A Billionth of a Gram Is not Much But…

By

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Paracelsus, a physician said this in the 16th century, and it became a quote for the ages.

"*What is there that is not poison? All things are poison, and nothing is without poison. Solely the dose determines that a thing is not a poison*."

This language uses poison broadly to describe a harmful substance and tells us even a good thing is bad if we get too much. For example, too much sun causes sun burn or sun poisoning. It also means a bad thing can be safe if the dose is small enough. And this applies to tonight's topic, Botulinum A toxin the most lethal substance known to humankind.

You may have heard of this toxin, and some may have received it or know of someone who has. If so, you are likely to know it as Botox, a widely advertised drug that today sells in the billions. They are the same!

This toxin, as a drug, came on the scene more than 30 years ago for treatment of crossed eyes and spasms of the muscles of the face and neck. Since then, its use has expanded to dozens of new medical conditions and, also for cosmetic treatment.

Since its introduction, Botox has gone from an orphan drug serving a small market to a blockbuster selling in the billions. Its only active ingredient is a pure toxin produced by the bacteria Clostridium botulinum and it does just one thing. It blocks acetylcholine, a neural mediator that affects the action of selected muscles and glands. For treatment a small amount of diluted toxin is injected at the target site. Used properly it acts locally with no systemic effect.

Botox, used worldwide by tens of millions, was first marketed by Allergan pharmaceuticals in 1990. Now an AbbVie brand, it accounts for 70% of the current world market which in 2021 was $ 4.6 billion.

Fulfilling Paracelsus' dictum, the therapeutic dose of Botulinum toxin is in the hundredths of a billionth of a gram. The usual therapeutic dose of Botox is between 25 and 200 units each containing 0.7 billionths of a gram. With a wide range of safety the dose lethal to a human is 3000 units. A fatal drug

overdose is less likely to occur than from a medicine we may already have at home.

If the tale ended here, this wouldn't be much of a story.

The U.S. has a well-regulated pharmaceutical industry that submits around fifty new drugs for FDA approval each year. These are developed by established companies investing billions and employing thousands. Product development can be arduous leading to the familiar term, "the drug is in the pipeline." Throughout the drug development process the FDA seeks answers to two questions: is the drug safe and is it effective?

Botulinum A toxin eventually followed a course confirming both. But the tale of how the toxin reached this point and became Botox is anything but ordinary and it began two and a half centuries ago.

In southern Germany, around 1780, unexplained deaths were occurring in epidemic proportion. These continued unabated into the next century in a war-torn population reeling from food shortage and poverty. These deaths were eerily alike. Beginning with paralysis of muscles around the eyes and throat weakness spreads down the body affecting breathing with death occurring in hours to days in an otherwise healthy individual.

By 1817 a newly appointed district health officer, Justinius Kerner, age 29, was ready to accept the challenge. After dealing with one hundred seventy patients half of whom died in the typical pattern he took action. Employing an epidemiologic approach, he isolated a common factor. It was a cheap and readily available food called blood sausage eaten by all the families who had experienced a death.

Kerner studied the contents of this "catch all" food mixed, stuffed in animal intestine, and boiled before eating. The only ingredients common to all were salt, blood, and a fatty slime. Discarding the first two, Kerner decided to focus on the fat and set out to determine if it was the cause.

He fed the fat flavored with honey, to a menagerie including bugs, insects and other small animals. They all died. Kerner then placed this toxic substance in a small incision in the flank of a rabbit and its leg muscles became weak. He was on to something!

In a final, daring phase of the experiment, Kerner put a dab of the poison on his finger and placed it on his tongue. It caused a tight feeling in his mouth which immediately felt dry. His conclusion was the fatty substance had the power and that it affected the excitability of nerves.

