Toxin to the Rescue

Tapping a deadly botulinum protein to treat neuromuscular disorders

By INGFEI CHEN

In a classic example of medicine harnessing the therapeutic powers of a poison, researchers have turned a potent toxin that causes botulism into a successful treatment for a number of neuromuscular diseases and anticipate unleashing it against several more.

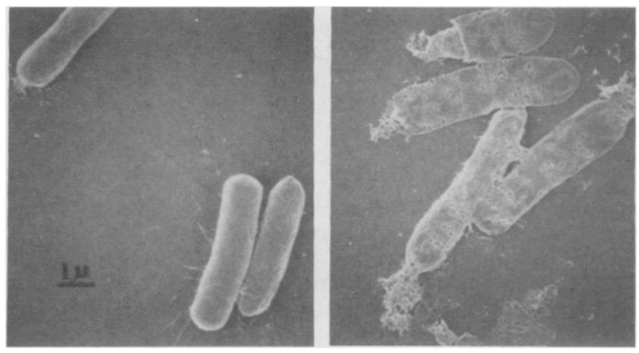
Through the decades, *Clostridium botulinum* has gained notoriety for inducing vomiting, dizziness and sometimes even paralysis and death in people who eat canned goods contaminated with it (SN: 2/7/76, p.93). But since the late 1970s, scientists have partially revamped this bacterium's nasty image by using tiny doses of its lethal product — called botulinum toxin — to treat individuals who suffer from muscular spasms of the eyes, face, throat, limbs or torso.

The organism follows a growth cycle "pretty unusual" even in the bacterial world, says microbiologist Eric A. Johnson of the University of Wisconsin-Madison's Food Research Institute, the only U.S. facility that produces the toxin for medical purposes. In the lab, cultures of *C. botulinum* turn a turbid yellow-brown within two days of anaerobic fermentation. Some 24 to 48 hours later, the cultures magically clear — after the organisms commit "mass suicide" by dissolving their own cell walls, releasing the toxin in the process.

While *C. botulinum* produces seven distinct neurotoxins, researchers have focused on one they call Type A. This complex protein consists of three functional regions: one that targets a muscle nerve ending and binds to its cell membrane, another that helps the toxin enter the cell, and a third that poisons the nerve ending by blocking its release of acetylcholine, a neurotransmitter that normally signals a muscle to contract.

Neurologists, ophthalmologists and other researchers have discovered over the past 15 years that minute doses of Type A toxin produce a temporary, local paralysis that can provide relief to people affected by certain disorders in which excessive muscle-contracting activity causes involuntary twisting, twitching and repetitive movements or abnormal postures. Roughly 100,000 to 200,000 individuals in the United States suffer from these conditions, known as dystonias.

Botulinum therapy "has been the most dramatic thing that has happened to these patients in a great many years," neurologist Roger C. Duvoisin said last November at a National Institutes of Health conference on the clinical uses of the toxin.



Eric A. Johnson/Food Research Inst. U. of Wis.

Left: Scanning electron micrographs depict cells of Clostridium botulinum, *the bacterium whose toxin causes botulism. Right: After growing in culture for a few days, the organisms commit "mass suicide," dissolving their cell walls and releasing the toxin.*

Type A botulinum toxin debuted in human medicine at the Smith-Kettlewell Eye Research Institute in San Francisco in 1976, when ophthalmologist Alan B. Scott used it to improve the vision of patients whose eyes crossed or turned outward. This condition, known as strabismus, can lead to double vision and deficient depth perception (SN: 5/7/77, p.296). Since then, researchers have tried the potentially lethal protein in "an ever-widening circle of conditions with muscle spasms," says Duvoisin, chief of neurology at the Robert Wood Johnson Medical School in New Brunswick, N.J.

Toxin injected into specific muscles damps excessive nerve firing in selected tissues just enough to prevent abnormal muscle spasms without producing undesired paralysis. In animals, this therapy "substantially" inhibits the release of acetylcholine in most targeted nerve endings, says Lance L. Simpson, head of environmental medicine and toxicology at the Jefferson Medical College in Philadelphia. Because dystonia-affected nerves are usually so overstimulated that even after the toxin blocks most of their nerve endings, these cells retain enough activity to maintain normal muscle function, he says.

