or coconut juice, made into heavy pancakes, and grilled —Chamorro tortillas, about an inch thick.

Go-Between

The mid-eighteen-hundreds were especially difficult years on Guam, which has had more than its share of natural and man-made disasters, and, in restrospect, those years are when it is possible to see hardship, *fadang*, and disease in the same context. Between 1847 and 1849, the island was struck by four typhoons, a tidal wave, and an earthquake. Again and again, crops died. During those years, natives relied especially heavily on cycad seeds to survive. Then, in 1856, Guam's Spanish governor, Felipe María de la Corte (according to a recent translation by the historian Marjorie G. Driver), cautioned against eating the seeds: "There are constantly epochs of the year during which a great portion of the population, being without maize and other articles of food used here, finds itself obliged to fall back on *federico* and other fruits and roots of the forest which cannot fail to do them injury either from their being essentially harmful, or because the organic system suffers from the repeated changes from one kind of food to another." The Governor urged that natives be dissuaded "gradually from using those articles which are harmful and which, according to best reports, are the origins of the country's endemic illnesses which have become hereditary, often causing premature aging and short life."

It doesn't appear that Guamanians followed the Governor's recommendation for long, if at all. At the turn of the century, William E. Safford, an American naval officer, a botanist, and Guam's vice-governor from 1899 to 1900, noted that after typhoons the natives, "who very seldom have a reserve on hand, are obliged . . . to go to the forest for wild yams and nuts of *Cycas circinalis*." In the nineteen-thirties, a man who lived in Merizo, the village next to Umatac, wrote in his journal (quoted in "Guam and Its Peo-

ple," by Laura Thompson) that his family harvested cycad seeds from January to June. And then, as one middle-aged Guamanian told me, "back in the Japanese occupation, when they kicked us out of our homes, we moved to the jungle and that's what we had to eat—*fadang*. We'd eat it more than once a day, along with whatever else was around."

Fifteen years after the war, Whiting and Kurland proposed to the scientific community that cycad seeds, processed and eaten or used as a medicine, were a plausible cause of ALS and parkinsonism-dementia on Guam—although, to be sure, not one case of ALS or parkinsonism-dementia had been directly tied to a cycad-seed meal or treatment. The theory was compelling. In the sixties and early seventies, the N.I.H. held six scientific conferences on the toxicity of cycad seeds. The ideas generated at the conferences generated experiments. Scientists around the world subjected birds, mice, rats, guinea pigs, cows, horses, pigs, and monkeys to cycad seeds, extracts, or flour. In Bombay, a neuropathologist, Darab K. Dastur, made pancakes using cycad starch and fed them to three rhesus monkeys for several months; he observed that one of the monkeys developed severe weakness and muscle wasting in one arm. In Japan, years earlier, chemists had discovered a cancer-causing substance in the cycad seed and named it "cycasin"; now other scientists showed that it was the most powerful natural carcinogen yet identified: when it was given to pregnant mice, tumors blossomed. In Bethesda, researchers gave doses of a cycasin derivative to pregnant rats and observed that the newborns had shrunken brains—an interesting but little-pursued observation. At King's College, London, the biochemists Arthur Bell and Peter Nunn discovered another cycad-seed toxin, beta-N-methylamino-L-alanine, or BMAA—an amino acid—and injected it into hatchling chicks. With an objectivity bordering on surrealism, they reported, "The birds tended to 'run backwards' (a surprising and often very rapid motion). Birds fell over and were unable to get up. . . . Some birds showed violent spasms during which they chirped continuously."

In the end, though, after all the attempts, no one was able to show that cycad material given to laboratory or farm animals led to a disorder resembling either ALS or parkinsonism-dementia, or that it specifically damaged the brain or the spinal ganglia involved in those disorders. And no test of cycad-seed chemicals had induced animal brains to form the telltale neurofibrillary tangles. Obvious though the cycad hypothesis seemed, it had been impossible to prove—or, for that matter, to refute.

Meanwhile, more bad news for the Kurland and Whiting theory came in from the field. In the mid-sixties, Yoshiro Yase, a neurologist at the Wakayama Medical College, in Japan, documented an outbreak of ALS and parkinsonism-dementia in the Kii Peninsula, southeast of Osaka; and although cycad trees grew in Japan and had been harvested in the past, Yase said that the patients in the Kii Peninsula had not eaten cycad-seed products. At around the same time, D. Carleton Gajdusek, a pediatrician and virologist at the N.I.H., in the course of investigating in New Guinea a neurological

disease known as kuru—work that later won him a share of the Nobel Prize in Physiology or Medicine—happened upon an ALS epidemic among the Auyu and Jakai groups, in the red-soiled coastal lowlands of Irian Jaya (formerly West New Guinea). Gajdusek, one of the most highly regarded and most outspoken medical scientists in America, said that cycad seeds had nothing to do with ALS in Irian Jaya.

With such discouraging reports from the lab and the field, most scientists concerned with the problem on Guam dismissed the cycad hypothesis. The theory, one scientist flatly asserted, was "unique but negative." It had been championed for so long against mounting criticism that some called it "Kurland's folly." At the last cycad conference, held in Chicago in 1972, it fell to Kurland to summarize where the hypothesis stood. He conceded only that "there is not sufficient evidence to support any action with regard to the use of cycad as a food on Guam since no toxic effect has been observed in feeding adult animals experimentally with a few samples of prepared cycad flour."

The lack of action still worries him. Once, in the sixties, he suggested to Guam's governor that an official warning be issued against the consumption of cycad seeds. The governor, Manuel F. Leon Guerrero, a proud man and only the second Chamorro to reach the office, wanted to know what sort of hard evidence Kurland had to show that the seeds actually caused *lytico* and *bodig*. *Fadang*, the Governor said, was a delicacy, a taste of home; it had got Guamanians through the war, and *he* wasn't about to announce that it brought on the scourge unless Kurland could prove it—and, of course, Kurland couldn't. "I personally like cycad," the Governor said, and, as Kurland remembers the conversation, they left it at that.

BY the time I went to Guam, in February of 1989, for a couple of weeks, I'd gathered that the epidemic was all but over, that the cycad hypothesis was being revived but that a local mineral imbalance had also been proposed as the cause of the disease, that no Guamanians really ate cycad seeds anymore, and that the island was basically a godforsaken rock where Air Force bombers stood behind chain-link fences like vultures dozing in the tropical sun. I'd formed just enough mistaken impressions to make the reality of the place interesting.

The largest and southernmost of the Mariana Islands, Guam is thirty-eight hundred miles west of Honolulu, fifteen hundred miles south of Tokyo, nine hundred miles north of the equator. Ever since Magellan "discovered" the island, in the early fifteen-hundreds, it has been important to people on their way someplace else. In Spanish times, it provisioned galleons on the Acapulco-to-Manila run. The United States grabbed it for a Pacific outpost in the Spanish-American War. For the Japanese Empire it was, briefly, a gateway to Micronesia. More recently, for the United States military, which owns a third of the island, it has been a dock and runway near Asia, and then some. During the Vietnam War, Guam lost a greater percentage of its men in action than any state did.

The island is shaped like a peanut: thirty miles from north to south, eight miles across at its widest, and four and a half at the waist. The northern and southern halves differ starkly in geology, community life, and patterns of neurological disease. The north is a coralline plateau, no more than a few hundred feet high—the lithified remains of reef deposits that aeons ago rose above the sea. At construction sites and roadcuts, the exposed rock looks as white as meringue. There are no permanent rivers or streams or ponds in the north; rainwater dribbles through the porous limestone, collecting in sea-level aquifers, and by the time it comes out of the tap it is high in calcium, and is about as hard as water can get. It clings to your skin and feels vaguely gritty.

Most of the island's hundred thousand residents and twenty-five thousand service personnel and dependents live in the north. Agaña, levelled in the war, now resembles an outlying section of San Diego: the echo of Spanish names, low-slung office buildings, the glare of sunlight on cars stuck in traffic, parking lots shimmering with heat. The big resort hotels are on Tumon Bay, a crescent beach northeast of Agaña which is trying hard to be Waikiki. The trade is primarily Japanese. A lot of the Japanese tourists I saw were young and retro-Americanized, sporting penny loafers and spit curls, and smoking Marlboros. Tokyo

businessmen find that it is cheaper to buy a condominium on Guam and fly there weekends for golf than to join a country club at home. In northern Guam, you see beefy Americans in the sing-to-the-video *karaoke* bars—one night a sunburned, crewcut guy gave a raucously patriotic interpretation of "Born Free"—and you see bashful Japanese women in the "Wild West" shooting galleries blowing away paper targets with Smith & Wesson .357s. Business booms. The Guam Hilton is the most heavily booked Hilton on earth.

