

Cultivated Corneal Epithelial Transplantation for Ocular Surface Reconstruction in Acute Phase of Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS), also known as the erythema multiform, is an acute, self-limited, inflammatory disorder of the skin and mucous membranes. Although the skin lesions are self-limited, the ocular disease gets worse and often results in bilateral blindness owing to a lack of corneal stem cells,¹ corneal scarring, and subconjunctival fibrosis. Prognosis of corneal transplanta-

tion in the acute phase is poor because of the difficulty of overcoming the severe inflammation and allograft rejection. Even in the chronic phase, it is difficult to control persistent inflammation, dry eye, and trichiasis, which induce persistent epithelial defect and allograft rejection. Although corneal stem cell transplantation and amniotic membrane (AM) transplantation, combined with dry eye treatment and strong immunosuppressive therapy, have been attempted at the scarring stage,² the management is difficult, and the visual prognosis is not satisfactory. However, if it were possible to control the severe inflammation and manage the corneal transplantation in the acute phase with less

scarring change, the visual prognosis could be greatly improved. Recently, attention has focused on cultivated corneal epithelial transplantation as a new approach for ocular surface reconstruction in limbal-deficient disorders.³ We ensured the suitability of the denuded AM as a carrier for the corneal epithelial cell culture⁴ and have successfully established a surgical system for cultivated corneal limbal epithelium transplantation in rabbits using AM as a carrier.⁵ We applied this procedure in 2 patients with the acute phase of SJS, and we achieved successful ocular surface reconstruction.

Human AM was obtained at cesarean section,⁵ and the amniotic epithelium was removed by EDTA

