

BOTULINUM TOXIN

A Poison That Can Heal

by Luba Vangelova

Botulinum toxin can heal as well as harm. The bacterial toxin that can paralyze and kill if consumed in contaminated food is now safely used, in a purified form, as a medicine to control certain conditions marked by involuntary muscle contractions.

The history and lethality of botulism would seem to make it an unlikely source for a curative substance. Although death rates from botulism poisoning are just a fraction of what they were 30 years ago, botulism continues to strike dozens of people every year—most of them infants, according to statistics from the national Centers for Dis-

ease Control and Prevention in Atlanta. Botulism-causing *Clostridium botulinum* bacteria and their spores are everywhere. Prevalent in soil and marine sediments worldwide, their spores are often found on the surfaces of fruits and vegetables, and in seafood. The bacteria and spores themselves are harmless; the dangerous substance is the toxin produced by the bacteria when they grow. There are seven varieties of botulinum toxin, designated by the letters A through G.

Botulinum toxin is "the most poisonous substance known," says Stephen S. Arnon, M.D., head of the Infant Botulism Prevention Program at the California Department of Health Services. For this reason, anyone with symptoms of botulism should receive emergency treatment, and public health officials should be notified to locate the source of the contamination and prevent other cases.

Once in the body, the toxin binds to nerve endings at the point where the nerves join muscles. This prevents the nerves from signaling the muscles to contract. The result is weakness and paralysis that descends from the cranium down, affecting, among other things, the muscles that regulate breathing.

Before the development of mechanical ventilators, the respiratory paralysis caused by botulism claimed many more victims than it does today. Between 1910 and 1919, for example, the death

rate from botulism was 70 percent. By the 1980s the rate had dropped to 9 percent, and in 1993 it was less than 2 percent. But recovery is still slow; assuming the patient receives proper care to ensure continued breathing, recovery occurs only when the affected nerves grow new endings, a process that can take several months, although the length of time varies greatly from case to case.

If botulism is caught in the early stages, injection of an antitoxin made from horse serum can lessen the severity of disease by neutralizing the toxin that has not yet bound to nerve endings. But because of the risk of serious side effects such as anaphylaxis, a life-threatening allergic reaction, and serum sickness (an unpredictable allergic reaction to the horse serum, which can lead to anaphylaxis), the equine antitoxin cannot always be used, and it is never given to infants.

The condition in which *C. botulinum* spores germinate and toxin is produced—absence of oxygen, low acidity levels, and temperatures between 40 and 120 degrees Fahrenheit (4.5 to 49 degrees Celsius)—can easily develop in improperly stored home-cooked or commercial foods, as well as in canned foods that have not been prepared with proper canning procedures. Infant intestinal tracts, which haven't yet developed the full range of beneficial bacteria, can also present an environment inviting to *C. botulinum* toxin production, as can some deep wounds.

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"Botulism is still lurking, and if our guard is not up, it will create a problem," says Richard C. Swanson, director of the Food and Drug Administration's division of emergency and investigational operations and one of the agency's representatives to the Inter-agency Botulism Research Coordinating Committee.

One of the most common culprits in food-borne botulism is home-canned food.

Three Types

There are three types of botulism poisoning, distinguished by the manner in which they are contracted: food-borne, wound and infant. In infant botulism the toxin is produced when *C. botulinum* spores germinate in the intestine. (Rarely, adults can acquire the disease this way.) In wound botulism, which is very rare, the toxin is produced by *C. botulinum* bacteria in an infected wound. In the food-borne form of the disease, the person ingests the toxin itself by eating food contaminated with it. Statistically, infant botulism, which was recognized in the mid-'70s, is the most common form of the disease. But the public still generally associates botulism with food poisoning in adults and children. The food-borne disease is the most avoidable form of botulism.

Symptoms usually develop within a day of eating the food, although they can take up to 10 days to manifest. Apart from weakness and paralysis, common complaints include fatigue, dry mouth, and difficulty swallowing. Unfortunately, doctors sometimes misdiagnose the symptoms as Guillain-Barré syndrome, stroke, intoxication, or a handful of other conditions. For this reason, federal health officials suspect that botulism poisoning is underdiagnosed.

Home Canning

One of the most common culprits in food-borne botulism is home-canned food, especially vegetables such as asparagus, green beans, and peppers. More than 90 percent of food-borne botulism outbreaks between 1976 and 1985 were due to home-processed foods.

