

Feature Article

Clinical Researcher Details the Discovery of Neurotoxin for Aesthetic Uses

By Andy Pickett, Ph.D., B.Sc., Founder and Director of Toxin Science Limited



For many, history is a nuisance that gets in the way of life today. To others, it is a rich source of knowledge and information, the foundation of who and where we are. Many fascinating and key facts from the past can positively contribute to our current lives, but agreeing on history – the facts, events and reality – can be fiercely argued, sometimes to extremes.

The discovery of botulinum toxin (BoNT) and how nature makes such a potent protein is well documented and universally agreed upon. Frank Erbguth, M.D., a professor in Nuremberg, Germany has often published on these aspects¹. However, the history of BoNT use for the benefit of man is another chapter that tells us a real story of discovery and ingenuity by two enterprising professionals.

Alan Scott, M.D., an ophthalmologist from the Smith-Kettlewell Institute of Visual Sciences in San Francisco, Calif., was extremely interested in strabismus² and was trying to find a way to improve treatment without using surgical techniques applied to the ocular muscles. Edward Schantz, a biochemist, worked on BoNT since the 1940s; originally for the U.S. Army Department of Defense laboratory at Fort Detrick (Frederick, Md.), and then at the University of Wisconsin (Madison, Wis.) in 1972. Dr. Schantz was fascinated by biological toxins and especially BoNT, to the point of considering medical uses, but he never advanced those aspects. Together, Dr. Scott and Dr. Schantz recognized how a protein with such high specific potency could be adapted to treat actual human conditions.

The earliest existing work on using BoNT for a medical investigation was published by Scott, Rosenbaum and Collins in 1973. They looked at using either BoNT, alcohol, α -bungarotoxin (a snake neurotoxin), or a chemical di-isopropyl-fluorophosphate as a means of affecting the ocular muscles in rhesus monkeys³. Although most of the publication is devoted to discussions on the use of BoNT, notably, a sentence at the end acknowledges A. E. Maumenee for the suggestion of actually using BoNT, which leads us to wonder; “who was Maumenee and what does that acknowledgment mean”?

Alfred Edward Maumenee Jr., M.D., was one of the great early American ophthalmologists. In a career spanning over 50 years, he had nearly 350 publications to his name in all areas of ophthalmology⁴. Maumenee’s life and times are described in detail in a fascinating interview published in 1994⁵.

In 1973, when Dr. Scott published his work, Maumenee was ophthalmologist-in-chief at Johns Hopkins Hospital and held The William Holland Wilmer Chair in Ophthalmology at The Johns Hopkins University School of Medicine. His knowledge of, and ideas about BoNT, however, will be reported at a later date, when historians have unearthed the mystery!

Botulinum Toxin Timeline	
1895	The bacterium <i>Bacillus botulinum</i> (later renamed <i>Clostridium botulinum</i>) was identified by Professor Emile Pierre van Ermengem.
1928	P. Tessmer Snipe and Hermann Sommer isolated the <i>Clostridium botulinum</i> toxin for the first time.
1949	Arnold Burgen’s group discovered that botulinum toxin blocks neuromuscular transmission through decreased acetylcholine release.
1973	Earliest existing data on using botulinum toxin for a medical investigation published by A.B. Scott, A. Rosenbaum and C.C. Collins. This study looked at using either botulinum toxin, alcohol, α -bungarotoxin (a snake neurotoxin) or a chemical di-isopropyl-fluorophosphate as a means of affecting the ocular muscles in rhesus monkeys.
1981	A.B. Scott filed a trademark for the neurotoxin Oculinum® (number 1212107). A few days later Scott announced this new name.
1985	By 1985 a significant number of patients were being treated for strabismus, spasmodic torticollis (cervical dystonia), and a range of other muscular conditions.

The early years of Dr. Scott and Dr. Schantz's work have been mostly described by Dr. Schantz and his successor Eric A. Johnson, M.S., Sc.D., who is currently a professor of bacteriology at the University of Wisconsin, and one of the world's leading researchers into many aspects of BoNT. Professor Johnson joined Dr. Schantz at the University of Wisconsin in 1985 and has since served as guardian of the history of the university's involvement, through Schantz, in the BoNT story⁶.

