

# TREATING STRABISMUS BY INJECTING THE AGONIST MUSCLE WITH BUPIVACAINE AND THE ANTAGONIST WITH BOTULINUM TOXIN

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## ABSTRACT

### Purpose

We report the results of injection of bupivacaine (BUP) and botulinum toxin (BT) into agonist and antagonist muscles, respectively, to treat horizontal strabismus.

### Methods

We treated both horizontal muscles of 7 patients with comitant horizontal strabismus, 2 patients with partial lateral rectus (LR) paralysis, and one elderly myopic patient with acquired esotropia, injecting the agonist muscle with BUP in concentrations of 0.75% to 3.0% and volumes of 3.0 to 5.0 mL, and the antagonist with BT in about half the usual therapeutic dose to prevent it from stretching the BUP-treated muscle during its regeneration following BUP myotoxicity. We re-injected BT in one patient with an inadequate response from the initial BT dose.

### Results

The 7 comitant patients were corrected (averages) 19.7 prism diopters (pd), from 28.3 pd to 8.6 pd, at 193 days after injection. Muscle volume increase after BUP injection was 5.8% at 158 days. One LR palsy patient without LR atrophy was changed 55 pd; the other, with LR atrophy, was corrected 4 pd. Two patients had transient vertical deviations from the BT injection. The myopic patient with esotropia was unchanged.

### Conclusions

Injections of BUP and BT corrected 7 patients with comitant horizontal strabismus an average of 19.7 pd, about double the correction reported from BUP injection alone. BUP injected muscles increased size by 5.8%. Of 2 patients with LR weakness, one without LR atrophy was changed by 55 pd, but another with LR atrophy was corrected only 4 pd.

## INTRODUCTION

In addition to its anesthetic effect, injection of the amino-amide anesthetic bupivacaine (BUP) into the fast muscle fibers, such as those of the extraocular muscles (EOM) damages the muscle fibers within minutes, probably by allowing excess  $Ca^{2+}$  ions to enter the cytoplasm from the sarcoplasmic reticulum. This results in separation of the muscle fiber sarcomeres at the Z band.<sup>1</sup> The damaged fibers and myocytes are then removed by macrophages leaving the cell membranes, nerves, and blood vessels intact.<sup>2</sup> Within a few hours of exposure to BUP, autocrine growth factor molecules such as IGF-I and mechano growth factor (MGF) are released from the damaged area. These molecules activate satellite cells that proliferate over the next 10-20 days to form new muscle fibers and myocytes to replace the damaged muscle.<sup>3, 4</sup> In EOM, proliferation continues on to build a muscle having greater contractile strength, intrinsic elastic stiffness, and size than before, with consequent effects on eye alignment.<sup>5</sup> These biomechanical alterations are not achievable with strabismus surgery. When this muscle response occurs inadvertently after retrobulbar anesthetic injection for eye surgery, misalignment or strabismus is produced.<sup>6, 7</sup> We are successfully harnessing this muscle response to improve eye alignment and correct strabismus.<sup>8, 9</sup>

We believe that yet another property of EOMs can be manipulated with BUP: the BUP-injected muscle will regenerate to the length at which it is held during the process of regeneration. In the present study, to further increase strabismus correction, we sought to shorten the agonist muscle during regeneration by paralyzing its antagonist with a small dose of botulinum toxin (BT). That induces the BUP-injected muscle to regenerate to a shorter length than if the antagonist were allowed to stretch it out during the time of regeneration.

## METHODS

Under a protocol approved by the Smith-Kettlewell Institutional Review Board, we treated 10 patients with injections of both BUP and BT. Seven of these patients had large comitant horizontal deviations or were previously unresponsive to injection of a single drug, either BUP or BT. We also injected the muscles of 2 patients with LR paresis in a similar fashion and those of one patient with esotropia from high myopia and a displaced LR muscle who asked to be treated in an attempt to avoid surgery. The averages reported are for the 7 comitant patients and do not include the data from these 3 patients. Using needles insulated except at their tips to record the EMG signal and thus determine the position of the needle tip, we injected BUP in concentrations of 0.75% to 3.0% and volumes of 3.0 to 5.0 mL into the medial rectus in exotropia or the LR in esotropia. Earlier MRI studies showed that BUP diffuses poorly along the muscle,<sup>6</sup> so we attempted to fill the whole muscle by injecting most of the BUP in the posterior third and the remainder in the middle of the muscle, allowing some BUP to move anteriorly along the needle track. Simultaneously, we injected the antagonist muscle with BT, using small doses to create mild paresis lasting under a month. Patient #6 had little paralytic effect from the initial BT injection and received a second injection. Examination by standard clinical methods and by MR imaging of the eye muscles was done before injection, immediately afterwards to determine the site of injection, and at intervals thereafter to determine eye alignment, comitance, and eye muscle size changes, as described earlier.<sup>5</sup>