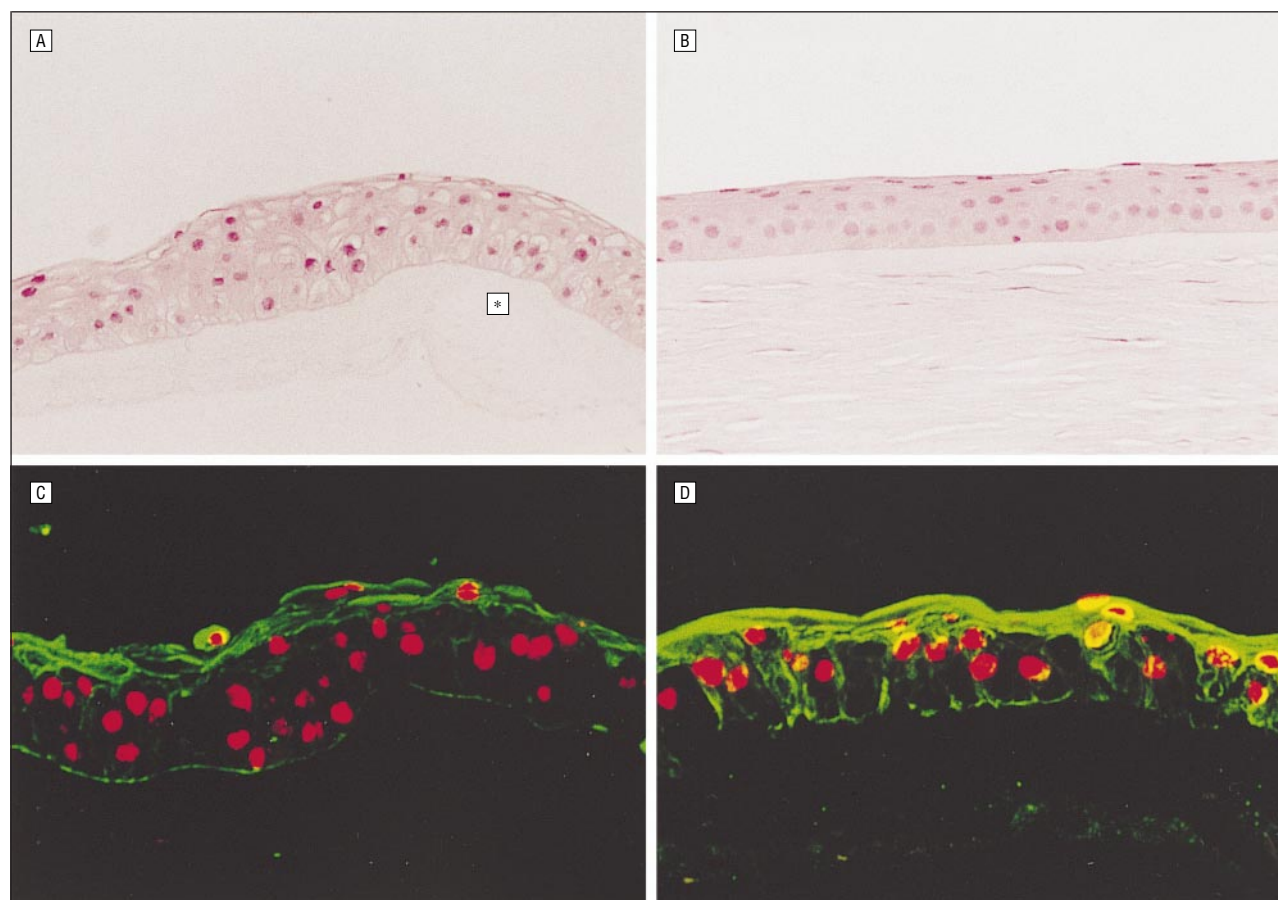


Figure 1. A, Cultivated corneal epithelium on amniotic stroma (asterisk) consists of 4 to 5 layers that are very similar in appearance to normal corneal epithelium (B) (hematoxylin-eosin, original magnification $\times 100$). C and D, Cultivated corneal epithelium stained with antibodies specific to corneal epithelium keratin 3 and keratin 12.