The south, everyone likes to say, is the old Guam. As you drive across the slope that divides the northern plateau from the southern range, you are suddenly climbing back in time, into wind-scoured bush where carabao are tied up in the shade and banana bunches hang from rickety porches. Starting just below the island's narrow midsection, rivers appear, flowing over volcanic rock. The south is a terrain of weathered ridges and valleys. Mt. LamLam, a few miles outside Umatac, is thirteen hundred feet high. Where the steep hillsides have eroded, the clays are exposed in great blood-red patches, as if skinned. The red comes partly from oxidized compounds of aluminum, a metal that has figured in recent theories about the origins of the neurological disease on Guam.

The road into Umatac winds over mountains, yielding spectacular pull-over views of the forested ravines and coast. The Japanese tour buses pull over. The Sunday-driving servicemen pull over. A few times on my way to Umatac, I pulled over at the legendary spot where, years ago, Kurland and another scientist once stood beholding the distant bayside village, the steeple of its white church visible above the palms. One afternoon, the story goes, Kurland and his successor at the Research Center, an infectious-disease specialist named Jacob Brody, stood on this precipice: one scientist facing an opportunity, the other turning away from it after a decade of frustrated searching. Kurland said how disappointed he was not to have found the sure answer. Brody, the new man, taking in Umatac with a sweep of the arm, said: "The answer is down there. If only we're not too stupid to find it."

I was accompanied on my first trip to Umatac by John Steele, a neurologist. Steele—Canadian, tall, blond, blue-

eyed, very polite—came to Guam in 1983 after five years in the Marshall Islands. He told me that, in the grand neurological tradition of Drs. Parkinson, Alzheimer, and Huntington, there was a disorder bearing his name: the Steele-Richardson-Olszewski syndrome, also called progressive supranuclear palsy, which he and his fellow-nomenclatees described in Toronto in the early sixties. Actually, he said, the more Guam cases he saw, the more some of them looked like *his* disorder, an unusual form of parkinsonism of unknown origin distinguished by impaired eye movements. He took me to meet one of his patients.

We stopped on the edge of the village, at the home of a man I'll call Pedro, who was then in his fifties (he has since died) and had developed both parkinsonism-dementia and ALS some years before. Pedro lived in a metal-roofed wooden house a few yards from Umatac Bay. Chickens were strutting around under the palm trees. You could fish off the front steps. Steele and I, following Chamorro custom, removed our shoes at the door. The front room was large and tidy. A couch and soft chairs and a big console television were at one end, and the kitchen was at the other. Pedro's wife, wearing a floral housedress, offered us a glass of orange juice, then sat at the kitchen table wearily smoking a cigarette. Pedro was in a wheelchair in front of the television watching "Airport '77."

He was a handsome man with short black hair, a square jaw, fine white teeth, bloodshot eyes. He was wearing a white T-shirt and a diaper, and a white towel was draped across his bare legs. His feet were bare and statue still. He greeted me with a firm handshake and a smile. Steele asked how Pedro was feeling. His wife said, "He is not feeling too well." Steele asked Pedro how his grandchild was. At that, Pedro's eyes narrowed, his shoulders began slowly pumping, and he began to cry, though with no tears and no sound. Steele asked him if he was sad. He nodded yes. "Pedro doesn't feel well," his wife said.

Steele held open one of Pedro's eyelids with a thumb and forefinger and told him to watch and follow his other hand, which he slowly lifted toward the ceiling. "Come on, Pedro, look up. See if you can do it, Pedro—look up, look up." Pedro's eyes were stuck. Steele asked Pedro's wife if it would be O.K. to film this exam—a video recorder was in the car—because it showed that Pedro had an important problem with his eye movement.

"Pedro is not feeling well today," she said. "Maybe some other time."

As we were leaving, Steele pointed out three black-and-white photographs near the door, hanging above a glass display cabinet in which many lovely shells were arrayed. One photograph was of Pedro's sister-in-law as a young woman, looking quite robust. Another showed her years later, her gaunt face against a pillow, her strength and her flesh stolen by ALS. The third showed Pedro and his wife many years before: they stood arm in arm in bright sunlight, she very pretty, with curled hair and a cheerful dress, and Pedro looking sharp in pleated trousers.

Driving into the village, Steele explained that Pedro had the impaired blinking reflex that is typical of parkinsonism, and, on top of that, had an ocular disorder known as "gaze palsy," which is a sign of the Steele-Richardson-Olszewski syndrome. Someone with gaze palsy can't roll his eyes, and when he tilts his head back to try to look upward, that doesn't work, either, because his eyes remain level, as a doll's do. Steele said Pedro also had a disorder of the brain stem, associated with ALS and parkinsonism-dementia, which prompts spontaneous outbursts of crying or laughing. Sometimes, Steele said, tears will be pouring down a patient's face, and if you ask him what's wrong he says "Nothing."

UMATAC is on a narrow terrace that fronts a U-shaped bay. Its situation is precarious. Facing southwest, the village gets hammered by storms—again and again, for Guam is at the center of a typhoon belt. A few hundred yards back from the sea, the hills rise steeply. Fresh water blesses the village, which for centuries was little more than a rest stop. A former Spanish governor said of Umatac in 1870, "It ekes out a wretched existence with the help of the ships which have to go there for water. It lies at the foot of a mountain range, which leaves it no room for fields; nor can it be reached by any road."

Driving down the neat, shoreside main street, you see that this is, as the travel writers put it, "Guam's most picturesque village." Along the street are some small houses; a couple of

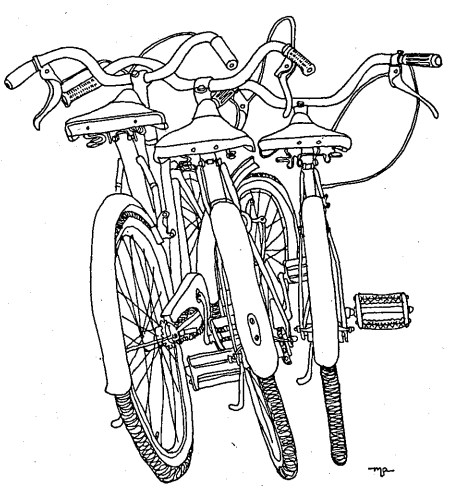
bodegas, where you can buy pickled slices of mango or Japanese radish out of big jars next to the cash register; a hamburger stand, whose proprietor, a middle-aged woman, told me, "We are tired of being guinea pigs, we don't want to be known as the *lytico* and *bodig* people"; a mission-style church, white with red trim; a typhoon-proofed elementary school; the village commissioner's windowless office, of whitewashed cinder block. Between the bay and the office is a small park, and in the shade of magnificent banyan trees are picnic tables, barbecue grills, and an obelisk with a plaque that reads "FERDINAND MAGELLAN LANDED NEAR THIS PLACE, MARCH 6, 1521."

The sixth of March, Discovery Day, is a bigger holiday than the Fourth of July, even though so many of the island's troubles began the moment the three ships that remained of Magellan's circumnavigational fleet appeared offshore. Magellan had been sailing for more than three months since rounding the Horn; many men had died of scurvy, and others, their gums bleeding with the effort, were now eating leather, rats, and sawdust. The ships were met by dugout canoes with sails of woven fronds, boats so fast that the Spaniards likened them to flying fish, carrying gargantuan, dark-skinned Chamorros, who had never seen ships, whites, or iron. Thrilled by the ships' iron fastenings, the *indios* tore some away, and they stole a skiff as well. Ashore a few days later, after provisioning the ships, Magellan's men, in retaliation, burned down forty or fifty huts and killed seven Chamorro men. Magellan then sailed for the Philippines, where he was killed. He had named the ocean Pacific, but called the island Isla de los Ladrones, or Island of Thieves. That name appeared on European maps for centuries. Guam has had a public-relations problem ever since.

Right across the street from Umatac's Magellan monument is the overgrown ruin of San Dionisio Church; it dates from the late seventeen-hundreds, about when Chamorros gave in to Catholicism. (During the seventeenth century, brutal wars against the Spanish, together with epidemics of unfamiliar infectious diseases, imported by missionaries and soldiers, nearly extinguished the Chamorro race, reducing the population from around forty thousand to three thousand. From then on, not surprisingly, the Chamorros were easily converted—a process that, ironically, the Spanish called *reducción*.) Behind the church ruins is an enormous old mango tree that figures in a legend about the origins of ALS and parkinsonism-dementia—a legend that shows how history, faith, and disease are entwined in the local philosophy.

