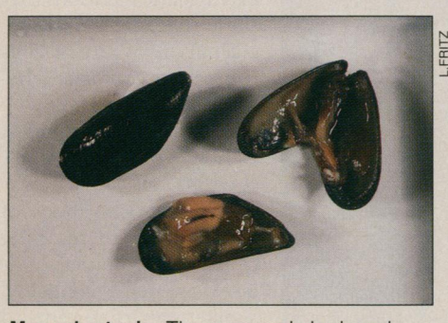
Hot Field: Neurotoxicology

In 1987, some inhabitants of Prince Edward Island, north of Nova Scotia, fell victim to a strange disorder after eating what looked like normal, tasty blue mussels. Although the initial symptoms were unpleasant enough (including diarrhea and disorientation) that the victims recall them vividly, some of the sufferers couldn't tell you what they had for breakfast today. The fact is, 5 years after their poisoning by domoic acid—a toxin produced by diatoms, one-celled marine organisms eaten by the mussels—several of the people who were poisoned continue to have trouble with their short-term memory.

This puzzling case illustrates how the young field of neurotoxicology is achieving a special place in toxicology and on the public health agenda. The reason: Not only are researchers finding more and more neurological toxicants in the environment, but in studying substances like domoic acid they're finding intriguing clues to forms of neurotoxicity that could be a key feature of chronic diseases such as Huntington's.

Domoic acid is by no means the only natural "excitotoxin" (agents that overstimulate and destroy never cells) researchers are finding. Take the grass pea, a plant often eaten during famine in Asia and Africa. This arid land legume contains an excitatory amino acid, beta-oxaloamino-alanine, that may cause the spastic leg movements of a condition called lathyrism. On Guam, there's a motor disease that resembles amyotrophic lateral sclerosis (ALS) and Parkinson's disease; it's linked to another plant amino acid, beta-methylamino-alanine.

Closer to home, researchers are finding indications that subtle metabolic changes can turn endogenous excitatory amino acids—those already present in the nervous system, such as glutamate, aspartate, and their analogs—into excitotoxins. Says John Olney, who launched the field in 1969 when he showed that monosodium glutamate fed to monkeys raised blood levels of glutamate, killing nerve cells in the hypothalamus, "We're seeing tantalizing evidence that excitotoxins make a contribution to chronic diseases."



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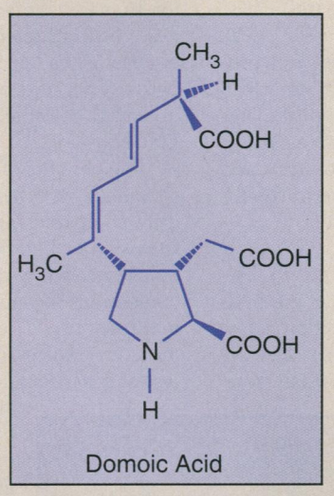
Muscular toxin. These mussels harbored high levels of domoic acid, an excitotoxin.

Some of the hottest research on excitotoxins is aimed at understanding how nerve cells die during Huntington's disease. One group of scientists is zeroing in on whether high levels of endogenous quinolinic acid in cerebrospinal fluid could be a cause of Huntington's (*Science*, 1 January, p. 25). Others are exploring a model that involves faulty metabolism of glutamate and its effect on neurons. Walter Koroshetz and Flint Beal of Massachusetts General Hospital and colleagues have shown that some Huntington's patients may be susceptible to overexcitation from glutamate because of damage to energy-producing mitochondria in the neurons. Supporting evidence for this idea appeared in the January issue of the *Journal of Neurochemistry*, in which a group led by Beal found that in rats, a toxin that disables mitochondria can produce nerve cell death characteristic of Huntington's.

The spotlight is also on glutamate in another neurodegenerative disease—ALS, which strikes about one of 75,000 people a year. In this case, researchers suspect poor transport of glutamate may kill motor neurons in the brain and spinal cord. In the 28 May 1992 issue of the *New England Journal of Medicine*, Johns Hopkins neurologist Jeffrey Rothstein and his colleagues describe data collected from nerve tissues of ALS patients and controls. In ALS patients, cell components called synaptosomes taken from the spinal cord, motor cortex, and somatosensory cortex were inefficient at transporting glutamate. Yet synaptosomes from other nerve tissues in ALS patients functioned normally—as they did in nerve tissues from non-ALS patients. The researchers hypothesized that poor transport leads to high levels of glutamate in the extracellular space and overstimulation of glutamate receptors.



Domoic Acid

Domoic acid, meanwhile, hasn't faded from researchers' attention. Several groups are focusing on how domoic acid triggers excitatory receptors in the hippocampus, a brain structure that has an important role in the formation and storage of memories. Frank Iverson, chief toxicologist at Health & Welfare Canada in Ottawa, and colleagues have found that rats given domoic acid developed lesions in the hippocampus. In the United States, toxicologists William Slikker and Andrew Scallet at the Food and Drug Administration's (FDA) National Center for Toxicological Research in Jefferson, Arkansas, have reported a similar effect on monkeys. Their results, now in press, show that the lesions are dose dependent and appear more readily in older animals. "We know the hippocampus is a sensitive target," Slikker says.

As neurotoxicologists explore the mechanisms of domoic acid poisoning, Canada and the United States have taken steps to guard against future outbreaks of poisoning. Shortly after the 1987 incident, Canada's National Research Council lab in Halifax developed techniques for screening shellfish to find domoic acid. In February 1992, the FDA expanded its shellfish monitoring program to include checks for contamination. Last fall, the program detected high levels of domoic acid in clams and Dungeness crabs off the coast of Washington and temporarily halted the harvest. FDA researchers are now developing methods of sampling water for the presence of domoic acid-producing diatoms as a step before sampling shellfish directly.

While the public attitude toward excitotoxins may be one of fear and loathing, drug companies see the promise of using these amino acids to treat chronic degenerative diseases, a prospect that is starting to generate "tremendous interest," according to Beal. Researchers at Eli Lilly & Co., in collaboration with Washington University's Olney, have begun studying the metabolism of excitotoxic analogs of aspartate; the basic research may lead to treatments for a range of neurodegenerative disorders. "The effects of excitatory amino acids," says Olney, "are more widespread than anyone imagined." And those wide-ranging effects have drawn myriad colleagues into a field where, two decades ago, Olney was all alone.

–Richard Stone