This led to Kerner's prescient comment:
"Some of the drops of the acid brought onto the tongue caused great drying out of the palette and the pharynx." " It can be expected that in outbreaks of sweat, perhaps also in mucus hypersecretion, the fatty acid will be of the therapeutic value." Then he paused and with this disclaimer said. "*What is said here about the fatty acid as a therapeutic drug belongs to the realm of hypothesis and may be confirmed or disproved by observations in the future"*

The condition that became known as Kerner's disease, later got a new name botulism poisoning after botulus the Latin word for sausage. Little else was recorded until 1895. Then, Microbiologist in Belgium demonstrated that the toxin was produced by a gram positive, anaerobic bacterium and named it Clostridium botulinum.

About this time a new industry brought epidemic botulism poisoning again to the forefront.

Near the beginning of the 19th century, the food process we know as canning began in France. At the time Napoleon was seeking a better way to nourish his far-flung troops. The government even offered a prize to anyone who could accomplish this.

Nicolas Appert, a chef, did so by placing different foods in glass bottles, securing the tops,

and boiling them for various periods before cooling. - It worked. - He earned the prize.

The commercial canning industry reached the United States around the middle of the 19th century starting successfully with Heinz ketchup and Campbell's soup. Then, in 1919 a serious problem arose as California began nationwide distribution of its canned foods. The crisis centered around California black olives.

The epidemic started in the summer when dinner guests at five separate locations from Montana to New York City died shortly after the meal. The only connection was all the deceased had eaten one or more black olives before their death from botulism poisoning. Investigation began in Canton Ohio, site of the first outbreak. It continued in Grosse Point Michigan where it was confirmed tainted olives traced to two California producers were the cause. In all thirty people died in five separate incidents

These events led to an overhaul of the food processing and canning laws in California with stringent guidelines for time and temperature in the process. These were adopted throughout the country and remain today ensuring safety in our canned foods .

Currently there are about one hundred new cases of Botulism poisoning each year in the United States. They were mostly from home prepared foods. Death occurs in less than 3% of adults affected, compared to 50% before 1950. and it is virtually zero in infants. Statistics say you are more likely to experience a lightning strike than acquire botulism poisoning.

In 1942 as World War II intensified, the British expressed concerns the enemy would employ chemical or biological warfare. They shared this with the President who responded by assembling a group of academics and industry leaders to form a

U.S. biological warfare center. By 1943 it was established at Camp Detrick in Maryland.

By spring 1943, a group of young men called to serve formed a core group of scientists. Many were in their twenties meaning they were young and only beginning their careers in science. Their task was to learn about agents that could be employed in war.

The team made rapid progress. One of their early accomplishments was to purify the Botulinum toxin molecule and explain how it affected the body. This effort spurred Briton's fear that this toxin would be used to poison their drinking water. These were put to rest when it was determined botulinum toxin was not suitable for use as an offensive weapon. The equivalent of Three teaspoons full could wipe out the world population, but it was just too difficult to deliver!

By 1945, the young scientists resumed civilian life, except for one. He was a biochemist named Doctor Edward Schantz. He would find a peaceful use for Clostridium botulinum toxin. He recognized its

value as a laboratory tool and supplied it free to basic scientists. A small amount was also taken by the CIA for their own unique purposes.

When he retired from Fort Detrick in 1971 to assume a position as Professor at the Wisconsin Food Safety Institute Schantz took the botulinum toxin with him. But a question remained – “who owns the toxin?” ‘ Finally in 1975 at a national security hearing called to learn more about clandestine CIA activities it became official. Dr Edward Schantz who was doing the right thing would be the sole custodian of botulinum toxin.

Earlier, as he was transitioning to the University of Wisconsin, Schantz was contacted by a young ophthalmologist working in San Francisco . This call in 1972 would forever change the role the toxin. The caller was a young part-time researcher. He asked for a small amount to study its effect on eye muscle function.

That young ophthalmologist, Alan Scott, completed residency ten years earlier then took a

novel approach to medical practice. Remaining in San Francisco, he worked each afternoon in his private office caring for patients and in the morning conducted clinical research in the laboratory associated with the California Pacific Medical Center. He worked on his own at no pay.

