chapter 32

CHEMODENERVATION THERAPY: TECHNIQUE AND INDICATIONS

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In this chapter we review the background of botulinum toxin injection for strabismus, the technique of its use, and the application of this treatment to various strabismic disorders. Once one becomes adept with the technique and comfortable with its applications, it will seem indispensable for many cases in which one wants to change ocular alignment but does not wish to operate. It should not, however, be regarded as a general replacement for incisional surgery.

Historical Perspective

The first thorough investigations of botulinum toxin were undertaken by Kerner (see Gruesser[9] for review of this topic) and published in 1817–1822. He followed the clinical course of 230 patients with botulism, making many original observations about causation, diagnosis, prognosis, and treatment. More importantly to our topic, he extracted the toxin from sausages, demonstrated its effects in animals, correctly concluded that it paralyzed skeletal muscles and parasympathetic function, and proposed its use as a therapeutic agent in neurologic diseases such as chorea that are characterized by excessive motor movement. Just when his experiments were defining the potential medical effects of botulinum toxin, his request to the Bavarian king for support was apparently turned down, because he abandoned his researches and turned toward holistic medical practice and romantic poetry, a scenario not foreign to us nowadays.

Over the next 75 years little was added until van Ermingen in 1896, after an epidemic of intoxication caused by improperly cured ham, described in great detail the organism, its toxins, and their effects in several mammalian species. Clinical botulism is mostly a result of improper food preparation and/or preservation. Public health and commercial interests at that time then supported the research, and a large literature developed on the organisms, their toxins, and the prevention and treatment of botulism. But it was 160 years after Kerner before the idea of therapy with botulinum toxin was implemented.

We began in 1970/1971 with injection of various drugs into extraocular muscles (EOMs) as an alternative to surgical treatment for strabismus.[29] Among these was botulinum toxin, considered also by others (Crone, Bach-y-Rita, Jampolsky, Maumenee—personal communications) and actually used by Drachman[6] to experimentally paralyze animal hind limbs without inducing systemic toxicity. Using crystallization techniques developed by the U.S. Army Chemical Warfare Department, Schantz[24] prepared and generously supplied us and many other investigators with botulinum toxin. We chose type A botulinum toxin because, of the several types involved in epidemics, it had a strong muscle-paralyzing effect. This approach is still used to prepare Allergan's Botox. The type A botulinum toxin from Porton Laboratories, Dysport (*dys*tonia—*Port*on), is purified by slightly different techniques. Mouse LD/50 potency tests on these products done in our laboratory gave results in units that were equivalent in side-by-side trials in human blepharospasm (Botox, right eye; Dysport, left eye of the same patient). However, as labeled by the manufacturers, the clinical potency equivalence is variable; the average of several reports is about 3 units Dysport to 1 unit Botox.

Chemistry

Botulinum toxin molecules are long protein sequences (150,000 daltons) with three domains (active portions of the molecule) (Fig. 32–1). The first domain binds to one of six receptors found exclusively on nerve terminals; these are specific receptors for clostridial toxin. At this time, nobody knows why they are there. Endocytosis then brings the toxin into the nerve terminal within vesicles. The second domain allows the toxin to enter the nerve cytoplasm from the vesicles. The third domain acts as an enzyme, each toxin

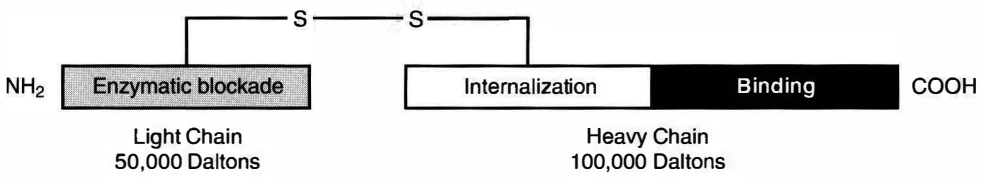

Figure 32–1. *Schematic localization of functional domains within botulinum toxin.*

type cutting a different and specific site on one of the three proteins required to dock vesicles to the nerve membrane for exocytosis of acetylcholine.

In the past few years, the seven toxin types, the six nerve membrane receptors, and the three substrate proteins involved in exocytosis have been identified and sequenced and the specific amino acid sequences of the botulinum toxin molecule that are involved in receptor affinity and enzymatic activity have been identified, all in great detail.

Mechanism of Action in Strabismus

Initially, we thought that botulinum toxin treatment of comitant strabismus worked because the EOMs were permanently weakened by the induced denervation paralysis. Spencer and McNeer[30] have shown changes in the outer (orbital) muscular layer of botulinum toxin–treated primate EOMs, lasting for many months. It is possible that this may reduce primary-position force (normally 8–10 g for a human horizontal rectus) without showing up in full active contraction (normally 60–100 g). But active contraction force returns fully to these muscles. We now believe that the muscles alter alignment of the eyes mostly by having changed their length when they were stretched or relaxed. Botulinum toxin is just a way of getting the eye into a new position so that the muscles can adapt their length.[27] The propensity for this internal sarcomere reorganization varies from one individual to another. It also is dependent on the dose response, on creating a large angular change of alignment from the botulinum toxin injection paralysis, and on its persistence for at least 1 month. Therefore, it is not surprising that clinical responses to initial botulinum toxin injection are variable.