## RESULTS

The Table summarizes the patient details and the results. On average, the comitant patients were corrected 19.7 pd at 193 days after injection. Figures 1 to 3 show the data for eye muscle sizes and eye alignment after injection. Figure 4 shows the stages of events after injection for patient #3. In patient #8, whose LR had 30 gm of active force before injection (normal 70 gm on the fellow LR) and whose LR was not atrophic, the treatment altered alignment by 55 prism diopters resulting in an overcorrection requiring surgical recession of the LR at 4 months after injection. At that surgery, the LR active force measured 35 gm and showed stiffness of passive rotation to adduction about twice that of the LR on the normal eye. This small increase in active force is well below that required to change alignment by 45 prism diopters, and implies that a reduction in length and/or increased stiffness of the LR were responsible for much of the alignment change. Treatment was ineffective for patient #9 with a severely atrophic LR muscle and for patient #10 with high myopia, esotropia, and a displaced LR. Two patients developed a transient hypertropia from medial rectus injection of BT, and two patients developed significant swelling and discomfort for a few days after BUP injections that had a strong weakening effect on the injected muscle.

*Table. Summary of patient data. Patients 1-7 had comitant horizontal strabismus. Patients 8 and 9 had LR paresis, and Patient 10 had high myopia and a displaced LR.*

Patient #	BUP Conc (%)	Vol (mL)	Botox® Units	Deviation Follow-up (days)	Initial Dev (pd)	Final Dev (pd)	Change (pd)
1	0.75	4.5	1	146	18	10	8
2	3.0	4	1.5	88	14	2	12
3	3.0	3	3	355	16	0	16
4	0.75	4	2	286	20	0	20
5	0.75	4	5	247	40	18	22
6	3.0	4.5	7.5	160	40	0	40
7	0.75	4.5	4	70	50	30	20
8	1.5	3.0	2.5	56	10	-45	55
9	0.75	5	1	44	10	6	4
10	0.75	4.5	3	110	30	30	0

