

## TOPICAL TREATMENT WITH NERVE GROWTH FACTOR FOR CORNEAL NEUROTROPHIC ULCERS

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### ABSTRACT

**Background** Corneal neurotrophic ulcers associated with impairment of sensory innervation of the cornea may lead to loss of vision, and there is no effective treatment for these ulcers. We evaluated the effects of nerve growth factor in patients with this disorder.

**Methods** Twelve patients (14 eyes) with severe corneal neurotrophic ulcers associated with corneal anesthesia were treated with topical nerve growth factor 10 times daily for two days and then 6 times daily until the ulcers healed. Treatment continued for 2 weeks after the ulcers healed, and the patients were then followed for up to 15 months. The evolution of the corneal disease during treatment and follow-up was evaluated by slit-lamp examination, photography, fluorescein-dye testing, and tests of corneal sensitivity and best corrected visual acuity.

**Results** Corneal healing began 2 to 14 days after the initiation of treatment with nerve growth factor, and all patients had complete healing of their corneal ulcers after 10 days to 6 weeks of treatment. Corneal sensitivity improved in 13 eyes, and returned to normal in 2 of the 13 eyes. Corneal integrity and sensitivity were maintained during the follow-up period (range, 3 to 15 months). Best corrected visual acuity increased progressively during treatment and follow-up in all patients. There were no systemic or local side effects of treatment.

**Conclusions** In this preliminary, uncontrolled study, topically applied exogenous nerve growth factor restored corneal integrity in patients with corneal neurotrophic ulcers. (N Engl J Med 1998;338:1174-80.)

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SEVERAL ocular and systemic diseases and circumstances, including fifth-nerve palsy, viral infections, chemical burns, corneal surgery, abuse of topical anesthetics, neurotrophic keratitis, diabetes mellitus, and multiple sclerosis, can cause corneal neurotrophic ulcers.<sup>1</sup> These ulcers result from loss of the sensory innervation of the cornea, which leads to a decrease in the number of corneal stem cells,<sup>2</sup> decreased metabolic and mitotic rates in the corneal epithelium (which increases cell permeability),<sup>3,4</sup> and reduced acetylcholine and choline acetyltransferase concentrations.<sup>5</sup> The result is progressive corneal damage, with epithelial defects, vascularization, opacification, ulceration, and ultimately, perforation, even in the absence of injury or infection. The standard treatments consist of cover-

ing the eye with a patch or a soft contact lens, tarsorrhaphy, and constructing a conjunctival flap, but they are often ineffective, and the outcome is often loss or severe impairment of vision.

Nerve growth factor is a well-characterized neurotrophin that is required for the development and survival of selected neurons, including sympathetic and sensory neurons.<sup>6</sup> It provides trophic support after neuronal injuries and reverses pathologic changes induced by peripheral-nerve injury.<sup>7</sup> In denervated skin, nerve growth factor induces sensory-neuron sprouting and restores the density of nerve growth factor receptors.<sup>8,9</sup> Skin ulcers caused by the impairment of sensory innervation, such as in patients with diabetes mellitus and leprosy and after trauma, may be the result of decreased concentrations of local nerve growth factor.<sup>10,11</sup>

Nerve growth factor receptors have been found on the normal and abnormal cornea and conjunctiva.<sup>12,13</sup> In this study, we evaluated the efficacy of topical application of nerve growth factor in patients with severe noninfectious corneal ulcers due to corneal anesthesia that were unresponsive to conventional therapy.

### METHODS

#### Patients

We studied 12 patients (14 eyes) who had noninfectious corneal ulcers associated with impaired corneal sensitivity, caused by essential neurotrophic keratitis (5 eyes), chemical burns (3 eyes), abuse of topical anesthetics (2 eyes), surgery for orbital tumor (1 eye), surgery for acoustic neuroma (1 eye), penetrating keratoplasty for unknown reasons (1 eye), and lamellar keratoplasty for a herpetic vascularized scar (1 eye) (Table 1). The mean age of the patients was 31 years (range, 4 to 56); six were female and six male. All the patients presented with corneal ulcer without ocular pain and photophobia or other signs of active inflammation (Fig. 1A). Corneal ulceration had been present for a mean ( $\pm$ SD) of  $45 \pm 24$  days. All had received conventional treatment, such as artificial tears and covering the eye with a patch or a soft contact lens,<sup>1</sup> and antibiotics with little or no benefit, and were referred to our center because of progressive worsening of the ulcer. The criteria for enrollment in the study were clinical evidence of corneal ulcer that was unresponsive to conventional therapy and the presence of corneal and conjunctival anesthesia. The exclusion