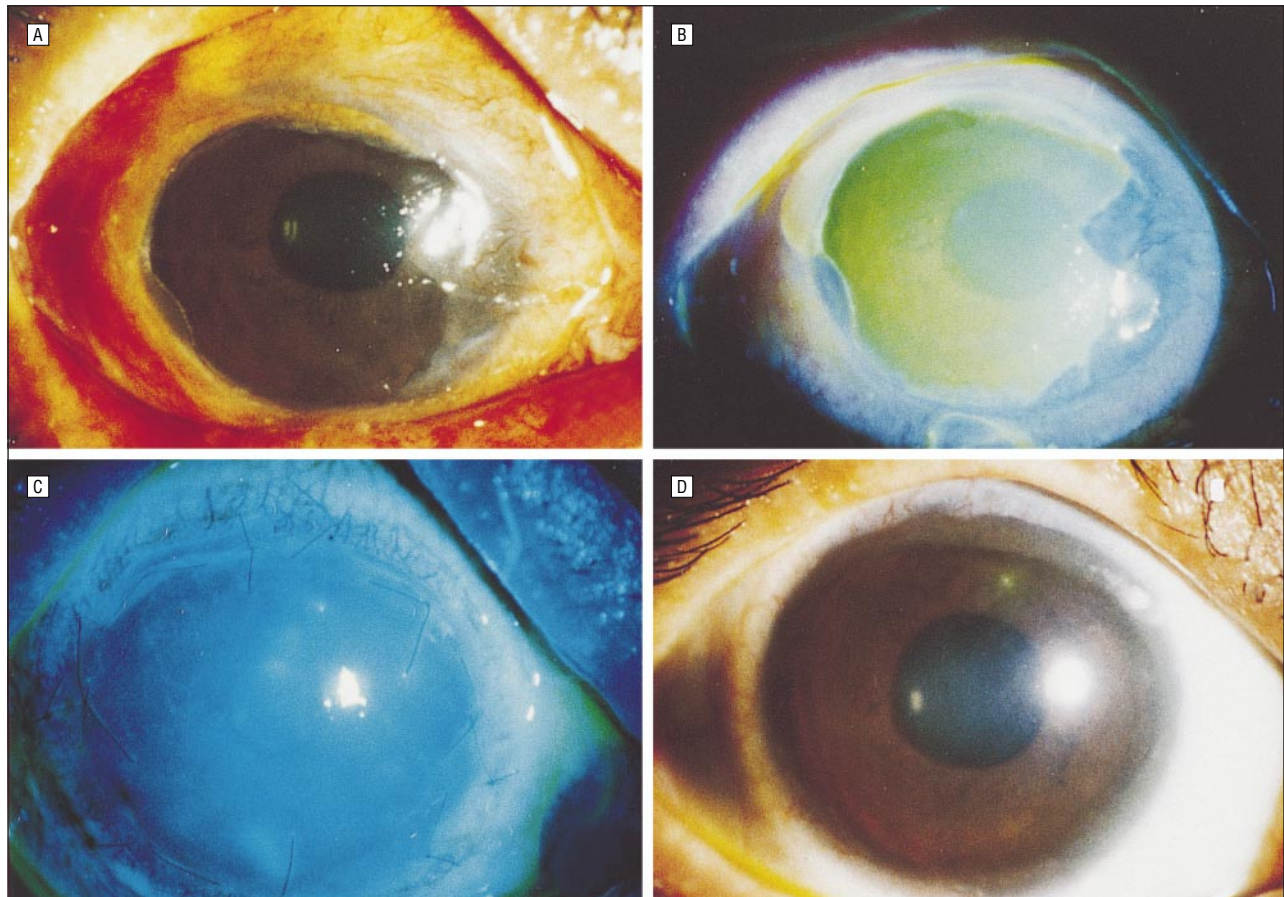


Figure 2. A, Persistent corneal epithelial defects of patient 2 (right eye) surrounded by inflammatory subconjunctival fibrosis. B, Fluorescein staining clearly shows the area of epithelial defect surrounded by conjunctival invasion. C, Two days after the cultivated corneal epithelial transplantation, corneal surface is covered with transplanted corneal epithelium, which shows no fluorescein staining. D, Three months after transplantation, a clear corneal surface is maintained, and visual acuity is 20/20 OD.

treatment.⁴ Small pieces of donor limbal cornea were cultured on acellular AM with 3T3 fibroblasts. The culture was submerged in the medium for 2 weeks, after which it was exposed to the air to promote epithelial stratification for 1 to 2 weeks. The cultivated corneal epithelium consisted of 4 to 5 layers, appeared very similar to normal corneal epithelium, and stained with antibodies specific for corneal epithelium keratin 3 (AE5) and keratin 12 (J7) (**Figure 1**).

Report of Cases. The patients were a 32-year-old man (patient 1) and a 21-year-old man (patient 2), each of whom had had SJS for 3 months. Their eyes showed persistent corneal epithelial defects surrounded by inflammatory subconjunctival fibrosis that was resistant to conventional therapy (**Figure 2**, A and B). They showed total stem cell deficiency. After informed consent from

the patients and approval from the university ethics committee were obtained, we performed the cultivated corneal epithelial transplantation on the right eye of patient 1 and in both eyes of patient 2. After removal of the conjunctival tissue on the cornea up to 3 mm outside the limbus, we treated the subconjunctival fibroblasts for 5 minutes with 0.04% mitomycin and vigorous saline washing. We secured the cultivated allocorneal epithelium on AM onto the corneal surface with 10-0 nylon sutures, then we covered it with a therapeutic soft contact lens. Postoperatively, 0.3% ofloxacin and 0.1% dexamethasone were instilled 4 times per day, and corticosteroid (1 mg/d), cyclosporin (150 mg/d), and cyclophosphamide (100 mg/d) were administered to prevent postoperative inflammation and allograft rejection. Forty-eight hours after transplantation, the corneal surfaces of the 3 eyes were clear and smooth, and the

entire corneal surfaces were perfectly covered with transplanted allocorneal epithelium that did not stain with fluorescein (**Figure 2**, C). The transplanted corneal epithelium was surrounded by a conjunctival epithelial defect at 360°, suggesting there was no contamination of host conjunctival epithelium. Five days after transplantation, all areas of the ocular surface were covered with transparent epithelium. Shortly after the transplantation, conjunctival inflammation rapidly subsided, and visual acuity recovered to 20/20 OD in patient 1 and 20/20 OU in patient 2. After a posttransplantation observation period of 6 months, their ocular surface epithelia were stable and without defects (**Figure 2**, D). We are carefully monitoring the transplanted allocorneal epithelial cells to determine their longevity.

