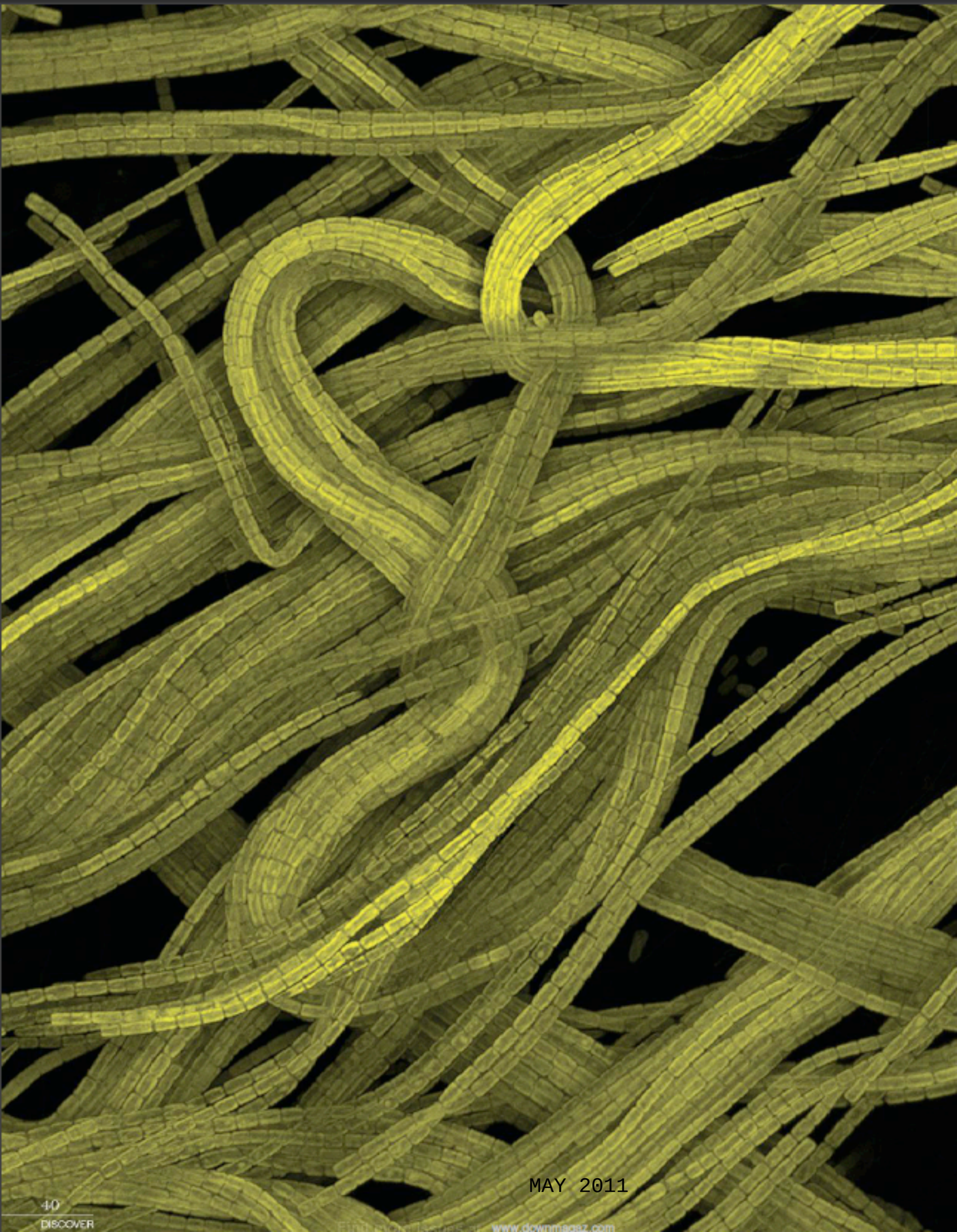

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THERE'S SOMETHING IN THE WATER

a trail of clues linking seafood to **ALS**, **ALZHEIMER'S**, and **PARKINSON'S** disease.