Human doses generally range from 0.1 to 0.5 nanograms, well below the 16 nanograms needed to induce even mild botulism poisoning. The treatment's long-term effects remain unknown and require further study. However, Duvoisin says, since the immediate and localized side effects of Type A toxin (such as drooping of the upper eyelid or difficulty in swallowing) are transitory, treatable and rarely serious when the toxin is properly administered, botulinum therapy appears safe and "relatively easy."

Indeed, the Food and Drug Administration last February approved Type A treatment for people 13 years and older afflicted with any of three dystonias: strabismus, benign essential blepharospasm (spasmodic closing of the eyelids) and hemifacial spasm (in which one half of the face undergoes sudden muscle contractions). Though the therapy appears promising for other disorders as well, its use in any condition other than those three remains experimental and requires special FDA approval.

Allergan Pharmaceuticals of Irvine, Calif., the only firm marketing Type A botulinum toxin in the United States, is currently seeking FDA consent to use the protein against other neuromuscular illnesses. Though Allergan won't disclose which ones, at the recent NIH meeting a panel of experts reviewing clinical studies of the past decade pronounced the botulinum treatment "safe and effective" for three additional conditions:

- Spasmodic torticollis, the most common dystonia, in which painful neck-muscle spasms twist the head to one side.
- Oromandibular dystonia, characterized by continuous spasms of the jaws, lips and tongue that may cause uncontrollable jaw opening or closing and difficulty in swallowing or speaking.
- Adductor spasmodic dysphonia, in which involuntary closing of the vocal cords interrupts the airstream and produces a strained, hoarse, choppy voice.

Researchers using Type A toxin to treat patients with constricted vocal cords

have achieved "quite remarkable success" in restoring vocal fluency, says Audrey L. Holland, a speech pathologist at the University of Pittsburgh School of Medicine. "By causing the vocal cords to become more flexible, [the toxin] allows speech to become more normal," she says.

Botulinum toxin may also offer relief for several other speech disorders, including some stuttering conditions, and for occupational hand dystonias – such as writer's or musician's cramp, in which intensive use of the hands leads to loss of control over the fingers. But while researchers feel optimistic about Type A's therapeutic potential, further studies must assess its effectiveness in these and other dystonias, the NIH panel concluded.

Physicians and psychologists once viewed dystonias as psychologically rooted illnesses, but scientists now believe that some of these disorders stem from an abnormality in the basal ganglia, an area of the brain responsible for smoothness and coordination of movement. The defect could be genetic, a consequence of environmental damage or a result of disease.

Except in certain cases of eye misalignment, Type A botulinum toxin provides only temporary, symptomatic relief "and does not address the disturbance in the central nervous system [underlying these disorders]," Duvoisin says. Because new nerve endings sprout after several months – reestablishing communication with the muscles – and the dysfunctional nerve endings eventually recover as well, patients require periodic injections. But the temporary nature of the therapy "is in some ways an advantage," Duvoisin says, "because the toxin's effect does reverse in time, so that there is some protection against overtreatment."

Dystonias have conventionally been treated with other drugs, and sometimes with surgery to sever or remove the troublesome nerves. The NIH panel described both approaches as "minimally effective." Past experience has shown that operations to correct dystonias not only are irreversible and sometimes unpredictable, but also carry the risk of disfigurement for what may be short-lived benefits.

For a patient with blepharospasm, surgical destruction of the nerves causing spasmodic eyelid closings costs $10,000 to $14,000, says O.G. Bruce, former president of the Benign Essential Blepharospasm Research Foundation, Inc., in Beaumont, Tex.

In comparison, treatment with Type A botulinum toxin costs $400 to $1,800 per visit, depending on dosage; patients usually require three or four injections a year. While these expenses do, in time, exceed the cost of surgery, Bruce points out that an operation doesn't provide a full cure either and often requires follow-up drug therapy.

Moreover, some dystonias cannot be treated by surgery because the affected muscles lie in areas too difficult or risky to operate on, such as the neck. In contrast, doctors can easily inject botulinum toxin almost anywhere. "That's really what's so wonderful about [the treatment]," Johnson says.

A permanent toxin-based therapy may lie upon the distant horizon. At least one researcher hopes to improve Type A's therapeutic potential by manipulating the molecule.