Comment. The concept that corneal epithelial stem cells reside in the

limbal basal epithelium was established in the 1980s.¹ Conventional stem cell transplantation has great potential as a treatment for stem cell deficiency. However, this procedure needs several weeks to cover the total corneal surface with migrated corneal epithelium from donor cornea, and the denuded corneal surface induces severe inflammation, especially in acute phase SJS. The patients we report here were in acute phase and would have been contraindicated for conventional stem cell transplantation. Our method of cultivated allogeneic epithelial transplantation allowed us to cover their ocular surfaces with clear and silent corneal epithelium during surgery, and subside their inflammation. In conclusion, cultivated corneal epithelial transplantation using AM as a carrier is an effective ocular surface reconstruction technique for acute phase SJS.

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Migraine Headache Associated With Latanoprost

Latanoprost is a phenyl-substituted isopropyl ester of prostaglandin $F_{2\alpha}$ that enhances uveoscleral outflow and lowers intraocular pressure. Its potency, once-daily dosing schedule, and low incidence of adverse effects led to widespread use immediately after its release in the United States. Since then, adverse effects such as anterior uveitis and cystoid macular edema¹ have been reported. This report describes 3 patients who experienced new onset of migraine headache after taking latanoprost; 2 patients had to discontinue the drug. This adverse effect previously has not been reported in association with latanoprost use. The trigeminovascular theory of migraine pathogenesis could explain this association.

Report of Cases. *Case 1.* A 65-year-old man with primary open-angle glaucoma that was previously well controlled with topical therapy became allergic to dipivefrin hydrochloride and dorzolamide hydrochloride. He was intolerant of β -blockers because of a cardiac arrhythmia. He was prescribed latanoprost for both eyes at bedtime. Although the patient had no prior history of migraine, in the ensuing months he began to have migraine headaches. The frequency and severity increased until the headaches were occurring daily. The pain was throbbing, bifrontal, and associated with lightheadedness and photophobia. It was not relieved by over-the-counter or narcotic analgesics, and the patient was virtually incapacitated. He consulted his neurologist, but because he had been examined 1 year previously for ver-

tigo, no new tests were performed. Eight months later he informed his ophthalmologist, and latanoprost treatment was discontinued. He had almost immediate relief, with only 1 migraine the following week. He was headache-free for the following 10 months.

The patient agreed to a challenge with latanoprost. After the second night of therapy, he woke up with another migraine headache. He continued the latanoprost for 2 more nights but again had to stop the drug because of incapacitating pain. Forty-eight hours later, his headache resolved. It has not recurred within 4 months of follow-up.

Case 2. A 67-year-old white man with primary open-angle glaucoma taking levobunolol hydrochloride at a dose of 0.5% was prescribed a nighttime dose of latanoprost for both eyes to treat a mild rise in intraocular pressure. The next morning he awoke with a severe bifrontal headache. It was throbbing in nature and associated with photophobia and slight blurring of vision. He did not normally suffer from headaches and described it as the worst headache he had ever had. It was not relieved with an over-the-counter analgesic. It intensified, and 4 days later he went to the emergency room. A computed tomographic scan and neurologic consultation were performed and found to be normal. On the sixth day, he realized the temporal association with latanoprost and called the eye clinic, whereupon he was instructed to discontinue the drug. His headache disappeared within 24 hours and has not recurred with 1 year of follow-up.

Case 3. A 54-year-old woman with primary open-angle glaucoma taking betaxolol hydrochloride at a dose of 0.5% for both eyes had mild progression of visual field loss in her left eye. Latanoprost was added nightly to her left eye. At approximately 3 AM on the night after her first dose, she was awakened by a severe unilateral pounding headache extending from the left eye and brow to the left cranium. There were no associated neurologic symptoms. The patient does not normally suffer from headaches. The headache was not relieved by acetaminophen

or codeine phosphate but spontaneously resolved the next day. It recurred for 3 more nights after instillation of latanoprost. On the fourth night, the headache did not occur. The patient continued to take the drug, and the headache has not returned.

