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*New York, N.Y., and Los Angeles, Calif.*

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Previous work on patients with muscular dystonia has shown that small intramuscular doses of botulinum toxin A eliminated hyperkinetic facial lines for approximately 6 months. The purpose of this study was to determine the efficacy of botulinum toxin A injections in eliminating facial wrinkles in aesthetic surgery patients who do not have muscular dystonia. Eleven healthy subjects were studied in a double-blind fashion. On both sides of the face, 0.2 cc of either normal saline or botulinum toxin A was injected into the forehead or into the periorbital wrinkles (crow's feet). Documentation of results was made by photographs taken of the patients during repose and during facial animation before and after injection. Assessment of facial wrinkles was done from a grading system in which the patient and the facial plastic surgeon were asked to judge the severity of the wrinkles on a scale from 0 to 3, with 0 reflecting no facial wrinkles and 3 reflecting severe facial wrinkling.

Nine of 11 subjects injected with botulinum toxin A noted a significant improvement in the severity of their facial wrinkles in comparison with the side of the face injected with saline, with a rating improvement of 2 points. Two of 11 subjects noted a moderate improvement, with a rating improvement of 1 point. No patient injected with saline reported an improvement in the severity of the facial wrinkles on the control side. There were no serious complications. Botulinum toxin A is an efficacious method of nonsurgically eliminating facial wrinkles and may play a role in the cosmetic enhancement of the aging face. (*Plast. Reconstr. Surg.* 94: 94, 1994.)

It is well known that hyperfunctional facial lines are the result of pull on the skin by the underlying facial mimetic musculature.[1] Facial wrinkles need to be differentiated from dynamic facial creases. In contradistinction to a hyperfunctional facial line, a facial wrinkle is caused by laxity intrinsic to the skin that is the result of age-induced changes in collagen of the dermis. Specifically, hyperkinetic lines formed by the corrugator supercilii, frontalis, and lateral aspects of orbicularis oculi muscles result in glabellar frown lines, deep forehead wrinkles, and crow's feet, respectively. There are numerous surgical procedures designed to eliminate or attenuate these hyperkinetic facial lines on the aging face, including rhytidectomy, liposuction, brow lift, dermabrasion, chemical peel, and collagen injections.[2,3] Rarely have any of these techniques available for eliminating facial wrinkles been scrutinized in a double-blind, placebo-controlled manner. Previous work with patients suffering from muscular dystonia has shown that small intramuscular dosages of botulinum toxin A eliminate hyperkinetic facial lines for approximately 6 months.[1] The purpose of this study was to determine the efficacy of botulinum toxin A injections in a double-blind, placebo-controlled fashion in eliminating hyperfunctional facial lines in healthy aesthetic surgical patients.

## Background and Pharmacology

The bacterium *Clostridium botulinum* produces eight serologically distinct toxins. The toxins exert their effects at the neuromuscular

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junction by inhibiting the release of acetylcholine. The result is a flaccid paralysis. There are three steps involved in the toxin-mediated paralysis: binding, internalization, and inhibition of neurotransmitter release. The binding is selective and saturable. It is the release of vesicle-bound acetylcholine that is inhibited by the toxin.

One international unit (IU) is defined as the $LD_{50}$ in mice. The $LD_{50}$ in humans is estimated to be approximately 2730 IU.[3] The toxin is shipped freeze dried in 100-IU vials. When used clinically in this study, the toxin is reconstituted with normal saline to a concentration of 2.5 to 5 IU/ml. The toxin takes 3 to 4 days to have a noticeable effect and lasts approximately 4 to 6 months.

*Injection Technique*

Toxin was freshly diluted to a concentration of 2.5 or 5 IU/ml and injected by means of a monopolar hollow-bore Teflon-coated electromyography needle which was connected to an EMG recorder. By a technique previously described, the needle was placed through the skin overlying the exaggerated facial lines.[1,4] With the needle in place, EMG readings commenced, and the patient was instructed to accentuate the lines with a squint or a frown. The needle was moved to the electrically most active portion of the muscle, and the toxin was then injected. No massaging of the site took place so as to keep the diffusion of the material to a minimum.

