

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF DIRECTOR**

ACTION REFERRAL

TO <i>Myers</i>	DATE <i>10-3-07</i>
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DIRECTOR'S USE ONLY	ACTION REQUESTED
1. LOC NUMBER 000178	<input checked="" type="checkbox"/> Prepare reply for the Director's signature DATE DUE <i>10-10-07</i>
2. DATE SIGNED BY DIRECTOR <i>Cleared 10/31/07, letter attached</i>	<input type="checkbox"/> Prepare reply for appropriate signature DATE DUE _____
	<input type="checkbox"/> FOIA DATE DUE _____
	<input type="checkbox"/> Necessary Action

APPROVALS <small>(Only when prepared for director's signature)</small>	APPROVE	* DISAPPROVE <small>(Note reason for disapproval and return to preparer.)</small>	COMMENT
1.			
2.			
3.			
4.			

108
Felicity
Williams

10-1-07

DHHS

RECEIVED

PO Box 8266

OCT 03 2007

Columbia SC 29202

Department of Health & Human Services
OFFICE OF THE DIRECTOR

Dear Ms Emma Fortner,

My son Raymond Williams is
scheduled for Stem Cell Transplant
on October 8, 2007 for his eyes. I

just found out that this is an
experimental procedure. It's been
done before but I think here will
be the first time. It will be done
in Columbia at Palmetto Health
Richland Hospital. The Doctor is
Julie Tsai. I've call CRS in Florence
and talked with someone there
and they informed me they will not
be able to help with the medicine.

I understand this medicine is
very expensive and very important
to have after the surgery. Raymond
has already lost vision in his right
eye and the surgery will ~~keep~~
~~his~~ sight in the left eye. I'm
writing this letter as a very

concerned parent who only want
the best care for my child. With
but this surgery he will go completely
blind. We really need the financial
assistant and help to make things
better and have a life as normal
as possible. Please give this your
immediate attention on such short notice.
I have enclose a copy of the
letter and procedure sent to me
by them,

Thanking you in advance
Levene Welch
Shelene Welch (mother)

Surgery Instructions for University Specialty Clinics-OPHTHALMOLOGY

Patient:

Raymond Williams **RECEIVED**

Your Surgeon Is: *Dr. Julie Tsai* OCT 03 2007

You will be reporting to

Department of Health & Human Services
OFFICE OF THE DIRECTOR

Palmetto Health Richland Hospital

Outpatient Surgery- 3rd floor in main hospital

Parking garage is located across the street from 4 Medical Park-Level P-3

OR

Palmetto Health Parkridge Surgery Center

190 Parkridge Drive

Suite 108

Columbia, SC 29212

From I-26, take exit 102B onto Highway 60 East. Turn right on Parkridge Drive side.

On Surgery Date:

October 8, 2007

EYE DROPS

- *If you are a patient of Dr. Richard M. Davis or Dr. Julie Tsai, and are scheduled for cataract surgery*, you will be given a prescription for eye drop(s) to start two days prior to surgery. The drop(s) should be used in the operative eye(s) four times a day. Please remember to start eye drop(s) and bring them with you the morning of surgery.

PRE-OP

- Days before your surgery, the nurses at Palmetto Health Richland or Parkridge will conduct a pre-operative interview over the telephone. They will ask you questions about your medical history. Please review **health** questionnaire in the back of your outpatient surgery book.

Dear Kerato Limbal Allograft Candidate;

Enclosed is material regarding the Kerato-Limbal Allograft (Stem Cell Transplant) Procedure: List of medications following the procedure, letter explaining the procedure and articles written about it. This is to help you/family members to understand the procedure a little more. It is very important that the criteria be met and understood before proceeding with surgery.

*The medications (immunosuppressive) following surgery are extremely important so the graft will not reject. These are expensive. (Cost varies depending on pharmacy and state/country you live in.) It is necessary to check with your insurance plan to see if they will cover any/all medications. This information is also submitted to your insurance company when we seek prior authorization.

*It will be necessary for you to see an Internist/Kidney Specialist who specializes in immunosuppressive medications. Dr. Tsai will want you to see him/her prior to surgery to get a baseline on certain blood levels. We will fax the order to them as soon as you let me know when your appointment is. Some of the medications you will be on are steroids. The blood levels are monitored monthly after the surgery.

Dr. Tsai wants to follow you post operatively for approximately two years. This will mean visits to either of her offices (Columbia/Irmo). You may see your ophthalmologist also in between visits if a problem occurs and you cannot get to Dr. Tsai.

*Due to the criteria for the Kerato-Limbal Allograft tissue, it may be necessary to reschedule your surgery, if no tissue is available. This is a risk greater for out of state/country patients, if flight arrangements have been made. If flying, you may want to let the airline know of this possibility. Please get a transferable/refundable ticket. (We will help in any way if necessary.)

We advise not leaving until you have spoken to Dr. Tsai's surgical coordinator.

*It will be necessary for you to make accommodations for approximately one week or arrange transportation for frequent visits to the office. A list of hotels near the hospital will be enclosed in your pre surgery packet, as well as directions.

Sincerely,

Katina Simms

Surgical Coordinator for Julie H. Tsai, M.D.

Combined Living Related Conjunctival Limbal Allograft and Keratolimbal Allograft Stem Cell Transplant Procedure

Patients with limbal stem cell deficiency due to severe chemical injuries, congenital conditions such as aniridia or severe inflammatory disorders such as Stevens-Johnson syndrome are unable to regenerate epithelial cells to properly repair and maintain a healthy ocular surface. These patients require limbal stem cell transplantation to repopulate a healthy epithelial cell layer.

Sources of limbal stem cells for transplantation include the patient's healthy fellow eye (conjunctival limbal autograft or CLAU), a living relative (conjunctival limbal allografts or lr-CLAL) or cadaver tissue (keratolimbal allografts or KLAL).

Patients with severe conjunctival scarring as well as corneal scarring benefit from replacement of conjunctiva as well as stem cells. The conjunctiva provides important components of the tear film. If both eyes of a patient are affected, an autograft cannot be performed. As an alternative, we look to a living relative for stem cell tissue. Potential donors must have healthy eyes and must not be long-term contact lens wearers. For siblings, HLA blood typing is done to find the best genetic "match".

Both the surgery for the patient and donor are done on the same day. Two to three clock hours are conjunctival limbal tissue are taken from the superior and inferior areas on the donor eye. The areas are then closed with 2-3 stitches. This can be done under local anesthesia. The donor is placed on antibiotic and anti-inflammatory eye drops for 3-4 weeks. The donor may feel mild soreness and foreign body sensation while the harvested areas heal. There is minimal risk to the donor as the remaining stem cells are more than adequate to maintain a healthy ocular surface. There have been no long-term reports of subsequent stem cell deficiency in a donor eye.