Comment. Migraine headache is a significant cause of morbidity and lost work time in the United States. About 6% of men and 18% of women experience regular migraines and have at least 1 attack per year.² Peak incidence of migraine onset is in the teens; onset after age 50 years is rare. Patients with a history of migraine are not usually examined unless "alarm symptoms" are present. These include sudden changes in attack duration, frequency, or severity; abnormal neurological examination results; or onset after age 50 years.³ All of the patients described in this report were older than 50 years and had no prior history of migraine headache.

Many theories of migraine pathogenesis have been proposed, but the exact mechanism is still not understood. People prone to migraine have underlying cortical hyperexcitability, and the attack is started by 1 or more triggers. Humoral mediators have been extensively investigated, but the exact role of each remains in debate.³ The visual aura is caused by a wave of depolarization called cortical-spreading depression. In animal experiments, this is accompanied by changes in cerebral blood flow similar to those seen in migraine, suggesting that the phases of vasoconstriction and vasodilation are only epiphenomena. A new theory of migraine pathogenesis suggests that the trigeminovascular system plays a key role via activation of pain fibers from the large cerebral vessels and dura, which lead centrally to the thalamus and cortical pain centers.⁴

Ocular abnormalities can cause headaches in several ways. Ciliary muscle spasm can cause pain referred to the brow but did not appear to be present in these patients because they did not display acute myopia. In addition, latanoprost causes relaxation rather than contraction of the ciliary muscle,⁵ which

may be how it increases uveoscleral outflow. Ciliary body irritation due to anterior uveitis was also considered, but this was not present on examination either.

Latanoprost may have caused migraine via activation of the trigeminovascular system. The parent compound, prostaglandin $F_{2\alpha}$, is a vasoactive agent. Clinical trials with the tromethamine salt of prostaglandin $F_{2\alpha}$ revealed a 50% incidence of conjunctival hyperemia, ocular pain, and headache.⁶ The ocular hyperemia induced by prostaglandin $F_{2\alpha}$ isopropyl ester is partially mediated by nitric oxide release, although the mechanism by which it causes headache has not been explained.⁷ Latanoprost stimulates the production of endogenous prostaglandins D_2 , E_2 , and $F_{2\alpha}$ in the ciliary body, all of which are vasoactive agents.⁸ Thus, a small concentration of the drug could lead to significant levels of vasoactive prostaglandin in the eye. In addition, if migraine can indeed be triggered by direct stimulation of the trigeminovascular system, the small amounts of latanoprost entering the eye could be sufficient to do so. The half-life of latanoprost in the aqueous humor and ciliary body is 3 hours,⁹ which could circumvent the advantage of low systemic absorption.

Migraine headache associated with latanoprost has not been previously described. However, it is a major adverse effect of a similar prostaglandin analog investigated for use in glaucoma.⁶ Because of the atypical initial symptoms, 2 of the patients had neurologic consultations, 1 of whom was investigated to rule out a serious neurologic problem. These 2 patients had to discontinue the drug for relief. New prostaglandin analogs are in clinical trials for use in glaucoma; there is reason to be concerned that they will cause headache as well. Ophthalmologists should first discontinue latanoprost in a patient developing headache, because they may spare their patient the inconvenience and risk of an investigation.

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Subperiosteal Hematoma of the Orbit With Osteoneogenesis

Although orbital surgeons work extensively with the bony structures of the orbit, the mechanism of bone healing has been a relatively neglected topic in the ophthalmic literature. A detailed understanding of the basic science of bone healing may pave the way for future innovations in surgical and medical management of problems of the orbital bones. One factor long thought to be important in bone healing is the hematoma overlying the fracture site.^{1,2} Some authors have proposed that it acts as a mechanical and biochemical bridge for the migration of cells that will eventually form a callus.³ Others, however, have suggested that it does not play an important role in the healing of bone fractures.⁴ In this report we describe a case of a traumatic orbital subperiosteal hematoma with no obvious underlying fracture and bone for-

mation within the hematoma. This stage in bone healing has rarely been captured histologically in a clinical setting, and appears to support the importance of the role of the hematoma in osteoneogenesis.