## PATIENTS AND METHODS

A total of 12 patients were included in the study. All patients were first screened by a facial plastic surgeon (Keen or Aviv). A thorough review of medical history, medications, and prior facial plastic surgery was obtained. Patients with contraindications to botulinum toxin A injections, such as patients with Eaton Lambert syndrome, patients with known hypersensitivity to the toxin,[3] and patients who could not complete the protocol, were not included in the study. Of the 12 patients enrolled in the double-blind trial, 1 was eliminated from the study because of failure to return for follow-up photographs and assessment. Of the 11 remaining patients, injections were performed in 9 patients with hyperfunctional forehead lines and in 2 with prominent crow's feet. Forehead injections included 8 injection sites with 10 units on one hemiforehead. Crow's feet injections were at 2 separate sites utilizing 5 units on the tested side. The ages ranged from 32 to 62 years, with a mean age of 42.8 years. There were 7 females and 4 males. Photographs of the injection site both at rest and during active wrinkling were taken to document the preinjection appearance. All photographs were standardized by using the same camera, lens system, flash system, and film. Photographs were obtained at 3 ft with a 105-mm lens oriented vertically utilizing Ekta Chrome 400 slide film and a ring flash. A set of close-up photographs at 2 ft with the camera oriented horizontally also were obtained. These photographs were repeated at 2 and 6 weeks after injection. All patients were followed up for a minimum of 1 year. Sites injected included forehead lines and crow's feet (Table I).

Subjects were studied in a double-blind fashion. On both sides of the face, 0.2 cc of either normal saline or botulinum toxin A was injected into either the periorbital wrinkles (crow's feet) or the forehead frown lines. The

*TABLE I*
Patient Data

| | | | | Rating Before Injection | | Rating After Injection | | Net Improvement (6 wks) | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | Age (years) | Sex | Region | Rest | Wrinkles | Rest | Wrinkles | Rest | Wrinkles |
| JB | 32 | M | Forehead | 1 | 2 | 0 | 0 | +1 | +2 |
| BB | 48 | F | Forehead | 2 | 3 | 1 | 2 | +1 | +1 |
| CC | 40 | F | Forehead | 2 | 3 | Did not return for follow-up | | | |
| MK | 36 | M | Crow's feet | 1 | 2 | 0 | 0 | +1 | +2 |
| LL | 32 | F | Forehead | 2 | 3 | 0 | 1 | +2 | +2 |
| DO | 62 | F | Crow's feet | 2 | 3 | 2 | 2 | 0 | +1 |
| CR | 37 | F | Forehead | 2 | 3 | 0 | 0 | +2 | +3 |
| IR | 47 | F | Forehead | 2 | 3 | 0 | 0 | +2 | +3 |
| GT | 44 | M | Forehead | 2 | 3 | 1 | 1 | +1 | +2 |
| AV | 42 | F | Forehead | 3 | 3 | 0 | 1 | +3 | +2 |
| EE | 50 | F | Forehead | 2 | 3 | 1 | 2 | +1 | +1 |
| WB | 44 | M | Forehead | 2 | 3 | 0 | 1 | +2 | +2 |