According to Dr. Schantz's account, his collaboration with Dr. Scott began around 1968, when he was still at Fort Detrick⁷. Dr. Scott's descriptions of the historical events are shorter but no less informative than those from Dr. Schantz^{8,9}. In particular, the ever-increasing use of BoNT in these earliest years, from treating ophthalmic conditions to larger muscle problems, is an exceptional story^{8,9}.

Word of this promising new approach to treatment of ophthalmic conditions soon spread around the world. In particular, clinicians from the U.K. visited and trained with Dr. Scott to learn his techniques with this new product. One of the first was John Lee, D.M., M.R.C.P., F.R.C.S., F.R.C.O.phth, from Moorfields Eye Hospital in London. Dr. Lee visited Dr. Scott in 1981 and returned from the trip with a few vials of the product in his pocket¹⁰. It was from these initial ophthalmic treatments that the first indications of effects on facial muscles in general were identified.

In those early days, many ophthalmic clinicians reported anecdotes of patients who returned for examinations after initial treatment with BoNT and declared that their face never looked better with less wrinkles, or even that their migraines had disappeared! Dr. Lee even wryly joked that had he realized the future cosmetic potential of BoNT, he would have been a wealthy man. Regrettably, none of these early observations were committed to case reports.

Interestingly, also in 1981, Dr. Scott and Dr. Schantz named their product Oculinum[®], since "the original name of the toxin, which is of course the most lethal substance known, is indeed scary to the patient¹¹." Dr. Scott filed the trademark Oculinum (number 1212107) just a few days prior to announcing the new name at a conference.

By 1985, four years before the product was licensed by the Food and Drug Administration (FDA), significant numbers of patients were being treated for strabismus¹², spasmodic torticollis (also called cervical dystonia)¹³ and a range of other muscular conditions⁹.

Allergan acquired the Oculinum trademark in July 1991 and subsequently changed its name (after the product was first licensed in the U.S. in 1989 for the treatment of strabismus). Dr. Scott reported that prior to this he had presented the product to Allergan and many other organizations and was turned down.

So the questions still remain: What was the earliest published report on the aesthetic use of a BoNT, and who actually discovered this use? Many physicians, including neurologists, would say this was not a discovery per se, since they always re-balanced the facial muscles after a BoNT treatment in order to obtain an acceptable aesthetic appearance for the patient. This was particularly the case in larger facial treatments requiring BoNT, such as hemifacial spasm. Apparently, treating unaffected areas of the face to obtain the correct appearance for the patient was always on their minds.

1989	<p>Oculinum receives licensing from the U.S. Food and Drug Administration for the treatment of strabismus.</p> <p>Also in this year, the journal <i>Plastic and Reconstructive Surgery</i> published the first verifiable report addressing the use of botulinum toxin for aesthetic treatment. Written by Richard Clark, M.D., and Craig Berris, M.D., from Mercy General Hospital in Sacramento, Calif., this short report defined the published baseline for aesthetic uses of botulinum toxin.</p>
1991	<p>Allergan acquires Oculinum[®] and subsequently changes its name to BOTOX</p> <p>Dysport originates in the U.K. to treat neurological conditions.</p> <p>Also in this year, Jean and Alistair Carruthers present their first data on aesthetic use of botulinum toxin at the American Society for Dermatologic Surgery annual meeting in Orlando, Fla.</p>
1992	<p>The Carruthers' study of 18 patients treated for glabellar lines titled: Treatment of glabellar frown lines with C. botulinum-A exotoxin was published in the <i>Journal of Dermatologic Surgery and Oncology</i>.</p>
1994	<p>A more extensive series of treatments (corrugator, procerus, and other conditions) with neurotoxin was documented by Guyuron and Huddleston of Mount Sinai Medical Center in Cleveland, Ohio.</p>
1995	<p>Benjamin Ascher's first published work explored botulinum toxin for the treatment of glabellar lines and crow's feet in 19 patients that were followed every month for 12 to 24 months.</p>

In August 1989, the journal *Plastic and Reconstructive Surgery* published the first verifiable report¹⁴ that addressed the use of BoNT for aesthetic treatment. Written by Richard Clark, M.D., and Craig Berris, M.D., from Mercy General Hospital in Sacramento, Calif., this short report described treatment of the frontalis on one side to re-balance a unilateral facial nerve paralysis. This defines the published baseline for aesthetic uses of BoNT.

There is no doubt that Drs Clark and Berris were working in the field of aesthetics. Their patient is clearly identified as having a two face lifts previously as well as surgical correction for crow's feet. Both are still practicing aesthetic surgeons today in Sacramento!

