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Early development history of Botox (onabotulinumtoxinA)

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Abstract

The development of Botox (onabotulinumtoxinA) began in the 1970s as Dr. Scott was attempting to identify an injectable substance that would weaken the extraocular eye muscles in patients with strabismus as an alternative to muscle surgery. This search led to botulinum toxin type A, which was tested and developed over the next 15 years. As botulinum toxin type A moved from an experimental drug to a product in need of licensing by the Food and Drug Administration (FDA), the first manufacturing methods and quality control procedures were developed for Oculinum, the botulinum toxin type A product that would eventually be sold to Allergan and become known as Botox.

Abbreviations: CBER = Center for Biologics Evaluation and Research, FDA = Food and Drug Administration, GMP = Good Manufacturing Practices, HSA = human serum albumin, IND = investigational new drug, IRB = institutional review board.

Keywords: blepharospasm, botulinum toxin, drug development, strabismus

Dr. Alan Scott

In the 1970s, the outcome of strabismus surgery was far from perfect—as many as 40% of patients needed reoperation. We began investigating different substances that could be injected into muscles to weaken them and create permanent alignment changes. With Carter Collins we developed Teflon coated injection needles which recorded the electromyograph, allowing us to identify and inject specific muscles. These are widely used today. I learned about the restricted local effect of injected botulinum toxin type A from a chapter by Daniel Drachman describing the toxin's effects on hindlimb development in chicks.[1] *Drachman had obtained botulinum toxin type A from Ed Schantz who was making toxin at the Food Research Institute at the University of Wisconsin. Ed Schantz generously supplied us with toxin for most of our subsequent experiments and clinical protocols.*

After various studies defined potency and effect on rats, mice, and cats, I injected the eye muscles of monkeys with botulinum toxin type A. Over the next few days, paralysis of the muscle and altered eye positions became apparent. The muscle weakness was quite specific and prolonged, with only a few local side effects and no apparent systemic toxicity. We reported these results in our 1973 paper.[2] *I could immediately tell the value of botulinum toxin type A and thought that it would be useful in blepharospasm and other conditions of skeletal muscle overactivity*[2] *(although I didn't foresee cosmetic use!).*

We conducted many subsequent studies to assess the stability, dosing, and toxicity of botulinum toxin type A. We formulated for human use the toxin Schantz sent to us; the neurotoxin requires a protein stabilizing agent and we changed from the gelatin used in laboratory work to human serum albumin (HSA), an approved drug, whereas gelatin was an unapproved animal product. Although the toxin amounts were initially given in nanograms or micrograms, we moved fairly quickly to using units based on the mouse LD_{50} test because we were interested in the biological activity rather than the mass of toxin. Given the studies we conducted in monkeys and the many similarities between monkeys and humans, we had a good idea of the doses to use in patients. Even so, the protocol established by the hospital required us to start at doses that were several orders of magnitude below those we believed would be effective.

Despite my previous experience characterizing and injecting botulinum toxin type A in monkeys, it was still an emotional experience to inject that first human patient. I didn't know if I'd be able to keep my hand steady for the injections. The first patient I injected had undergone retinal detachment surgery and was left with an eye pulling to one side. He was eager to receive

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This historical narrative was compiled based on review of the literature and interviews with the authors, and the quoted portions reflect the personal observations and reflections of the individuals who were interviewed. In some instances, this article describes uses for which Allergan, an AbbVie Company, has not sought and/or received regulatory approval in individual countries and are mentioned for historical context or background only.

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Please refer to the approved indications and relating warnings and precautions in the Botox and Botox Cosmetic prescribing information, at https://www.rxabbvie.com/pdf/botox_pi.pdf and https://www.rxabbvie.com/pdf/botox-cosmetic_pi.pdf, and https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/20190626-Botox-Cosmetic-Insert-72715US10-Med-Guide-v2-0MG1145.pdf.http://dx.doi.org/10.1097/MD.0000000000032371

botulinum toxin type A as an experimental treatment. We didn't expect any significant adverse reactions, but under the protocol we were required to keep him in the hospital's intensive care unit for 3 days after the injections. The protocol required a very small initial dose, which had the correct effect of straightening the eye but lasted only a few weeks.