The toxin is called **BMAA**. And it's in the

by KATHLEEN McAULIFFE

ELIJAH

STOMMEL, A NEUROLOGIST AT THE DARTMOUTH-HITCHCOCK MEDICAL CENTER in New Hampshire, often has to deliver bad news to his patients, but there is one diagnosis he particularly dreads. Amyotrophic lateral sclerosis, or ALS, kills motor neurons in the brain and spinal cord, progressively paralyzing the body until even swallowing and breathing become impossible. The cause of ALS is unknown. Though of little solace to the afflicted, Stommel used to offer one comforting fact: ALS was rare, randomly striking just two of 100,000 people a year. ¶ Then, a couple of years ago, in an effort to gain more insight into the disease, Stommel enlisted students to punch the street addresses of about 200 of his ALS patients into Google Earth. The distribution of cases that emerged on the computer-generated map of New England shocked him. In numbers far higher than national statistics predicted, his current and deceased patients' homes were clustered around lakes and other bodies of water. The flurry of dots marking their locations was thickest of all around bucolic Mascoma Lake, a rural area just 10 miles from Dartmouth Medical School. About a dozen cases turned up there, the majority diagnosed within the past decade. The pattern did not appear random at all. "I started thinking maybe there was something in the water," Stommel says. ¶ That "something," he now suspects, could be the environmental toxin beta-methylamino-L-alanine, or BMAA. This compound is produced by cyanobacteria, the blue-green algae that live in soil, lakes, and oceans. Cyanobacteria are consumed by fish and other aquatic creatures. Recent studies have found BMAA in seafood, suggesting that certain diets and locations may put people at particular risk. More worrisome, blooms of cyanobacteria are becoming increasingly common, fueling fears that their toxic by-product may be quietly fomenting an upsurge in ALS—and possibly other neurological disorders like Alzheimer's disease and Parkinson's as well.

The stakes are so high that 21 research teams from 11 countries are now investigating the potential dangers of BMAA. "One group has vociferously denied the hypothesis," says Walter Bradley, a neurologist and leading authority on ALS at the University of Miami Miller School of Medicine. "But more scientists are realizing this is a viable hypothesis, and papers on the topic are beginning to snowball."

HINTS ABOUT THE POTENTIAL HEALTH threat of BMAA stretch back half a century to the remote Pacific island of Guam. There, in the aftermath of World War II, U.S. Army physicians encountered an outbreak of a strange syndrome that the native people called lytico-bodig—the term *lytico* signifying paralysis and *bodig* dementia. Some victims had ALS-like symptoms, others exhibited the rigid posture of Parkinson's disease, and still others displayed the mental fogginess typical of Alzheimer's.

An American team headed by neurologist Leonard Kurland of the Mayo Clinic determined that the highest incidence of lytico-bodig occurred in Umatac, an enclave of thatch-roofed huts on Guam's southern coast. At the peak of the epidemic, in the 1950s, almost every household in the village had at least one afflicted member. The island's indigenous people, the Chamorros, were heavily affected. Filipinos who had immigrated to Guam and adopted native customs also developed the disease at high rates, but typically only if they had lived on the island for at least 10 years. That pattern suggested an infection with a long incubation period or a toxin that accumulated over time.

Medical researchers from around the world flocked to Guam, hoping that lytico-bodig would provide a window into the broader mysteries of neurodegenerative disease. They quickly zeroed in on a distinctive component of the diet in Umatac, primitive palmlike plants called cycads, whose seeds were ground into a flour that the Chamorros made into tortillas. Perhaps some compound in the cycads was to blame.

In the 1960s, British biochemists Arthur Bell, Peter Nunn, and Armando Vega of King's College analyzed cycad

seeds and focused on a compound in them, BMAA. What drew their attention was its molecular structure: BMAA resembles beta-oxalylamino-L-alanine (BOAA), a substance found in Asian chickpeas that is known to cause a paralyzing disease. Test-tube experiments showed that BMAA can kill motor nerve cells in the spinal cord, the very ones destroyed by ALS. More evidence came from a study of monkeys fed high doses of the compound. The monkeys began to move more slowly and to tremble, and their faces froze in a masked expression, mirroring some of the symptoms of lytico-bodig. On autopsy, moreover, the animals' brains showed damage to motor neurons.

Those findings initially fed hopes that science had nabbed a brain-ravaging killer. Other researchers raised doubts, however. Neuroscientist Mark Duncan of the National Institutes of Health pointed out that enormous doses of BMAA had been required to produce symptoms in the monkeys. A Chamorro, he calculated, would have to eat almost a ton of cycad flour per month to get an equivalent dose. It was unfathomable how the toxin could be consumed in such high amounts on Guam. No other plausible causes of lytico-bodig turned up. By the early 1990s, the epidemic was in decline and the trail of clues had grown cold.

JUST WHEN RESEARCH SEEMED TO have come to a dead end, the issue was revived by Paul Cox, then the director of the National Tropical Botanical Garden on the Hawaiian island of Kauai. As part of his research there, Cox studied bats, and that work led him to a flash of insight. He noted that the Chamorros of Guam liked to eat a local fruit bat, to such an extent

Blooms of **CYANOBACTERIA ARE BECOMING INCREASINGLY COMMON**, fueling fears that **THEIR TOXIC BY-PRODUCT** may be quietly **FOMENTING AN UPSURGE IN ALS, ALZHEIMER'S**, and **PARKINSON'S**.