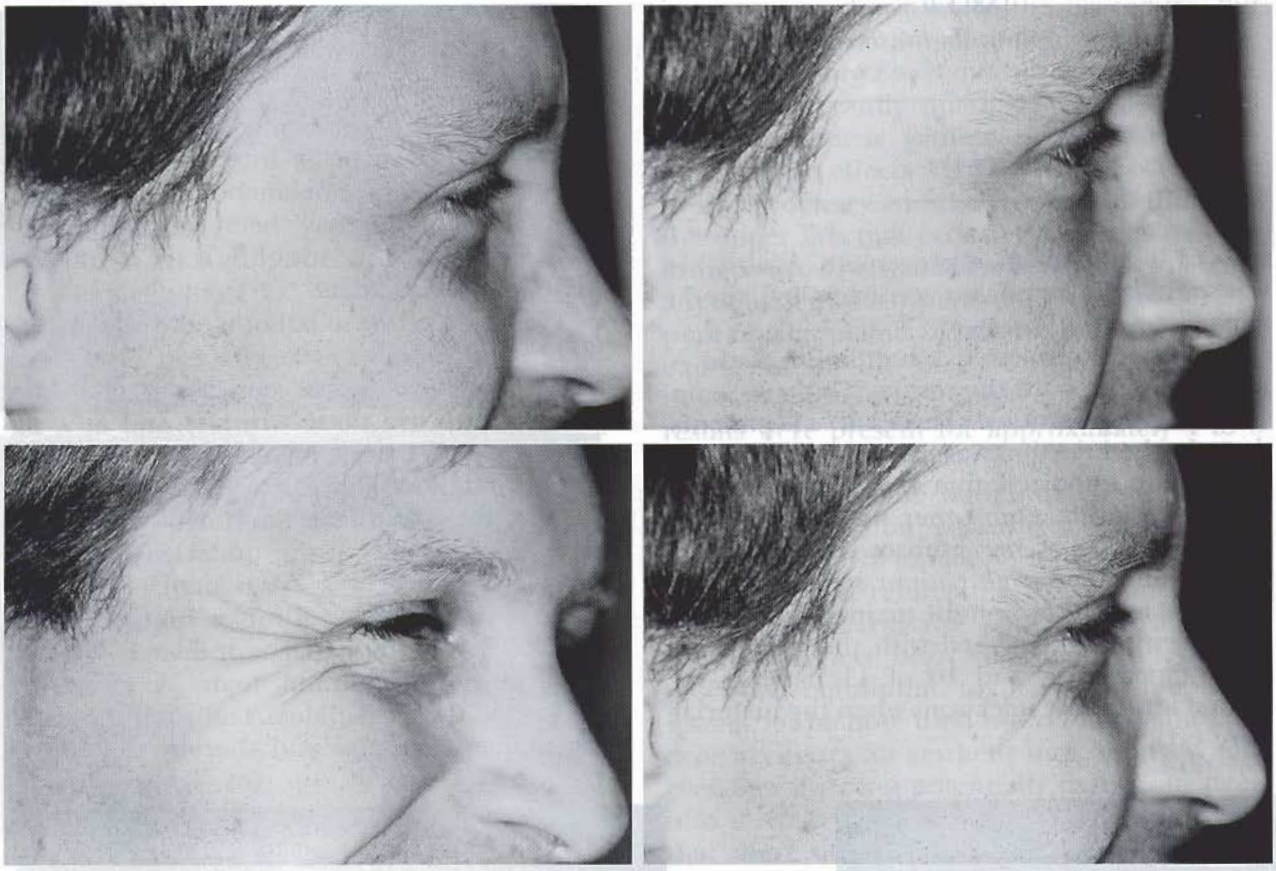

FIG. 1. (*Above, left*) Close-up of crow's feet at rest before injection, right eye. (*Above, right*) Same patient 2 weeks after botulinum toxin injection to lateral portion of orbicularis oculi at rest, right eye. (*Below, left*) Same patient before botulinum toxin injection squinting, right eye. (*Below, right*) Same patient with crow's feet attenuated by botulinum toxin injection 2 weeks after injection, squinting, right eye.

patients were asked to rate their wrinkles before injection and 2 weeks after receiving bilateral placebo-controlled injections. Patients had access to their prior responses when grading their wrinkles. Photographs taken at both visits were randomized and presented to the senior author for judging. The data were analyzed by paired $t$ analysis.

A total of 5 units was utilized for the crow's feet, and 10 units was utilized for the forehead injections. After 6 weeks, patients were offered an injection of toxin on the control side.

Prior to the injections, all patients were asked to assess their facial wrinkles by looking in a mirror and grading the severity of the wrinkles. The rating system devised by our group is based on a scale of 0 to 3, with 0 reflecting no facial wrinkles, 1 signifying mild facial wrinkles, 2 denoting moderate facial wrinkles, and 3 representing severe facial wrinkling (Table II).

These assessments were made both in repose and during animation. At this time, no grading was performed by the surgeons, and no cues were given by the surgeons. The surgeons graded the wrinkles from slide projections of the photographs at a separate sitting approximately 2 months after the testing was completed. The surgeons did not have access to the patients' grades, and they were blinded.