Kurland heard it on one of his earliest trips to Umatac. "When we talked to the patients and their families, most of them wouldn't tell you anything," he recalled. "They would clam up when you wanted to go into the background of why the diseases were here. Then we heard the legend, and traced it back to around 1815. The story was that someone aroused the ire of the Umatac priest by repeatedly stealing mangoes from the tree in the churchyard. The priest kept warning him not to do it. Finally, the priest cursed the man and his family with this terrible disease. So, many of the people we spoke to believed that if you developed the disease you were in effect admitting that you were a descendant of a thief. It certainly didn't make history-taking any easier."

DEBBIE QUINATA is a sort of freelance liaison-activist for *lytico* and *bodig* patients. She lives on an oceanfront ranch on the south edge of Umatac. Her husband, Cory, banged together their plywood-and-two-by-four house after a fire wrecked their last place. It has no screens or glass in the windows, no front door. Geckos scurry up and down the walls, chirping. You especially notice the lizards' chirping, because snakes have killed all the songbirds on the island, leaving the forests spookily silent. Looking around the Quinatas' property, you conclude that the wilderness has won. But beneath the tangles of vines are fruit trees, and at a roadside stand the family sells papayas, coconuts, oranges, mangoes, star apples, and ice-cream bananas more luscious than the name implies.



Debbie worries that researchers are too cold with villagers and patients. When some doctors resurveyed Umatac for disease a while ago, she tried to lead what she calls a "revolt of the specimens." Her cousin Greg Quinata did revolt, and she wanted me to meet him. He seemed to be the village cynic. We sat on her porch. Greg, who was in his late forties, sported a sky-blue baseball hat emblazoned with a palm tree, a rainbow, and the slogan "Have a Chamorro Day!" Debbie served coffee and Twinkies.

"This is the *bodig* stuff right here, man," Greg said, reaching for a Twinkie. "My complaint is that the doctors don't come back and say, 'Your blood turns yellow when it goes to the lab,' or whatever," he went on. "They come and they bang on your joints, they look in your ears, they take your blood, your hair. All these different doctors who keep coming through here—they should compare notes. At one time, they blamed the disease on the water in the south. I don't know why they always blame the south."

When I asked about the cycad hypothesis, he said, "They jumped the conclusion. People have *lytico* in the States, they don't eat *fadang*, so what the hell? To blame the disease on that particular fruit, the *fadang*— Christ, the process you have to go through to get that stuff cured! Good grief, *everybody* ate that stuff. In my recollection, they use raw *fadang* material for open wounds. It works pretty good, too. I never used it, but I've seen it used like that. I still eat *fadang*. It's delicious."

Debbie, who belongs to a medical-ethics committee at the University of Guam, showed me a transcript of a scientific conference of many years ago, at which Kurland referred to Umatac as a "living laboratory" for the study of nervous-system diseases. The offending phrase was heavily underlined. She also showed Greg and me a joke on the great medical mystery. It was a jigsaw puzzle made from a large color photograph of Umatac and its bay. There was one piece missing. It said, across the top, "THE UMATAC PUZZLE" and, across the bottom, "Help

find the missing piece . . . just call Dr. Steele."

A MAN I'll call Juan lives with his family in a typhoon-proofed cinder-block home on a hill in Umatac. His wife has ALS. The day I stopped by, she was in a wheelchair, wearing a pretty cotton dress, and she greeted me with a huge, radiant smile. She speaks in a way that only Juan and her children comprehend. Afflicted now for two decades, she is among the longest-surviving ALS patients anywhere. She sat becalmed in the living room watching a game show while Juan and I sat on the shady concrete patio in the back yard. Sometimes a rooster squawked, feebly, as if he were about to conk out from the heat. Juan, in his mid-fifties, is wiry and, like a lot of Guamanian men, has a military aspect; he smokes cigarettes, has short hair, wears a white T-shirt around the house. On a chain around his neck hung a gold crucifix.

"I have to keep in mind that she's not going to get well," he said. "She's going on twenty years now with the disease. My youngest son is twenty-one. He was one year old when she came down with it. I remember when she was stricken. She was putting my son to bed one night, and she noticed there was a numbness in her hand. I massaged her hand with coconut oil and Vicks. A few days later, she said, 'The numbness is going up, in both arms now.' It just kept going like that. In four or five years, it was all over her body. She can still move her hands, but not her feet. I have to move her feet for her. When I got out of the service, I worked first for the senior citizens. Now I work at the Department of Mental Health, as a psychiatric technician. I know we don't have it that bad here. We have computers and cars and other things. I know there are places where children are poor and starving. So many people have brought my wife gifts, jewelry, and so forth. I told her, 'You have so many chains and necklaces, you look like Mr. T.' "

When I asked Juan about cycad seeds, he said, "During the war, my wife's family was strict about food, especially *fadang*. They said you have to soak the *fadang* for two weeks or more before eating it. Actually, they hardly ate *fadang*. I don't believe that *fadang* is the cause of *lytico* and *bodig*. A lot of people have been eating that, and they aren't sick. All these doctors come by here. The last time, they wanted to take blood and some hair from my wife. I asked, 'When are you going to tell me the results?' I still haven't heard from them. But I never really had problems with doctors. I say, 'Send them down.' I welcome anybody who comes to this house for information. I don't think of us as guinea pigs. If they find a cure, I'm happy not just for us but for the whole world."

IN the seventies and early eighties, after the downfall of the cycad hypothesis, the Guam research took some curious turns. The then dominant scientific camp, led by Gajdusek, who had assumed control of the Guam N.I.H. Research Center, argued that the disease was related to an unusual mineral imbalance—a chronic dietary deficiency of calcium coupled with an excess intake of aluminum. The theory was based partly on the observation that in the north, with its hard water and chalky, calcium-rich soils, the disease was much less common than in the red-earth south, where, the scientists suggested, Guamanians consumed too little calcium and too much aluminum. Furthermore, analyses of soil and water taken from the two other ALS clusters in the western Pacific—in the Kii Peninsula of Japan and on the lowland delta of Irian Jaya—turned up the same odd lack of calcium and abundance of aluminum.

According to the theory, a lifelong diet deficient in calcium would so starve the body of the essential mineral that its tissues, to compensate, would absorb from food, and then retain, far more than the usual quota of metals such as iron and aluminum; these metals, which may be toxic to cells, over the years would damage specific nerves of the brain and spinal cord, leading to ALS and parkinsonism-dementia. (The general notion that a grave mineral deficiency could devastate nerve function was not without precedent; for instance, Gajdusek and others had shown that a pregnant woman who has not consumed enough iodine risks giving birth to a cretin.) The size of the Guam epidemic, to be sure, had gradually diminished after its peak, in the early sixties, and the reason for the decline, the mineral camp argues, was that Guamanians had meanwhile adopted a more Americanized diet, presumably higher in calcium. And so Gajdusek and his colleagues, including

the neurologists Yoshiro Yase and Kwang-Ming Chen and the anthropologist Ralph M. Garruto, advocated the low-calcium, high-aluminum theory for years. They performed experiments in which they raised rabbits and primates on low-calcium, high-aluminum diets, and found that some of the animals had mildly damaged brains. And the researchers published papers in distinguished journals which convinced a number of medical scientists that the answer had at last been discovered. The good news also spread to the people of Guam. In 1984, the Guam legislature honored Chen, a friendly and devoted physician, for his two decades of caring for patients on Guam and for his "brilliant work" on the mineral theory. "It appears," the legislature happily proclaimed, "that the etiology of this most elusive disease . . . may have been found, and its prevention or treatment may be on the horizon."

On the horizon, though, the mineral theory ran into serious trouble. The most persuasive argument against it was simply that southern Guamanians do not and probably never did consume too little calcium. In one remarkably straightforward criticism, presented at a scientific meeting in 1988, Steele arranged for the assay of a few springs near Umatac, and found that the only low-calcium spring is the one that Gajdusek's team happened to test; the other local springs have normal if not unusually high calcium levels, indicating that Umatac's fresh water did not lack the mineral. Other researchers have shown that locally gathered foods have plenty of calcium. For instance, traditional Guamanians, who live close to the land (and have the island's highest rates of disease), tend to eat a great deal of local fish; these are small fish from coastal waters and are typically eaten whole, calcium-rich bones included. Kurland, summing up the confusion created by the mineral theory, characterized the work of the rival researchers by a word that for him must be the equivalent of "obscene": "sloppy." He said to me, "It always struck me as odd that they would propose a shortage of calcium on an island that is mostly coral." Expressing a not uncommon opinion of Gajdusek, Kurland added, "He's had a brilliant scientific career, but that doesn't mean he hasn't made some mistakes."