Indications and Clinical Results

The indications for botulinum toxin injection in strabismus are similar to indications for surgery, but there are important differences. Botulinum toxin injection in EOMs is most efficient in nonrestrictive strabismus. Severe restrictions caused by scarred, inelastic muscles favor surgery, because botulinum toxin depends on reciprocal agonist-antagonist readjustments of length-tension elasticity. Scarring and paralysis restrict the inherent ability of the muscle to alter its length-tension characteristics. Smaller deviations (horizontal or vertical) with minimal sensory changes have a superior prognosis and may routinely be managed successfully using botulinum toxin injection. Large-angle deviations, more frequently found in long-standing adult strabismus, can be expected to respond favorably, although repeated injections often are needed, resulting in a longer interval from the initiation of therapy to optimal correction. Despite this apparent disadvantage, a significant number of adults choose chronic botulinum toxin injections to achieve the desired result in place of surgery.

Tables 32–1 and 32–2 show that larger deviations are less fully corrected by one injection, that esotropia and exotropia generally respond similarly, and that children and adults respond alike. In general, there is a 30% to 40% chance that one injection will correct the deviation to 10 PD or less. Biglan and colleagues[1] obtained a 38% correction rate with 1.3 injections, and Carruthers and Kennedy[5] achieved a 29% rate in large-angle exotropia with one injection. Botulinum toxin has only a transient alignment effect in strabismus resulting from permanent nerve paralysis but an important effect on contracture of the antagonist to the paralyzed muscle. Botulinum toxin fills a void as a nonsurgical therapeutic method.

PARALYTIC STRABISMUS

Sixth Nerve Paralysis

Acute cases of any age or origin are followed without treatment for 3 to 4 weeks. If healing begins within a month, it typically will be progressive and complete. Adults will be rehabilitated and children seldom lose binocularity if alignment is restored in a month. After 1 month, if disabling diplopia persists and recovery is not progressing, or if a child remains esotropic in all gaze positions so that binocularity is threatened, then injecting the medial rectus (MR) on the affected side(s) is appropriate, even though many of these cases would resolve over time. In a randomized trial in ambulatory adults with paresis of diabetic or vascular origin, there was little long-term difference in recovery between a botulinum toxin–treated (86%) and an observed control group (80%).[12] Thus, for these patients who have a generally good prognosis, the value of botulinum toxin treatment lies in earlier rehabilitation.

For more *severe paresis* of traumatic origin or those caused by intracranial pathology, recovery is often delayed several months or takes place very slowly. During this time, MR contracture progresses and esotropia increases. Botulinum toxin injection of the MR in these nonacute cases allows the lateral rectus (LR) to recover against an equally weak MR of normal length, rather than against a strong and shortened MR. There is virtually no risk of permanent overcorrection and the patient's alignment is improved, serving both functional and cosmetic goals while awaiting healing of the LR. The data from Metz and Mazow[20] indicate that there is a higher percentage of correction in such cases (Table 32–3).

Persistent esotropia 6 to 12 months after onset may be due to limited LR recovery or to MR contracture in varying

Table 32–1. Effect of Botulinum Toxin Injection on Strabismus in Children*

	No. of Patients	Average Deviation (PD)		% Change	Final Deviation of 10 PD or Less	
		Preinjection	*Postinjection*		*No. Patients*	*% Patients*
Esotropia						
By Number of Injections						
1 injection	146	28	9	68	101	38
>1 injection	115	35	11	69	77	30
All patients	261	31	10	68	178	68
By Initial Deviation						
8–24 PD	81	16	7	56	63	78
25–39 PD	108	30	11	63	68	63
40+ PD	72	50	11	78	47	65
All patients	261	31	10	68	178	68
Exotropia						
By Number of Injections						
1 injection	66	26	12	54	32	34
>1 injection	29	27	15	44	13	14
All patients	95	26	13	50	45	47
By Initial Deviation						
10–24 PD	43	17	7	59	29	67
25–39 PD	32	29	16	45	8	25
40+ PD	20	42	19	55	8	40
All patients	95	26	13	50	45	47

*Results in 356 patients (ages 2 months–12 years) with follow-up of 6–65 months (average, 27 months). Reduction rate of strabismus is broken down by number of injections and initial deviation as measured in prism diopters.

Table 32–2. Effect of Botulinum Toxin Injection on Strabismus in Adults*

	No. of Patients	Average Deviation		% Change	Final Deviation of 10 PD or Less	
		Preinjection	*Postinjection*		*No. Patients*	*% Patients*
Esotropia						
By Number of Injections						
1 injection	216	28	9	68	142	38
>1 injection	159	32	14	57	68	18
All patients	375	30	11	63	211	56
By Initial Deviation						
10–24 PD	132	17	6	62	95	72
25–39 PD	142	29	10	65	81	57
40+ PD	101	49	18	62	35	35
All patients	375	30	11	63	210	56
Exotropia						
By Number of Injections						
1 injection	133	28	11	61	77	27
>1 injection	154	34	13	61	72	25
All patients	287	31	12	61	149	52
By Initial Deviation						
10–24 PD	93	17	8	53	62	67
25–39 PD	112	30	11	64	60	54
40+ PD	82	50	18	64	27	33
All patients	287	32	12	60	149	52

*Results in 662 patients (ages 12–90) with follow-up of 6–83 months (average, 17 months). Reduction rate of strabismus is broken down by number of injections and by initial deviation as measured in prism diopters.