In unpublished experiments, Simpson has engineered a new agent by removing the toxin's cell-poisoning region and inserting a deadlier substitute: a cell-killing fragment, isolated from a plant toxin called ricin, that works by blocking the cell's ability to make protein. If, when injected, this modified Type A toxin successfully binds and kills overstimulated nerve endings in patients with dystonias, it might provide a one-shot cure, he says.

"Nature has provided us with a starting material [in botulinum toxin]," Simpson says. "But I think if we re-engineer the toxin, we can come up with even better therapeutic agents." □

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beans 16,000 and peanuts 5,000 to 7,000.

Maybe we should serve more soybeans, mung beans or peanuts with our beer, or else switch to dandelion wine. If I were concerned about cirrhosis, I'd up my intake of dandelions, milk thistle and artichokes, all of which contain hepatoprotective compounds. Or maybe I'd just add dandelion flowers to a bean paté.

James A. Duke
Economic Botanist
USDA Agricultural Research Service
Beltsville, Md.

Refuge from refuse

John Gillis (Letters, SN: 11/24/90, p.323) asks, "Can anyone seriously think that this vastly empty country of ours is lacking in space for trash disposal?"

True, my corner of rural America is devoid of the swarm of humanity that fills Mr. Gillis' hometown of New York City. But it is filled with wildlife and flowers, and with trees that give us oxygen to breathe and paper for publications such as this. There is more to an ecology than just human presence.

I agree with Mr. Gillis on one point: The real disposal problem of today is political, not physical. It is the political problem of persuading everyone to accept responsibility for the consequences of their own consumption, rather than expecting that they can dump those consequences in someone else's (apparently) empty backyard. We need to work on the technology to solve that one, so that I don't have to trade my wildflowers and wild animals for city dwellers' trash and rats and noxious chemicals leaking into the groundwater. Maybe we can even come up with something that will let New York City keep its trash at home rather than barging it all over the world.

As a member of our town landfill committee, organized a few years ago when local landfills were almost full, I conceived the plans that became our recycling center. I assure you that even with apparently abundant space, rural areas still have problems disposing of waste. Burying it is not the answer, and for that and all other solutions, the technology and economics are really not congenial.

Bruce McCulley
Troy, N.H.

Mr. Gillis may be correct when he reasons that "garbage disposal has never been a major engineering problem." However, his attempt to place the blame on the "not-in-my-backyarders" fails to tell the whole story.

Landfills leak, even those with engineered liners and leachate collection systems. Even the EPA has admitted this. Alas, though garbage disposal may not be a major engineering problem, it is a major environmental problem – and if the political process stimulated by those who sponsor a "not-in-my-backyard" philosophy causes us to rethink the way in which we dispose of our wastes, and causes us to rely upon more benign forms of disposal such as recycling and composting, then we as a country with vast resources of land will be in a much better position to pass those resources on to the next generation of garbage producers.

Paul G. Beaulieu
Granby, Mass.

Civilization's colossal creation

Staten Island's Fresh Kills landfill is not only the biggest landfill in the world ("'Big dig' unearths clues to garbage decay," SN: 11/24/90, p.324). By the time you read this, it will be the largest human-made structure of any kind, surpassing even the Great Wall of China. Its 2.3 billion-plus cubic feet equals the displacement of the Great Wall, and every new "baggie" expands its record.

How sad.

K.A. Boriskin
Bellingham, Mass.

Glaucoma and beyond

While some cases of glaucoma do involve headaches, halos and blurred vision, as anecdotally described in "Eyeing the Optic Nerve" (SN: 11/24/90, p.330), readers should recognize that the majority of cases exhibit no symptoms aside from a barely perceptible, gradual loss of peripheral vision.

Mrs. R.L. Border
Las Vegas, Nev.

The laser techniques devised by Dr. Weinreb promise new benefits beyond the measurement of retinal changes in glaucoma. This noninvasive technology could aid in the assessment of degenerative changes that signal the onset or progression of a variety of retinal diseases, giving physicians a new tool with possible wide application in the diagnosis and management of many ocular disorders.

David F. Weeks
President, Research to Prevent Blindness, Inc.
New York, N.Y.