Surgery is then performed on the recipient. The harvested CLAL is then secured to the eye superiorly and inferiorly. Keratolimbal tissue is used to fill in the gaps nasal and temporal to provided 360-degree ring on stem cell tissue around the diseased corneoscleral limbus. This is done in an exceedingly meticulous fashion, in order to ensure that the epithelial cells from the donor tissue migrate smoothly across the surface. Postoperatively, patients are placed on varying doses of topical and systemic immunosuppressive therapy to prevent rejection of the transplanted tissue.

The combined living related CLAL and keratolimbal surgery is technically challenging procedure. Close follow-up is needed to monitor the epithelial healing as well for side effects related to the systemic immunosuppression.

Our typical immunosuppression regimen includes:

Prograf-our typical starting dose is 2 mg twice a day (comes in 1mg tablets); we check a trough level 3-5 days after starting the medication and change the dose accordingly; therapeutic levels may vary depending on the laboratory, but are usually 5-20 ng/ml. We aim toward the lower range (5-10 ng/ml), if the level is subtherapeutic, but the patient is doing well clinically, we usually do not change the dosage.

CellCept-usual dose is 500 mg twice a day.

Prednisone-usual starting dose is 40 mg once a day (about 2/3 mg/kg/day), we taper down to 10 to 15 mg/d over 3 months; from there we taper very slowly from 3 months to 1 year. Need to consider calcium supplementation to help prevent osteoporosis.

We typically check Tacrolimus, Complete Blood Count, and Creatinine levels once a month to check for toxicity.

Call us with any additional questions. (803)434-6836
Katina Simms
Surgical Coordinator for Julie H. Tsai, M.D.

KERATO-LIMBAL ALLOGRAFT POST OPERATIVE MEDICATION ESTIMATE

This is a general estimate of medications that be used after you "Stem Cell Transplant." All these medications are necessary. Please check with your insurance plan to see if they are covered. If you need assistance, let me know. I have information on a Patient Assistance Prescription Drug Program.

Medication	90 Day Supply	180 Day Supply
Vigamox 0.5%	\$ 175.00	\$310.00
Restasis	\$ 249.00	\$489.00
Prednisone Forte 1%	\$ 58.00	\$120.00
Cellcept 500 MG	\$1839.00	\$3680.00
Prograf	\$2360.00	\$4719.00
Prednisone 10 MG	\$ 19.65	\$ 26.65
Prilosec 20MG	\$ 59.98	\$ 119.00
Percocet 5/325**	\$ 48.65	\$ 48.65
Promethazine 25MG	\$ 50.64	\$ 50.64
Artificial Tears	\$ 25.00	\$ 50.00
** One Time Dispensing		
Total Estimate	\$ 4884.92	\$12,251.29

**EYE DROPS AND ORAL MEDICATIONS FOR
KERATO-LIMBAL ALLOGRAFT PATIENTS**

Julie H. Tsai, M.D.

**USC Ophthalmology
4 Medical Park, Suite 300
Columbia, SC 29229
(800) 922-1278
(803) 434-1571
FAX (803) 434-1581**

This is a list of eye drops and oral medications you may be on following the Kerato-Limbal Allograft Procedure. The ones that are highlighted you could be on up to two years. (These are anti-rejection medications.) Please check with your insurance company to see if any of these are covered. If this is a Workman's Compensation claim, they need to be aware of these medications to approve this procedure.

Eye drop

**Pred Forte 1%
Vigamox
Restasis
Non-Preserved
Artificial Tears**

Oral Medications

**Prograf
CellCept
Prilosec
Percocet
Prednisone**

All these medications are necessary with this procedure. Some of these you will tapered down over time. The anti-rejection medications you could be on for up to two years. This is important to know before the procedure, due to the

fact these medications are very expensive, but very necessary so you will not reject the graft.

Also, Dr. Tsai wants follow up care with her. So this will result in coming to her office(s) periodically for the next two years.

The criteria for Kerato-Limbal Allograft tissue:

- 1) Donor tissue cannot be preserved longer than three days of death.
- 2) Age of donor no older than sixty years old.
- 3) Tissue is from the Minnesota Lions Eye Bank.
(Tissue is flown in day before your surgery)

This makes it a risk for the out of state/country patients. but please understand it is very important this criteria is meant for the success of your surgery. It is necessary that you call our office before leaving to come here for this procedure.

Adolescent Medicine

Janice Bacon, MD
Julia Ballance, MD
Judy Burgis, MD
Bryant Fortner, MD

Genetics

Kate Clarkson, MD
Randy Colby, MD
Ken Corning, M.S.
Amy Toburen, M.S.

Neurosurgery
Lenwood Smith, MD**Newborn**

Penny Buckman, RN, CPNP

Allergy/Immunology

David Amrol, MD
Michael Bykowski, MD

**General/Ambulatory/
Adolescent**

Jennifer Amrol, MD
Julia Ballance, MD
Jason Hawn MD

Ophthalmology

Wilson McWilliams, MD
Edward Cheeseman, MD

Cardiology

Sharon Kammer, MD
Ozzie Shuler, MD
Matthew Wienecke, MD
Luther Williams, MD

Orthopaedics

Fred Plehl, MD
Mark Locke, MD

Child Abuse and Neglect

Susan Luberoff, MD

Pediatric Ear, Nose & Throat

Fred Garner, MD
William Giles, MD

Community Pediatrics

Marlon Burton, MD
Ellen Humphries, MD
Susan Luberoff, MD
Eileen Walsh, MD

Gastroenterology

Rathna Amamath, MD

Pharmacology

Jennifer Bair, Pharm D.
Holly Watson, Pharm D.