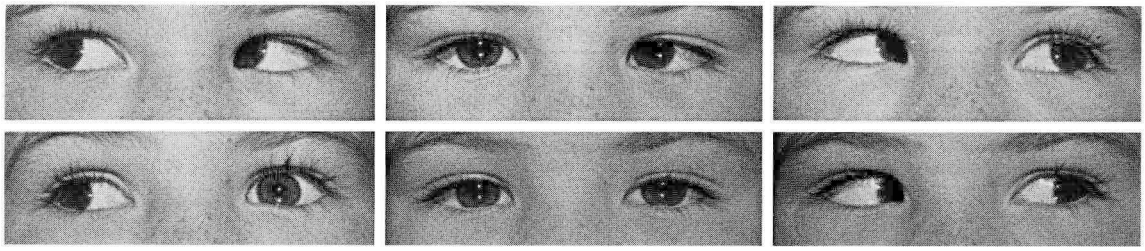

Figure 32–2. *Seven-year-old boy with comitant 30 PD of esotropia 3 months after spontaneous onset of left lateral rectus palsy.* Top, *Before injection.* Bottom, *One week after 1.2 units of botulinum toxin was injected into left medial rectus. Left abduction is full, indicating that the esotropia was due to medial rectus contracture.*

proportions. If there is abduction beyond the midline, good abduction saccades, or good LR force (30 g or more), then release of the MR contracture by botulinum toxin injection alone will often be fully curative. Of course, these patients respond well to simple recess-resect surgery, but the almost magical effect of botulinum toxin injection of the MR makes this simple office procedure attractive (Fig. 32–2).

In cases of *permanent paralysis* there is no place for botulinum toxin injection alone, because recurrence is inevitable. Surgery by lateral transposition of the superior rectus (SR) and the inferior rectus (IR) gives the largest amplitude of single binocular vision.[22] The value of botulinum toxin here is twofold. First and most important, botulinum toxin injection lengthens and preserves the short MR so that this muscle, now the only active horizontal mover, has a large range of contraction-relaxation. In contrast, surgical recession of an already short and contracted MR restores alignment but leads to further shortening and a further reduction in range of motion. Also important is that botulinum toxin leaves the anterior ciliary artery supply of the MR intact, obviating the threat of anterior segment ischemia. The ability of botulinum toxin to release MR contracture makes it appropriate to wait a full 6 months after the onset before undertaking transposition surgery. Botulinum toxin injection may be done a few weeks before surgery or deferred until the time of surgery to allow accurate traction testing of the MR. It is then easily done under direct visualization. Injection is best deferred until postoperative alignment can be determined in cases in which MR contracture is mild—it may be unnecessary, and overcorrection could result. Injection several months after surgery has corrected several undercorrected transposition cases and may need to be repeated.

Third Nerve Paresis

Saad and Lee[23] corrected three of four cases that had some residual MR function, and Metz and Mazow[20] similarly corrected a majority of their cases using botulinum toxin. Botulinum toxin is very useful in late aberrant third nerve regeneration, where small deviations interfere with primary-position alignment. The muscles seem to be especially sensitive, and small doses should be used.

Table 32–3. Botulinum Toxin Correction of Nonacute Sixth Nerve Paresis

		% Recovered	
	No. Patients	*Botulinum Toxin Treated*	*Control*
Unilateral	34	70	31
Bilateral	11	90	42

From Metz HS, Mazow M: Botulinum toxin treatment of acute sixth and third nerve palsy. Graefes Arch Clin Exp Ophthalmol 1988;226:141–144.

Fourth Nerve Paresis

Botulinum toxin injection is beneficial in unilateral fourth nerve paresis. Lozano Pratt[14] corrected 9 of 9 acute cases with 17 to 30 PD of vertical deviation before injection at 12 months' follow-up. Buosanti[2] corrected 9 of 15 (3 others partially improved). One of us corrected 4 of 6 patients observed over 12 months. It is interesting that a series of inferior oblique (IO) injections done 15 years ago did less well, so that this treatment approach was (temporarily) abandoned. Higher doses and better technique explain the current results. All cases just mentioned were injections of the overacting IO muscle. Garnham and colleagues[7] found botulinum toxin injection of the yoke IR more useful in both acute and chronic fourth nerve paresis. We agree that this is valuable in cases in which the vertical deviation is more pronounced in downgaze.

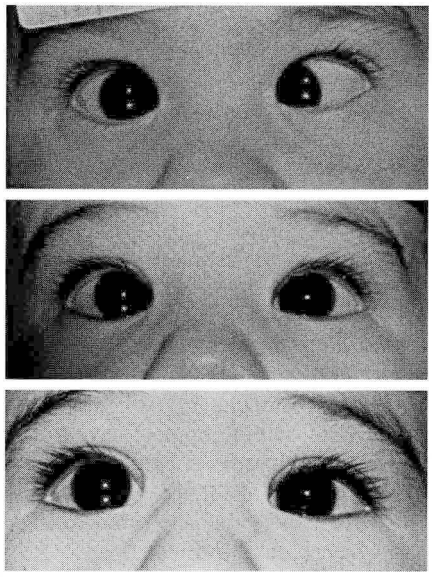

Figure 32–3. *Infantile esotropia.* Top, *Age 6 months, before injection.* Middle, *Age 9 months, 3 months after first bilateral medial rectus injection at 6 months of age.* Bottom, *Age 14 months, 5 months after second bilateral medial rectus injection.*