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TABLE 1. BASE-LINE CHARACTERISTICS OF THE 12 PATIENTS WITH CORNEAL NEUROTROPHIC ULCERS AND CORNEAL ANESTHESIA.

PATIENT No.	AGE (yr)/SEX	CAUSE OF ULCER	PREVIOUS OCULAR CONDITIONS	ASSOCIATED SYSTEMIC DISEASES*	DURATION OF ULCER (DAYS)	DIAMETER AND DEPTH OF ULCER	BEST CORRECTED VISUAL ACUITY
1	9/F	Essential neurotrophic keratitis	Microphthalmos†	Hemifacial hypoesthesia	20	7 mm; 2/3 of the stroma	0.025
2	26/F						
Left eye		Essential neurotrophic keratitis	Recurrent keratoconjunctivitis	Hemifacial hypoesthesia; temporal spike on EEG	60	7 mm; entire stroma	0.02
Right eye		Essential neurotrophic keratitis	Recurrent keratoconjunctivitis	Hemifacial hypoesthesia; temporal spike on EEG	15	3 mm; 1/3 of the stroma	0.05
3	35/F	Essential neurotrophic keratitis	Perforated ulcer†	Neurofibromatosis	30	4 mm; 1/3 of the stroma	0.05
4	7/F	Essential neurotrophic keratitis	Recurrent keratoconjunctivitis	Ectodermal dysplasia	40	4 mm; 1/3 of the stroma	0.1
5	4/F	Orbital surgery	Orbital teratoma	None	60	5 mm; 1/3 of the stroma	0.02
6	30/F	Neurosurgery	None	Previous acoustic neuroma	60	7 mm; 2/3 of the stroma	0.02
7	34/M	Topical-anesthetic abuse	Corneal abrasion	None	20	5 mm; entire stroma	0.02
8	44/M	Topical-anesthetic abuse	Corneal abrasion	None	90	4 mm; 1/3 of the stroma	0.02
9	25/M	Penetrating keratoplasty for unknown reasons	Perforated ulcer†	None	30	5 mm; 1/2 of the stroma	0.05
10	56/M	Lamellar keratoplasty for herpes zoster	None	None	60	7 mm; 1/3 of the stroma	0.02
11	50/M	Lamellar keratoplasty for alkali burn	None	None	80	5 mm; 1/3 of the stroma	0.02
12	56/M						
Left eye		Alkali burn	None	None	30	4 mm; 1/3 of the stroma	0.05
Right eye		Alkali burn	None	None	30	8 mm; 2/3 of the stroma	0.02

\*EEG denotes electroencephalogram.

†Enucleation of the other eye had been performed.

criteria were the presence of corneal infection and the presence of other ocular diseases.

Before starting treatment with nerve growth factor, the patients were treated with preservative-free artificial tears (one drop every two hours) for 10 days. If no tendency to heal was observed or if the ulcer progressed toward ocular perforation, all topical and systemic treatments were discontinued and topical treatment with nerve growth factor was commenced. The study protocol was approved by the ethics committee of the Hospital of Venice, and written informed consent was obtained from all patients.

**Study Protocol**

The patients were evaluated at base line, daily for 1 week during treatment with nerve growth factor and then weekly until the corneal ulcer was completely healed, and thereafter every month for up to 12 months after treatment was discontinued. The treatment used was murine nerve growth factor (200 µg in 1 ml of balanced salt solution), purified from submaxillary glands according to the method of Bocchini and Angeletti.<sup>14</sup> Each patient was treated in the hospital until corneal healing began (after 2 to 14 days). The patients received one drop (approximately 50 µl) of nerve growth factor in the conjunctival fornix of the affected eye every two hours from 6 a.m. to midnight for two days, followed by a dose of one drop six times a day until the ulcer healed. After the ulcer healed, one drop of a lower concentration of nerve growth factor (100 µg per milliliter) was administered four times daily for two weeks.