Report of a Case. A 9-year-old boy was struck in the right periocular region by another boy's head while participating in a sporting event. There was no immediate change in vision or onset of symptoms other than a dull periorbital ache. The following morning the vision was subjectively blurred with increased periorbital edema and ecchymosis. Five days following the injury the right eye became proptotic and the patient complained of vertical diplopia. Medical attention was sought.



Figure 1. Coronal computed tomographic scan demonstrating hematoma in a subperiosteal location in the right superior orbit.

The patient's medical history was unremarkable; the only medication he was taking was acetaminophen for the ache in the right eye. Ophthalmologic examination revealed a best-corrected visual acuity of 20/40 OD and 20/20 OS. Pupils were symmetrically round and reactive without a relative afferent pupillary defect. Ocular motility was full in the left eye but significantly limited in supraduction and mildly limited in horizontal gaze in the right eye with negative forced ductions. External examination results were unremarkable, and fundus examination revealed a bulge in the supertemporal quadrant without any chorioretinal folds. Hertel exophthalmometry measured 19 mm OD and 15 mm OS with a base of 83 mm. There was 3 mm of hypoglobus in the right eye, and soft tissue could be palpated through the right upper eyelid. No resistance to retro-pulsion was appreciated.

Orbital computed tomography revealed a large right superior orbital mass contiguous with the orbital roof (**Figure 1**), suggesting a subperiosteal location with inferior displacement of the extraocular muscles and globe. A diagnosis of right superior orbital subperiosteal hematoma was made.

An urgent anterior orbitotomy through an upper eyelid crease incision was performed to improve vision and relieve the mass effect. Approximately 10 mm posterior to the

superior orbital rim, a bluish-tinged mass was identified beneath a thin, bulging periosteum. A 6 × 5-mm patch of this periosteum was removed and submitted for histopathologic examination, with care being taken to avoid the underlying bone and the medial portion of the orbit to preserve the trochlea and neurovascular bundles. This resulted in expulsion of a large volume of liquefied and coagulated blood, which was completely irrigated. No fracture of the underlying bone was identified. On follow-up examination 2 weeks postoperatively, the patient's vision had returned to 20/25 OD, and he was orthophoric in all positions of gaze. Hertel exophthalmometry readings were 14 mm OD and 15 mm OS.

The gross specimen consisted of a triangular piece of black tissue measuring 6 × 5 × 4 mm. Light microscopic examination of routinely stained sections (**Figure 2**) revealed red blood cells and numerous polymorphonuclear and mononuclear inflammatory cells within a highly vascular connective tissue matrix, consistent with granulation tissue. In the granulation tissue was an island of osteoblasts within the lacunae of an osseous matrix. A diagnosis of subperiosteal hematoma with granulation tissue and foci of osteoneogenesis was made.

Comment. While the etiology, epidemiology, and histopathology of orbital hematomas have been described in the ophthalmic literature,⁵⁻⁹ the relationship of these hematomas to bone repair has not been described. The sequence of events leading to osteoneogenesis after fractures has been a subject of interest in the nonophthalmic literature.^{1,10,11} However, the exact biochemical and cellular mechanisms remain unclear and are a subject of controversy among clinicians and basic scientists. The healing process at the site of a fracture has conventionally been divided into 3 overlapping morphologic stages: (1) an initial inflammatory stage, (2) a reparative stage, and (3) a remodeling stage.¹ The duration of each stage is variable and depends on factors such as the size and severity of the bony defect, as well as mechanical