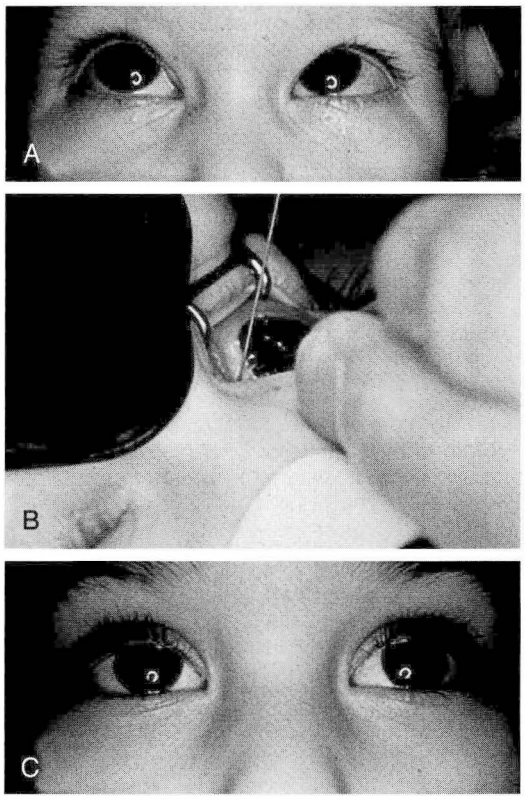

Figure 32–4. *Photographs of infantile esotropic patient treated with bimedial botulinum toxin injection.* A, *Patient at preinjection age of 12 months displays characteristic deviation of infantile esotropia.* B, *Patient receives bimedial 2.5 units of botulinum toxin in intramuscular injection under nitrous oxide anesthesia.* C, *Patient is orthotropic at both distance and near fixation 53 months after injection.*

CHILDHOOD STRABISMUS

Infantile Esotropia

Treatment of infantile esotropia by simultaneous bimedial botulinum toxin injection is quite successful (Figs. 32–3 and 32–4). Table 32–4 shows the results of several independent series.[3, 8, 18, 28] All these reports include 2 years or more of follow-up and show high correction rates of 60% to 80% with multiple injections. Opinions from these investigators suggest the following therapeutic program:

1. Perform simultaneous bimedial injection.
2. Inject as early as age 3 months. The good results in the series of Campos and associates[3] were all in patients injected before age 8 months.
3. Repeat simultaneous bimedial injection with recurrence of esotropia exceeding 15 PD, increasing the dose unless ptosis is a limiting side effect.
4. Examine patient frequently, correcting any hyperopic refractive error.

The following comments are pertinent:

1. Large overcorrection to 20 to 40 PD of exotropia, lasting 3 to 6 weeks, is usual and desirable.
2. Over one third of infants presenting with esotropia and no refractive error when first seen will develop significant hyperopic/astigmatic refractive errors and thus develop accommodative esotropia. The appropriate treatment is full-strength lens correction.
3. All authors remark that the incidence of dissociated vertical deviation (DVD) and V- and A-pattern strabismus appears to be lower after successful bimedial botulinum toxin treatment than with surgical correction, but no comparative data are available.

Table 32–4. Infantile Esotropia Treated by Botulinum Toxin (No Prior Surgery)

Authors	No. Patients	No. Injections	% Corrected to 10 PD or Less
McNeer et al[18]	76		89
Scott et al[28]	61	1.6	66
Gomez de Liano et al[8]	107	1.6	73
Campos et al[3]	50	1.0	76

Accommodative Esotropia

Bimedial rectus botulinum toxin injection has been very useful for correcting a high accommodative convergence/accommodation ratio with residual esotropia at near and for the nonaccommodative angle in accommodative esotropia.[19] Consecutive exotropia has not been seen. Initially, low-dose simultaneous bimedial injection of 2.5 units should be used and repeated as needed (Fig. 32–5).

Acquired Esotropia

Acquired esotropia here refers to strabismus developing after infancy that is neither paretic nor accommodative. Bimedial injection of 2.5 units of botulinum toxin can be expected to provide motor alignment, but it is less stable and effective with intractable amblyopia. The best responses

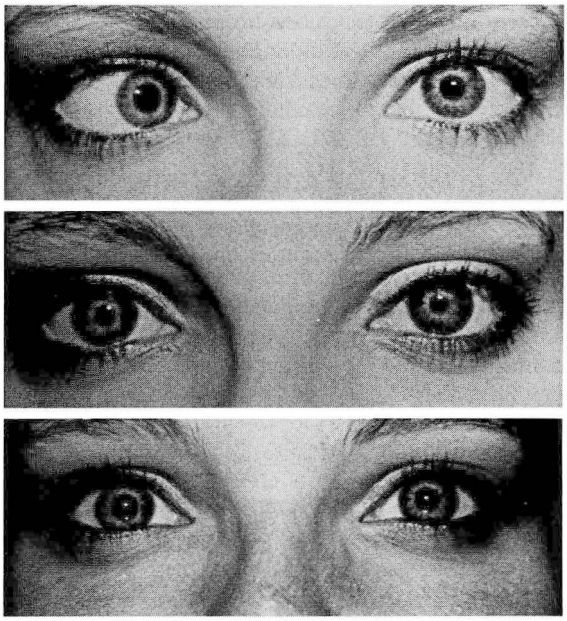

Figure 32–5. *Loss of fusion from removal of hyperopic correction.* Top, *Esotropia while wearing full contact lens correction.* Middle, *Two months after injection of right medial rectus with botulinum toxin.* Bottom, *Eighteen months after injection of right medial rectus.*

are achieved if amblyopia can be improved or reversed before injection. Unilateral MR injection will often enhance or create hypertropia. Therefore, the hypotropic eye should be injected even if it is the fixing eye to help correct rather than worsen such vertical deviations.

Intermittent Exotropia

In children, the recommended schedule is simultaneous 2.5-unit doses in both LR muscles. This avoids the secondary vertical deviations and ptosis common after higher doses or unilateral injection. As with surgery, an exotropic deviation recurs in the majority of patients. An acceptable result thus means a lesser exotropic angle that can be comfortably controlled. In an investigation limited to botulinum toxin treatment of childhood intermittent exotropia,[31] 32 patients were treated by one or more simultaneous bilateral Botox LR injections and followed 3 years from the final injection. Sixty-eight percent developed a stable deviation of 10 PD or less. Seven of the patients required surgery during the study period when injection failed to prevent recurrent exotropic drift. The response between ages 3 and 5 years was much better than in younger or older patients. With evidence of exotropia exceeding 10 PD, injection should be repeated.