Critical Care

Richard Cartie, MD
Robert Hubbard, MD
Greta Harper, MD
Mark McDonald, MD

Hematology/Oncology

Kevin McRedmond, MD
Ron Neuberg, MD
Laura Pirich, MD
Carla Roberts, MD

Pulmonology

Daniel Brown, MD
Trey Brown, MD

Dermatology

Lee Carson, MD, Ph.D.
Annette Lynn, MD

Infectious Disease

C. Warren Derrick Jr., MD
George Kotchmar, MD
Nandini N. Narayan, MD

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Robin Welsh, MD
Ashley Noojin, PhD

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Richard Ferrante, PhD.
Betsy Grier, PhD
Shelly Holstrum, MD
Graeme Johnson, MD
Patrick Owen, PsyD.
Mark Posey, PhD
Mary Quattlebaum, MSP
Lawrence Siegel, MD
Mary Ellen Warren, Ph.D.
Donald Wuori, MD

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Kirk Bass, MD
Victor Iskerys, MD
Ritu Lall, MD
David Marsh, MD
Ravi Rao, MD
Stephen Watson, MD

Radiology

Rod McPhearson, MD
Shiela Jones, MD

Rheumatology

James Fant, MD
Tasha Ruth, MD

Nephrology

Rob Holleman, MD
Abdullah Sakarcan, MD

Sports Medicine

John Batson, MD
Jeff Guy, MD

Surgery

Stanton Adkins, MD
Juan Camps, MD
James Glasser, MD
Prithvi Reddy, MD

Neurology

Kristen Griffin, PNP
Tim Livingston, MD
Lawrence Mauldin, MD

Emergency Medicine

Ron Fuerst, MD
Jim Lloyd, MD

Urology

Jeff Ethreth, MD

Endocrinology

Makala Jackson, MD

David Schwartz, MD

Laura Szadek, PNP

Ocular Surface Transplantation

An overview of techniques, indications, and postoperative management.

BY EDWARD J. HOLLAND, MD, AND GARY S. SCHWARTZ, MD

Severe ocular surface disease is one of the most challenging ailments in the realm of ophthalmology. Affected patients have profound visual loss, chronic inflammation of the ocular surface and cornea, chronic discomfort, and a poor prognosis for standard keratoplasty. Recent advancements in the various techniques of ocular surface transplantation have led to significant improvements in the overall success rate in the management of these patients.¹⁻¹⁰

Procedures for ocular surface transplantation can be divided into autografts and allografts. A conjunctival autograft takes tissue from the same eye or the fellow eye to manage a conjunctival deficiency. Limbal tissue is not used, because this

method is not meant to treat limbal disease. In a conjunctival limbal autograft, a normal fellow eye is used as a donor for severe, unilateral limbal deficiency. When limbal disease is present in the fellow eye, it is important that the conjunctival graft include limbal tissue. For bilateral disease, an allograft procedure is required. The two main sources of donor tissue are cadavers and living relatives.

TECHNIQUES

Keratolimbal Allograft

The cadaveric donor procedure, also known as *keratolimbal allograft*, utilizes one or two donor corneoscleral rims in which peripheral cornea, a scleral rim, and a small conjunctival skirt are used to transfer limbal stem cells (Figure 1). The technique is readily available and affords a large quantity of limbal stem cells to be transferred to the recipient eye.

Living-Related Conjunctival Limbal Allograft

Living-related conjunctival limbal allograft is a surgical method in which normal limbal tissue and the conjunctival carrier are harvested from a patient's living relative and

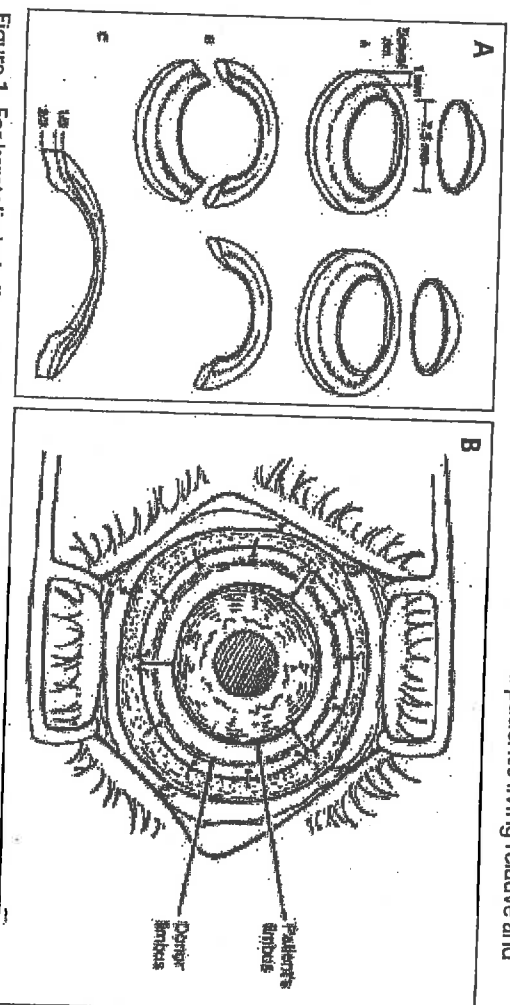


Figure 1. For keratolimbal allograft, the authors prepare tissue from a cadaveric donor for transplantation (A). Both corneas from the same donor are used to provide three lenticules of 6 clock hours of limbal tissue. The keratolimbal allograft method utilizes three donor limbal tissue crescents positioned at the limbus of the recipient's eye (B).

transplanted onto the diseased eye. Two trapezoidal limbal grafts, including approximately 6mm of the limbus and extending 5 to 8mm posterior to the limbus, are transplanted (Figure 2). This technique supplies conjunctival tissue as well as limbal cells. However, a smaller number of stem cells are transplanted when compared to the keratolimbal allograft procedure. Additionally, the living-related conjunctival limbal allograft depends on the availability of a relative who agrees to donate.

Ex-Vivo Expansion

Newer methods of stem cell transplantation utilize the technique of ex-vivo expanded limbal cells. Limbal tissue from a donor is expanded in culture before transplantation. Cells can come from a normal fellow eye, a living relative, or a cadaver. This technology is still being developed and is not utilized as commonly as the aforementioned allograft procedures.

Amniotic Membrane Transplantation

Amniotic membrane transplantation is also used in ocular surface reconstruction. The membrane is harvested from a human placenta and can be stored frozen for extended periods of time. These transplants can provide basement membrane that can then be utilized as a substrate for epithelial cell growth. Additionally, amniotic membrane can replace conjunctival tissue in which there are no conjunctival sources available. However, amniotic membrane transplantation alone does not provide stem cells and should not be used as a solitary procedure in patients with significant limbal stem cell deficiency.

POSTOPERATIVE MANAGEMENT

Compared to conventional penetrating keratoplasty, limbal allografts are associated with a significantly higher risk for rejection because the grafted tissue does not have the same immune privilege status as a central corneal graft. The vasculature of the limbal area allows the donor tissue greater access to the immune system. Also, most eyes with ocular surface disease have preoperative inflammation due to the disease state.