If the scientific controversies surrounding the Guam research were as remote from daily life as, say, the race to find some transient subatomic particle, the groping for answers wouldn't matter much to anyone besides the scientists. But the problem on Guam is a most human one. It's fair to assume that in the seventies and eighties some islanders accepted the idea that a mineral imbalance caused the local disease, and, thus reassured, gave little thought to the not disproved dangers of eating cycad-seed products. The false security that the calcium theory offered had another effect: it was one of the reasons that N.I.H. officials in Bethesda felt justified in closing the Guam Research Center, which they did in 1986.

Gajdusek believed that the facility had become an unnecessary drain on diminishing N.I.H. resources, especially in the light of certain reports claiming that the disease had all but disappeared from the island. "If anybody wants to work on Guam," he told me, "it's no problem to just go there, and one can get anything done with zero logistical support in forty-eight hours or two weeks or forty-eight days, or whatever it takes. My attitude is that all that can be scientifically done can be done without the lab."

Kurland, who had founded the center thirty years before, said that shutting it down was "a shame." Olivia Cruz, a Chamorro physician who has worked for the N.I.H. intermittently for twenty years, suggested that the lab's closing wasn't fair to the island's people, who had coöperated with the researchers for so long. "All of a sudden, the N.I.H. dropped it," she said. "And, really, they didn't ask the people of Guam. They didn't ask the doctors —you know, 'We are thinking of closing up the unit. What is your feeling?' Nothing. The N.I.H. just pulled out."

By that time (to take inventory), during three decades of doing research and providing free medical care on the island the N.I.H. had spent many millions of dollars; no one had found an indubitable explanation for the disease; ALS had been diagnosed in approximately four hundred and sixty people on Guam, and parkinsonism-dementia

in three hundred and forty. (True, a total of eight hundred cases in three decades isn't terribly impressive; two and a half times as many people are murdered in New York City in a year. But in any other population the size and age distribution of Guam's about twenty cases of ALS would occur, not four hundred and sixty.) Around the time that the N.I.H. lab finally shut its doors, Jacob Brody, formerly the lab's director, captured the sense of fruitless intellectual yearning when he wrote, in a largely scientific article, "What can be sadder than an epidemiologist investigating a disease that has no pattern?"

ALUMINUM is often associated with dementia, but whether or not it plays a role in the disease on Guam remains an open question; Daniel P. Perl, a neuropathologist at the Mt. Sinai School of Medicine, in Manhattan, hopes to answer it. Perl, in his late forties, has dark hair, a mustache sprinkled with gray, and a "Know what I mean?" delivery right out of Queens, where he was born. A professor of psychiatry and pathology, he is a leading authority on Alzheimer's disease. He became interested in Guam, he told me one afternoon in New York, after "the pots-and-pans thing."

It was a study by Perl and his colleagues in the late seventies that, perhaps more than anything else, prompted Americans to worry that eating food prepared in aluminum cookware might lead to Alzheimer's disease. Working at the University of Vermont, the scientists aimed an X-ray probe at brain tissue taken from some people who had died of Alzheimer's; the nerve cells had abnormally high levels of aluminum. The scientists couldn't explain the finding. They didn't say that aluminum *caused* the Alzheimer's—only that a lot of the metal was present in the diseased, tangle-filled nerve cells of the few specimens they tested.

Still, not long after they published their observations, in *Science*, in 1980, the aluminum scare was on, spread mainly by some apocalyptic news reports. Perl himself thinks that Americans should *not* worry about aluminum cookware. The aluminum that most of us encounter every day appears to pose no threat, he said. Aluminum is the third-most-abundant element on earth, and we're all exposed to it all the time, in soil, dust, food. Antacids such as Maalox contain aluminum hydroxides. Perl said of our considerable daily intake of garden-variety aluminum, "If you've got normal kidneys, you pee it right out." In spite of serious doubts about the role of aluminum in Alzheimer's, a nagging fear of aluminum products persists. See Perl quoted and pictured in *Newsweek;* he's got a pickled brain in his hands and a "Go figure" expression on his face. When the press calls him, he issues a standard line: "Take the bargain on aluminum cookware, and tell your congressman to get more money for Alzheimer's research."

Perl does believe that other aluminum compounds—other species of the metal—may have the potential to get into the brain and damage nerve cells. When aluminum chlorohydrate, an ingredient of antiperspirants, is in spray form, Perl said, it's a kind of aluminum that a person might want to avoid using, since studies in his lab reveal that the brain absorbs aluminum directly from the nasal passages. But the fact is that no one has identified the source of the aluminum that accumulates in the brains of Alzheimer's victims, so the risk involved in exposure to aluminum compounds is uncertain. "What do we really know about aluminum speciation?" Perl asks. "Damned little."

The place to settle the aluminum question, in Perl's view, is Guam. Several years ago, after hearing about the dementia and ALS on Guam, Perl X-ray-probed some diseased brain tissue from the island, which he had obtained from Gajdusek's group, and found that the aluminum in those brains was nearly off the scale. "Normally, the background level of aluminum in a neuron is from one to three parts per million," he told me. "In the diseased Guam brains we're getting from three hundred to six hundred parts per million. That's a remarkable figure. It's as if there were *chunks* of aluminum in those neurons. Our hypothesis is that the aluminum is playing an active role in the disease. We're not going to say what that role is. We don't know. Somewhere along the line, you're going to have to explain what all this aluminum is doing in these brains. That's going to have to be part of this equation. Yeah, you *can* say the aluminum is secondary, it's down the road from an already damaged brain, and all that. Yes, the evidence is circumstantial, but every time you see this abnormality—the tangles in Alzheimer's, the tangles on Guam—it's this one element, it's aluminum. It's not all elements. It's not other elements with it. It's aluminum. What the hell's going on? Why should it be that specific? Why should this one element go to this one place in the middle of the brain? I don't really know. The disease on Guam may be caused by a combination of things. It is certainly not simple exposure to aluminum in the soil—I could name fifty places all over the world that have aluminum-rich soil. The answer may be that it's two things on Guam that come together—cycad and aluminum, or some kind of thing—and that if you had cycad alone it wouldn't do it, if you had aluminum alone it wouldn't do it. Who knows?

THE WISDOM GRAVY

Goose down on the warm curve of a pail.
Hundreds of young rooks flying into the tree.
John: *I'd like to get good at it, at being married.*
Me: *Well, you can't do better than that.*
John: *She thinks I can do much better than talk about wanting!*
I said to her, I know I haven't done well
these last two years, these first few years,
but I want to get good at it. I'm good at being alone.

A.'s jealousy. B.'s jealousy. Of life.
All night I sucked at wisdom like a shooting tooth:
this morning life's a light garment, a garment of light,
like in our paradise. A. keeps the manger, B. keeps it, too, forever
and ever. This gravy is wide and deep, saltier and stranger.
I've carried it home to you under my white hat.

—JEAN VALENTINE

• •

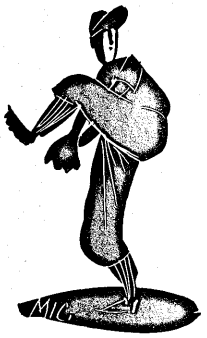
But maybe that's why the answer doesn't stare us in the face."

SOME recent studies suggest that the answer *has* been staring scientists in the face all along. A neurotoxicologist named Peter S. Spencer is now reviving the cycad hypothesis, much to Kurland's satisfaction. After looking at all the earlier data with a fresh eye and adding some findings of his own, Spencer has concluded that "the weight of evidence" supports the cycad seed as a cause of the disease on Guam. Like most scientists who have approached the epidemic, Spencer, who was reared and educated in England and is now a professor at the Oregon Health Sciences University, in Portland, sees Guam as a test case for a larger idea: he believes that natural substances in food are being overlooked in the search for the origins of neurodegenerative disorders.