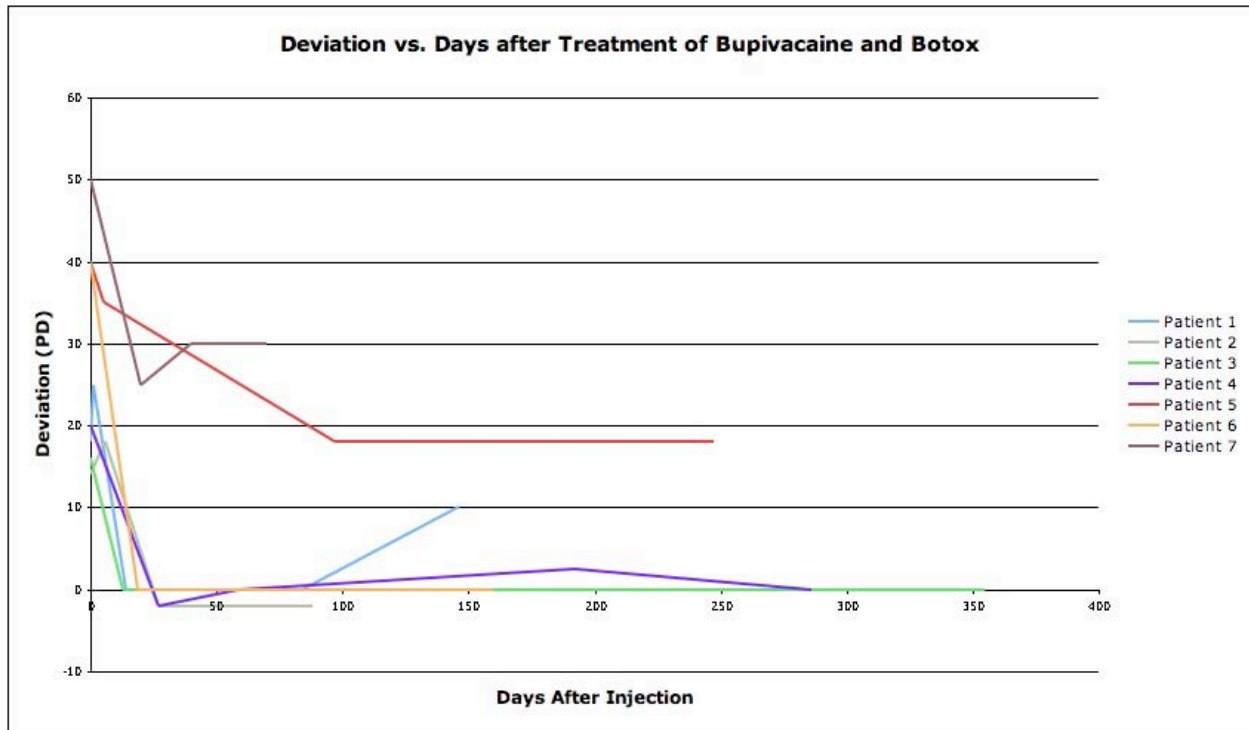


Figure 1. The changes in deviation over time are shown.

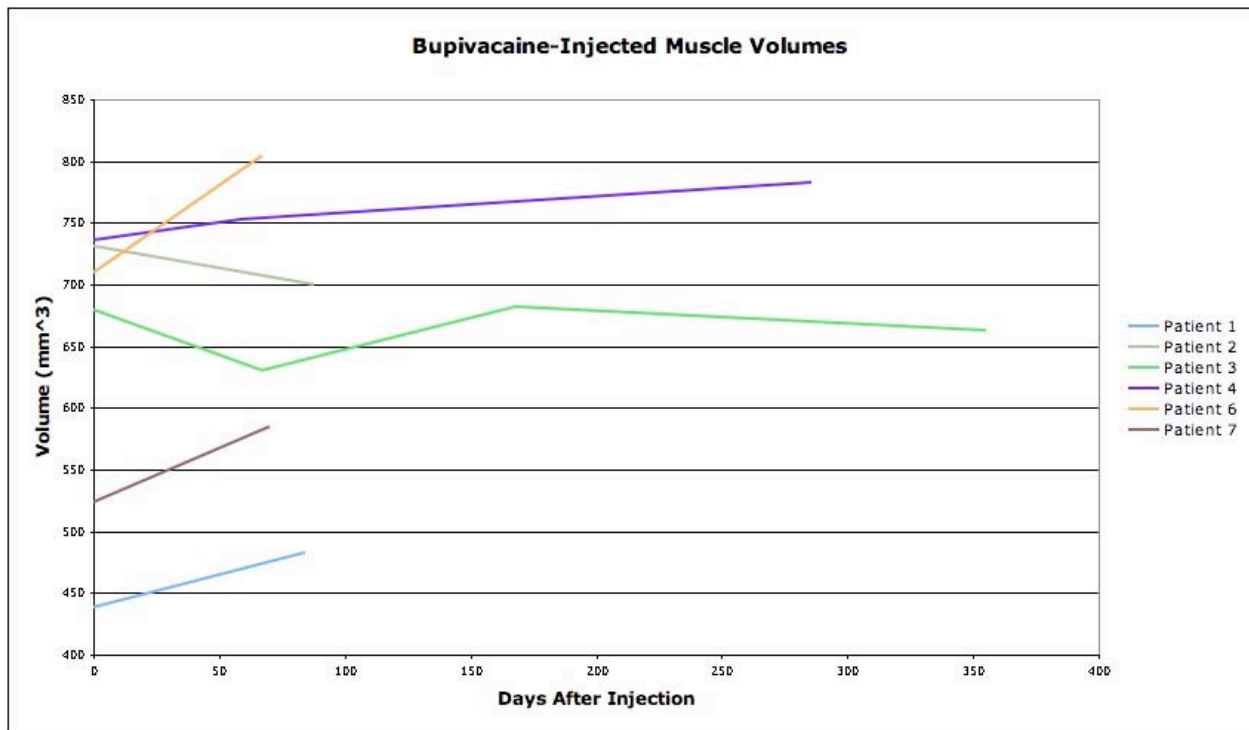


Figure 2. The changes in the size of the muscles injected with BUP are shown. The colors correspond to individual patients in each graph.