Table 32–5. Botulinum Toxin Dosage for Initial Injections

	Units
Horizontal strabismus*	
Under 25 PD	2.5
Over 25 PD	2.5–5.0
MR injection for LR palsy	
Early (1–3 months)	1.0–2.0
Later or in conjunction with transposition surgery	2.5
Later for partially or fully healed palsy but with MR contracture	2.5
Vertical muscles	
IR for comitant deviation	2.5
IR for thyroid	5.0
IO	2.5
SR (rare)	2.0
Children with infantile esotropia or exotropia (bilateral injections)	2.5
Weak muscles—myasthenia, external ophthalmoplegia, aberrant regeneration, cerebral palsy	1.0–2.0
Retrobulbar injection for nystagmus	25.0

MR, medial rectus; LR, lateral rectus; IR, inferior rectus; IO, inferior oblique; SR, superior rectus.
*Further refinements: Smaller doses for MR, larger for LR. Smaller doses for smaller squints, larger for larger squints. Smaller doses for small women (occasionally very sensitive).

Cerebral Palsy

Strabismus surgery for neurologically impaired infants and children is less predictable than in normal subjects; it has a high rate of overcorrection, and side effects of general anesthesia are more frequent. Botulinum toxin injection offers an alternative with a very low overcorrection rate (about 3%). Low-dose bimedial injections of 1.25 to 2.0 units are preferred with esotropia because the dose-response ratio is less predictable. Exotropia responds less strongly. The usual beginning dose is 2.5 units. Reinjections are often necessary, increasing the dose as indicated (Table 32–5). Although overcorrection is possible in esotropia, it has not been seen in exotropia. Strabismus in older children with cerebral palsy is treated by unilateral injection to avoid past pointing and balance problems from the induced paralysis.

TREATMENT OF ADULT STRABISMUS

Multiply Operated Strabismus

Multiply operated strabismus patients unhappy with the surgical outcome are frequent candidates for botulinum toxin injection. The strabismus is often complicated by cicatricial restrictions, excessive muscle recession, and poor fusion. Evaluation of comitance, versions, and forced ductions will be useful in making a prognosis. Botulinum toxin injection will be less predictable, often yielding small corrections requiring multiple injections. But the ease of injection and the frequently excellent outcome warrant a trial in most such cases. Because suppression and amblyopia are frequent, the effects of botulinum toxin-induced paralysis on the sensory status is often of no concern. The series of Carruthers and Kennedy,[5] with 29% correction after one injection, is representative of this group.

There is a significant incidence of restrictions from injury or prior retinal or strabismus surgery, of secondary strabismus due to overrecessed muscles, and of permanent paresis in adult strabismus. None of these are ideal cases for botulinum toxin injection (or for surgery). These and previously unoperated large-angle deviations can be expected to respond to repeated botulinum toxin injections over time. Despite this apparent disadvantage, a significant number of adults choose repeated botulinum toxin injections to achieve a partial result. Indeed, in one exceptional subset of 80 patients, 8 to 20 injections were given as chronic treatment.[13] Smaller deviations with minimal sensory changes had a better prognosis. The intervals between recurrences gradually increased, and a number of patients became stable. Our experience is similar. The chance of creating a greater strabismus problem with botulinum toxin injection is minimal, affording both the patient and surgeon security that little is at risk from trying it.

Post–Retinal Detachment Strabismus

The prognosis for curing strabismus resulting from retinal detachment surgery is guarded if there is severe scarring (Fig. 32–6). These patients have normal binocular vision in their favor. In most cases, the strabismic angle is modest, and it is always worth trying botulinum toxin injection. Scott[26] corrected 60% of cases with one injection, and Pettito and Buckley[21] corrected 80%. Scarred EOMs often require larger doses or a repeat injection. Injection of two muscles (e.g., the LR and IR simultaneously) is common.

Thyroid Ophthalmopathy

Botulinum toxin is useful in acute or active cases to relieve diplopia (Fig. 32–7).[15, 25] Maintaining alignment to prevent or treat chronic cases is much less secure; surgery

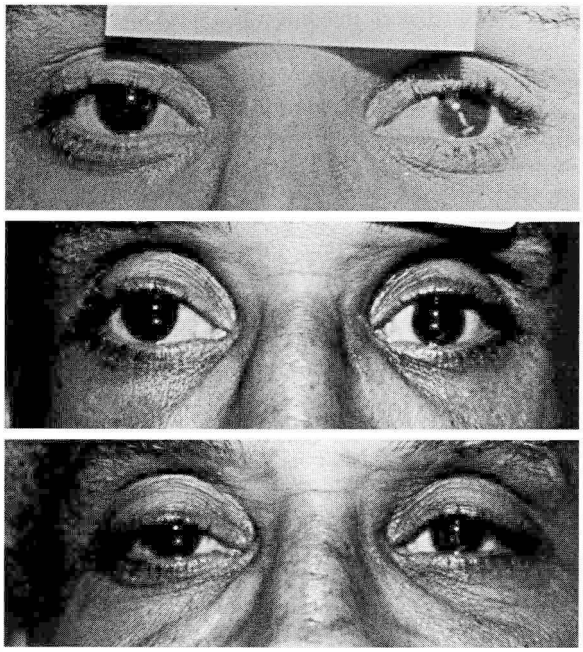

Figure 32–6. *Retinal detachment with loss of vision, left.* Top, *Before injection of botulinum toxin showing left exotropia.* Middle, *One year after injection of left lateral rectus.* Bottom, *Five years after injection.*

is avoided in 25% to 30% of cases. Most late EOM restrictions are fibrotic scars, precluding benefit from botulinum toxin injection. However, an occasional remarkable loosening of IR contracture shows that some restrictions are caused only partly by fibrosis and that internal muscle shortening plays a role. There is no way to predict this clinically except to perform a therapeutic trial.