**Procedures**

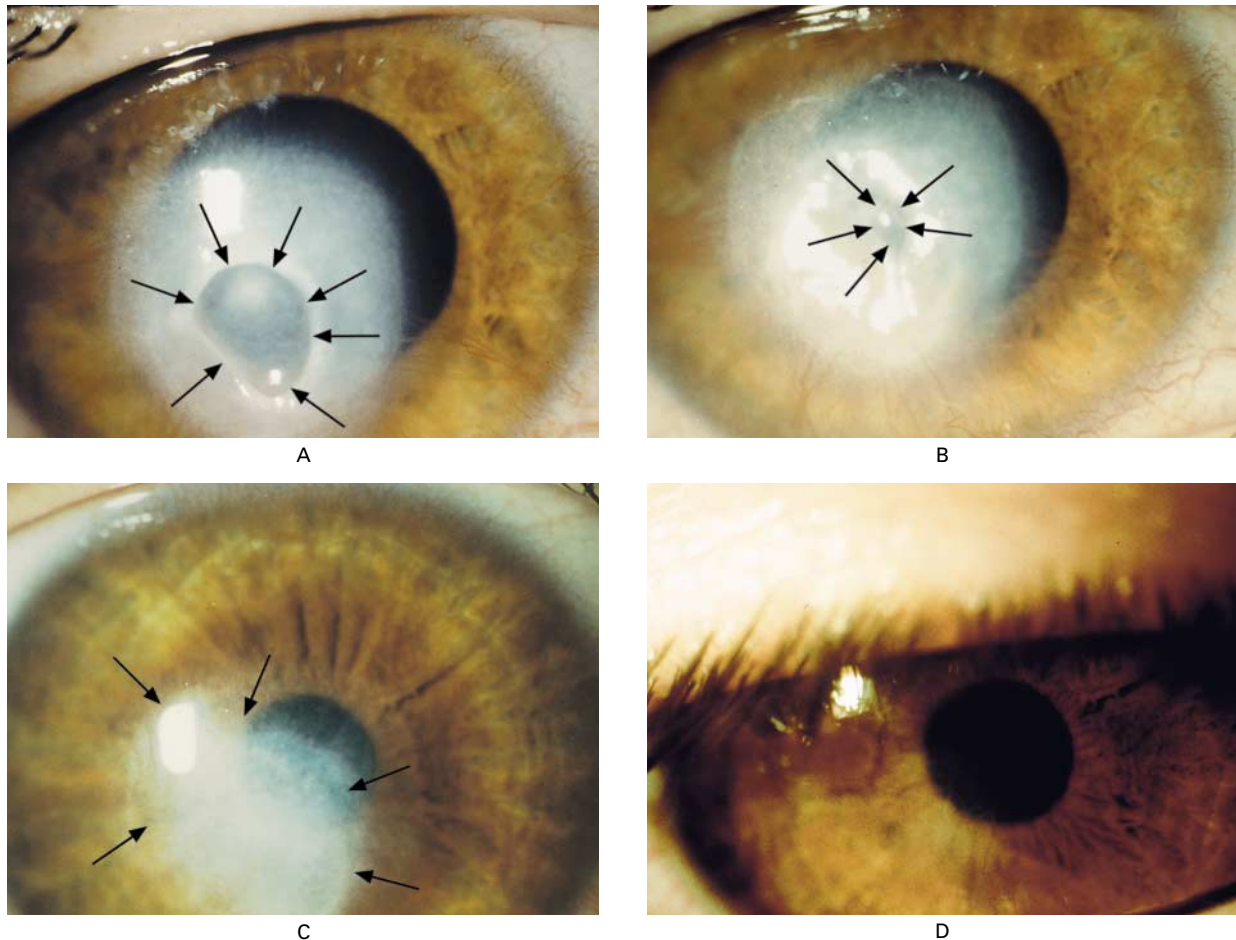
All patients were evaluated at base line by a complete eye examination (slit-lamp evaluation, tonometry, fundus oculi evalua-

tion when possible, photography, fluorescein-dye test, corneal-sensitivity tests, estimation of best corrected visual acuity, and Schirmer's test). A general history was obtained and physical examination and routine hematologic and chemical tests were performed to rule out systemic disease. Cranial magnetic resonance imaging was also performed in the patients with essential neurotrophic keratitis to rule out anatomical lesions of the central nervous system or the cranial nerves.

