

## Botulinum Toxin: Lethal Weapon or Magic Bullet?

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By Katayoun Chamany

Like penicillin botulinum toxin could become a legend. Until recently, the toxin was known primarily as the cause of botulism, a type of deadly food poisoning produced by improper canning. In the late 1980s, Canada approved use of the toxin to treat strabismus (also known as cross-eyes), and Americans suffering from this ailment began crossing the border for medical relief. In 2001, Canada approved an additional use for the toxin--the removal of facial wrinkles--and in 2002, the FDA in the United States followed suit. (1, 2). Subsequently, the neurotoxin has become a household name as clients line up at local gyms, parties, and spas for their quarterly Botox injections, in order to temporarily rid themselves of wrinkles and sweaty armpits. The toxin now enjoys a type of celebrity caché, for better or worse, and has been featured comically on popular sit-coms and comic strips (3-8).

Profits are expected to hit an all time high as the toxin makes the leap from therapeutic drug to beauty aid, and this financial trend is likely to grow, since a number of new therapeutic applications may be developed and approved for use in the next few years. Dr. Mitchell F. Brin, vice president of Allergan, claims that botulinum toxin type A could treat up to ninety-three human disorders (5, 9). Meanwhile, Elan pharmaceuticals has secured rights to specific clinical applications of botulinum type B (10). Both companies hope to secure a unique financial niche, and scientific investigations of botulinum toxin action suggest that the versatility of the toxin will make this possible. By investigating how the toxin goes about disrupting neurological function, scientists have begun to learn a great deal about the basic properties of neuronal transmitter release and cellular secretion pathways (11-14). These findings may lead to new treatments for neurological and endocrine disorders such as cerebral palsy, Parkinson's Disease, Graves Disease, and Cushing's Disease (9, 15-17). Perhaps most surprising is that the lethal toxin is being engineered as a delivery vehicle for oral vaccines such as those used for cancer (18). So the stakes are very high--both for those who suffer from debilitating diseases and the pharmaceutical companies who will develop and sell the medical applications.

There is also another side to this story, which is perhaps not as well known, but is just as important: namely, the use of the toxin as a lethal agent. *Clostridium botulinum* is the bacterium that produces the world's most deadly toxin. A small dose of the toxin can kill 10 million people within 48 hours. If aerosolized, the bacterial spores linger in the air for up to two days. These spores germinate once they have entered a human host and, if the conditions are right, begin to release the neurotoxin (13, 19, 20).

With potency 10,000 times stronger than any other biological poison, the botulinum toxin was recruited as a biological weapon many years ago, and it continues to be used today. During WWII, Stanley Lovell, an American officer in the Office of Strategic Services, ordered the manufacture of gelatin capsules containing the toxin. The plan was for Chinese prostitutes to hide these capsules behind their ears and then slip them into the meals of high-level Japanese officials(20). More recently, in 1993 the Iraqi leader

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Saddam Hussein admitted to manufacturing and stockpiling 19,000 liters of the toxin, despite having signed the 1972 Biological Weapons Convention Treaty which forbids such actions (19, 21-23). And between 1990-1995, the terrorist cult group Aum Shinrikyo unsuccessfully launched three botulinum attacks in Japan (13). State and local health officials are on heightened alert for bioterrorist activities using botulinum toxin, so much so, that in preparing for the millenium celebration, Saint Lukes Hospital in New York stockpiled antitoxin.

Despite the ongoing threat of a bioterrorist attack via botulinum toxin, President Bush has refused to ratify the Biological Weapons Convention Treaty. He argues that the surveillance protocols threaten biotechnology commercial interests. Instead, he has asked for increased federal funding for prevention and treatment of symptoms caused by biological weapons (24, 25).

Unfortunately, little research has been conducted in the way of prevention and antidote for botulism. Presently, the Centers for Disease Control (CDC) has a limited supply of a horse antitoxin that can be shipped via air upon request by a State Health Department (13, 22). Although there is no approved vaccine to prevent botulism, the CDC does possess an investigational toxoid vaccine whose access is restricted to military personnel and researchers. However, some advances are being made. In 2001, the Senate Appropriations Committee for Bioterrorism put forth a bill that called for a \$520 million budget to improve food safety, protect US agriculture, and increase spending for vaccine and treatment development (26). Nevertheless, current methods of prevention are inadequate, and researchers are just beginning to develop high-throughput assays to identify botulism treatments and more effective vaccines (22, 27-29). We clearly have a long way to go.

No longer just regarded as a deadly food poisoning caused by grandma's pickling or canning, *Clostridium botulinum* and the toxin it produces have jumped to the forefront of military and anti-terrorist campaigns, scientific research, pharmaceutical ventures, and the vane worries of an aging and wrinkling populace. The potential medical benefits of the toxin provide great hopes, but it's use as a weapon holds an equal potential for harm. By learning more about both the underlying science of the toxin and the role it may play in our lives, we will hopefully be able to make informed choices about how to maximize the benefits and minimize the destructive potential of the single most poisonous substance currently known to humankind.

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