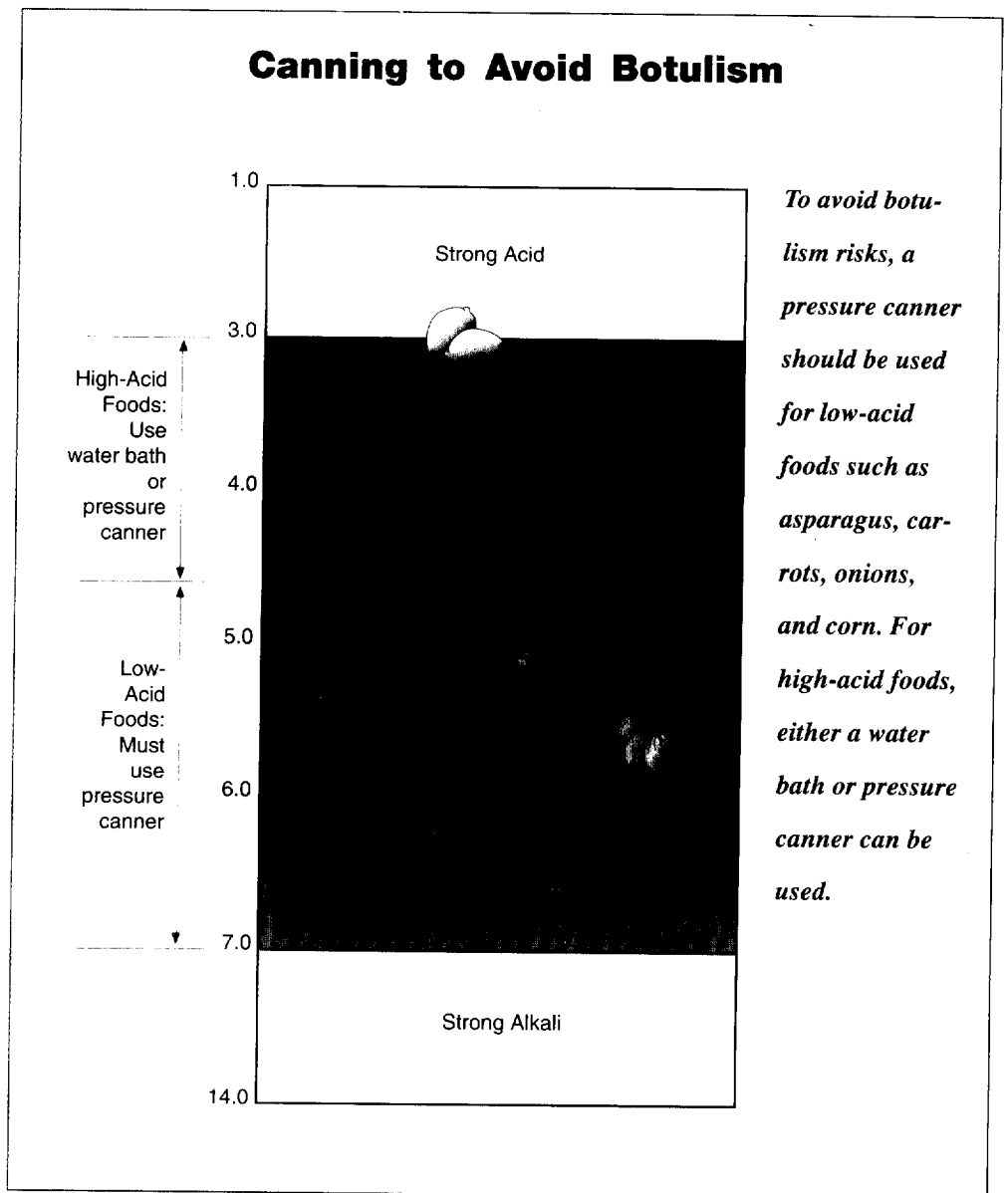
"If you home-can products, make sure you use proper equipment, proper containers to can in, and use the up-to-date process," Swanson advises. U.S. Department of Agriculture home canning guidelines are available from county extension offices. One basic recommendation is to cook food to be canned in

pressure cookers because they can maintain temperatures high enough (above 212 F, or 100 C) for 10 minutes to kill the spores, which are remarkably heat-resistant.

Foods cooked at home should not be left at temperatures between 40 F and 140 F (4.5 C to 60 C) for more than four hours. Toxin that may have formed can

readily be destroyed by boiling the food for 10 minutes.

Commercial foods have also been involved in botulism outbreaks. Some outbreaks have been attributed to improperly handled food, such as potato salad, served in restaurants. But many commercial food outbreaks are due to consumer mishandling, such as disregarding



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labels that indicate the food should be refrigerated. Some food companies acidify their products or lower their moisture content as an extra precautionary measure in case the refrigeration warning is not heeded. Consumers can best protect themselves by reading the labels and following the storage instructions, Swanson says, and by discarding rusty, swollen or otherwise damaged cans.