Our current immunosuppression protocol includes topical corticosteroids as well as topical cyclosporine. All patients receive systemic immunosuppression with three agents: (1) corticosteroids used 1mg/kg/day and tapered during a 6-month period; (2) tacrolimus, 1 to 4mg b.i.d.; and (3) mycophenolate, 500 to 1,000mg b.i.d. A multitrug regimen is necessary with limbal allograft transplantation to achieve adequate immunosuppression. Additionally, it allows the use of lower doses of individual medications, thereby reducing the risk for side effects. The level of immunosuppression can be justified

for this group of patients, because they are highly dependent on the survival of their grafts for functional vision. The necessary duration of immunosuppression depends on a patient's preoperative diagnosis, postoperative course, and whether the rejection of a transplant has occurred. The drug regimen is continued for at least 12 to 18 months for the vast majority of patients, with the corticosteroids reduced to less than 1mg/kg/day for the first 3 months postoperatively.

A number of patients, particularly those with noninflammatory disease such as aniridia, can successfully taper off all systemic immunosuppression at 12 to 18 months. However, patients with underlying inflammatory conditions such as Stevens-Johnson syndrome will often have signs of chronic inflammation and are at risk of rejection upon the discontinuation of systemic immunosuppression. If inflammation persists, or an impeded rejection reaction occurs, it may be necessary to maintain the patients on long-term immunosuppression.

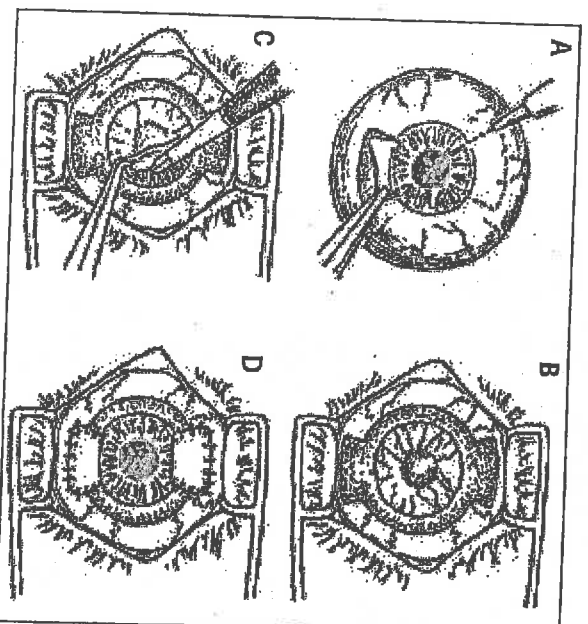


Figure 2. When performing the living-related conjunctival limbal allograft transplantation technique, tissue is harvested from a donor eye. The dimensions of the conjunctiva are marked using a gentian violet pen. Harvesting begins in the conjunctiva and proceeds anteriorly (A). To prepare the recipient for the donor tissue, the authors perform a 360° limbal conjunctival peritomy and allow the conjunctiva to recess. Recipient beds of 3 clock hours are created at the 12- and 6-o'clock meridian (B). Abnormal corneal epithelium and fibrovascular pannus are removed using necessary techniques (eg, peeling, blunt and sharp dissection) (C). Conjunctival allografts are transferred to corresponding anatomic positions on the recipient's eye and secured with 10-0 nylon sutures (D).

TABLE 1. AN ALGORITHM FOR THE TREATMENT OF PATIENTS WITH SEVERE OCULAR SURFACE DISEASE¹¹

Management of Glaucoma Tube shunt for patients on more than one topical medication	
Correction of Eyelid and Eyelash Abnormalities Exposure: lagophthalmos, ectropion Mismatched lashes: entropion, trichiasis, distichiasis	
Suppression of Inflammation Topical corticosteroids and cyclosporine A Systemic immunosuppression Oral corticosteroids Tacrolimus or cyclosporine A Mycophenolate or azathioprine	
Ocular Surface Transplantation Conjunctival limbal autograft for unilateral disease Keratolimbal allograft for bilateral limbal deficiency with minimal-to-moderate conjunctival disease Living-related conjunctival limbal allograft for bilateral limbal deficiency with moderate-to-severe conjunctival disease Combined conjunctival-keratolimbal allograft for bilateral limbal deficiency with severe conjunctival disease	
Keratoplasty Lamellar keratoplasty for patients with stromal opacification with normal endothelial function Penetrating keratoplasty for patients with stromal opacification with loss of endothelial function	

RECOMMENDED TREATMENT ALGORITHM

Based on our experience with severe ocular surface disease, we have established a sequential paradigm for the management of patients with ocular surface disease (Table 1).

Glaucoma Management

On the patient's initial presentation to our clinic, we evaluate IOP. We recommend the aggressive management of elevated IOP by the early placement of a tube shunt in patients who are on more than one topical glaucoma medication. After stem cell transplantation, many patients experience an increase in their IOP. Moreover, their long-term use of multiple topical medications not only becomes less effective but can be toxic to the transplanted epithelial surface. Therefore, it is important that a patient's IOP be stable before ocular surface transplantation.

Eyelid Function

We evaluate the status of the eyelid and lashes before performing ocular surface transplantation. Patients with significant exposure, lagophthalmos, entropion, ectropion, trichiasis, or distichiasis are referred to the oculoplastic service. Significant eyelid abnormalities can cause a breakdown of the epithelium and secondary microbial infection in patients with ocular surface disease. Oculo-

plastic procedures should improve the function of the eyelids as much as possible prior to ocular surface transplantation.

Ocular Surface Inflammation Management

Limbal allografts transplanted to an inflamed ocular surface have a significantly poorer prognosis than those in which the inflammation has been reduced. If significant conjunctival inflammation is present, topical and systemic immunosuppression should begin weeks to months before transplantation to improve the overall success rate of the procedure.