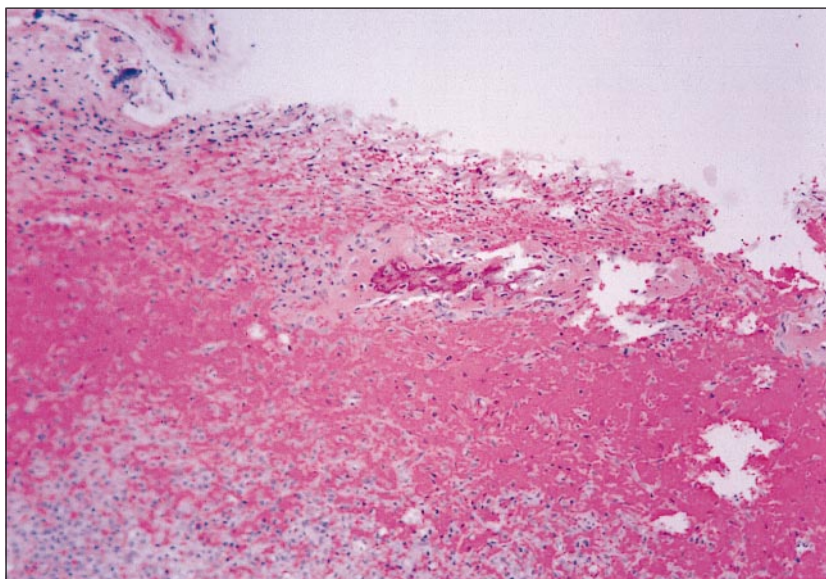


Figure 2. Photomicrograph demonstrating an island of osteoblasts within an osseous matrix developing within granulation tissue (original magnification ×80).

and biochemical influences at the site of fracture. Our patient exhibited features of both stages 1 and 2. Stage 3 is a long-term process in which local forces and stress act to remodel and establish the final shape and contour of the healed fracture and surrounding bone, and was not considered in this case.

The first stage of bone fracture repair, the inflammatory stage, is characterized by hematoma formation and inflammatory exudate from ruptured blood vessels in bone, periosteum, and/or surrounding tissues.¹¹ Within hours, platelets aggregate at the site of the injury, releasing cytokines, which cause a marked inflammatory response and vasodilation. The ends of the ruptured blood vessels soon clot off, and the loss of nutrition results in necrosis of local tissues and osteocyte degeneration within 24 hours. Monocytes, multinuclear phagocytes, and osteoclasts soon engulf and digest this necrotic debris, including acellular bone.

The second stage, the reparative stage, is characterized by the formation of a fracture callus and its subsequent transformation to mature bone. A proliferation of blood vessels and loose connective tissue creates a bed of granulation tissue within the periosteal tissues and marrow. The sources of the pluripotent mesenchymal cells that transform into new bone are marrow, endosteum, periosteum, endothelial cells, circulating cells, and surrounding muscle.¹²⁻¹⁸ These mesenchymal cells differentiate into osteoblasts, chondrocytes, and fibroblasts, each laying down its own respective extracellular matrix. The factors from fractured bone that attract and trigger the differentiation of these osteoprogenitor cells remain elusive, but data obtained to date indicate that these factors are numerous and have very complex interactions.¹⁹ The proteins most extensively studied have been the bone morphogenetic proteins^{11,20,21} of the transforming growth factor β supergene family.

The process of differentiation of these primitive osteoprogenitor cells begins within 2 to 3 days and is most marked by 1 week. By the fourth day, nests of cartilage cells are

apparent, and are soon replaced by bone tissue.^{15,16} By the end of the first week, the tissue has matured to form a callus, which is of firmer consistency than a hematoma and provides a natural internal fixation for the fracture. Subsequently, mineralization and ossification of this new osteoid tissue progress, and new bone tissue becomes visible radiographically as flecks of radiodense material within approximately 1 to 3 weeks.

A hematoma occurring at the site of a bony fracture has long been suggested to play a critical role in bone healing,² and the absence of a fracture hematoma, whether due to surgical drainage or anticoagulation by heparin, has been shown to result in a decrease in callus production. In an interesting study using a rat animal model, Mizumo et al²² demonstrated that the hematoma surrounding a bony fracture has inherent osteogenic potential, and that the osteogenic factor arises from bone marrow.

Figure 2 shows an osseous fleck developing within a subperiosteal hematoma. The specimen was collected 5 days after the development of the hematoma. The surrounding chronic inflammatory exudate shows that this tissue is predominantly in the latter stages of the stage I inflammatory process. In our patient, osteoneogenesis occurred without any radiographic or clinical evidence of an underlying fracture. The absence of an underlying fracture raises questions about the hypothesis developed by Mizumo et al, that the osteogenic factor lies within the marrow. With further understanding of these processes, it may be possible in the future to devise less invasive and more satisfactory interventions in the management of orbital fractures.

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