## RESULTS

There was no significant change in facial wrinkle assessment before and after injections of saline, as measured by both patients and examiners. When measuring the severity of facial wrinkles in patients injected with toxin, patients in repose reported a mean reduction in wrinkles of 1.3 rating points (out of 4). The surgeons rated the mean reduction to be 1.5 points. This was a significant improvement, with paired $t$ analysis revealing $p < 0.01$. When patients were asked to contract the injected muscles, the results were even more impressive. A profound improvement was noted, with the patients reporting a mean improvement of 2.0 full rating points and the surgeons concurring

TABLE II
Facial Wrinkle Grading System

| |
|---|
| 0 = no wrinkles |
| 1 = mild wrinkles |
| 2 = moderate wrinkles |
| 3 = severe wrinkles |

with a 1.9-point mean improvement. Again, this was statistically significant according to paired $t$ analysis ($p < 0.01$).

All subjects requested a botulinum toxin A injection to even off the results. There were no serious complications. Three of 11 patients thought the injection was painful, and 2 of the 11 patients reported that their eyebrow had dropped slightly. One other patient reported that the shape of her eyebrow had changed slightly, and that same patient stated that her forehead felt "heavy" on the toxin-injected side. All patients were pleased with the change in their appearance, and 10 of 11 patients returned for further injections when the material wore off.

## DISCUSSION

Hyperfunctional facial lines involving the forehead and the lateral orbital region are common cosmetic deformities. These excessively prominent lines can be interpreted as anger, anxiety, fear, fatigue, melancholia, and aging. In the past, these lines have been treated by surgical excision, yielding unsightly scars, or injected with collagen, silicone, or even the patient's own fat in an effort to balloon out the skin and flatten the folds.[1–3] Face lifts and brow/forehead lifts are surgical endeavors that only partially improve these wrinkles and at a significant cost in terms of scarring and healing. These treatments do not adequately address the fact that these face lines are functional and are related to the pull of the underlying mimetic facial musculature. Just as a patient with a facial paralysis does not have a line on his or her face, the flaccid paralysis that is induced by small quantities of botulinum toxin A effectively eliminates these wrinkles. The toxin weakens the mimetic muscles and thereby physiologi-