Thyroid-induced esotropia offers the best prognosis for botulinum toxin injection. The medial rectus muscles are frequently affected in thyroid disease and the horizontal deviation is usually modest. Because multiple muscle surgery in thyroidal eye disease carries a higher risk of ischemia, use of botulinum toxin for the esotropia while operating on the vertical deviation is very useful.

Post–Cataract Strabismus

Immediate diplopia after cataract surgery in previously fusing adults usually presents as hypotropia of the operated eye secondary to IR contracture after retrobulbar anesthesia. When prisms are inadequate and the patient wishes to avoid IR recession, botulinum toxin injection of the IR will correct over 60% of cases with a single injection. A second useful application is in long-standing unilateral cataract with exotropia and diplopia after cataract removal. Injection of the LR will restore alignment and subsequently maintain fusion in over half of these patients.

Postoperative Adjustment

Avoiding multiple surgical procedures is an integral part of strabismus treatment. Botulinum toxin injections are an alternative to additional surgery for strabismus, particularly if the intended goal has not been achieved by recent surgery. Botulinum toxin may be used either early or late in the postoperative period[17] or in conjunction with surgery, especially if the planned surgical procedure (e.g., transpositions, additional surgery on rectus muscles) may compromise the vascularity of the anterior segment.

Intrinsic Muscle Disorders

Unexercised EOMs and other tissues stiffen markedly in some persons. Strabismus in chronic myasthenia and progressive external ophthalmoplegia is surprisingly responsive to botulinum toxin when the eye is stiff on traction testing. The response is much less when the eye is readily moved.

Nystagmus

Carruthers[4] improved vision by 3 lines after direct intramuscular injection of botulinum toxin in 3 of 4 cases with purely horizontal congenital nystagmus. This resulted in vision of 20/40 (6/12) or better for several months. Acquired nystagmus with oscillopsia and reduced vision usually has a vertical or rotary component. A single retrobulbar injection creates ophthalmoplegia for 3 to 4 months to dampen such movements.[18] This has dramatically improved vision in several cases from 20/400 to 20/40 (6/120 to 6/12). Because the induced ophthalmoplegia creates diplopia and marked spatial/balance problems, this works best for wheelchair-bound patients. Only one eye of an ambulatory patient should be injected in this manner.

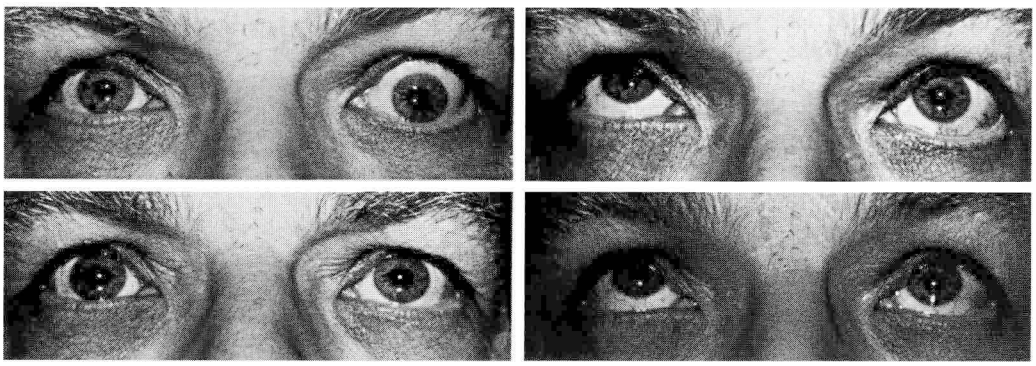

Figure 32–7. *Thyroid eye disease, left hypotropia.* Top, *Before injection.* Bottom, *Sixty-seven days after injection of left inferior rectus showing improved alignment in primary gaze* (left) *and better upgaze* (right).

Technique

INFORMED CONSENT

Informed consent should include reference to the intended overcorrection and its cosmetic implications, as well as possible diplopia and spatial disorientation lasting 1 to 2 months. This will require patching in about a third of adult cases, mostly for the first week or two, followed by adaptation that allows its discontinuance. A trial of patching should be considered for 1 or 2 days before injecting adults without suppression. Some elderly persons are physically unstable, and many busy adults are unable to drive and work with only monocular vision. Children adapt in a few days, even if fixing with the injected eye. About half of patients need retreatment within 2 years. Eye perforation has occurred in 1 in 1000 cases, but no patient has lost vision. Partial ptosis and vertical deviation occur mainly with MR injection, at a rate of about 25%. Fewer than 1% of patients still have ptosis 6 months after the injection. It helps patients to know that the injection itself is more frightening than painful, that the eye is made numb so that pain is minimal, and that the technique takes less time than the preoperative discussion and paper work. Advantages include the use of local anesthesia and doing a less-invasive procedure.