Spencer was introduced to Kurland at a scientific meeting in Washington, D.C., a decade ago. I picture them talking in a hallway outside some fluorescent-lit conference room, an encounter of opposite styles: Kurland, the smaller man, a senior scientist, mocked for his folly, adhering to the cycad hypothesis, awaiting vindication but unable, as a clinician and population watcher, to test directly the question of causality; Spencer, then in his early thirties, six feet four, edgy, quick-talking, an experimentalist uniquely qualified to try out the cycad hypothesis in the lab. They showed more than a polite collegial interest in each other's work. Kurland had once predicted that "there might be an analogy" between ALS on Guam and lathyrism, a paralytic disorder endemic to parts of Ethiopia, Bangladesh, and India. Spencer had lately been studying lathyrism, in the lab and abroad, and to him the basic similarity of lathyrism and Guamanian ALS was obvious: lathyrism afflicts poor rural people who have consumed excessive amounts of a toxic seedstuff during periods of hardship and famine.

Doctors since Hippocrates have known that eating too much *Lathyrus sativus*, or grass pea, causes an irreversible paralysis. Not until a few years ago, however, following some earlier leads of Indian and British scientists, did Spencer and his co-workers actually demonstrate which compound in the grass pea destroyed nerves. The grass-

pea neurotoxin, they showed, is beta-N-oxalylamino-L-alanine, or BOAA, another amino acid. Amino acids are the building blocks of protein, the pearls on the string. But besides performing that structural function, certain amino acids modulate the nervous system, carrying chemical messages across the infinitesimal synapses between nerve cells. The brain is awash in its own stock of amino acids, which either calm or excite impulses. In addition, foods contain amino acids that seem able to affect brain chemistry, and thus one's mood, if not one's health: the tryptophan in milk makes it a good nightcap; the glutamate in MSG and the aspartate in NutraSweet are said to give some people headaches. Spencer's group, in its studies of the BOAA from grass pea, showed that this amino acid stimulated nerves so potently that they literally burned themselves out. When his group fed macaque monkeys large amounts of the grass-pea neurotoxin, or of grass pea itself, the animals showed the initial signs of lathyrism: they became weak and stiff-legged. Significantly, though, they did not develop full-blown paralysis, regardless of how much of the grass pea or its neurotoxin they received. "It is a bitch to produce lathyrism in animals," Spencer said. "You can't produce it in rats or mice at all. Scientists in India and elsewhere have been trying to do that for a long time, and they've failed. I don't know why. In our experiments on monkeys we were able to produce only the very early, reversible stage of the disease. So it's a real problem, producing animal models of disease brought on by excitatory amino acids."



Spencer's studies of the grass pea laid the foundation for his work on the BMAA in cycad seeds, which has a chemical structure (and thus a name) similar to that of the grass-pea neurotoxin. It was BMAA that the biochemists at King's College discovered in the sixties, injected in chicks with such bizarre effect, and then gave up on. Spencer contacted Peter Nunn in London, and the two of them picked it up. When they added pure BMAA to a culture of mouse-brain tissue—the fetal brains had been removed, sectioned, and kept in a warm, serumlike buffer for a few weeks while the nerves kept developing—the BMAA prompted weak but undeniable excitatory responses.

In 1986, while Spencer was the director of the Institute of Neurotoxicology at the Albert Einstein College of Medicine, he led a team of seven scientists in a study that was published in *Science*, which gave the story big play by putting it on the cover. In the study the scientists tube-fed large doses of BMAA to thirteen macaques every day for as much as thirteen weeks. The animals were videotaped. Wrinkled hands and a curved posture and seemingly grizzled faces make macaques, like primates generally, look old even when they're young; these animals appeared to age before one's eyes. After a few weeks of exposure to BMAA, some of them became weak. The muscles of their arms lost bulk. They couldn't pick up small objects anymore. These initial symptoms, Spencer has said, were not unlike those of someone in the early stages of ALS. Over the three months, some of the animals became apathetic, listless. They stopped grooming themselves. Their hands trembled. Their faces slackened. They stared. They stooped and shuffled. Watching the videotapes, even those scientists who disagreed with Spencer were struck by how the animals now seemed to have a mild case of parkinsonism.

Two of the afflicted monkeys received the drug L-dopa, a treatment for Parkinson's; within thirty minutes, the animals appeared more alert and expressive, and had regained some use of their hands. Several of the experimental animals were anesthetized and put to death and quickly autopsied. In their brains were signs of degenerative changes, such as swelling and discoloration of some neurons. The degeneration was particularly evident in the motor cortex, where movements are initiated, and where in ALS victims the damage is usually extensive. There was also some damage to the spinal cord, and even to the substantia nigra, the target of Parkinson's disease.

But this experiment does not "prove" the hypothesis, as Spencer points out. The brains of the experimental animals that were fed BMAA did not have in detail the advanced

pathology of ALS or parkinsonism-dementia; there were no neurofibrillary tangles in their neurons, for one thing. Nor were the sick animals' symptoms precisely those of human beings with those diseases. Spencer, building in a few escape hatches, says only that the experimental animals exhibited "some features" that were "reminiscent" of the disease on Guam.

A macaque confined to a cage in a lab in New York and fed BMAA is, as analogies go, fairly remote from a Chamorro boy hiding in the forest who eats *fadang* and develops ALS a few years later, but that is the closest anyone has come to getting the disease on Guam to occur in a laboratory setting. Spencer wonders how close science will ever come to reducing the disease to barren fundamentals, given its close association with hard times. Malnourishment, he suggests, enhances the susceptibility of humans to cycad-seed toxins. "But that idea is going to be impossible to test," he said. "We cannot in good conscience raise experimental animals in such a way as to starve them."

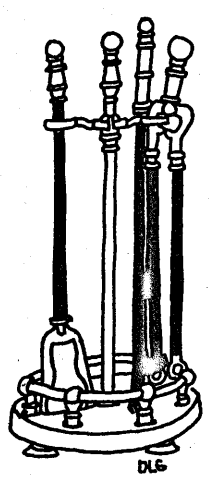
How a single toxin might give rise to such a variety of symptoms and pathology as is expressed in ALS and parkinsonism-dementia is a matter of speculation. Spencer suggests that a person's age and metabolism and the amount of toxin consumed influence the form that the disease ultimately takes. A poorly fed adolescent who receives a high dose of cycad-seed toxin, or whose body handles the toxin poorly, might be destined for ALS in months or years. A middle-aged person who has received somewhat less toxin might end up with parkinsonism-dementia in years or decades. Even less toxin in an older person might eventually lead to dementia minus the parkinsonism—to something resembling Alzheimer's disease.

The disease on Guam can take a great deal of time to develop, and that delay confounds researchers. "Cases of ALS have been known to occur among Guamanians as long as 13 and possibly 34 years after leaving Guam," Dwayne M. Reed, an epidemiologist working at the Research Center in the sixties and seventies, and Jacob Brody wrote in 1975 in the *American Journal of Epidemiology*. "Exposure to something in the traditional way of life, involving either a cumulative effect, or more likely, a long latent period" could account

for the delay, they continued. On Guam, then, years and even decades may intervene between action and reaction. It might be called a non-Newtonian disease, crying out for an idea as counterintuitive as the quantum. And so Spencer has introduced the idea of the slow toxin.

The amino acid BMAA, he says, may be a slow toxin, even though in the lab setting at high doses it seems to work acutely. BMAA itself is probably not the whole story, Spencer adds. He is even more concerned now about cycasin, the potent cycad-seed chemical that seems to be doubly dangerous, capable of triggering both tumors in rodents and neuromuscular disease in goats. And cycasin, unlike BMAA, is abundant in a cycad seed, making up from two to four per cent of its weight. If the culpable agent is ingested in a meal of *fadang* or absorbed into the bloodstream from a topical medicine made of unprocessed cycad seeds, Spencer says, it may damage nerve cells in a manner that doesn't show up for quite a while.

Assuming that such a thing as a slow toxin exists, there are a couple of ways it might work. It might kill off a small fraction of the neurons in the substantia nigra, say, but not give rise to parkinsonism until neighboring neurons have died of old age. (Starting in our mid-forties, about ten per cent of our brain neurons die off per decade.) Only with aging, then, would the loss of the killed-off neurons be felt. (In forwarding this concept, Spencer elaborates on the work of the neurologists William Langston and Donald Calne.) If one thinks of a dose of neurotoxin as a blinding punch, the toxin-plus-time theory is analogous to what happens to some boxers long after they step out of the ring: traumatized young, they don't tremble and falter with parkinsonism until the years, too, have exacted a price.