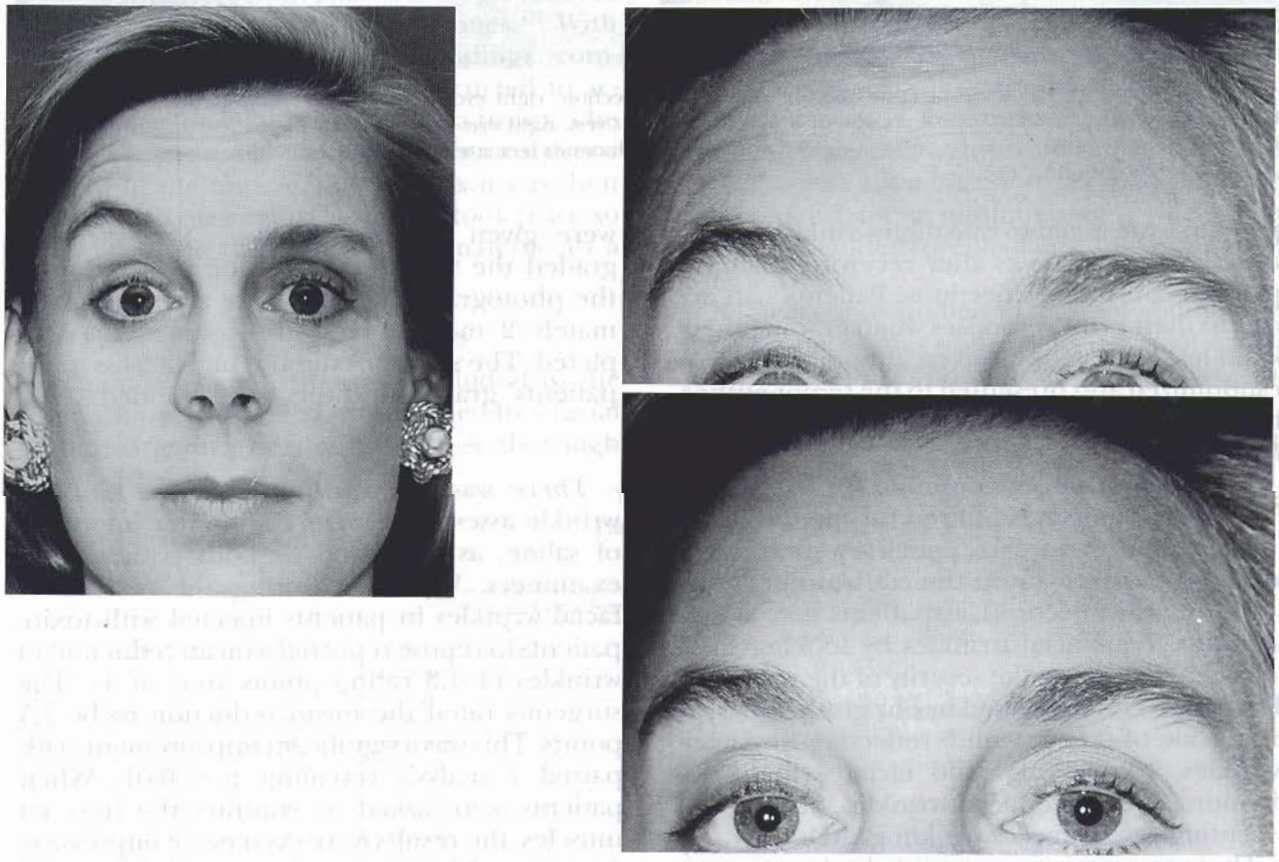

FIG. 2. (*Above, left*) Full-face view of double-blind forehead injection at 2 weeks. Note elimination of wrinkles on the botulinum toxin side, elevating eyebrow. (*Above, right*) Close-up, elevated eyebrow. (*Below, right*) Same patient 2 weeks after having control side injected with toxin to balance off aesthetic appearance, elevating other eyebrow. Note lack of wrinkles.

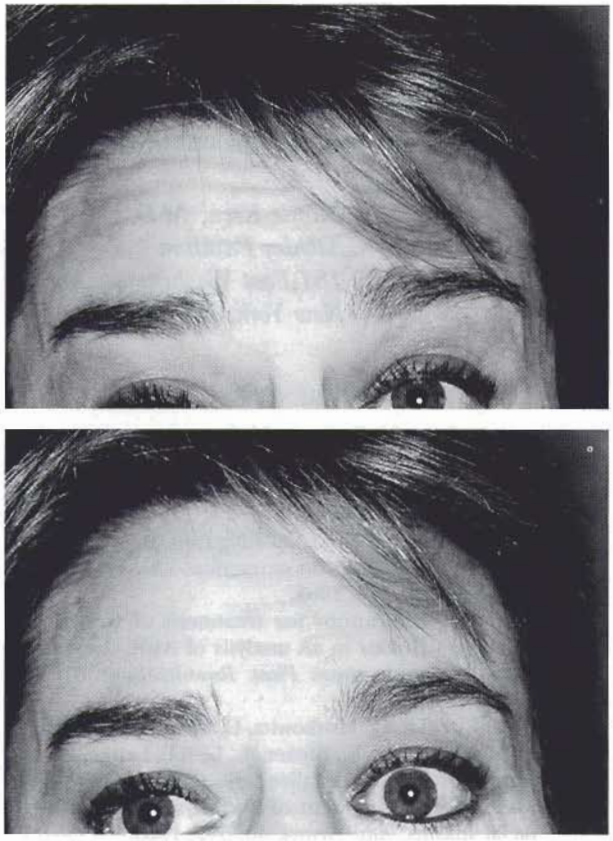

FIG. 3. (*Above*) Before injections, elevating forehead. (*Below*) Same patient after botulinum toxin injections laterally and saline in the midline, 2 weeks after injection, elevating forehead.

cally lessens the wrinkles that are the product of the muscular contraction.[1,4–9] Not all facial wrinkles are caused by the tension of the underlying mimetic muscles. Laxity of the skin that is related to the age-induced changes in dermal collagen also can cause facial wrinkles. Indeed, our poorest result was in our eldest patient, in whom these factors played a significant role in the origin of the wrinkles. The toxin can be injected easily on an ambulatory basis with minimal discomfort. By utilizing EMG control with small volumes of concentrated solution, one can precisely localize the injection. This can be accomplished with minimal side effects.