Scott's aim was to create a novel nonsurgical technique to treat misaligned eyes. He hoped to do this by injecting tiny amounts of a substance to selectively weaken eye muscle action. He already had snake venom and, a substance whose commercial use was as an insecticide as nerve agents, and he would also try alcohol**.** *He had read about Botulinum toxin an wanted to try it but needed a source*.

Scott contacted a young neurologist at Johns Hopkins, who had reported injecting the toxin in a chick embryo while studying causes of club foot. This man had received his toxin from the lab at Camp Detrick. Scott contacted Dr Edward Schantz who had supplied the Hopkins researcher and within weeks Alan Scott had his own supply of Botulinum A toxin.

Scott's first task was to determine a safe dose. Using Swiss mice, the LD/50, or lethal dose to half of the mice injected, was 0.7 billionths of a gram. He called this a mouse unit. By extrapolation, the LD/50 for a 150 lb. human would be 3,000 mouse units.

He injected each of the four poisons separately in an eye muscle of a monkey. Of the four, only botulinum toxin was both effective and safe. It would be Scott's choice going forward. He reported this in 1973 recording the first attempt to use botulinum toxin as a treatment.

Based on success in monkeys using extremely low doses, Scott received Investigator New Drug approval from the FDA in 1977. This meant he could continue to study the toxin for use in a human but now under watchful eyes.

In 1978, Scott was the first person to inject botulinum toxin in a human. It caused no harm**.** The initial dose was weak with no effect**.** But it met the first FDA requirement, the drug was <u>safe.</u> Now it

was time to increase dosage to see if it worked in a human.

By 1981 Scott had injected forty-two patients with good results. He presented his findings at the American Ophthalmological Society. In conclusion he said, “It appears that botulinum toxin can be of some use in treating strabismus.” This researcher was cautious, and never made claims he couldn’t support but he did confirm Kerner’s prophesy made one hundred sixty-one years earlier

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From here Scott, with FDA approval, moved ahead with a full-scale drug trial. This involved two hundred clinical investigators and required botulinum A toxin in sufficient volume to complete the studies. Drug trials are conducted in three phases. Scott’s work reported in 1981 confirming the drug was safe and effective in forty-two patients was the first phase for botulinum toxin.

The second phase would require several hundred patients effectively confirming results of phase one. Then a third phase including thousands of patients would provide additional information about safety, effectiveness and side effects.

I had met Alan earlier, was aware of his work, and joined the study around 1981 at the beginning of phase two clinical trials. Scott and I were about the same age and had the same type of practice, pediatric ophthalmology and strabismus including clinical research, on a much smaller scale by me, and began practice about the same time.

Our team at Indiana University School of Medicine used the trial drug, now called Oculinum, treating strabismus patients. Later adult patients came to us suffering from muscle spasm of the eye lids, face, and neck. Many travelled a long distance to receive this new experimental treatment.

We soon established an “Oculinum clinic” treating patients who returned for injections usually

at three-to-five-month intervals. Patients consented to receiving an experimental drug and there was no charge to the patient for the treatment.

Alan Scott saw value in treating more than eye muscles and encouraged the many investigators who visited his clinic to treat other conditions encountered in their own patients. Scott was also aware that treatment around the face smoothed worry lines, "crow's feet" and wrinkles from aging. This didn't interest him. Mostly he let others pursue expanded use for the toxin. He concentrated on treating eye muscles.

By the mid-eighties, Alan Scott was distributing ten thousand vials of the toxin each year to clinical researchers. To meet FDA requirements for reliable manufacturing, he formed a company he called Oculinum Inc. and found a regular manufacturer to package the toxin. Because he had no outside funding, Scott mortgaged his home and began asking for donations from investigators. This novel approach provided the major funding for the project.