Or a slow toxin, Spencer says, may work like a carcinogen, wreaking cellular havoc by fouling up the genetic material, DNA. The odd thing about mature nerve cells is that (except for olfactory-nerve cells, which regenerate one by one every month or so) they don't just keep dividing, like other cells. Not long after birth, the majority of the nerve cells stop dividing. Since they don't divide, adult nerve cells are incapable of growing wildly into tumors. In Spencer's view, a nerve cell exposed to a tumor-promoting chemical such as cycasin might react in some unfortunate way other than by transforming into a tumor. Perhaps its DNA processing is altered, so that the cell slowly degenerates and dies. Thus, Spencer says, cycasin may be a "neurotoxin masquerading as a carcinogen"—a slow toxin.

"Maybe there is a link between cancer and neurological disease which no one has ever thought about before," he told me. "No one has asked, 'What happens to a nondividing nerve cell exposed to a carcinogen? What the hell does it do?' Maybe it starts making foreign proteins, or something. So we're looking for a mechanism of that sort, something that might take years and years for a nerve cell to express. There's got to be something like that. That's where we're going."

Spencer will travel some distance to make a point. After he did the BMAA study, he felt that it was crucial to determine whether cycad seeds played a role in the clusters of ALS and parkinsonism-dementia outside Guam. In the fall of 1987, he went to Irian Jaya. He hired a boat, two local health workers, a guide, and a guard with a machine gun, and, with a colleague, Valerie Palmer, who is the head of the Third World Medical Research Foundation, he steamed up the Ia River, retracing some of Gajdusek's movements. In Auyu villages, Spencer and Palmer interviewed two men with ALS and three with parkinsonism. They showed them photographs and seeds of cycad trees, and asked, "Any of these around?" They were led some distance from the river ("No wonder Gajdusek missed it," Spencer said), to a small stand of cycads. It was the local pharmacy. An Auyu man explained that the seeds were used to treat warts, open sores, abrasions. A poultice was made by mixing fresh crushed pith of the seeds with their own milky juice, he said, and applying the sodden material to the damaged skin, with a leaf as a bandage. The poultice would be freshened daily over days or weeks. They interviewed a twenty-

nine-year-old man who was in the early stages of ALS. When he was fifteen, the man said, he had used fresh poultices for a month to treat a sore on one ankle. He showed Spencer the scar. The man's mother had taught him the remedy; she, too, had been paralyzed.

"It was an incredible revelation, a fantastic moment," Spencer said.

I said that it must have been exciting to stumble on such a thing.

"But it wasn't stumbling—don't you see?"

From Irian Jaya, he went, with a few colleagues, to Japan, where he sought another link between ALS and cycads. He recounted his "witch-doctor bit" for me one afternoon in his lab at Einstein, while we were standing next to an enormous top-opening deep freeze. In a village on the Kii Peninsula, he had visited the shop of a *kitoshi*, or dispenser of traditional medicine. "She was about ninety-nine years old," he recalled. "Her son was there, too. He was about seventy-five. She said, 'Come on, come on, what's your problem?' " Spencer, towering, with a British accent, did a comical imitation of the wizened *kitoshi*. "I said I had very bad diarrhea, and the translator told her. She said, 'No problem a-tall, I'll pray for you.' She walked me up to the quote-unquote altar. She banged on a drum, she muttered some things. She patted me on the shoulder with a piece of wood. She waved a knife around and muttered some more. Then she issued my prescriptions. The first was for some herbal. The second was for another herbal." He opened the freezer, and, as he reached in, a cloud of condensed air rose up and around him, a sorcerer over a steaming brew. "The third was for cycads." He handed over a plastic bag that had a Japanese label and contained what looked like peeled chestnuts. "I went around the corner to the equivalent of a drugstore to fill the prescription. I asked the man there how many I should take. He said to take as many as I liked."

On another trip to the Kii Peninsula, Spencer went to Iseji, the village that was the epicenter of the disease, where he saw in yards and public gardens a great many *sotetsu*, or *Cycas revoluta* trees, heavy with toxic seeds. He interviewed a woman whose daughter had died some years before, at twenty-five, of ALS. He and his co-expeditionists

summarized the case in a letter to the British journal *The Lancet:*

> Her mother told how the child every year from the age of 1 to 12 had received a basket of young *sotetsu* seeds collected by her grandmother from cycad trees. They were used as marbles, to form necklaces, or fashioned into whistles for use by the young child. The mother agreed that repeated oral contact with the neurotoxic pulp of the seed probably took place during the first years of her child's life. The child walked before the age of 1 and had no unusual childhood illnesses. She developed into a healthy teenager and did well in long-distance running races until, at the age of 18, she began to complain of backache and spasm of the calf muscles. At age 20, she was said to have leg weakness . . . and ALS was diagnosed. The disease appears to be less common in Iseji today, and children no longer play with *sotetsu* seed.

As far as Spencer was concerned, there was now enough evidence to sound a warning on Guam. He held a press conference on the island in the spring of 1988, at which he urged Guamanians not to eat cycad-derived foods, and called for an outright ban on medicines that made use of fresh unprocessed cycad seeds. Remarkably, not since Governor de la Corte's 1856 decree had anyone officially advised Guamanians to avoid cycad seeds.

But his public-health warning, like de la Corte's, was not all that effective. His critics accused him of showboating. Kurland, who has mixed feelings about having once restrained himself from making a similar public-health recommendation, who credits Spencer with reviving scientific interest in Guam, and who remains convinced that cycad seeds are at the root of the epidemic, nonetheless believes, in his conservative way, that Spencer went too far—overstepped the evidence. An editorial in Guam's paper, the *Pacific Daily News*, shared Spencer's concern but seemed annoyed by his tone: "We're not sure a formal ban is necessary. The Chamorro people are not stupid. They are now well aware of the link between the fadang and lytico-bodig. We're certain that any local people who can read or hear have now been informed on the connection."

ON Guam, the reluctance to follow Spencer's recommendation runs deep, as I gathered during a conversation with Governor Joseph Ada. The Governor, a cheerful man with aquiline good looks like Danny Thomas's, has a gift for irony. In his office, in the pride of place behind his desk, hangs a large, sunny painting that depicts a friendly seaside exchange between Magellan's beplumed landing party and several naked Chamorros. Yet one of the Governor's first official acts, he told me, was to thank the Philippine government for the favor its people did Guam in killing Magellan. The Governor's policy toward *fadang* is similarly ambiguous. His first reaction to Spencer's recommendations was "There goes my favorite food!" Officially, he said, he was anti-*fadang*. But then he said, smiling, that he continues to enjoy it. When he goes to fiestas, Chamorro women stack *fadang* tortillas on his plate, and he doesn't want to disappoint them. "If I see it, I eat it," he said. He told me that he was personally not much concerned about safety, because the people who cook for him know how to detoxify cycad seeds. I lost some confidence in his biomedical judgment when, as he graciously led me out of his office, he handed me, as a memento of my visit, a cigarette lighter with his name on it.

Steele was another authority sending mixed *fadang* signals. For a while, he collaborated eagerly with Spencer, championing the cycad theory. He even publicized the cases of a Saipanese mother and son—she had parkinsonism and he had ALS—who had eaten *fadang* only once, years before they were stricken; they remembered the occasion because the mother had never prepared *fadang*, and it had tasted horrible. Steele had concluded from this case study that it was not impossible for a person to develop ALS a long time after one meal of improperly prepared *fadang*. (On the basis of that case study, I decided that I wasn't going to try *fadang* even once.)

Then, a year after Spencer's announcement, Steele declared a change of heart. The occasion was a symposium of the Guam Lytico and Bodig Association, which consists of patients, their families, doctors, and volunteers. The symposium took place during my stay on Guam, and I was sitting next to Cynthia J. Torres, a founder of the association. Addressing about a hundred people in a banquet room of the Guam Hilton, Steele said, "A number of people have been unable to reproduce Spencer's animal studies," and, he went on to say, "We doubt that it's the

BMAA of the cycad seeds accounting for this, but there could be yet another toxin in the cycad seed that we've not identified yet."

Mrs. Torres turned to me, and, summing up the current Guamanian view of medical authority, said to me in a stage whisper, "*Scientists!*"

During a question-and-answer period, a gray-haired, bespectacled woman wearing a blue Hawaiian shirt went to the front of the room, took the microphone, spoke in Chamorro, and had most of the audience in stitches. The woman, Mrs. Torres told me, was saying that scientists always blame the disease on *fadang* because people ate *fadang* during and right after the war. Her theory was a little different. She said that the strange thing that Chamorros first ate back then, an equally likely cause of disease, was Spam. She called for more research.