Ocular Surface Transplantation

Once the IOP stabilizes, lid anatomy and function are restored, and the ocular inflammation is reasonably controlled, ocular surface transplantation may be performed (Figure 3). The selection of technique is based on several factors. If the patient has unilateral disease, a conjunctival limbal autograft is the procedure of choice because it does not run the risk of failure secondary to immune rejection. For patients with bilateral disease, the most common choices of donor tissue are the cadaveric procedure (keratolimbal allograft) or the living-related conjunctival limbal allograft. For the vast majority of patients with limbal deficiency without extensive conjunctival disease, we advocate

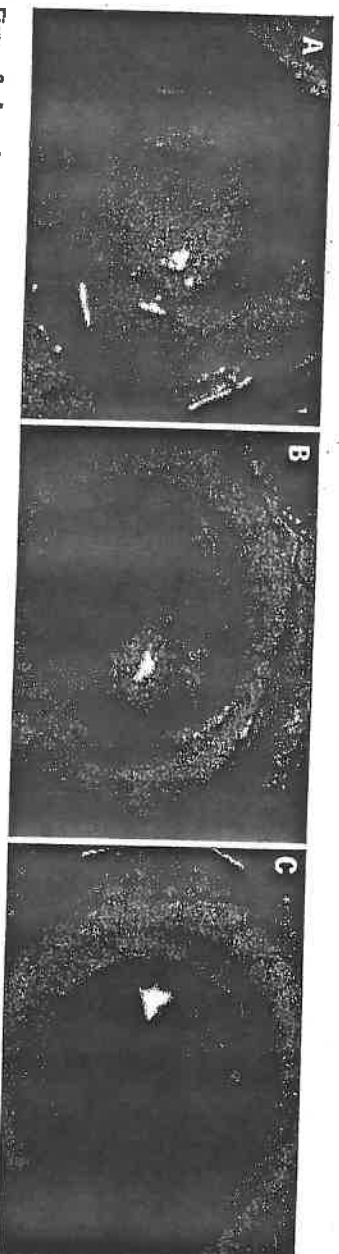


Figure 3. A patient suffered a severe alkali injury (A). Three months after the authors performed a keratolimbal allograft, the patient achieved a normal corneal epithelium and experienced a regression of neovascularization (B). In another 3 months, the authors performed a successful penetrating keratoplasty (C).

the use of keratolimbal allograft because of the availability of cadaveric donor tissue and the increased quantity of stem cells available for transplantation.

If patients have extensive conjunctival disease, we believe the living-related conjunctival limbal allograft provides much needed healthy conjunctival cells in addition to limbal tissue. Most recently, we have combined keratolimbal allograft with living-related conjunctival allograft in patients who have the most severe ocular surface disease. This combination maximizes the advantages inherent to each procedure.

Keratoplasty

In patients whose IOPs are controlled, whose ocular lid function is reasonably healthy, and who have a stable ocular surface, we will consider keratoplasty as a means of visual rehabilitation. The vast majority of patients with a failed ocular surface have subsequent stromal scarring and loss of vision even if the ocular surface has been restored. These individuals then undergo a penetrating or a lamellar keratoplasty for visual rehabilitation. If there is significant stromal scarring but good endothelial function, a lamellar keratoplasty will reduce problems with endothelial rejection. If the endothelium is involved in the disease process, a penetrating keratoplasty is required.

SUMMARY

Ocular surface transplantation has changed greatly during the last decade. Patients with severe ocular surface disease now have a chance of obtaining reasonable visual function. Surgeons need not only address the corneal and ocular surface problems, but they must also aggressively treat glaucoma and oculoplastic problems prior to ocular surface transplantation. It is extremely important to control inflammation both pre- and postoperatively with systemic and topical immunosuppression to maximize outcomes.

Improvements in the success rates of transplantation procedures are still needed, because patients with the most severe ocular surface damage and total conjunctival

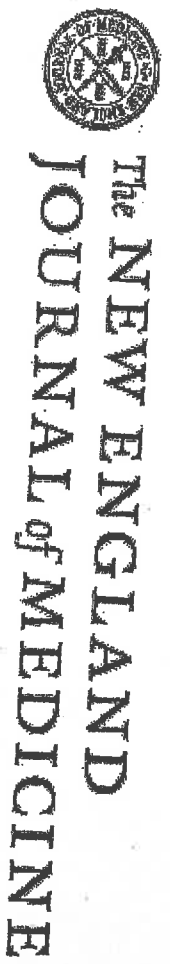
failure are not candidates for ocular surface transplantation. The development of conjunctival substitutes, as well as techniques to reverse severe keratitis sicca, will allow patients with total ocular surface failure the opportunity for visual recovery. ■

Edward J. Holland, MD, is Director of Cornea at the Cincinnati Eye Institute and Professor of Ophthalmology at the University of Cincinnati in Ohio. He states that he holds no financial interest in any company or product mentioned herein. Dr. Holland may be reached at (859) 331-9000, extension 3064; eholland@fuse.net



Gary S. Schwartz, MD, is in private practice at Associated Eye Care in St. Paul, Minnesota. He states that he holds no financial interest in any company or product mentioned herein. Dr. Schwartz may be reached at (651) 702-0436; gsschwartz@associatedeyecare.com.

1. Kenyon KR, Tseng SCG. Limbal autograft transplantation for ocular surface disorders. *Ophthalmology*. 1988;96:708-723.
2. Tsai RJF, Tseng SCG. Human allograft limbal transplantation for corneal surface reconstruction. *Cornea*. 1994;13:389-400.
3. Tsubota K, Tada I, Saldo H, et al. Reconstruction of the corneal epithelium by limbal allograft transplantation for severe ocular surface disorders. *Ophthalmology*. 1995;102:1486-1495.
4. Kwitko S, Ramirez D, Barceno S, et al. Allograft conjunctival transplantation for bilateral ocular surface disorders. *Ophthalmology*. 1995;102:1020-1025.
5. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. *Trans Am Ophthalmol Soc*. 1996;196:71-743.
6. Holland EJ, Schwartz GS. The evolution of epithelial transplantation for severe ocular surface disease and a proposed classification system. *Cornea*. 1996;15:549-556.
7. Crossable CR, Schwartz GS, Mallory JV, et al. Keratolimbal allograft: recommendations for tissue procurement and preparation by eye banks, and standard surgical technique. *Cornea*. 1999;18:52-58.
8. Holland EJ, Schwartz GS. The evolution and classification of ocular surface transplantation. In: Holland EJ, Mennin MJ, eds. *Ocular Surface Disease*. New York: Springer; 2002:146-157.
9. Daga SM, Holland EJ, Mennin MJ. Living-related conjunctival limbal allograft. In: Holland EJ, Mennin MJ, eds. *Ocular Surface Disease*. New York: Springer; 2002:201-207.
10. Schwartz GS, Tsubota K, Tseng SCG, et al. Keratolimbal allograft. In: Holland EJ, Mennin MJ, eds. *Ocular Surface Disease*. New York: Springer; 2002:208-222.
11. Holland EJ, Schwartz GS. The Paton lecture—ocular surface transplantation: 10 years' experience. *Cornea*. 2004;23:425-431.