In 1987, he California pacific Medical Center cut ties with Oculinum Inc. on the advice of their liability insurers without cause. With this action Scott was no longer able to supply toxin to investigators in the trials. Seeking a path forward. he approached eight pharmaceutical companies offering to sell his company, Oculinum Inc. All declined for good reasons. The market as predicted by Scott was small. Moreover, anyone buying Oculinum would be dealing with the world's deadliest toxin. Another disincentive was disclosure in the 1973 paper that ruled out the possibility of a patent.

On December 29, 1989, based on data Scott complied from the trials, Oculinum received FDA approval for treatment of strabismus, blepharospasm, and neck muscle dystonia in patients twelve years and older. Scott immediately arranged an exclusive license agreement with Allergan pharmaceuticals. This took the pressure off, but it meant little regarding recovery of money already

spent. Then in 1991 Allergan purchased Oculinum for $9 million. Scott's comment at the sale: "I was OK in the lab and a pretty good clinician, but I was a lousy businessman." When pressed later he said, "It was a good deal at the time."

The new owner Allergan re-named Oculinum Botox and experienced a steady increase in sales based on new medical indications with the drug used mostly 'off label.' Even more important to growth in sales was the success of a Canadian ophthalmologist, who Scott trained. Jean Carruthers promoted Botox for cosmetic use and spread the word worldwide. Today Botox is the market leader and available from AbbVie. Sales are projected to reach 7 billion dollars putting this drug in the top echelon of *all* drugs.

While money was never a motivation for Alan Scott it still is an interesting feature of the life of the drug Botox. By Scott's accounting the total outlay of money from all sources including those given 'in kind' during the development of this drug amounted to a mere $4 million. More than half of the cost was covered by the $2.5 million in donations from the

clinical researchers. This was unprecedented in the history of drug development.

When Scott completed the sale with Allergan, he rewarded an underpaid but loyal staff and gave $750,000 to Dr Edward Schantz who had supported the project with high quality toxin for twenty years at no charge. After these post sale dispersals, Scott retained little more than a modest purse in return for thirty years of effort.

Scott and his wife Ruth raised five children and lived a modest but fruitful life based on Scott's earning from his private practice.

How does the cost of developing Botox compare with that of other drugs. While it is not easy to get accurate reports from drug companies, according to the best information available the number is $1 billion. On average fifty drugs gain approval by the FDA in a year. A current top selling drug was said to cost a whopping $6 billion. At $4 million and change, Botox development was on a shoestring.

Today Botox treats only 3 to 4% of strabismus patients. Although this was the driving force for Alan Scott's work it is barely a tic in the market and the drug might never have succeeded for this purpose alone. Strabismus treatment is estimated to account for less than 1% of Botox sales, the remaining 99+% is shared equally between medical indications and cosmetic/aesthetic use. In medicine it treats conditions from migraine headache to sweaty palms and dozens more. Not all are FDA approved but indications are legitimate, and the drug can be employed safely to treat on the open label policy.

A drug now selling worldwide in the multi billions of dollars and expected to increase in sales was developed by a part time researcher interested solely in asking questions and finding answers. He worked with little help in a simple laboratory and found the money to move ahead on his own. When not in the lab he practiced medicine and with his wife raised a family.

In 1965 now with three young daughters added and a little outside help he built an earthquake resistant, energy efficient – passive solar, low maintenance, home that he lived in until his death in 2021. Its current worth is $2.7 million. He was a pretty good builder!

After selling Oculinum Inc. as the sole owner, Scott relinquished all official ties with Botox. He moved on seeking better ways to treat strabismus and never did anything to indicate he missed the multimillions he could have received in royalties or from selling his company outright. Active until the very end of his life, but still dealing solely with strabismus, Dr. Alan Scott died on Dec. 16th, 2021, at age 89.

Scott's response when asked shortly before his death about his failure to negotiate a better deal when he sold Oculinum said, "I guess I had all the fun and Allergan made all the money." This I believe is an honest answer.

The monumental accomplishment and selfless behavior of Alan Brown Scott, as he tamed the world's deadliest toxin was quite a feat!

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