The best corrected visual acuity was defined as the best vision that the eye can achieve after correction of its refractive error. Visual acuity was measured by having the patient read the smallest-possible line on a visual chart and expressed as a fraction of the normal value (normal vision is defined as 1.0, or 20/20). Corneal culture was performed to rule out bacterial and fungal infection, and corneal scrapings were analyzed with the polymerase chain reaction to rule out herpesvirus infection.

Corneal ulcers were classified according to their widest diameter and depth on slit-lamp examination. To test corneal sensitivity, we removed and twisted the tip of a cotton swab and then slowly advanced it until it touched the central corneal zone of the patient.<sup>15</sup> All tests of corneal sensitivity were performed between 9 and 11 a.m. Corneal sensitivity was considered to be normal if there was a blink reflex when the cornea was touched. If the patient felt contact but had no blink reflex, corneal hypoesthesia was diagnosed, and if no response was present, corneal anesthesia was diagnosed. To test for the presence of sensitivity to chemical stimulation, we determined whether the patient noted a burning sensation after conjunctival instillation of a pungent substance<sup>15</sup> (a commercial mydriatic drug [Visumidriatic 1 percent, Merck Sharp & Dohme]).

The eye examinations were repeated daily while the patient was hospitalized, weekly during treatment, and then monthly during



**Figure 1.** Photographs of the Eye of a Patient with a Corneal Neurotrophic Ulcer before, during, and after Treatment with Nerve Growth Factor.

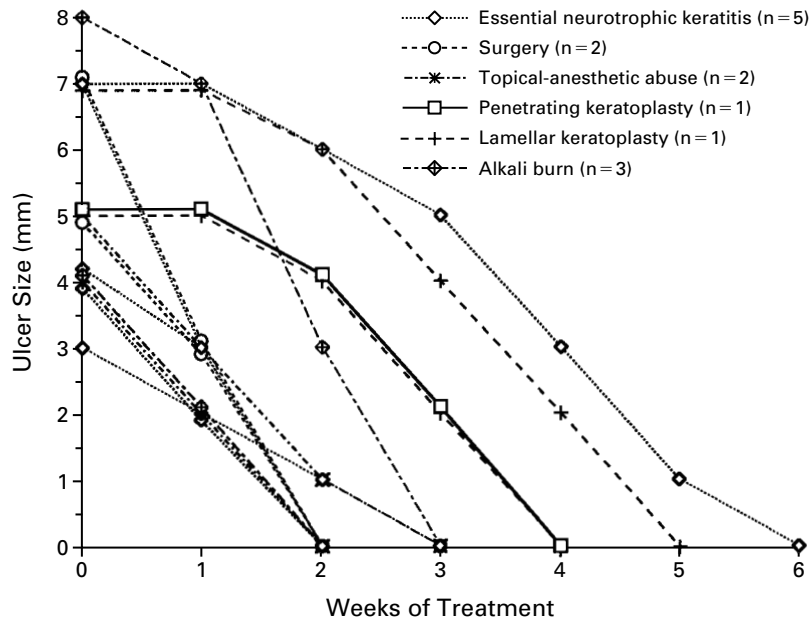
The patient had had a corneal ulcer in the right eye for 20 days. Slit-lamp examination showed a large and deep central corneal ulcer overlying a circular edematous area that was approximately 7 mm in diameter (arrows in Panel A). After four days of treatment with nerve growth factor, the corneal ulcer had shrunk to approximately 2 mm in diameter (arrows in Panel B). At this time the patient had eye pain and intense photophobia. After 12 days of treatment, the cornea was completely healed, and treatment was discontinued after 15 days. A central scar (arrows in Panel C) and corneal sensitivity were present. After 12 months of follow-up, the corneal scar was transparent (Panel D) and the patient had a best corrected visual acuity of 0.70.

follow-up. To assess the efficacy of nerve growth factor, we evaluated the results of the slit-lamp examinations, changes in ulcer size, best corrected visual acuity, and changes in corneal sensitivity. The effects of treatment on best corrected visual acuity were compared with paired t-tests at base line, at the time of discontinuation of therapy, and 6 and 12 months later.