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EDITORIAL

Epithelial Stem-Cell Transplantation for Severe Ocular-Surface Disease

The treatment of patients with severe ocular-surface disease has been largely unsuccessful. Superficial keratectomy (the excision of abnormal cells on the corneal surface) can lead to invasion of the corneal surface by goblet cells derived from the conjunctiva ("conjunctivalization"). Standard procedures of corneal transplantation (penetrating or lamellar keratoplasty) provide a stable ocular surface only for as long as the donor epithelium survives. After the inevitable sloughing of the donor epithelium, conjunctivalization will occur.

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The ocular surface is composed of the tear film and the epithelium of the cornea and conjunctiva. Stratified, nonkeratinized epithelium covers the entire cornea as well as the bulbar and palpebral conjunctivae. The corneal epithelium is constantly being sloughed and renewed. The cells responsible for the proper renewal of the corneal epithelium are located at the corneoscleral junction, which is also known as the limbus.^{1,2,3} The renewal process involves centripetal and circumferential cellular migration from the limbus in addition to the vertical movement of cells from the basal layers.

An important difference between the limbus and central cornea is the presence of blood vessels at the limbus. These vessels provide limbal epithelium with both increased nutrition and increased interaction with blood-borne cytokines. The ocular surface can be compromised by disruption of epithelial stem cells or the conjunctiva. The loss of epithelial stem cells may result in neovascularization, persistent epithelial defects, scarring, ulceration, and perforation of the cornea. Conjunctival disease may lead to scarring, the formation of symblepharon (adhesions of lid conjunctiva to globe conjunctiva), dry eye, and mucin deficiency, all of which contribute to further destabilization of the ocular surface.

Severe ocular-surface disease causes loss of vision in thousands of patients in the United States each

year. Aniridia (the congenital lack of an iris), iatrogenic deficiency of epithelial stem cells, contact-lens-induced keratopathy, and neoplasia result primarily in deficiency of the epithelial stem cells. Chemical injury, thermal injury, the Stevens-Johnson syndrome, and ocular pemphigoid lead to conjunctival and epithelial deficiencies.

Surgical procedures aimed at replacing diseased epithelium have been developed over the past decade.^{4,5,6,7,8,9,10} In this issue of the *Journal*, Tsubota et al. present the results of their study of epithelial stem-cell transplantation for severe ocular-surface disease.¹¹ They evaluated 70 transplantations performed on 43 eyes and found that 51 percent of the eyes (22 of 43) had corneal epithelialization after transplantation. In the 28 eyes in which standard corneal transplantation was performed simultaneously, 15 of the grafts (54 percent) survived. To those not in the field, these results may appear unimpressive. However, without epithelial transplantation, none of these patients would have had clear corneas. All would be functionally blind. By comparison, the patients with clear corneas could distinguish the largest symbol on the visual-acuity chart from a distance of 5 m, a level consistent with the ability to perform the activities of daily living.

Treatment usually appears to be successful in the immediate postoperative period in most patients with ocular-surface disease, regardless of the type of rehabilitative procedure used (including penetrating keratoplasty), because the transplanted donor epithelium will survive for a few months. The success of surgery can therefore be evaluated only after at least six months. Success depends on the continuous turnover of stable corneal epithelium, which must be supplied from a viable source of epithelial stem cells. Tsubota et al. should be commended for following all their patients for at least one year after surgery.

Important questions regarding the transplantation of epithelial stem cells remain to be answered. Which patients will benefit the most from this procedure? When should additional surgery, such as procedures to treat glaucoma or penetrating or lamellar keratoplasty, be performed? What is the best postoperative medical management — specifically, what is the role of systemic immunosuppression? Why does ocular-surface failure occur in some patients two years or more after otherwise successful epithelial stem-cell transplantation? Which of the techniques for epithelial stem-cell transplantation is preferable?

Epithelial stem-cell transplantation appears to be potentially beneficial for patients with a wide variety of ocular-surface diseases. However, because of limited availability of tissue and the need for postoperative systemic immunosuppression, we believe that this approach should be reserved for patients with the most severe disease and the poorest prognosis with standard therapies.

Tsubota et al. used corneal scleral buttons (obtained from cadaveric donors and stored for a mean of 5.9 days), from which they harvested and transplanted the epithelial stem cells attached to the peripheral corneal scleral rims. When they performed simultaneous penetrating keratoplasty, they used the central corneal button from the same donor eye. It is our impression that the success rate of such transplantations is higher when the transplanted epithelial tissue is allowed to stabilize before penetrating keratoplasty is performed. Therefore, we recommend waiting approximately three months after epithelial transplantation before attempting standard corneal transplantation.¹² In the United States,

the eye-bank system is organized so that it may be feasible to perform procedures on such patients at two different times, using two or preferably three donor eyes. The relative shortage of corneal tissue in Japan, as compared with the United States, may make it necessary to perform the two procedures simultaneously, using a single donor eye.

In most patients, systemic immunosuppression is required to prevent rejection of the transplanted stem-cell tissue. In contrast, the tissue transplanted in penetrating keratoplasty usually survives without systemic immunosuppression because it is avascular. Tsubota and coworkers used an immunosuppressive regimen of cyclosporine and a short course of corticosteroids; we typically use cyclosporine, azathioprine, and corticosteroids. How long systemic immunosuppressive medications should be continued is unclear, and comparative data on the various regimens are needed. When cadaveric tissue is used, tissue typing, although possibly beneficial, is not practical. It would decrease the pool of potential donor eyes and increase the time a patient would have to wait for surgery.

We have seen stem-cell transplantations fail more than one year after surgery. This failure could represent chronic low-grade rejection or stem-cell death from nonimmunologic causes. The reason cannot be determined by clinical examination; rather, it will probably require histologic study. The postoperative care of such patients is complex because of the need to use systemic immunosuppressive agents, with which most ophthalmologists do not have extensive experience. Therefore, the treating ophthalmologist must work hand in hand with clinicians who are experienced in using immunosuppressive agents.

A potential source of stem cells is a living related donor, from whom the patient could receive a conjunctival epithelial allograft. In this procedure, conjunctiva acts as a vessel conveying the fragile epithelial stem cells from the healthy eye of a living relative to the diseased eye of the patient. The risks to the donor are minimal. Because less than half the stem cells are removed and because the eye is otherwise normal, the remaining stem cells can maintain a viable ocular surface. Although HL-A tissue typing is used to help find the best match, the recipients usually require systemic immunosuppression.