PREPARATION

The amplifier should be checked to ensure that the batteries are working. The needle should have an intact tip and a good coating of Teflon. A spare should be available in case the needle gets damaged or contaminated. The minute amount of white material in the bottom of the botulinum toxin bottle is the correct content. It is mostly salt, some protein, and 100 units of the toxin itself. Reconstitution with 2.0 mL of nonpreserved saline yields a solution of 5 units/0.1 mL; 4.0 mL gives 2.50 units/0.1 mL. Tuberculin syringes are remarkably accurate; fractions of the dose may be accurately given by varying the volume injected. First, one should aspirate the volume of the proposed dose plus an additional 0.1 to 0.2 mL into the syringe. Then the injection electrode is firmly attached, and the excess is injected through the needle electrode to check for patency and spot a leak at the syringe/needle junction. Because an awkward position is often required to read the syringe marks, one should fill with the exact volume desired and empty it completely into the EOM. If there are two muscles to inject (e.g., bimedials in children), a second syringe can be filled, or the needle transfered to the second syringe, again with the exact dose.

DOSAGE

Nearly all initial doses are 2.5 units (see Table 32–5). Subsequent doses may be increased as much as 100% depending on the response to the earlier injection. Notice that dosage is not decreased for children and may even be increased for those with large deviations.

ANESTHESIA

Proparacaine (or tetracaine, cocaine, or 4% lidocaine) in a minimum of a drop a minute for three doses is used. A vasoconstrictor drop (e.g., epinephrine), given before instilling anesthetic drops, makes it easier to avoid the anterior ciliary vessels and enhances anesthesia. After the drops, a subconjunctival injection of 0.1 to 0.4 mL lidocaine over the muscle does not diminish electromyographic (EMG) activity and reduces discomfort, especially in a previously operated patient with scar tissue.

SEDATION

Diazepam or a similar oral drug, given an hour before the procedure, is helpful for the very apprehensive patient.

INJECTION TECHNIQUE

Placement in the muscle is crucial. The neuromuscular junctions, centered halfway back in the EOM, should be the target.[11] Injection outside the muscle reduces the treatment effect and increases the likelihood of affecting adjacent muscles. Because the drug diffuses along needle tracks, a single accurate placement is most reliable. Steps that help in injecting horizontal muscles in an alert patient using an electromyogram amplifier are as follows:

1. Prepare the syringe with the appropriate dose of botulinum and attach the monopolar needle electrode as described earlier. Note the position of the needle bevel so the orientation in the orbit can be determined.
2. Attach a ground lead to the patient—at the forehead for the MR and laterally for the LR. Wipe this area beforehand with alcohol to ensure adhesion of the usual electrocardiographic leads.
3. Turn on the amplifier to half the volume and test the connections by touching the needle tip to the conjunctiva; it should make a loud "tick."
4. Have the patient gaze at a target away from the field of action of the muscle. (For example, the patient should look temporally during injection of the MR.)
5. Insert the needle electrode, its bevel facing the muscle, through the conjunctiva 8 to 10 mm from the limbus and, avoiding large vessels, push it 5–6 mm posteriorly, keeping to the orbital wall side of the muscle, away from the globe. Slowly move the gaze target to the primary position to activate the target muscle.
6. While listening to the EMG signals, advance the needle tip toward the area giving off the loudest sound. When a crackling sharp EMG signal is heard, inject the fluid slowly. It is a good sign if the EMG sound diminishes with the injection, indicating that the solution pushed the nearby muscle fibers away from the tip. Leave the tip there for 15 to 30 seconds until the pressure of the solution diminishes. Withdraw the needle slowly while the patient maintains primary gaze. Make a note of how reliable the EMG response and injection were, for future reference.

Special Considerations in Children

A child should know what is happening and why, couched in positive terms. After age 6 years in an intelligent child, the technique can often be performed as in adults. Because it is hard to predict which child will cooperate, we often attempt it in the office, knowing that a substantial number

of procedures will not be completed. For the successful ones we have saved time, anesthesia, and cost.

1. A quiet setting is essential. The parents should be present and holding the child's hands. Proceed slowly. Telling the patient that to fear something approaching the eye is a normal protective mechanism helps to gain cooperation. The child is shown that the eyes can be anesthetized with drops and that the second set of drops (a vasoconstrictor such as epinephrine 0.1%) will be cold but will not sting. It takes more to anesthetize children: plan on five instillations. Demonstrate that a moist cotton-tipped applicator will be able to touch the eye and not be uncomfortable. The child should be told that, toward the end of the procedure, there may be some aching or sense of pressure, but that this signals the end of the procedure. (These techniques are similar to those one uses for other procedures with children such as foreign body removal.) A somewhat abbreviated version may be useful for anxious adults.
2. For children aged 1 to 6 years and for those unable to cooperate, ketamine or nitrous oxide sedation can be added (see Fig. 32–4*B*). Intravenous ketamine, 0.5 to 1.0 mg/kg, will preserve EMG activity and keep the patient relatively quiet for 2 to 5 minutes. This is less than the usual anesthetic dose. The anesthesiologist should be informed that general anesthesia is not desired but rather some degree of akinesia, amnesia, and light sedation. Remarkably little hallucination and postoperative effects are noted with intravenous ketamine. Topical anesthetic drops given before ketamine are essential. Intramuscular ketamine, 2 to 3 mg/kg, has a much longer duration of effect. The recovery period is also longer and hallucinations do occur.