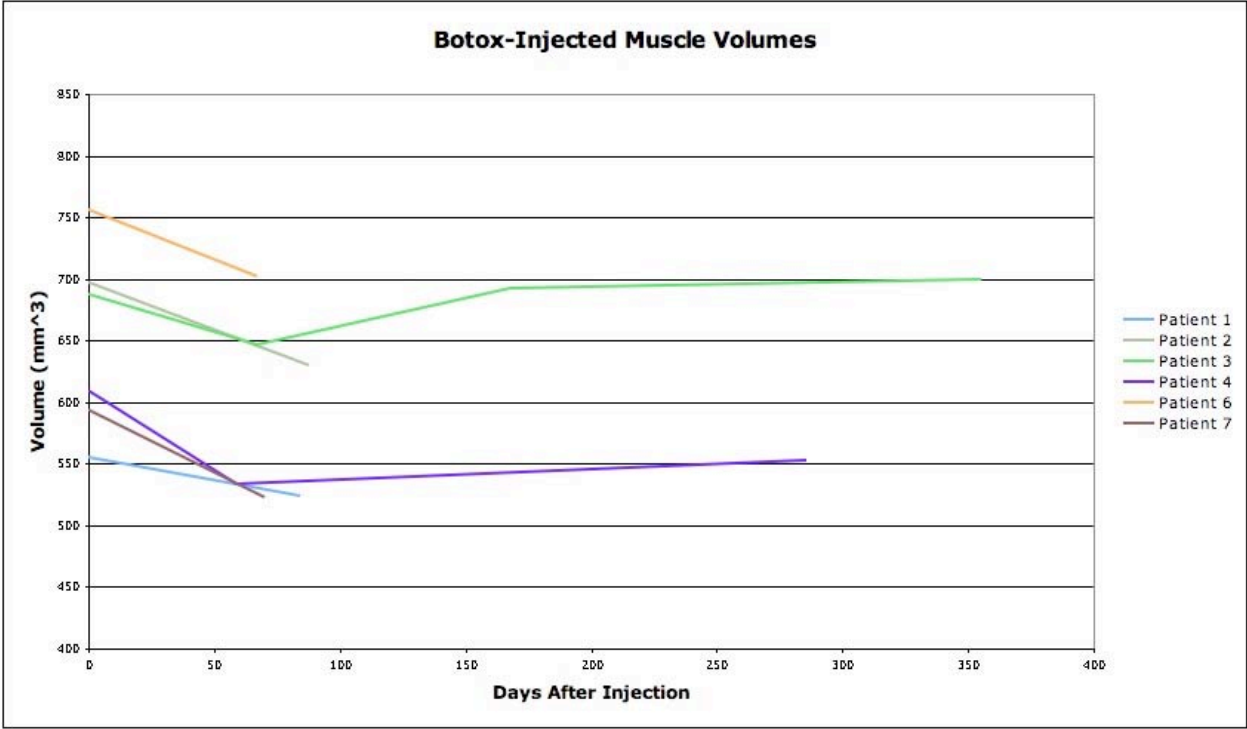


Figure 3. The changes in the size of the muscles injected with BT are shown.