Both procedures have advantages and disadvantages. The use of living related donors affords some degree of tissue matching because the tissue is from a relative. In addition, the tissue is fresh, which means that the stem cells may be healthier than those obtained from stored tissue. The conjunctiva that carries the stem cells also provides healthy conjunctival tissue, which is important in the rehabilitation of the ocular surface. Surgery, however, must be performed on two persons. A parent, sibling, or child must be available and willing to donate. The total amount of transplanted stem cells is less than that in the cadaveric donor procedure, since caution must be used to prevent the subsequent development of iatrogenic deficiency of epithelial stem cells in the donor.

In the past, little could be done to restore the vision of a patient with severe ocular-surface disease. Through recent advances, many patients who would previously have been blind for life can regain useful vision. Unfortunately, even with these advances, almost half such patients will not have much improvement after epithelial stem-cell transplantation. The encouraging results of Tsubota et al. provide a basis for further progress.

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References

1. Potten CS, Loeffler M. Epidermal cell proliferation. I. Changes with time in the proportion of isolated, paired and clustered labeled cells in sheets of murine epidermis. *Virchows Arch* 1987;53:286-300.
2. Potten CS, Morris RJ. Epithelial stem cells in vivo. *J Cell Sci Suppl* 1988;10:45-62.
3. Ebato B, Friend J, Thoft RA. Comparison of limbal and peripheral human corneal epithelium in tissue culture. *Invest Ophthalmol Vis Sci* 1988;29:1533-1537. [\[Abstract\]](#)
4. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. *Ophthalmology* 1989;96:709-723. [\[Medline\]](#)
5. Turgeon PW, Naunheim RC, Roat ML, Stopak SS, Thoft RA. Indications for keratoepithelioplasty. *Arch Ophthalmol* 1990;108:233-236. [\[Abstract\]](#)
6. Tsai RJ, Tseng SC. Human allograft limbal transplantation for corneal surface reconstruction. *Cornea* 1994;13:389-400. [\[Medline\]](#)
7. Tsubota K, Toda I, Saito H, Shinozaki N, Shimazaki J. Reconstruction of the corneal epithelium by limbal allograft transplantation for severe ocular surface disorders. *Ophthalmology* 1995;102:1486-1496. [\[Medline\]](#)
8. Kwikko S, Marinho D, Barcaro S, et al. Allograft conjunctival transplantation for bilateral ocular surface disorders. *Ophthalmology* 1995;102:1020-1025. [\[Medline\]](#)
9. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. *Trans Am Ophthalmol Soc* 1996;94:677-743. [\[Medline\]](#)
10. Holland EJ, Schwartz GS. The evolution of epithelial transplantation for severe ocular surface disease and a proposed classification system. *Cornea* 1996;15:549-556. [\[Medline\]](#)
11. Tsubota K, Satake Y, Kaido M, et al. Treatment of severe ocular-surface disorders with corneal epithelial stem-cell transplantation. *N Engl J Med* 1999;340:1697-1703. [\[Free Full Text\]](#)
12. Crossdale CR, Schwartz GS, Mallory JV, Holland EJ. Keratolimbal allograft: recommendations for tissue procurement and preparation by eye banks, and standard surgical technique. *Cornea* 1999;18:52-58. [\[Medline\]](#)

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- Nishida, K., Yamato, M., Hayashida, Y., Watanabe, K., Yamamoto, K., Adachi, E., Nagai, S., Kikuchi, A., Maeda, N., Watanabe, H., Okano, T., Tano, Y. (2004). Corneal Reconstruction with Tissue-Engineered Cell Sheets Composed of Autologous Oral Mucosal Epithelium. *NEJM* 351: 1187-1196 [\[Abstract\]](#) [\[Full Text\]](#)
- Schwab, I. R., Isseroff, R. R. (2000). Bioengineered Corneas -- The Promise and the Challenge.

NEJM 343: 136-138 [[Full Text](#)]

- Fontes, P. A, Thomson, A. W (1999). Stem cell technology. *BMJ* 319: 1308-1308 [[Full Text](#)]

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April 15, 2003

Stem Cell Transplants Offer New Hope in Some Cases of Blindness

By GWEN KINKEAD

A little-known operation restores hope for people who lose sight from chemical or heat burns of the eye or certain rare diseases. The procedure, 50 to 100 percent effective in healing corneal damage, is used worldwide, including Iran, where it helps restore sight for victims of Iraqi mustard gas attacks.

A variation on corneal transplants, the surgery grafts stem cells from a donor or a patient's good eye to the injured eye. The cells are from the limbus, a rim around the cornea. The cells resheath the cornea's surface, the 50-micron-thick epithelium, to maintain it as a transparent window. When burns or disease wipe out the limbal stem cells, the epithelium clouds over with scar tissue, causing blindness.

Grafting even a small piece of limbus can lead the stem cells to regrow clear epithelium -- and keep it clear -- thus restoring sight. The cells even recover transplanted corneas. Stem cell transplants and corneal transplants are frequently performed one after the other if corneal damage extends below the epithelium.

The discovery of the cells 17 years ago and clinical proof that they keep working in any eye with an intact tear system has opened a new era in eye surgery.

"It's an outstanding breakthrough and has, at least in the short run, cured a number of patients," said Dr. Richard S. Fisher, director of the corneal disease program at the National Eye Institute in Bethesda, Md.

The stem cells are adult, not fetal tissue, and join bone marrow and skin as the third adult stem cell in wide use to repair organs.

In the United States, officials estimate that 300 a year are performed and that the transplants are increasing because they are the sole alternative to plastic corneas for desperate burn cases, industrial accidents, damage from contact lenses and a few rare diseases that cause blindness. In operations on one eye, 90 percent to 100 percent restore vision, because the patients' own stem cells from the good eye can be transplanted without rejection.

In one eye, the surgery is "basically a slam dunk," said its originator, Dr. Kenneth R. Kenyon of Boston.

"When we first saw a number of challenging cases of mostly chemical burns," he said, "the eyes were chronically inflamed, with ulcers and blood vessels growing into the cornea, hallmarks, we now know, of limbal stem cell deficiency."

In a paper in 1989, Dr. Kenyon and Dr. Scheffer C. G. Tseng reported that ulcers and inflammation

healed and invading blood vessels withdrew after the surgery. Vision improved immediately for many patients. Patients who later needed the entire cornea transplanted because other layers were scarred also had better prognoses. Those transplants were more accepted because the new stem cells resurfaced the new corneas, keeping them transparent.

"I have some patients 20 years out with good vision," Dr. Kenyon said. "I believe these last a lifetime."

Stem cell transplants on one eye are now standard, said Dr. R. Doyle Stulting, editor of the journal *Cornea*. "They are clearly successful and they are permanent," Dr. Stulting said.