### RESULTS

All patients had complete resolution of the corneal ulcer after 10 days to 6 weeks of treatment with nerve growth factor (Fig. 1 and 2), at which time the dosage was reduced for 2 weeks and then discontinued. The mean duration of treatment was 34 days (range, 24 to 56). The healing process began two days after the initiation of treatment in three patients and within two weeks in the other patients

(Table 2). The rate of healing was not related to the severity of the ulcer, its depth in the stroma, the age of the patient, or the cause of the ulcer. The first signs of healing were an advancement of epithelial cells from the margin toward the center of the ulcer and the occurrence of mild-to-moderate conjunctival hyperemia and were accompanied by pain and photophobia in all patients. Subsequently, superficial or deep corneal neovascularization occurred in 9 of the 14 treated eyes. All ocular symptoms disappeared once the corneal ulcer was completely healed. Corneal sensitivity improved after ulcer healing in 13 of the 14 eyes (sensitivity returned to normal in 2 eyes and improved to hypoesthesia in 11 eyes), and after healing, all patients reported a burn-



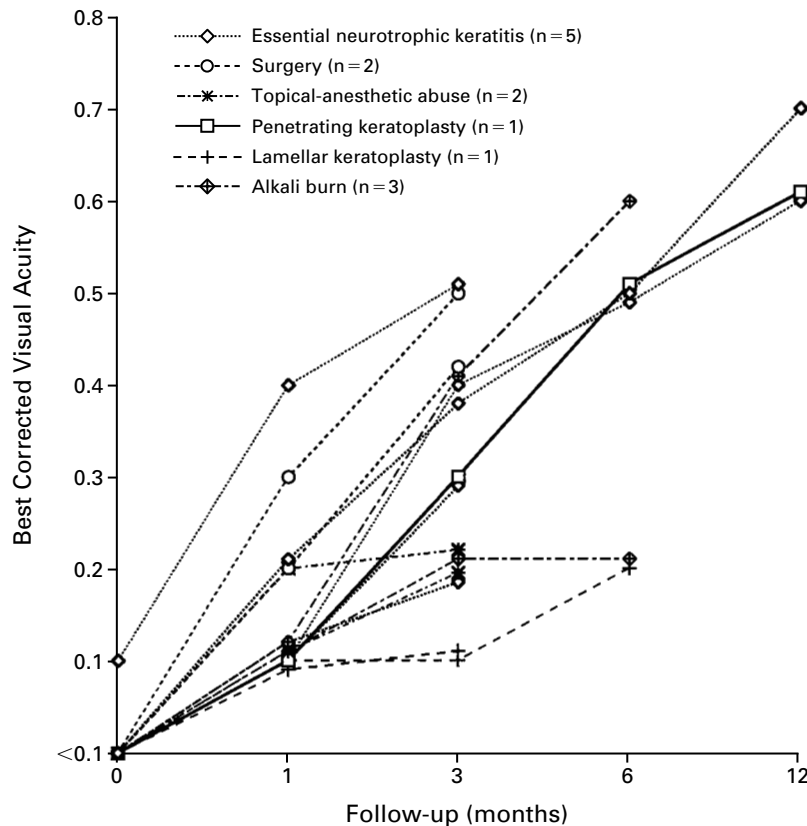
**Figure 2.** Effects of Treatment with Nerve Growth Factor on Ulcer Size in 12 Patients (14 Eyes) with Corneal Neurotrophic Ulcers from Various Causes.