Water sampling at Copco Reservoir in Northern California. Previous pages: Cyanobacteria at 300X magnification.

DAVID MOLANNAURORA PHOTOS. PREVIOUS PAGES: JOSE R. ALMODOVAR RIVERA, MICROBIOLOGY CENTER BIOLOGY DEPARTMENT, UNIV. OF PUERTO RICO, MAYAGUEZ. COURTESY NIKON SMALL WORLD. INSET: ISTOCK

that the animals had been hunted to near extinction by the late 1980s. Cox was intrigued by the diet of those bats: They feasted on cycad seeds. He proposed that BMAA had become concentrated—or as he put it, "biomagnified"—in the bats to levels many times higher than those found in cycad flour. Among people who regularly ate fruit bats, he hypothesized, the cumulative dose of BMAA might have been sufficient to inflict brain damage. Moreover, the increasing scarcity of fruit bats (specifically, the kind called flying foxes) on Guam might explain why the outbreak of lytico-bodig had petered out.

Best known for discovering prostratin, an anti-AIDS drug derived from the mamala tree of Samoa, Cox was well respected in ethnobotany, but veterans of the Guam epidemic regarded him as a newcomer unlikely to succeed where the giants of neuroscience had failed. That did not stop him from trying. Enlisting the help of Sandra Banack, an expert on Pacific bats at California State University, Fullerton, Cox tested three specimens of fruit bat collected on Guam in the 1950s, at the height of the epidemic. In 2003 they published the results. All of the bats were chock-full of BMAA.

Cox then set about getting brain tissue samples collected during autopsies of six Chamorros who had died of lytico-bodig. He compared those samples with brain tissue taken from 15 Canadians, two who had died of Alzheimer's and 13 with no signs of neuropathology before death. He contacted Susan Murch, a biochemist at the Hospital for Sick Children in Toronto and an expert in finding biomolecules in human tissues, to test the samples in a double-blind study. All six of the Chamorros' brains contained BMAA. Stunningly, so did the two Alzheimer's brains from Canada, while the 13 controls had not a trace. "Suddenly, this was not a story about a remote people on a small island," Cox says.

At this point, Cox had a fresh mystery on his hands: How did BMAA find its way into the brains of Alzheimer's victims so far from Guam? An answer came when he traced the origin of the BMAA in cycad seeds to cyanobacteria growing in the plant's roots. It was not the plant but the associated microbes that were churning out the toxic chemical. The reach of BMAA, Cox concluded, extended far beyond the cycad trees of Guam. Cyanobacteria are among the most ubiquitous organisms on earth. They are routinely found in soil but also in water, where the microbes form blooms familiar as the slimy green film often seen on the surfaces of rivers and lakes. Constituting the foundation of the aquatic food chain, cyanobacteria are a favorite meal of fish and mollusks, which are in turn eaten by us.

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

When Cox pondered cyanobacteria's central role in the planet's food web, he says, "I felt for a moment as if I were staring into the abyss."

TODAY THE DIRECTOR OF THE INSTITUTE for Ethnomedicine in Jackson Hole, Wyoming, Cox is on a one-man crusade to shine a scientific spotlight on the dangers of BMAA. When I first met him at a symposium on the topic, held at the University of Miami in 2009, his efforts had already spawned a veritable cottage industry: Some 50 BMAA researchers from around the world had gathered there, each bringing along a different piece of the puzzle.

Cox is a large-framed man in his midfifties with a thatch of dark hair flecked with gray, and he speaks in a colorful, down-to-earth style. He describes BMAA as a molecular gatecrasher. It is an amino acid, he explains, a chemical relative of the 20 molecules that make up all of the proteins in our cells. Most people's bodies can metabolize or excrete the chemical interloper, but that may not happen in some genetically susceptible individuals. When they consume BMAA-tainted food or drink—be it bat stew, shellfish, or contaminated water—the molecule is not discarded; instead, it is taken up and deposited in the brain, forming what Cox calls a "toxic reservoir." Once there, he says, "BMAA gets incorporated into proteins, potentially causing them to truncate or even collapse." That is how it triggers neurological malfunction and disorders like Alzheimer's, he believes.