At that time, Jean Carruthers, M.D., was working as an ophthalmologist at the University of British Columbia in Vancouver¹⁵. Dr. J. Carruthers and her husband Alistair Carruthers, M.D. report that they first encountered BoNT in 1988¹⁵ using it for the treatment of strabismus in adults¹⁶, not for aesthetic treatment. Their first data on aesthetic use of BoNT seems to have been presented at the *American Society for Dermatologic Surgery* annual meeting in Orlando, Fla., in 1991¹⁷. Their data on 18 patients treated for glabellar lines was published a year later¹⁸.

In 1994, a more extensive series of treatments (corrugator, procerus, and other conditions) was documented by Guyuron and Huddleston of Mount Sinai Medical Center in Cleveland, Ohio.

In February 1995, Benjamin Ascher, M.D., a plastic surgeon in Paris, France, published the findings from his study which explored BoNT for the treatment of glabellar lines and crow's feet in 19 subjects. Patients were followed every month for 12 to 24 months. At the time, this was considered a long study¹⁹. Dr. Ascher reported an increase in effectiveness with repeated injections.

According to published literature and available information, the aforementioned chronology is accurate, which begs the question; Did the early publicized work of the Carruthers capture the imagination of many plastic surgeons and encourage their use of BoNT, or was this work already ongoing in various places and in various guises? The general indications suggest that many clinicians were realizing the potential of BoNT for aesthetic uses at that time and were already engaged.

What, if anything, can we learn from this history? First and foremost, there is no evidence that any one person "invented" the use of BoNT for aesthetic purposes. Based on the information available, published and unpublished, the aesthetic effects of neurotoxin were acknowledged early on, but its full potential was not realized for many years. The earliest published report predates anything claimed today. Therefore, stories claiming that investigators have not "benefitted" from the invention are baseless²⁰.

It is also clear that the therapeutic uses of BoNT fuelled the aesthetic uses, which is common in medicine. Science as a whole is full of chance discoveries, fateful events and surprising results.

Also, we can observe distinct grey areas between these two worlds of BoNT use, in which doses are similar (strabismus and glabellar lines), muscles are the same, and targeting is essential (both conditions suffer from the same side effects of BoNT if not administered correctly).

We also realize that the intense interest in aesthetic applications is promoting both an advanced understanding of how BoNT is applied in practice (for example the number of cadaver dissection workshops being offered that look at facial muscles in detail), and new applications not previously considered, such as wound healing, scar elimination and its effects on skin quality^{21, 22}. Many of these developments are equally applicable in both worlds.

Finally, there is a simple lesson to be learned: If you observe something new or novel when using BoNT, regardless of the application, publish it.

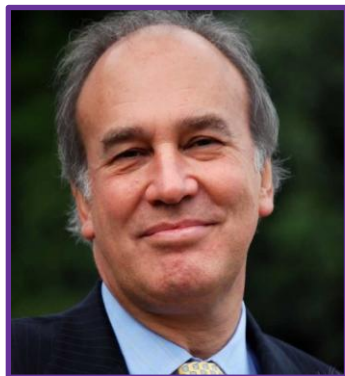
2002	BOTOX® Cosmetic receives FDA approval in the U.S. for dosing specifically to temporarily improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in people 18 to 65 years of age.
2003	Vistabel begins receiving international approval for aesthetic use outside of the U.S.
2009	Azzalure begins receiving international approval for aesthetic use. Dysport receives FDA approval for temporary improvement in the appearance of moderate to severe glabellar lines, or frown lines between the eyebrows, in adult patients.
2010	Bocouture / Xeomin begins receiving international approval for aesthetic use.
2011	Xeomin receives FDA approval for temporary improvement in the appearance of moderate to severe glabellar lines, or frown lines between the eyebrows, in adult patients.

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For over 30 years he has worked in the pharmaceutical industry on a wide-range of biological products, and especially botulinum toxin for the last 23 years.

His responsibilities provided scientific and product support, as well as technical expertise on botulinum toxin structure, function, physiology, assay technologies, quality, regulatory and production areas.

For the last several years, Dr. Pickett has focused on translating the science and technology of botulinum toxin to enable clinicians, dermatologists, plastic surgeons, rehabilitation specialists and medical students to have a clear understanding of the toxin products available, how they work and how they can be used.

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