Infant Botulism

Infant botulism differs from food-borne botulism in that the toxin itself is not ingested. Instead, *C. botulinum* spores swallowed by the infant germinate and produce the toxin in the favorable environment of the baby's large intestine.

Because the spores are nearly everywhere in the environment, children and adults regularly ingest them, yet very rarely suffer ill effects. In a few cases, adults who have had intestinal surgery or whose intestinal tracts have otherwise been altered have contracted the disease the way infants do. This has led researchers to conclude that infants' as-yet "incompletely-developed intestinal flora," may be to blame, says Arnon, one of the co-discoverers of infant botulism in 1976.

Infant botulism is serious, but rare and not usually fatal. From 1976 through the end of 1993, 1,206 infant botulism cases were confirmed in the United States. About 75 to 100 cases are reported annually, about half of them in California (presumed to be due to the prevalence of *C. botulinum* spores in the state, its high number of births, and the pediatric community's familiarity with the disease, which results in more correct botulism diagnoses). All of the infant cases involve babies less than 1 year old; the disease is most common in the second month of life.

Infants' immature intestinal tracts offer a "window of vulnerability, and if a baby has the bad luck to swallow a botulism spore during that period, the spore has an opportunity to germinate," Arnon

says. The spores travel with microscopic dust particles, so the researchers have concluded that most affected infants have simply inhaled the spores. "They mix with saliva, they're swallowed, and that's how they reach the intestine," Arnon says. Unfortunately, there is no way to prevent the disease in such cases.

But parents and other caregivers can prevent babies acquiring infant botulism from one source—honey. California researchers have isolated *C. botulinum* spores from about 10 percent of store-bought honey samples, and although less than 5 percent of infant botulism patients contract the disease from honey, health officials and pediatricians agree that honey should not be fed to infants under 1 year of age (it is perfectly safe for older children and adults).

The first sign that an infant has botulism is usually constipation, although this isn't always apparent to parents. Often the baby isn't brought to a doctor until parents notice other symptoms, such as lethargy and poor feeding as the paralysis begins to affect the baby's gag reflex and swallowing ability.

Because breathing is affected in the most severe stage of botulism-induced paralysis, researchers suspect a link between infant botulism and sudden infant death syndrome (SIDS), also known as crib death. One study done 15 years ago showed that about 5 percent of children in California whose deaths were attributed to SIDS actually had died from infant botulism. Because of the difficulty of conducting such studies, the link between SIDS and infant botulism remains poorly understood.

The infant botulism fatality rate is less than 2 percent, and recovery is usually complete. Often, however, infants have to spend weeks or months on a ventilator. Horse-derived antitoxin is not given to infants because of the risk of side effects such as anaphylaxis and serum sickness. But in February 1992, the California Department of Health Services began a new clinical trial that may provide a way of lessening the effects of the disease.

With funds from the FDA's Orphan Products Grants Program, the trial is evaluating a human-derived antitoxin obtained from laboratory workers who for occupational safety reasons have been immunized with botulinum toxoid, which is toxin whose poisoning potential had been removed.

The California investigators will assess whether infants given the antitoxin will have shorter hospital stays, fewer complications, and a halt to the progression of disease. Infant botulism represents the only opportunity to evaluate the safety and efficacy of human-derived botulism antitoxin (known formally as Botulism Immune Globulin) because of the sporadic and even less frequent occurrence of food-borne and wound botulism.

Use as Medicine

Meanwhile, purified botulism toxin is the first bacterial toxin to be used as a medicine. FDA licensed botulinum toxin as Oculinum in December 1989 for treating two eye conditions—blepharospasm and strabismus—characterized by excessive muscle contractions. It is now marketed under the trade name Botox.