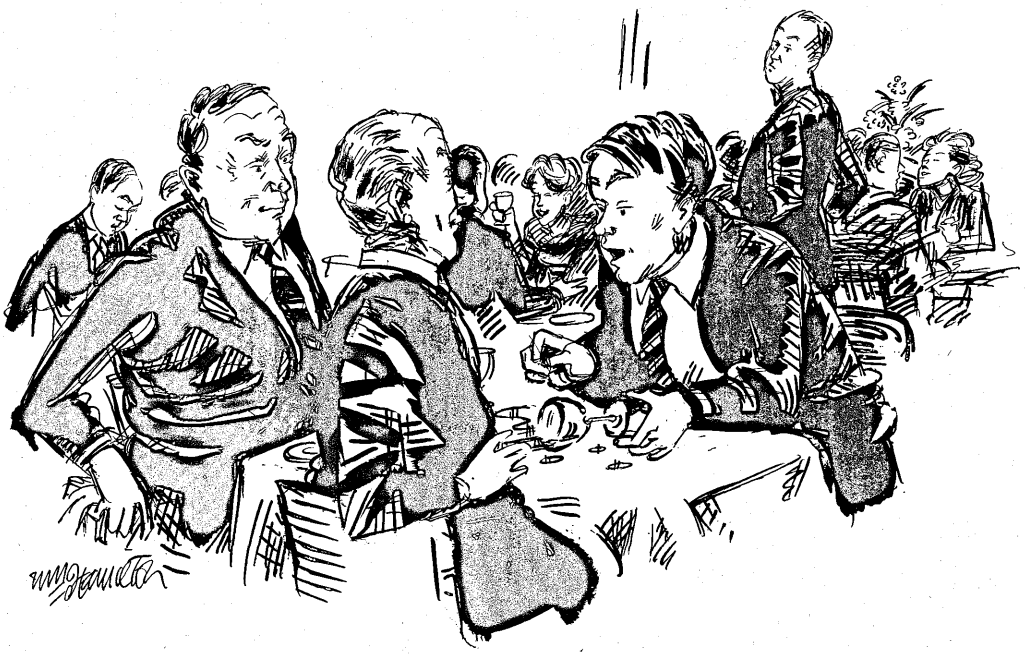
Mrs. Torres and I caught up with the woman and a friend of hers after the symposium, on their way out the door. The woman was Rosario Santos, who is in her mid-seventies and is the mother of twelve. She stood broomstick straight, with her arms folded across her chest. She looked exceptionally fit. Her English is Chamorro-accented—high-pitched, singsongy, buoyant. I asked her if she still ate *fadang*.

"Myself, I'm not scared. I know how to do it," she replied.

Mrs. Santos's companion said, "I don't think that *fadang* is causing the *bodig*. My parents are raised up on *fadang*, my grandfather, my father. Up to these days, I am still eating the *fadang*."

Mrs. Santos said, "The younger generation, they don't want *fadang*. A friend said to me, 'If the answer is *fadang*, it is a disgrace to my people.' I said, 'Carry your head high. It is not our fault. The disease is with us, and the *fadang* is not the only reason.' " She made the sign of the Cross, and said goodbye.

Later on, Steele told me he had lost faith in the latest cycad studies mainly because he thought Spencer wasn't acknowledging the fact that raw cycad seeds contain very little BMAA, and processed *fadang* has practically none.



"Oh, sorry. It wouldn't have happened if I weren't with persons larger than life."

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Whatever Steele's reasons, his public reversal that day was curious. Aspects of the cycad hypothesis are eminently criticizable. Nevertheless, even though it's remotely possible that cycad seeds play no role in the disease, even though someone might prepare a toxin-free batch of *fadang*, even though not everyone who eats *fadang* comes down with the disease, and even though some people who have come down with the disease say they have never eaten *fadang*, clearly the prudent thing is to avoid the stuff. That some Guamanians should cherish *fadang* as an expression of their native culture is understandable. Still, the failure of researchers to state unambiguously the dangers of doing so seems scandalous. If Perrier pulls every one of its bottles off the shelf because of a trace of benzene found in some samples—that is, because of the *perception* of a *possible* threat—how odd that doctors should hesitate to discourage Guamanians from using as a food and medicine something that, as was said more than a century ago, "cannot fail to do them injury."

EARLY one night, I attended a village meeting in Umatac. It was held outdoors, on a concrete apron adjacent to the commissioner's office. The air felt warm and humid. About two dozen of us sat in folding chairs or on a set of metal bleachers. A young girl passed around paper cups of corn soup. Albert Topasna, then the Commissioner of Umatac (he is now the mayor), presided at a standup microphone. With perfect ceremony and courtesy, he introduced the speakers and fielded questions. The meeting went on for three hours. A policeman talked for a long time about teenage rowdiness, underage moped drivers, and speeding by customized-low-rider pickup trucks. A government official spoke about land claims—an extremely complicated and very important subject. The Commissioner was reassuring, and he always addressed the audience as "my people." A few times he said, "Don't worry, be happy."

Topasna—everyone calls him Chief—had been the Commissioner of Umatac for most of the previous twenty years. As a matter of policy, he never drinks or plays cards in public, and never goes to illegal cockfights. "If people are drinking and I am drinking, who is going to take care of them?" he explained. One morning, at a village gathering outside his office, he sat enthroned on a folding chair, and when some young girls arrived they first went over and kissed his hand. "This is the closest community on the island," he told me. "I know everybody's problems

from top to bottom. We are all very close."

Topasna has broad shoulders, a royal midsection, deep-set eyes, and a flattop haircut. He is partial to Hawaiian shirts, worn with a triangle of undershirt showing at the neck. He is widely acknowledged to be the island's greatest diver and fisherman. He takes to the water many Thursday nights, having been sent out by his wife for Friday's supper. He speaks English as melodically as he speaks Chamorro, his first language. His voice is bassoonlike, deep and reedy—so beautiful that I asked him to recite for me some of the village song. He said:

In our dear old southern home,
Situated right by the sea,
Where the brave Magellan landed
When he crossed the silent sea,
In our dear old Umatac by the sea.

In our dear old southern home,
Situated right by the sea,
Where the oldest Spanish forts
And the capital used to be,
In our dear old Umatac by the sea.

Our conversations took on a pattern. I would ask about village life in general and then uneasily get around to the subject of the disease, the doctors, and *fadang*. My last day on the island, I found Topasna in his office. It was early morning. Dew moistened the grass; plumeria sweetened the air. We sat in a windowless room, the air-conditioner thrumming away. We talked about fishing. For a few days each spring, snappers chase schools of mackerel into Umatac Bay. With Topasna leading the catch, dozens of people wade into the water and drag enormous nets toward the shore—"scooping the mackerel," he says, with a gleeful look. Once, they hauled in twenty-six tons in three days. We talked about the latest Magellan controversy. Two University of Guam professors have rereckoned Magellan's landing, and concluded that it wasn't in Umatac but farther north, maybe in Tumon Bay. "Can the historians prove he didn't land here?" Topasna asked. "What is wrong with them? Are they young? Why don't they come down here and get the input? 'I'm sorry, Mr. Professor. My golly, sir, I think you are the one who is causing the trouble. Now that you're at the University of Guam, you're going to turn everything around. Mr. Professor, sir, you're telling us we're celebrating nothing?' " He then hinted that if the scholars did show their faces in Umatac they might run into some rigorous peer review.

Like the Governor, Topasna is known for his appetite for *fadang*. "I ate it ever since I was born," he said. "I'm still eating it. I love it. It is all over the jungle. You barbecue the fish and eat them with the *fadang* tortillas." He pretended to roll a fish in a tortilla, and smiled broadly at the thought of this delight. Of the disease he said, "It is really bad. Not only here but in the other villages, too. We have to make the people understand that the reason the doctors keep coming back is that they are not through yet. It is a problem that reaches my heart. When I speak to groups about it, and I speak in Chamorro, I look out into the crowd and everybody is crying."

I asked him if his family had been touched by the disease.

He shifted in his chair, leaned forward, folded his big arms on his desk. "For the *lytico* and *bodig*, not that I know on my mother's side. I am too young when my father's brother died, but I think he was part of that. I know that some of my father's side had it. I don't know too much about my father. I was only eight years old when he was killed by the Japanese. So I don't know whether he was going to have *lytico* and *bodig*. But I know that some of my uncles had this. I'm not denying anything. There is only one who is giving out this disease, and that's the One up there."