For patients blind in both eyes, stem cell transplants remain effective in half the cases after five years, principally because of rejection. Donor cells from eye banks or relatives are used, and patients require extensive antirejection drugs. In addition, injuries to both eyes from diseases like aniridia, an iris condition; Stevens Johnson syndrome, an allergic reaction to medication; and ocular cicatricial pemphigoid, an inflammatory disease, often damage lower corneal layers and require multiple operations before sight is restored.

Surgeons report progress in those cases. Dr. Edward J. Holland, director of corneal services at the Cincinnati Eye Institute, has written the lone textbook on reconstructing the ocular surface. Last year, he announced results from 74 blind patients who received donor stem cells in both eyes.

Seventy-three percent developed clear new corneal surfaces. In patients with no other problems, that would have meant great vision. But for those complicated cases, half of whom had aniridia, the mean vision improved, from 20/1700 before surgery to 20/200 after surgery.

"Twenty/200 is legal blindness, but most aniridics can't get better vision," Dr. Holland said, because their retinas have genetic damage that cannot be repaired. "At 20/200, they can get around and read large print books with functional aids."

This year in the journal *Ophthalmology*, Dr. Holland reported on 23 more people blind in both eyes from aniridia. Their vision had improved from an average of 20/1000 to 20/165 four years after stem cell and cornea transplants.

Twelve years ago, Shawn Smith, a jewelry designer, was cleaning 100 carats of rough emeralds in acid when the beaker exploded, splashing acid and emeralds into his eyes. Suddenly, he was blinded.

Two years ago, Mr. Smith sought help from Dr. Holland.

"He could only sense light," Dr. Holland recalled. "Both his eyes were covered with a thick dense scar we couldn't see under."

Dr. Holland peeled back the white scar tissue with scissors and scalpel to find the intact eye. He sutured four crescents of limbus donated by Mr. Smith's half-brother. In a week, the stem cells had grown a new transparent surface, indicating that they were up and running. Three months later, Dr. Holland transplanted other layers of the cornea. That night, Mr. Smith watched television. The next day, he could read the fourth line on the eye chart.

"It's an awesome world out there," Mr. Smith said, "and you just don't know it until you lose it. Then I went to school to see if I could recognize my son. I did."

Mr. Smith's sight is now 20/50.

Dr. Holland also reports success with Stevens Johnson patients, those with the worst prognoses. Stem cell transplants give them a 50-50 chance at sight, he theorizes.

Dan Merton was a union representative in Detroit until he contracted the syndrome a year ago. His skin peeled off, his lung collapsed and his kidneys stopped working. But worst of all, he could not see. "All I could do was sit on the bed," Mr. Merton said. "I didn't have the motivation to get up."

Dr. Holland grafted stem cells from the daughter of Mr. Merton onto his left eye, and he regained very low vision. That improved considerably after Dr. Holland transplanted his cornea. "I am so happy I don't know what to do," Mr. Merton said. "I can see everything. I can't see it clear. But I can see my kids. I am just so blessed."

Some ophthalmologists, however, say they will not accept limbal stem cell transplants as a breakthrough until studies on hundreds of patients confirm the results.

"This is so new we don't know if this will have later complications that'll revert or if it's a temporary solution or a permanent cure," said Dr. Kirk R. Wilhelmus at the Baylor College of Medicine in Houston.

Others, like Dr. Stulting, see the procedure as life-changing. "Someone who is seeing like midnight in a coal mine and can't find anything or move anywhere without being led, who tomorrow can see enough to tell where a door is or a truck is," he said, "is functionally different. They can walk, they can protect themselves. They're not even close to 20/20. They're maybe 20/400. Counting fingers instead of barely seeing light."

"People with stem cell deficiencies who have severe inherited disease or disease from birth or chemical injuries do have a big difference made in their lives if an operation suddenly enables them to read with a magnifying glass and work."

More could be helped, advocates say, if rejection could be eliminated or if donated corneas matched recipients' tissue types. Researchers have grown limbus in the laboratory, but the Food and Drug Administration recently stopped transplants of the bioengineered stem cells in humans, calling for lengthy clinical trials.

Work, however, continues in Italy, Japan and Taiwan as scientists try to find limbus cells that are pure stem cells. The goal is to grow sheets and sheets of limbus, making it a commercial product like bioengineered skin.

In Iran, dozens of victims of mustard gas in the Iraq-Iran war, most of them soldiers, can see after these operations, said Prof. M. A. Javadi, head of ophthalmology at the Shahid Beheshti University of Medical Sciences in Tehran.

The effects of invisible mustard gas are not felt for at least 30 minutes. It burns the skin, lungs and, above all, eyes. Soldiers who think they have survived an attack often blind themselves by wiping saturated uniforms across their faces. The chemical denatures proteins on the epithelium, melting it off. The effects can appear 10 or even 30 years later.

The delayed effects of the gas destroy the limbal stem cells, making corneal transplants alone useless,

said Professor Javadi, who has treated hundreds of gas victims. "Currently," he said, "stem cell transplanation with or without corneal transplants seem the most promising treatment."

People with mild cases can regain some sight, said Dr. Ali Khodadoust of Yale, who consults on hard cases in Shiraz, Iran, where he grew up. Half regain some or most of their sight, but severe cases cannot be reversed, because the gas has stopped the tear system.

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State of South Carolina
Department of Health and Human Services

Mark Sanford
Governor

Robert M. Kerr
Director

October 31, 2007

Ms. Leverne Welch
404 King Street
Bennettsville, SC 29512

Dear Ms. Welch:

Thank you for writing our South Carolina Department of Health and Human Services (SCDHHS) Director, Emma Forkner, regarding your son Raymond Williams. SCDHHS will do whatever we can to support medically necessary care for him.

We have talked with Raymond's attending physician, Dr. Julia Tsai, and are assured that she is a great advocate for getting him the care he will need. We are working with her to help confirm that the South Carolina Medicaid Program can support the specialized treatment, procedures and medications he will need to restore him to good health. SCDHHS is also working with Raymond's health insurance carrier, First Health of South Carolina (Select Health), to keep them abreast of his progress.

Your concerns regarding the experimental nature of the proposed treatments and medication are being addressed by his physician, First Health, and our agency. Meanwhile if you have further concerns or need to speak with us, please give me a call at (803) 898-2500 or (803) 255-3400. Thank you again for contacting us regarding Raymond's care. We will continue to monitor his progress and we are hoping for his full recovery.

Sincerely,

A handwritten signature in cursive script that reads "Marion Burton".

O. Marion Burton, MD
Medical Director

OMB/mk