Vision Change After Sheet Transplant of Fetal Retina With Retinal Pigment Epithelium to a Patient With Retinitis Pigmentosa

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Objective: To report the subjective and objective improvement in vision in a patient with autosomal dominant retinitis pigmentosa after transplantation of a sheet of fetal neural retina together with its retinal pigment epithelium.

Design: A sheet of fetal neural retina with its retinal pigment epithelium was transplanted into the subretinal space under the fovea unilaterally in a patient with retinitis pigmentosa with visual acuity of 20/800 in the treated eye. Early Treatment Diabetic Retinopathy Study visual acuity testing, scanning laser ophthalmoscope, tissue typing of the donor and recipient, fluorescein angiography, multifocal electroretinogram, multifocal visually evoked potential, and clinical examination were used.

Results: No clinical evidence of rejection was observed. There was no retinal edema or scarring. The transplant sheet lost its pigmentation by 6 months.

Main Outcome Measures: A change in visual acuity from 20/800 to 20/400 (7 months), 20/250 (9 months), and 20/160 (1 year) was observed by Early Treatment Diabetic Retinopathy Study visual acuity testing. Independently, scanning laser ophthalmoscope testing at a different institution at 9 months showed a visual acuity of 20/270 at a 40° field of view.

Conclusion: This study indicates that fetal retina transplanted with its retinal pigment epithelium can survive 1 year without apparent clinical evidence of rejection and show continued improvement in Early Treatment Diabetic Retinopathy Study visual acuity.

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PREVIOUSLY, IT HAS BEEN REported that intact sheets of fetal retina together with its retinal pigment epithelium (RPE) can be safely transplanted to patients with retinitis pigmentosa (RP).[1] Retinitis pigmentosa is a group of inherited diseases with mutations in photoreceptor or RPE genes.[2] In these diseases, blindness is due to specific degeneration of the photoreceptors and/or RPE cells even though the inner retina that connects to the brain may still remain functional.[3-5] If the diseased photoreceptors and/or RPE can be replaced and the new cells make appropriate connections to the functional part of the host retina, eyesight may be improved.

Using an implantation instrument and procedure originally developed by Aramant and Seiler[6] for use in rats with retinal degeneration, clinical studies have been performed in patients with RP[1,7] to transplant intact sheets of fetal retina with or without the RPE. Although no objective improvement in vision was reported, these clinical studies demonstrated the safety of the procedure.

METHODS

The study protocol was that of an interventional case series in which patients with RP and a visual acuity of 20/800 or worse in one eye were studied without a control group for comparison after approval from both Norton Audubon Hospital, Louisville, Ky, and the University of Louisville human studies committee. The study was conducted under the Food and Drug Administration (FDA) investigational new drug number BB-IND 8354.

The patient who received the transplant gave informed consent after extensive counseling regarding the realistic expectation of the procedure. In accordance with our selection criteria, this patient had a visual acuity measurement of 20/800 in the eye that was operated on for at least 1 year with a diagnosis of RP, was older than 21 years, was not pregnant, and was willing to return for follow-up visits. The patient, a 64-year-old woman, was tested preoperatively on 3 separate occasions, 1 month apart, by Early Treatment Diabetic Retinopathy Study (ETDRS) so that she was accustomed to the chart. The person measuring the ETDRS visual acuity was masked as to which eye had the surgery. The patient underwent protocol refraction each time by the masked observer. The ETDRS protocol for visual acu-