After our initial success in strabismus, we began injecting patients for other neuromuscular conditions such as blepharospasm that we thought would benefit from focal muscle weakening. I did the initial injections in torticollis patients and then passed on this experience to Joseph Tsui, a neurologist in Canada. I also did injections for two multiple sclerosis patients with spasticity in the hip muscles. Eventually, other physicians became interested in using botulinum toxin type A and we began to receive many requests for the medication. It became obvious that we needed to increase our manufacturing capability to meet the need, even though my primary interest was in research and not in developing a product. Our lab had a patent policy under which we declared items or processes of possible patentability. The lawyers found that our 1973 paper had published the concepts of how toxin worked, even though that was years before demonstration of clinical effectiveness, so we never applied for a patent.

Mr. Dennis Honeychurch

By the time I joined Alan Scott in 1983, he had already generated data on the safety and efficacy of botulinum toxin type A for treatment of strabismus in clinical studies[3,4] *but lacked the license to move it out of investigational new drug (IND) status to an approved biological product status (*Fig. 1*). We needed a product and establishment license issued by the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), typically issued to large corporations under single management. The drug manufacture and testing had to be moved out of the research facility and into a more suitable location.*

The first step toward licensing was to establish Good Manufacturing Practices (GMP) and Quality Assurance, which included standard operating procedures and quality control—in total more than 100 procedures. I had experience with GMP in my work as a radiopharmacist with the Navy, and that experience helped develop these procedures.

However, we didn't have the funds or expertise to establish a manufacturing and testing facility and big pharma wanted to keep their distance. In fact, I think most companies hung up the phone whenever Alan Scott called and mentioned the word "toxin." Fortunately, the FDA showed appropriate flexibility in their licensing requirements and allowed us to contract out some of the manufacturing steps as long as one of our staff oversaw the process. In addition to overseeing the manufacturing process, Alan or I would gown up and enter the class 100 clean room used for manufacturing. We were both immunized against the effects of the toxin and as such would make the first two critical dilutions. This would give us a diluted toxin solution that was safe for the technicians to process. I remember that the first run with the automated filling machine was not quite a success—it broke nearly all the vials. After that, the process was moved to a clean room and vials were filled by hand. The technicians became very efficient and able to produce batches of 10,000 vials, which were packaged with dry ice and shipped back to San Francisco. Back then we were required to declare the dry ice as a hazardous item, but botulinum toxin type A was exempt!

Dr. Alan Scott

In the early days, we asked for donations of $25 for each vial of botulinum toxin type A we sent out and the money went to Smith-Kettlewell to pay for our research studies. After we hired