**TABLE 2.** EFFECTS OF TREATMENT WITH NERVE GROWTH FACTOR IN 12 PATIENTS WITH CORNEAL NEUROTROPHIC ULCERS.\*

PATIENT NO.	SIGNS AND SYMPTOMS DURING TREATMENT	ONSET OF HEALING	TIME FROM START OF TREATMENT TO COMPLETE HEALING	CORNEAL SENSITIVITY†	BEST CORRECTED VISUAL ACUITY†	LENGTH OF FOLLOW-UP
1	Hyperemia, pain, photophobia	2	12 days	Normal	0.7	15
2						
Left eye	Hyperemia, neovascularization, pain, photophobia	8	6 wk	Hypoesthesia	0.6	12
Right eye	Hyperemia, neovascularization, pain, photophobia	7	3 wk	Hypoesthesia	0.3	4
3	Hyperemia, neovascularization, pain, photophobia	4	13 days	Hypoesthesia	0.2	3
4	Hyperemia, neovascularization, pain, photophobia	3	14 days	Hypoesthesia	0.5	3
5	Hyperemia, pain, photophobia	2	14 days	Hypoesthesia	0.4	4
6	Hyperemia, pain, photophobia	3	13 days	Hypoesthesia	0.5	4
7	Hyperemia, neovascularization, pain, photophobia	4	3 wk	Hypoesthesia	0.2	3
8	Hyperemia, pain, photophobia	6	10 days	Hypoesthesia	0.2	4
9	Hyperemia, pain, photophobia	14	4 wk	Anesthesia	0.6	12
10	Hyperemia, neovascularization, pain, photophobia	14	5 wk	Hypoesthesia	0.2	8
11	Hyperemia, neovascularization, pain, photophobia	12	4 wk	Hypoesthesia	0.1	4
12						
Left eye	Hyperemia, neovascularization, pain, photophobia	2	2 wk	Normal	0.6	8
Right eye	Hyperemia, neovascularization, pain, photophobia	7	3 wk	Hypoesthesia	0.2	8

\*None of the patients had systemic side effects.

†The results are those obtained at the time of the last follow-up visit.



**Figure 3.** Best Corrected Visual Acuity before, during, and after Treatment with Nerve Growth Factor in 12 Patients (14 Eyes) with Corneal Neurotrophic Ulcers from Various Causes.

ing sensation after conjunctival instillation of a mydriatic drug.

After healing of the ulcer, all patients had a corneal scar; both the scarring and the corneal neovascularization disappeared during follow-up. The improvements in corneal sensitivity and visual acuity were maintained throughout the follow-up period (Fig. 3). Follow-up lasted 3 months in the case of three patients, 4 months in four patients, 8 months in two patients, 12 months in two patients, and 15 months in one patient. After three months, all patients had photophobia during slit-lamp examination. One patient had no corneal contact sensitivity despite the presence of photophobia during slit-lamp examination and a burning sensation after the instillation of a mydriatic drug, both of which had been absent before treatment.

When compared with the values at base line (mean,  $0.03 \pm 0.02$ ), best corrected visual acuity significantly improved after healing of the corneal ulcer in all 14 eyes (mean,  $0.20 \pm 0.02$ ;  $P < 0.001$ ). The improvement was even more evident after 6 months (mean of six eyes,  $0.40 \pm 0.18$ ;  $P = 0.002$ ) and 12 months (mean of three eyes,  $0.63 \pm 0.06$ ;  $P = 0.002$ ) (Fig. 3).

None of the patients had systemic or ocular side effects during treatment with nerve growth factor or follow-up. Moreover, none had a relapse of their eye disease, and corneal integrity and sensitivity were maintained during follow-up.

## DISCUSSION

The results of this study indicate that topical administration of nerve growth factor is effective therapy for patients with severe corneal ulcers with sensory-nerve impairment and corneal anesthesia. These ulcers, although uncommon, have devastating effects on the cornea, frequently leading to ocular perforation and visual loss. There is no effective medical treatment. The only treatment is surgical, with the use of such procedures as tarsorrhaphy, construction of a conjunctival flap, or lamellar or penetrating keratoplasty.<sup>1</sup> The main goal of these procedures is to preserve the anatomical integrity of the eye; they do not restore visual function. In most cases, the prognosis regarding visual function is very poor, and relapses of the ulcer are frequent.