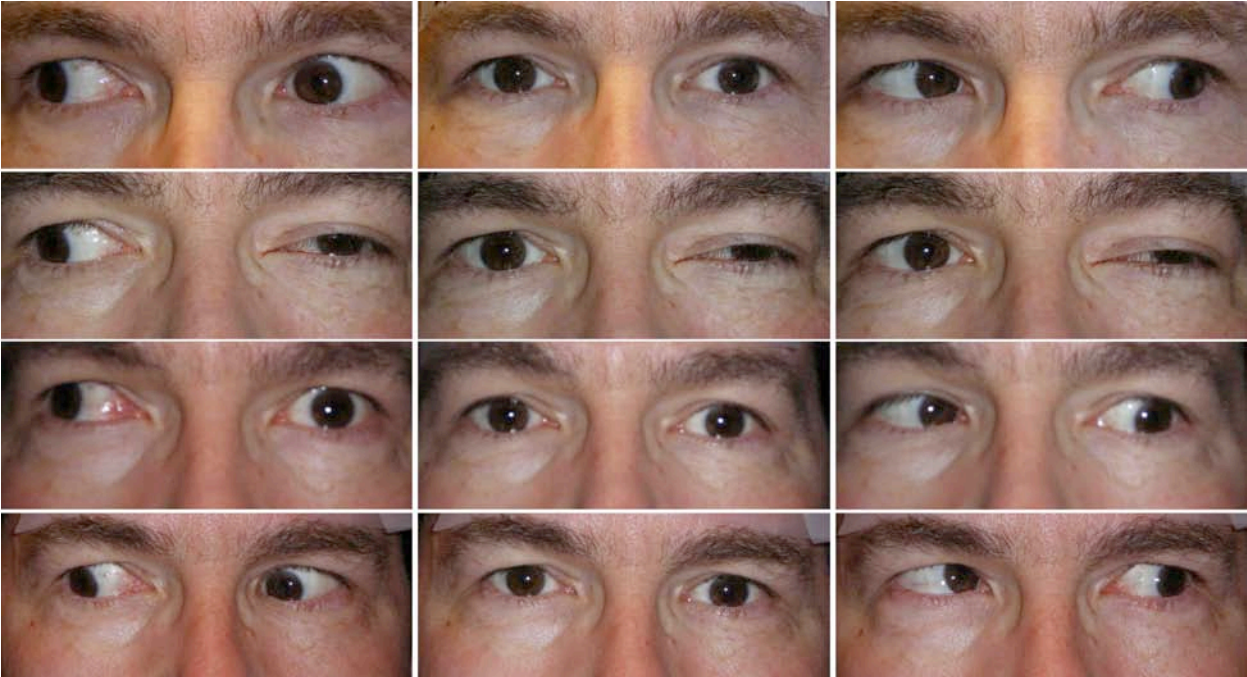


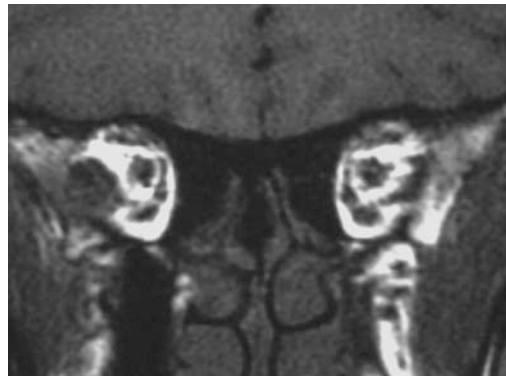
Figure 4. Case #3. Top row: Pre-injection, 16 pd exotropia. Second row: 30 minutes after injection, with paralysis of the LMR. Third row: 13 days after injection, 16 pd exotropia, with paralysis of both the LMR and LLR. Bottom row: 355 days after injection, straight.

## CASE REPORTS

Case 2. A 35-year-old man had diplopia and difficulty with binocular fusion from 14 pd residual esotropia following surgery for 30 pd esotropia. A first injection of BUP into the RLR was done. This markedly weakened abduction and increased the esotropia to 25 pd. On day 76 abduction had fully recovered and the esotropia had returned to 14 pd in all gaze directions. Injection of BUP into the RLR was done again, adding 1.5 units of Botox® to the RMR. (See Table) Twenty-one days after this second injection, the eye was straight. Both abduction and adduction were moderately reduced in amplitude, representing moderate paresis of both injected muscles. Thereafter, motility was gradually regained, and on day 88 the eye was 2 pd esotropic in the primary position. MRI scan showed the RLR muscle substantially enlarged in the posterior area. In gaze to the right, the strong RLR retracts the right eye 1-2 mm and causes 6 pd exotropia. See Figures 5 and 6.



*Figure 5. Case #2. Eye rotations 88 days after injection. Right gaze, below, showing retraction and exotropia.*



*Figure 6. Case #2. MR coronal plane image 88 days after injection, showing local enlargement of RLR injected with BUP.*

Case 6. A 26-year-old man had been operated on for 90 pd exotropia by 12 mm recession of each LR and 8 mm resection of the LMR. A residual 40 pd exotropia remained. The RMR was injected with BUP and the RLR with Botox®. Five days later adduction was fully paralyzed by the BUP injection and the eye was even further exotropic. The medial conjunctiva was swollen and red for several days. The RLR was only minimally paralyzed by the Botox® dose used; it was injected with additional Botox® on day 5, paralyzing the muscle and reducing the exotropia. On day 29 both RLR and RMR were regaining function and the eye was aligned. Full rotations and straight alignment were present on day 160 when last seen. The RMR is clearly larger than the LMR. Mild swelling of the RE remains. See Figure 7.