Graded weaknesses can be achieved by utilizing low dosages initially and then repeating the injections, if necessary, to achieve the desired effect. If too much weakness is achieved, the toxin gradually wears off in 4 to 6 months. By starting with a low initial dose, undesirable side effects can be avoided. The injections need to be repeated every 4 to 6 months in order to sustain the results. This may be considered an inconvenient drawback to the procedure, but this represents an improvement over collagen, which lasts only 2 to 3 months, and to silicone, which is currently not legally available. Full function returns without any long-term sequelae. Side effects were limited to occasional brow asymmetry and the resultant puffiness of the upper lids that occurred secondary to the brow ptosis. This was addressed by not injecting any wrinkles within 1 cm of the eyebrow. There were no complaints of adverse or limited facial expression in the sites we injected, nor was there any ptosis or ectropion of the eyelids. The results were present for approximately 4 to 6 months.

Antibodies to the botulinum toxin A have been described in patients receiving much larger dosages for longer periods of time.[5,6] The antibodies can render the toxin noneffective but do not harm the patient. No antibody production has been described in patients receiving botulinum toxin A for blepharospasm.[7–9] The dose used is two to five times the dose necessary for aesthetic indications. Whenever one injects a potentially dangerous drug into normal individuals, one must be certain that there are no long-term deleterious side effects. It should be noted that there have been no long-term adverse effects with the use of botulinum toxin A for blepharospasm and Meige's disease.[7–9] Muscle biopsies taken from patients after repetitive injections have failed to show any long-term evidence of permanent degeneration or atrophy, and these patients have received dosages that were two to five times the dosages used for aesthetic improvement of their wrinkles and have been studied for over 7 years.[10,11] Local or transient effects of botulinum toxin A have shown that excessive neuronal sprouting and muscle fiber atrophy occur. These changes are not permanent, nor are they clinically significant.[12] Aside from pain—the injection is painful—and a slight droop to the eyebrows, we did not report any other adverse reactions or side effects. Clearly, this is a short-term method of eliminating facial wrinkles and will need to be repeated two or three times a year in order to achieve a lasting result. A word of caution is necessary to the surgeon who has not had experience with this drug. Although we are recommending relatively low doses of the toxin, there is a very real danger of injecting too much toxin in the wrong areas of the face and achieving an unsightly facial palsy. This is so

because the toxin takes 3 to 5 days to give an effect, and there is no way to monitor exactly what wrinkles will be eliminated with each specific injection. We recommend the EMG injection technique as a way to ensure the correct placement of the toxin. A week after the original injections, a second "touch-up" shot may be necessary. Once a surgeon has experience with the injection technique, the control afforded by the EMG electrode may not be necessary. We are presently studying this by injecting one side with the EMG electrode needle control and the other side without it. This will be the subject of another report. Since everyone's reaction to the drug is different, it is vitally important to underdose at the first session in order to ascertain the individual patient's reaction to the medication. After injection, one must wait for the toxin to be metabolized, since there is no medication that can readily reverse the metabolic effect.

A larger study is currently being implemented to further define the aesthetic surgical indications of botulinum toxin A in eliminating facial lines. This study will include approximately 200 patients from two different cities (New York and Los Angeles) who will be injected in five different sites (forehead, frown lines, crow's feet, nasolabial folds, and platysma bands), photographed, and followed for at least 1 year. In this efficacy study, we did not attempt to define the optimal dosage, duration of effects, necessity for the use of EMG, or extrapolation of the technique to other sites. The parallel study is under way to answer these and other questions. The sole purpose of this study was to prove the efficacy of utilizing botulinum toxin A for elimination of hyperfunctional facial lines. Preliminary results indicate that the toxin seems to be most beneficial in the 30- to 50-year-old age group and most effective in the upper third of the face (crow's feet and forehead frown lines). These results will be the subject of another report.

## CONCLUSIONS

We conclude that botulinum toxin A is a safe and efficacious method of nonsurgically eliminating facial wrinkles in the aesthetic surgical patient for a period of 4 to 6 months. Botulinum toxin A may play an increasingly important role as an adjuvant treatment in the cosmetic surgical enhancement of the upper third of the aging face. Botulinum toxin A injections address the need for a short-term reversible therapy to "touch up" the aging face.

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