I turned the tape recorder off, thinking he had finished. He kept talking, and now his eyes grew teary. "I don't know," he said. "Maybe I will get it, too. Maybe someday you'll come back and I'll be sitting here with my head down." He rested his chin on his chest. "I don't know. My children, I don't know if they will get it. It is up to—" He looked skyward. "My godfather was a strong man who was six feet tall. He got the disease, *bodig* or whatever. When he died, he was like this"—and Topasna measured out a yard.

THE Guam problem stays with scientists long after they have left the island. "There's like a club of people hooked on this thing," Daniel Perl said a while ago, "and everybody's waiting to see how it turns out." Dwayne M. Reed sees the plusses of the cycad hypothesis but still considers the question open; when I telephoned him at his office in Honolulu and mentioned

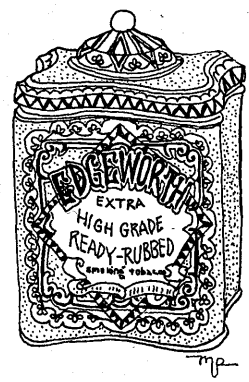
the word "Guam," he said, "*Argh!* The bane of my existence! I've been racking my brain on that for thirty years! Over and over and over! All these wonderful clues—the answer is there somewhere." D. Carleton Gajdusek, who says that "the cycad boys" don't have the answer this time, either, and supports the mineral-imbalance theory but admits that it's not a sure thing, said, "We jumped on Guam—we had to—and we've learned a tremendous amount, but it didn't yield the answers we were looking for. ALS on Guam has decreased to a fiftieth or a hundredth of what it was. The phenomenon eluded us before we could figure it out. It's unfortunate—not from the Guamanians' point of view, of course, but from ours." Marjorie Grant Whiting has been waiting, like a captain's wife pacing a widow's walk, for substantiation of the idea she launched thirty-five years ago—the cycad hypothesis. She lives in Honolulu now, and when I visited her there one day she was wearing a floral muumuu, Clark Kent glasses, a necklace made from the eggshell of a Kalahari ostrich, and Birkenstock sandals. She walked with a cane, her hair was white, and she roared with laughter every time she detected one of several attempts I made to learn her age. In a corner of a friend's disused lab at the University of Hawaii she had an office that consisted of a metal desk piled high with papers next to a chemical-fume hood filled with papers. Her book "Neurotoxicity of Cycads: An Annotated Bibliography for the Years 1829-1989," a collecting labor of decades, was published in April of this year. "I'd like to see this thing put to bed in my lifetime," she said. "We've certainly taken a firm enough stand on it."

Shortly after I got back from Guam, I met Spencer for brunch at a restaurant near LaGuardia Airport (he was between flights). In a double-breasted navy blazer and gray slacks, he looked the part of the British voyager-scientist. When we joined the buffet line, he helped himself to eggs Benedict and beef sausage; impressed by this toxicologist's dietary abandon, I did the same. He said no to champagne and coffee. I mentioned that I'd spoken with many Guamanians who not only didn't believe in the cycad theory but blithely, even ecstatically, ate *fadang*.

He said, "There are some suggestions of cows' becoming addicted to

cycads, of course. And some of our studies suggested that BMAA, and maybe other agents in the cycad kernel, interact with virtually the same receptor sites on neurons that PCP does—and PCP, as you know, is highly addictive."

I told him that some of the Guamanians I'd spoken with—like Greg Quinata, the Umatac cynic—said they found the cycad theory hard to believe, because not everyone who had eaten *fadang* got ALS or parkinsonism-dementia.



"Well," Spencer said, with a here-we-go-again roll of his eyes, "that's rather how people used to think about smoking and lung cancer, isn't it? And it's the way people think about lathyrism: 'How can this food that keeps me alive be poisonous?'" Concerning Greg's other comment—that most people in the world who get ALS have never touched a cycad—Spencer said something like "Yes, well, that's the great task ahead, isn't it? To determine whether dietary or occupational or environmental chemicals play a role in triggering some form of ALS."

As a result of Spencer's work on the excitatory amino acid BMAA, researchers in several labs have begun work on the substance, and others are screening other plants for similar neurotoxins that may function the way the ancient cycad's poisons seem to do—as a defense, as an explicit chemical stop signal. "There's no reason to believe that plants have evolved for our benefit," Spencer said. "We're at a very primitive level of understanding what kinds of foods are good for us and bad for us. Certainly the general notion that what's 'natural' is good and what's 'synthetic' is bad is totally without rational scientific basis. I think that additional factors have to be considered in the origination of the disease on Guam, such as other factors in the environment there, and other compounds in the cycad seed besides BMAA. We might think of the cycad as a chemical factory producing a large number of agents that have neurotoxic potential. But I'm very, very strongly convinced that the cycad seed will prove to be an important trigger of the disease."

Science is by nature and virtue unpredictable, so anything could happen, but it is not obvious how scientists are going to crack this code, how they'll squeeze the broad context of the Guam disease into a test tube, given that its origins seem to be tied in with historical and cultural as well as physical forces: with centuries of oppression, with war, with crop-destroying winds, with family likes and dislikes, with ethnic pride and even resentment. Guamanian ALS and parkinsonism-dementia have an irreducible quality, like an unknown that is combusted in the crucible and leaves a mysterious ash. The brain, longing to know, has never had much luck comprehending what it endures.

Kurland won't quit, and speaks now of Guam with the urgency of a man given a last shot. Nearly forty years after he first went to the island, no longer a young researcher with a reputation to make but a white-haired veteran with every license to putter around a vacation trailer he keeps on the banks of the Mississippi River, he'll be going back to Guam occasionally. Recently, the National Institute on Aging approved a five-million-dollar grant that Kurland had applied for along with Perl, with a proposal titled "Epidemiology of Neurodegenerative Disorders in Micronesia." The money essentially reëstablishes a research station on Guam. Kurland will run the project, as he ran the first one, but this time mostly from Rochester. In New York, Perl will seek tangles and senile plaques and aluminum in brain tissue sent from the island by air courier. On Guam, Steele, among others, will help keep track of patients, and David Williams, who studied with Kurland, will head the village research—doing what his teacher calls shoe-leather epidemiology.

Contrary to some reports, the epidemic on Guam has not ended but only shifted, Kurland told me on the phone the other day. The most recent survey of Umatac and another village (the survey results were analyzed after my trip to Guam) shows that ALS has fallen somewhat but that parkinsonism-dementia may well be as common as ever and—what is most significant—that an extraordinary number of those surveyed have symptoms of dementia without the parkinsonism. Perl says the

disease closely resembles Alzheimer's.

Kurland, ever restrained, doesn't leap to any conclusion. "We're calling it Marianas dementia, because we don't know if it's Alzheimer's or not," he said. "We haven't done enough pathology yet. But we are seeing in those southern villages a rate of dementia that is generally four times as high as what we see here in Rochester. About forty per cent of the people over seventy that we surveyed were demented. We also saw signs of dementia in ten per cent of those between fifty and sixty. These are unprecedented findings. The epidemic seems to be changing course. It appears as though some people who survived the period in their lives when they were most vulnerable to ALS or parkinsonism-dementia are developing dementia alone. It could be a dose-response thing." He was referring to Spencer's theory that people who have been exposed to small amounts of cycad-seed toxins over a long period are perhaps prone to dementia alone, as opposed to ALS or parkinsonism-dementia. "The cause has not been established, although I personally still think that the cycad seed is the most likely explanation," Kurland added.

I asked if he believed that the dementia there was linked to the continued eating or medicinal use of cycad-seed products.

He said he could not rule that out. "There is the aluminum question, but we don't know whether that's a cause of the disease or an effect," he went on. "Maybe it's a combination of things. I favor the cycad hypothesis, but I don't care whether it's aluminum or cycad, as long as we get the answer. Understand, if a toxin were found to produce features of three neurodegenerative diseases that we've always regarded as distinct—ALS, parkinsonism, and dementia—it would have tremendous repercussions for neurology. My own view is that on Guam, anyway, these are all caused by the same thing." He paused. "I think it's an emergency. What is happening on Guam is very strange." —TERENCE MONMANEY

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7 PM (2) (8) (9) (15) THE CIVIL WAR (CC)—Documentary; 2 hrs., 30 min. 1865 . . . Part 8 and the conclusion: Sherman marches to the sea; Richmond falls; Grant surrenders to Lee at Appomattox. [Last show of the series.]—*TV Guide.*

Just as well.