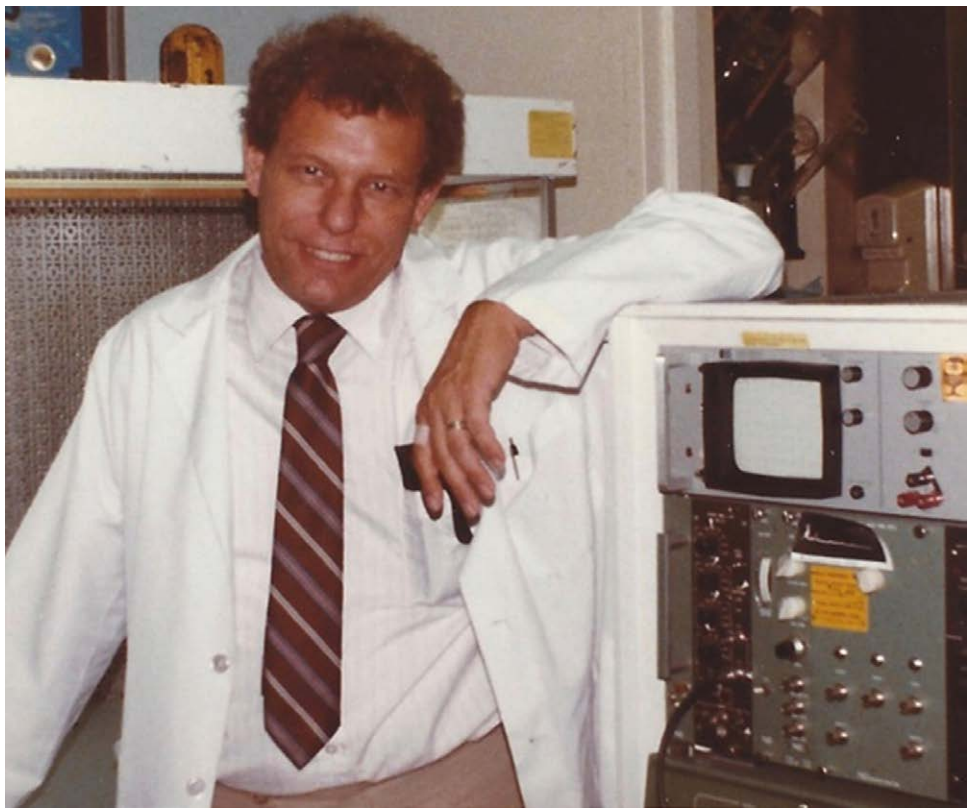

Figure 1 . Dennis Honeychurch in Oakland, California, ~1985. Photo provided by Dennis Honeychurch.

additional personnel to help with the testing and statistics, we raised the requested donation to $40 per vial, but we definitely weren't getting rich. In fact, Dennis and I mostly worked for free and I had to mortgage my house to pay for some of the equipment and costs.

Eventually, we had to stop production of botulinum toxin type A—which by this time was called Oculinum—because neither the Board at Smith-Kettlewell nor the insurers wanted us distributing toxin for human use, so we had to shut down. By this time, Oculinum had become a major treatment for blepharospasm and patients were extremely upset when they could no longer get it. They sent the FDA an avalanche of letters, which caused the FDA to get actively involved.

Dr. Mitchell Brin

*I remember when this happened—I was a clinician using the toxin at Columbia University. We had to go to the Institutional Review Board (IRB) with the insurance letter. They said we could continue to treat patients who were already enrolled in the protocol but couldn't enroll anyone new. This was true for nearly all investigators at the time, although investigators at the National Institutes of Health could use the drug for new patients (*Fig. 2*).*

Mr. Dennis Honeychurch

After leaving Smith-Kettlewell, we moved all testing, storage, and shipping to a building in Berkeley across the street from an animal testing facility. This was convenient because the animal facility had procedures and documentation in place to meet FDA requirements that complied with the participation portion for licensing. For example, after preparing botulinum toxin type A doses for potency, safety/identity, staff would cross the street and inject the mice. Our new facility provided the space needed for the numerous product testing procedures, labeling, storage, shipping and office space.

Again, the limited budget forced us to be creative. We had a laminar flow hood to perform sterility testing but needed a clean space with positive pressure to place the hood. Alan and I built a room within a larger room to isolate the hood. We modified the hood so that a small amount of the hood's air intake would be taken from the main room via an intake vent. This provided adequate differential to place the enclosed room under positive pressure.

Since our product was dried under vacuum, we needed to validate the process. The final product had only 1.4 milligrams of excipients [0.5 mg of human serum albumin, and 0.9 mg of sodium chloride] and we had to test down to the microgram range. We couldn't afford the instrument the FDA used, so we had to come up with a creative solution. We ended up connecting several vials with tubing, applying heat, then sweeping them with dry nitrogen into a less expensive instrument that could read microgram amounts of moisture.