   Inhalational anesthesia is an acceptable alternative that does not require intravenous access. However, the EMG signal is much diminished, and many injections will be given without the benefit of complete EMG guidance. This is probably acceptable for the medial rectus muscle, which is the usual target in children and the least variable in position. A small posterior conjunctival incision allows injection with the needle tip 10 to 15 mm posterior to the insertion under direct visualization. This is an excellent alternative when access to an efficient facility and anesthesia coverage are available.
3. From age 3 to 12 months, depending on the strength of the child, it is usually possible to anesthetize the eyes with drops and simply hold the infant down for the injection. A papoose board and additional hands to hold the head are imperative. Avoid using a lid speculum; if one must be used, it should have a firm stop to avoid continuous pressure on the lids. A bottle may sometimes keep the child at ease during the procedure, at least until the time of muscle penetration and injection. Parents need to be told that the procedure is mildly uncomfortable, just like immunization shots; that it is routinely performed under similar conditions in adults; and that, if successful, it will spare the infant a general anesthetic. If cooperation for the second eye is marginal, proceed deliberately. Waiting until the child stops crying will not help and should not be allowed to interrupt the procedure. However, if the head of a strong infant cannot be held still, terminate the procedure and plan to do the injections under anesthesia.

Injecting Cyclovertical Muscles

Inferior Rectus. The IR is injected through the lower lid in thyroid or other cases with restricted supraduction. The needle must be angled nasally 23 degrees (straight back puts the needle into the LR!). If the IO is encountered, continue right through it—the IR should be behind it. One should be sure to wait 30 seconds after injecting and remove the needle slowly to avoid back-flow of botulinum toxin into the IO.

Superior Rectus. SR injection is just as effective as injection of any other EOM; but because of the induced ptosis, the SR should be treated *only* when a hypertropia cannot otherwise be treated. The ipsilateral IO is usually injected simultaneously. Full ptosis can be expected for 2 months. Sometimes residual ptosis of 0.5 mm may persist!

Inferior Oblique. The IO is very close to the conjunctival surface inferotemporally when the eye is looking upward. Injection is done rather anteriorly to avoid the IR.

Superior Oblique. Injecting this muscle is not recommended. SO overaction and SO myokymia have been the indications, but ptosis occurs uniformly; there is a resulting SO palsy, and the basic condition recurs after a few months.

TECHNICAL COMPLICATIONS AND DIFFICULTIES

Sometime the target muscle cannot be found. An unusually positioned muscle may be found by carefully tilting and translating the whole needle and syringe. Multiple needle thrusts should be avoided because they can cause hemorrhage, especially if the thrusts are made deep into the orbit.

The LR takes a course going backward and downward below the horizontal in some patients. Recognizing this normal anatomic variant and repositioning the needle and syringe as just described are usually effective.

The EMG signal will be decreased for many weeks after the first injection and may remain so even after clinical muscle activity has returned to normal.

Partial ptosis occurs in about 16% of adults and 25% of children. Complete ptosis is truly rare, and no case of amblyopia due to ptosis has been documented.

Vertical strabismus after treatment of horizontal rectus muscles of one eye occurred in 17% of adult patients. It persists for longer than 6 months in fewer than 1% of patients and is much more common in MR injection than in LR injection. The induced vertical deviation is usually a *hyper*tropia after MR injection and a *hypo*tropia after LR injection. One can take advantage of this phenomenon by injecting the MR of the *hypo*tropic eye for esotropia and the LR of the *hyper*tropic eye for exotropia whenever possible. The induction of vertical strabismus is much less common in children treated bilaterally; any vertical effect seems to balance out.

The rate of overcorrection at 6 months is 1.7%. Cases with muscles that respond strongly to botulinum toxin, resulting in overcorrection, are also easily reversed by in-

jecting the antagonist. Smaller doses (1.0–2.0 units) should be used.

Scleral perforation may be prevented by keeping the needle tangential to the globe until it is posterior to the equator and using the EMG signal to guide it. Highly myopic eyes, eyes where the injection is near a previous surgical site, and eyes with scleral buckles are particularly at risk.

Diplopia is the most common and annoying side effect. The patient should appreciate that an overcorrection is necessary for a long-term beneficial effect. Adults may require patching but may also be able to use a head turn to align the eyes. Patching is avoided in visually immature children except to prevent or treat amblyopia.

Because we usually treat the nondominant eye, few patients develop spatial disorientation or past pointing because of the induced paralysis. Those who do are usually alternators or have part-time fusion. Patching the eye treats the problem, and adaptation usually occurs after a week.

Retrobulbar hemorrhage has occurred in about 0.2% of cases, usually after prior surgery. There is report of one eye decompressed by conjunctival incision, but this case and all others resolved without visual complications. The expected paralytic effect is not reduced.

Pupillary dilatation (Adie's pupil) has occurred rarely, probably from needle injury to the ciliary ganglion.

Systemic effects have not been encountered with the doses used to treat strabismus.

Estimating the surgical dosage for residual strabismus after unsuccessful injection requires waiting for stabilization to occur, typically 5 to 6 months.

Future Developments and Other Locally Acting Muscle Drugs

Toxin types B, C, F, and G will be helpful in large-muscle disorders in which development of antibodies to large doses of type A has become a problem. There is no advantage to using these in strabismus and blepharospasm in which antibodies to the small doses do not develop and systemic effects do not occur.

Large doses of local anesthetics are unpredictably myotoxic and are not therapeutically effective.

Lidocaine 2%, 0.2 to 0.5 mL, injected as for botulinum toxin, is useful diagnostically to reduce suspected overaction of an EOM and as a therapeutic trial in difficult cases before botulinum toxin injection or EOM weakening surgery.[16] No adverse myotoxicity has occurred in this clinical application.

Collagenase has been injected into fibrotic EOM (e.g., thyroid, orbit injury) in eight clinical cases. Only transient effects have resulted so far, but this does indicate the range of unexplored approaches to strabismus management.

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