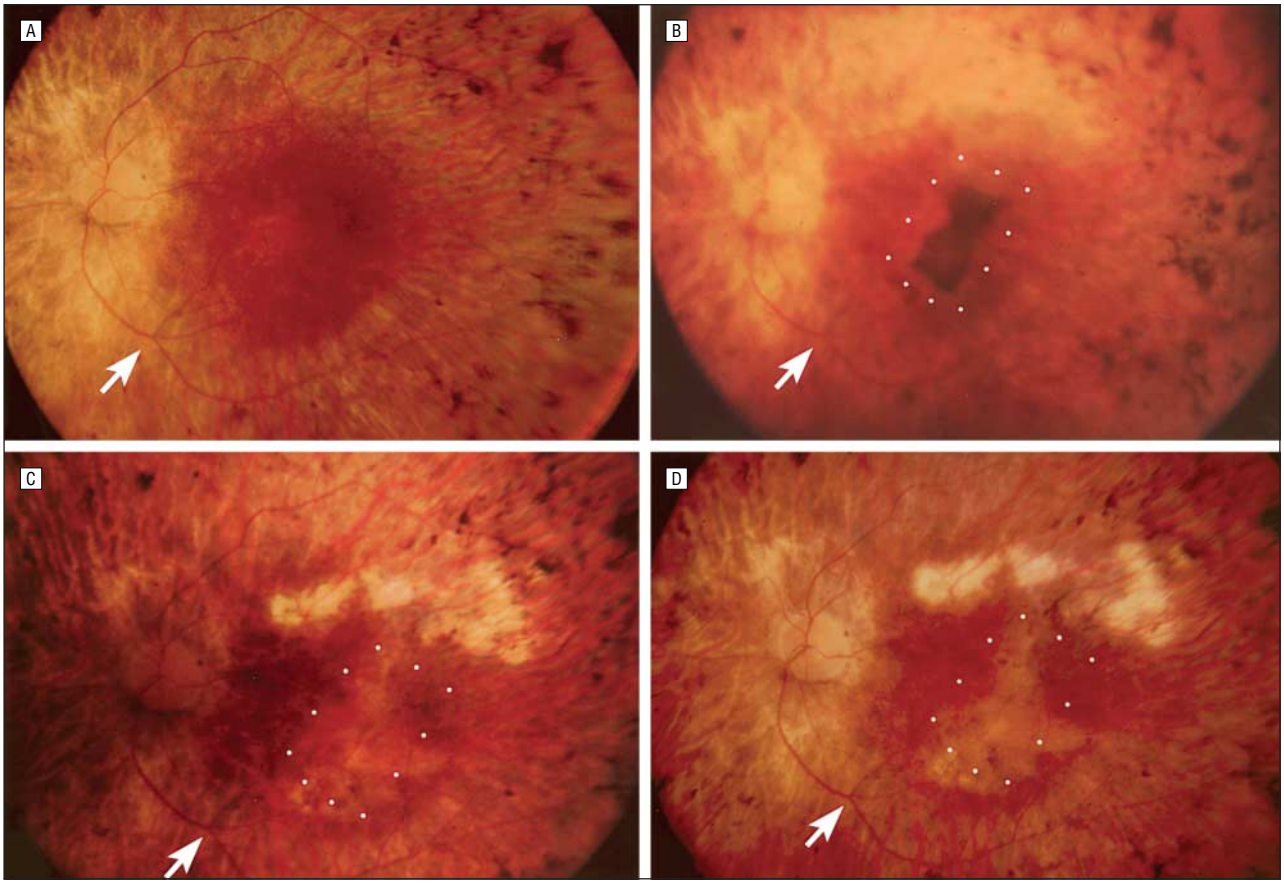

Figure 1. Fundus images: Arrows indicate the same blood vessel landmark in all images. A, Three weeks prior to transplantation. B, Two weeks after transplantation, showing heavy pigmentation of the transplant. The transplant area is outlined by white dots. C, Six months after transplantation, there is a loss of pigment. A white scar is recognizable at the retinotomy site. White dots outline the same area as in B. D, Twelve months after transplantation, there is no change compared with 6 months.

ity testing was followed as previously described.[8] The right eye, which was not operated on, was tested first.