*Figure 7. Case 6. Top: Before injection, the left eye is still healing from prior surgery. Bottom: 160 days after injection, the eyes are straight.*

Case 8. A 62-year-old woman had a pontine hemorrhage in 1994 resulting in a partial RLR paresis. Three horizontal muscle procedures had been done, leaving her with 14 pd esotropia, increasing to 25 pd in right gaze due to abduction weakness. She declined surgical intervention on the left eye. Measured isometric RLR active force was 30 grams but the RLR was not atrophic on MRI imaging. Injection of the RLR with 3.0 mL of 1.5% BUP was done. Seventy days after this injection, the esotropia had improved only to 10 pd esotropia, and eye rotations had returned to the pre-injection level. A second injection of 3.0 mL of 1.5% BUP was then done to the RLR with the addition of 2.5 units of Botox® to the RMR. On day 7 after the second injection the eye was 10 pd exotropic and there was -3 abduction and -3 adduction, representing moderate paresis of both injected muscles. On day 56 the eye had moved to a position of 45 pd exotropia where it remained until post-injection day 113. Adduction was limited, but adduction saccades appeared sharp and of normal speed. She asked then that the eye be straightened and a 6.5 mm recession of the RLR was done. At that surgery, the measured RLR isometric active force was 35 gm, only a slight increase above the initial 30 gm force. The RLR stiffness by traction test, however, was estimated to be twice that of the normal LLR. The RMR isometric active force was 55 gm, within normal limits. The eye measured 5 pd exophoria on postoperative day 7, with a further reduction to zero on postoperative day 138. There is single binocular vision over a useful area.

## **DISCUSSION**

The alignment correction achieved using BUP+BT was twice what we reported from BUP injection alone.<sup>6</sup> Since BT alone has been found ineffective in changing eye alignment in the low doses used, we believe that it acted through the mechanism of temporary paresis of the antagonist, preventing stretch of the agonist as the latter was being rebuilt. The average muscle size increase of 5.8% was very similar to the 6.2% we found from use of BUP alone.<sup>5</sup> The decrease in size of the muscles injected by BT is not unexpected, but has not been reported for eye muscles. This must play some part in the alignment change and both alignment and muscle sizes will be monitored further. Case #2 and case #8 show that eye position during regeneration greatly influences the outcome of BUP injection. Each case received minimal effect after BUP alone, but much larger effect after injection of both BUP and BT. Case 6 shows that the BT paralysis must be sufficient to disable the antagonist RLR and prevent it from stretching the RMR muscle injected with BUP. While the total BT fully paralyzed the LR, a correction of 40 pd from a single injection of BT alone would be extraordinary, so we credit the enlargement of the medial rectus as the major factor correcting this deviation. The specific changes induced in these muscles by BUP are unclear. Increase in myofibrils within the muscle cells increases size, strength, and stiffness. Intracellular deposition of non-contracting molecules has been postulated to account for the increase in size and stiffness without concomitant increase in force production after BUP injection in rat muscles.<sup>10, 11</sup> This would be expected to increase muscle stiffness, as in case #8, a desirable outcome for strabismus correction. This case, with a large angular correction and increased stiffness of the BUP-injected LR without much increase in muscle strength, suggests a role for these mechanisms as part of the action of BUP injection. In treatment of strabismus, strengthening, shortening, and

stiffening of the muscle would all be beneficial changes. In our earlier reporting on injecting BUP alone in horizontal strabismus, the stability of the alignment changes and the persistence of muscle enlargement up to 500 days were striking.<sup>8,9</sup> Stability seems to be present in these patients too, although follow-up time is shorter. Orbital inflammation from the muscle damage was the likely cause of the inflammation in case 6. While not a serious or limiting factor in these cases, swelling from injection of multiple muscles or of even one muscle in a compromised orbit with thyroid eye disease might compress the optic nerve.

Case #8 shows that a large correction can be obtained even in a muscle that is partly paralyzed, so long as it is not atrophic. Further, it shows that muscle shortening and stiffening, both desirable in stabilizing strabismus deviations, are major components of the muscle change in addition to muscle strengthening. Patient #9, who had LR paresis with atrophy, received little clinical benefit or change in size of the BUP-injected LR. Perhaps there is a relative absence of satellite cells as a part of the atrophy,<sup>12</sup> or perhaps there is a lack of muscle tissue to be injured and thus produce the signaling autocrine proteins. This leaves open the possibility that signaling molecules like MGF<sup>13</sup> given directly, rather than indirectly through the effects of BUP on muscle, would be effective and useful for these patients. Laboratory studies are underway to answer many of these questions.

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### b. Financial Disclosures

None

### c. Contributions of Authors in each of these areas

*Design of the study* (ABS, JMM)  
*Conduct of the study* (ABS, JMM)  
*Data analysis* (ABS, JMM, KRS)  
*Manuscript* (ABS, JMM, KRS)

### d. Approvals

This study was approved by and carried out under the supervision of the Institutional Review Board of the Smith-Kettlewell Eye Research Institute.

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