Dr. Alan Scott

*After moving to the Berkeley facility, we incorporated under the name Oculinum, obtained insurance, and continued production while searching for a pharma company that was interested in taking on the product (*Fig. 3*). Around 1984 I approached 6 drug companies, including Allergan, to manufacture the drug. All refused because of risk, limited market, or lack of patentability. After licensure of the drug to Oculinum Inc., we were hesitant to get into the commercial business of selling the drug. By this time many papers on toxin application in various disorders had been published and thousands of vials had been used. Allergan sent a representative to research meetings and they became interested in the drug's potential. We agreed to furnish the drug to Allergan, which would market it.*

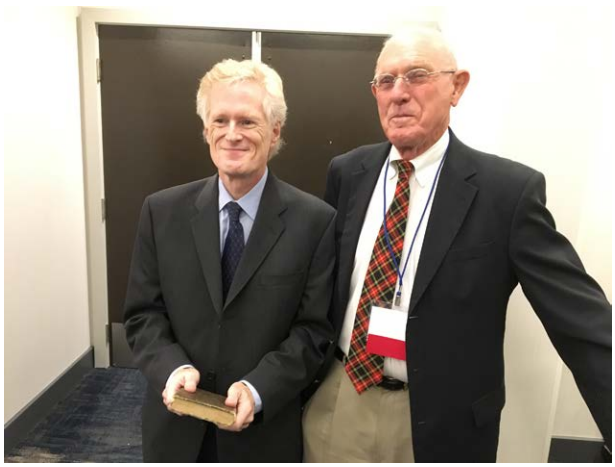

Figure 2 . Mitchell Brin (left) and Alan Scott (right) at a meeting in San Francisco, 2017. Photo provided by Mitchell Brin.

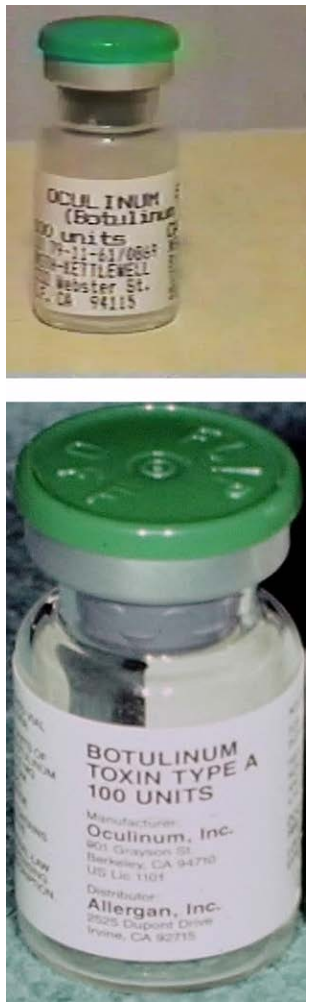

Figure 3 . Top: Oculinum research vial, ~1987. Oculinum commercial vial ~1990. Photos provided by Mitchell Brin.

Mr. Dennis Honeychurch

Once Allergan bought Oculinum, I stayed on as a consultant for 4 years. It was difficult to leave because I had many good colleagues there.

Dr. Mitchell Brin

Oculinum was licensed by the FDA on December 29, 1989 for the treatment of strabismus and blepharospasm associated with dystonia in patients 12 years of age and older. Allergan had a distribution agreement with Oculinum Inc., from which it later acquired the Oculinum product in 1991. It was renamed Botox in 1992 (originally coined [5] as the same product manufactured by Alan Scott). As Alan Scott predicted, Botox proved useful for spasmodic torticollis (cervical dystonia)[6] and other conditions of muscle overactivity such as limb spasticity.[7] Use eventually expanded to hyperfunctional facial lines.[8,9] As discussed elsewhere in this volume, the mechanism of action of botulinum toxin type A is not limited to skeletal motor neurons, but also extends to neurons of the autonomic nervous system as in axillary hyperhidrosis[10,11] and overactive[12] and neurogenic bladder,[13,14] in addition to select sensory fibers as in chronic migraine.[15,16] These mechanisms led to the use and approval of Botox and Botox Cosmetic in 15 indications in the United States and 26 indications across approximately 100 countries, with indications varying according to local labeling.

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Author contributions

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