Topical administration of nerve growth factor healed the ulcer in all the patients and improved cor-

neal sensitivity in most within 10 days to 6 weeks, and no patient had a relapse during follow-up. The first sign of corneal healing was a line of epithelial cells advancing from the border of the ulcer in association with conjunctival hyperemia. These findings suggest that the nerve growth factor had a direct action on the epithelium, in agreement with the results of a previous *in vitro* study in which nerve growth factor as well as other growth factors stimulated the proliferation and differentiation of rabbit corneal epithelial cells<sup>16</sup> and the evidence that human corneal epithelium has high-affinity receptors for nerve growth factor.<sup>13</sup> Nerve growth factor may also act indirectly by inducing neurogenic inflammation. There is increasing evidence that nerve growth factor stimulates the release of several neuropeptides and growth factors that can stimulate the healing process.<sup>17-20</sup>

During epithelial proliferation, all patients had photophobia and burning of their eyes during slit-lamp examinations, and most patients had improvement of corneal sensitivity, which suggests functional recovery of corneal innervation. This finding may be related to the well-known ability of nerve growth factor to induce neuritic sprouting by neuronal cells *in vitro* and nerve regeneration *in vivo* in denervated skin, as well as in the central and peripheral nervous systems after surgical, chemical, or ischemic injury.<sup>6,9,21</sup> Systemic treatment with nerve growth factor also induces hyperalgesia in animals and healthy subjects.<sup>22,23</sup>

The murine nerve growth factor that we used is closely homologous to human nerve growth factor.<sup>24</sup> Because of its trophic and regenerative actions on the central and peripheral nervous system,<sup>6</sup> nerve growth factor has been proposed for the treatment of several neurologic diseases.<sup>25</sup> In two clinical studies, intracerebral administration of murine nerve growth factor in patients with Parkinson's disease<sup>26</sup> and Alzheimer's disease<sup>27</sup> was of some benefit and caused no side effects. In our study, ophthalmic administration of murine nerve growth factor produced no local or systemic side effects.

The maintenance of corneal sensitivity after treatment with nerve growth factor suggests that such treatment completely restores sensory innervation of the cornea. This possibility is consistent with the known pathophysiologic role of sensory innervation in corneal wound healing. The cornea is a virtually avascular tissue, but it has very dense innervation (40 times more than the tooth pulp and 400 times more than skin). Thus, any inflammatory reaction and subsequent healing are controlled by this neuronal innervation.<sup>28</sup> Experimentally, corneal-nerve damage induces severe alterations in the metabolism and vitality of the epithelium, and clinically, surgical damage (as may occur during trigeminal-nerve manipulation or penetrating keratoplasty) or chemical damage (such as that caused by abuse of local anes-

thetics) of corneal innervation impairs epithelial healing and induces trophic ulcers.<sup>29-31</sup>

Our results are in line with the current hypothesis of the pathogenesis of corneal neurotrophic ulcers. It has been thought that corneal nerves release a trophic factor that maintains the integrity of the corneal epithelium and that nerve damage compromises the integrity.<sup>32,33</sup> The finding that exogenous nerve growth factor restored corneal integrity and sensitivity suggests that the progressive corneal damage that occurs in some patients with corneal sensory-nerve deficits could be due to a deficit of endogenous nerve growth factor. This hypothesis is in agreement with the effects of this factor in other biologic systems. For example, in animals with a targeted mutation of the gene coding for the low-affinity nerve growth factor receptor, ulcers and lesions of the feet occur,<sup>34</sup> and exogenous nerve growth factor accelerates the rate of wound contraction in mice.<sup>35</sup> Moreover, concentrations of nerve growth factor are decreased in ulcerative tissue from patients with systemic conditions such as diabetes mellitus, leprosy, and nerve trauma.<sup>10,11</sup>

In conclusion, in a preliminary, uncontrolled study, treatment with nerve growth factor induced prompt healing and restoration of corneal sensitivity with no local or systemic side effects in patients with corneal neurotrophic ulcers.

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