After hearing about Cox's theory, neuroscientist Deborah Mash, who directs the University of Miami's Brain Endowment Bank, became convinced that he was onto something. A petite woman with wavy brown hair and piercing green eyes, Mash seems as impassioned about BMAA as Cox himself. In her laboratory, housed in a squat redbrick building on the university's downtown medical campus, she describes how her team attached a radioactive label to BMAA, injected it into rodents, and tracked it. Her results seemed to bolster Cox's interpretation.

"The BMAA gets taken up by the brain, and then its level plateaus, which suggests that it is being incorporated into proteins—it is being

trapped," she says. "That sure sounds like a toxic reservoir to me."

At Cox's urging, Mash set out to conduct an independent study of ALS and Alzheimer's brains using samples from her own human brain bank. Many of these specimens came from donors who had spent much of their lives outside of Florida and whose lifetime exposures to BMAA therefore were probably quite varied. To run a meaningful experiment, Mash wanted to replicate Cox's methodology precisely, so she sent a colleague, neuroscientist John Pablo, to the lab at Jackson Hole. There, Pablo studied Cox's technique to distinguish BMAA from similar, naturally occurring amino acids—a method that still provokes debate. Once versed in the details, Pablo returned to run his tests.

The Miami team found **BMAA** in **23 OUT OF 24** samples from 12 **ALZHEIMER'S** patients.

The results were dramatic. The Miami team found BMAA in 23 out of 24 samples derived from 12 Alzheimer's patients but in only 2 out of 24 samples taken from 12 controls. They also tested samples from 13 ALS patients, all of which tested positive for BMAA.

To explore whether the chemical might be a result of any disease that kills neurons, rather than a specific cause, Mash and Pablo ran another experiment. They tested neural tissue from people who had died from Huntington's disease, a degenerative disorder of nerve cells in the base of the brain. Huntington's is known to have a purely genetic cause. The outcome looked very different this time. In 16 samples from eight people, there was barely a trace of BMAA.

Whether someone will fall ill from the neurotoxin probably depends on many factors, Mash speculates. These include the amount of lifetime exposure and individual differences in biochemistry that affect whether BMAA is absorbed by the gut, destroyed by the liver, or allowed to cross the blood-brain barrier. "More pieces of the puzzle need to be figured out," she says, "but obviously the health implications for humans could be huge."

In 2006 Larry Brand, an expert on phytoplankton and a colleague of Mash's at the Rosenstiel School of Marine and Atmospheric Science at the University of Miami, started gathering more evidence in the case against BMAA. Brand has spent a lot of time at sea over the past 15 years studying cyanobacteria blooms. "When Paul Cox came out with his paper saying that cyanobacteria produce BMAA," he says with a lingering Texan twang, "I thought, whoa, we'd better look into this because here in Florida we get some really big blooms."

Worldwide, he reports, blooms of cyanobacteria and algae are happening more frequently and over larger areas of both freshwater and salt water. The microbes reproduce more rapidly in warmer waters and thrive on runoff from sewage and agriculture. If fish eat more cyanobacteria and accumulate more BMAA in their bodies, he reasons, then the health impact on humans could well get worse.

Brand is attempting to understand that risk by tracking how BMAA moves through the food chain in Florida waters where regular cyanobacteria blooms occur. Many of the fish and shellfish specimens he sent to Mash's lab contained no BMAA, but quite a few did. Bottom-feeders registered notably high, perhaps because cyanobacteria accumulate not only on the ocean surface but also along the seafloor. Compared with the amount of BMAA found in the fruit bats of Guam, the levels of the toxin Brand found in Florida oysters and mussels were moderate. But pink shrimp, largemouth bass, and blue crabs—all eaten by humans—contained levels comparable to or even exceeding those in the bats. One blue crab topped the charts with 7,000 parts per million of BMAA, twice as much toxin as found in a Guam bat.

"That was a shocker," Brand says. He wondered if it was a fluke, but blue crabs collected by his team from bloom areas in the Chesapeake Bay had similarly high levels of BMAA. Last year Swedish researchers also found the neurotoxin in bottom-feeding fish living in the Baltic Sea, a hotbed for cyanobacteria blooms, although at lower levels than seen in the Chesapeake Bay and along the Florida coast.

THE CORRELATIONS BETWEEN BMAA and neurological disease seem strong—but as skeptics point out, correlation does not prove causation. And that is just one problem they have with Cox's theory.

The field has been dogged by clashing findings, leading some critics to question whether BMAA truly is a potent neurotoxin. "You can stuff mice with as much BMAA as you like and you simply don't see it in the brain," says Christopher Shaw, a neuroscientist at the University of British Columbia in Vancouver. Furthermore, he says, no known mechanism can explain how an amino acid that is alien to human biology could travel across the blood-brain barrier, get incorporated into proteins, and then trickle out to cause disease.