Small doses of the toxin are injected

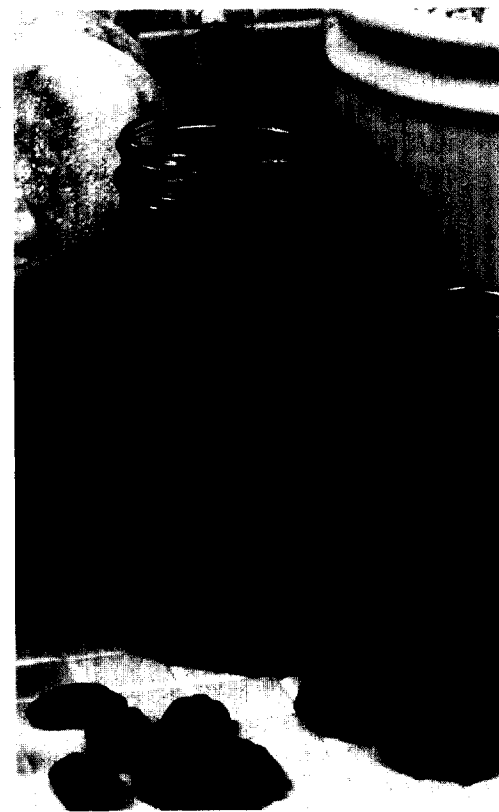
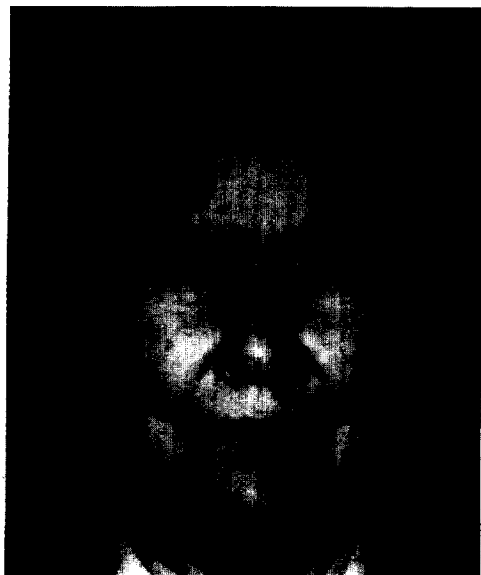


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At left, a patient with blepharospasm before injection with Botox is unable to open her eyes due to abnormal muscle contractions. At center, still pre-injection, she uses her fingers to keep her eyes open. At right, after injection, her eyes stay open without difficulty.

(Photos courtesy Joseph Jankovic, M.D., professor of neurology, Baylor College of Medicine, Houston, Texas)

into the affected muscles. As happens with botulism, the toxin binds to the nerve endings, blocking the release of the chemical acetylcholine, which would otherwise signal the muscle to contract. The toxin thus paralyzes or weakens the injected muscle but leaves the other muscles unaffected. The injections "block extra contraction [of the muscle] but leave enough strength for normal use," says Barbara Karp, M.D., deputy clinical director of the National Institutes of Health's National Institute of Neurological Disorders and Stroke.

Although the two eye conditions are the only indications for which it is licensed, botulinum toxin has been used investigatively for a variety of other conditions. "The main disease [group] the toxin is being used for is dystonias—neurologic diseases involving abnormal muscle posture and tension," Karp says. Examples include spasmodic torticollis (contractions of the neck and shoulder muscles), oral mandibular dystonia (clenching of the jaw muscles), and writers' and musicians' cramps.

Other investigational uses include: spasmodic dysphonia (which results in speech that is difficult to understand), urinary bladder muscle relaxation (such

as in cases where muscle contraction is severe enough to require catheterized urination), esophageal sphincter muscle relaxation, and the management of tics.

Experience shows that "it works better for some things than others," NIH's Karp says. For example, "it works better for disorders that involve small muscles than large muscles," she says. But for about 2 to 5 percent of patients, the injections simply don't work at all, she adds.

Injections usually have to be repeated, as the effects usually only last about

three to four months, although sometimes they can last over a year. Because of this, up to 10 percent of patients eventually develop antibodies to the toxin; this is more likely in patients who receive higher doses at more frequent intervals. Therefore, the makers of the biologic recommend that its dosage be kept as low as possible.

There are seven different types of botulinum toxin, and the currently marketed therapeutic toxin is type A. NIH is studying whether patients who have become immune to injections of type A toxin can successfully be treated by toxins of other types. So far, the research indicates that using type F to treat people with antibodies to type A seems to work, Karp says.

Botulinum toxin has "an amazing safety record," says Bill Habig, Ph.D., the recently retired deputy director of FDA's division of bacterial products in the Center for Biologics Evaluation and Research. "Considering it's one of the most toxic materials known and there was a lot of concern about it, it's turned out to be very safe," he says. ■

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Not for Wrinkles

Botulinum toxin type A has been promoted for use as a wrinkle remedy. Apparently, some practitioners have been injecting the substance to ease wrinkles by weakening face muscles. In a Nov. 18, 1994, *Federal Register* notice, FDA denounced the promotion of such unapproved use as "an egregious example of promoting a potentially toxic biologic for cosmetic purposes."