Raising further doubt, a team led by Douglas Galasko, director of the Alzheimer's Disease Research Center at the University of California, San Diego, twice tried to find BMAA in Chamorros and North Americans who died of brain disease—and both times came up empty-handed, though using a different method of chemical identification than the one employed by Cox and the Miami team.

David Thurman, a neurologist and epidemiologist at the Centers for

PEOPLE living around the lakes may have breathed in **BMAA FROM THE AIR**, eaten fish **CONTAMINATED** with it, or swallowed it while swimming.

Disease Control and Prevention in Atlanta, adds that even if BMAA is doing what Cox believes it is, it appears unlikely to be a major factor behind neurological disorders like ALS and Alzheimer's. Most experts, he notes, think these brain afflictions have multiple causes, including genes, poor diet, lack of exercise, and a variety of environmental agents, including pathogens and pesticides.

Surprisingly, Cox agrees that the overall risk from BMAA is probably low. In fact, he eats shrimp and crab with relish. "ALS is very rare, and only a few people are genetically at risk," he says. "Even if BMAA causes common disorders like Alzheimer's and Parkinson's, that still doesn't mean we should shun seafood." Commercial fishermen generally are not working in areas heavily contaminated with cyanobacteria, he notes, so the danger of exposure in the United States and Canada should be modest for those who eat typical store-bought or homegrown food and avoid drinking—as Cox puts it—"green, smelly" water.

Nevertheless, Cox and his colleagues press on, for the same reasons that researchers flocked to Guam in the 1950s: If BMAA exposure accounts for at least some of the most devastating neurological disorders, learning more about this obscure compound could have huge implications for understanding the underlying disease. Recently, Cox and colleagues have been studying ALS clusters on the Kii Peninsula in southeastern Japan, and he has joined forces with University of Miami neurologist Bradley to study a heightened incidence of the disease among American veterans of the first Gulf War.

In conjunction with Elijah Stommel, the ALS specialist at Dartmouth, Cox is also investigating the peculiar clusters of cases in New England. As word about their work has spread, more doctors have come forward to report cases in the region, with the number of ALS victims jumping from the 200 in Stommel's original database to 800 today. Sometimes a disease can be more prevalent in one spot than another due to random fluctuations, so the two researchers are working with epidemiologists who are using geographic software programs to distinguish true clusters from artifacts.

The data suggest that ALS is 2.5 times more common than average within one-half mile of a lake or pond where cyanobacteria have bloomed. Stommel hypothesizes that people living around the lakes may have breathed in BMAA from the air, eaten fish contaminated with it, or accidentally swallowed it while swimming. He and Cox are conducting tests of brain bank tissue to see if the ALS patients in these regions do in fact have elevated levels of BMAA.

WHILE THE EVIDENCE MOUNTS, COX IS already thinking about ways to detect toxic exposure before it causes disease. He recalls the intriguing case of a woman who died of an ALS-like illness called progressive supranuclear palsy. For decades before her death, she had a habit of cutting her hair, dating it, and putting it in her diary. Since virtually everything consumed leaves a trace residue in hair, Cox and biochemist Murch realized they had an opportunity to see if the woman had been exposed to BMAA. Her hair, they discovered, had been accumulating the toxin as early as 1939, with the level creeping upward over the next two decades. By 1957 the neurotoxin had reached the kind of abundance that Cox had measured in Alzheimer's patients. The amount peaked around 1962 and then began to decrease, with none detectable at the time of the woman's death.

"If we had a time machine," Cox reflects, "we could have gone back in 1957, taken a hair sample, and told her, 'You are accumulating a very weird neurotoxin.' We would have found out how she was getting exposed and might have prevented her disease."

In the future, doctors might routinely test for BMAA overload. They might even be able to counteract its effects. Before health officials are likely to consider limiting environmental exposure to BMAA, however, they will need stronger proof of harm. To that end, Mash would like to see the compound tested again in primates. "The one monkey trial ever done was certainly very provocative," she says. To her frustration, funding agencies have been reluctant to spend money on a theory so contentious.

For now, Mash and Cox grasp at each clue hoping it will prove the clincher. Researchers in France and Sweden have, over the past couple of years, shown that when BMAA is injected into rodents it gets incorporated into their eyes, where it could build up and potentially cause damage to cells in the retina. Almost half of the Chamorros who died of lytico-bodig showed damage to retinal cells. Most experts attribute that damage to a parasite, not BMAA. But John Steele, a neurologist at Guam Memorial Hospital who led some of the key research on the disease, adds a detail that sounds...fishy: Despite intensive research, no one has yet identified what the parasite could have been.