Fetal tissue of 13 weeks' gestational age was obtained by informed consent. Donors were not compensated. After the donors had decided to terminate their pregnancy, they were approached to donate tissue for research. The harvesting procedure of fetal retina with RPE has previously been described.[1] A 1.5×3.1-mm piece of the fetal retina with its RPE was cut out and implanted subretinally under the fovea of the left eye, using a custom-made implantation instrument with a flat plastic nozzle tip at a 130° angle.[1,6,7] The loaded instrument was inserted under the retina through the retinotomy site, and the donor tissue was placed into the target area with the correct orientation, the RPE toward the choroid.

Donor tissue that was dissected away was used for the tissue typing of the donor at the histocompatibility lab at Jewish Hospital, Louisville. The donor DNA was extracted using a DNA tissue extraction kit (QIAGEN, Valencia, Calif) and typed for the HLA antigens HLA-A, HLA-B, and HLA-DR by polymerase chain reaction amplification using sequence specific primers (Pel Freeze, Brown Deer, Wis). Anti-HLA antigen antibodies in the recipient were detected using 2 techniques, both using sensitive flow cytometric procedures. Screening for antibodies was performed using a pool of normal T cells. The specificity of the antibody was determined using HLA antigen–coated beads (One Lambda, Canoga Park, Calif).

Complete assessments (ocular examination, fluorescein angiography, ETDRS protocol for visual acuity testing, multifocal electroretinogram [mfERG], and multifocal visually evoked potential [mfVEP]) were performed preoperatively and repeated postoperatively. To assess potentially corresponding physiologic changes in the region of the transplant, photopic mfERGs and mfVEPs were recorded with VERIS Science software (EDI Inc, San Mateo, Calif) using techniques and parameters previously described.[7,9] Recordings were performed 3 times before surgery and at 2 weeks and 1, 3, 6, and 12 months postoperatively.[7]

The patient was tested at 9 months postoperatively at an independent testing site with the scanning laser ophthalmoscope (SLO) using a small, dim stimulus. The examiners at this location did not know which eye had received the transplant. To compensate for the patient's eye movement after each measurement, the reference cross was fixed by manual tracking at clearly defined vascular landmarks.[10] The patient declined the opportunity for preoperative testing, which makes this portion of the study difficult to interpret. However, the SLO testing postoperatively and the ETDRS testing correlated very well. The SLO testing was in addition to information obtained from the other clinical tests and not in the experimental protocol.

RESULTS

The transplant could be observed easily after surgery by indirect ophthalmoscopy because of its heavy pigmentation (**Figure 1** A and B). During the follow-up examinations, the area of pigmentation eventually disappeared (between 3-6 months) (Figure 1C). The appearance of the fundus in the transplant area remained unchanged between 6 and 12 months (Figure 1C

and D). Fluorescein angiography showed no dye leakage in the area of the transplant at 6 to 12 months (**Figure 2**). There was no evidence of vitritis or vitreous cells. Although the clinical appearance of rejection in the retina is still somewhat unclear, no clinical evidence of tissue destruction, subretinal fibroses, or necrosis of the retina was seen in our patient. No systemic or intraocular immunosuppression medications were used.

Tests of the medium surrounding the tissue before implantation for sterility and endotoxin levels were well within normal limits (data not shown). The HLA antigen types for donor and recipient are listed in the **Table**. As expected, the donor and recipient were not matched. The donor and recipient shared only a single HLA-B antigen (B14) and no HLA-DR antigens, indicating this was an allogeneic graft.

No donor-specific antibodies were seen in the patient at 6 months. Anti–major histocompatibility complex class I antibodies specific for the HLA-A1 antigen carried on the graft were found before transplantation and did not change at the time of the transplant. However, at approximately 3 months after transplantation, the titer of this class I antibody increased and continued to increase through the last sample collected 12 months after surgery. However, all other antibodies, including antibodies with specificities to antigens not expressed by the graft, increased concurrently. No anti–major histocompatibility complex class II antibody was detected at any time before or after the transplant.

The patient's vision in the eye that was operated on showed improvement both subjectively and objectively, as assessed with ETDRS visual acuity testing at 7 months to 1 year. The patient declined the opportunity for preoperative SLO testing but agreed to postoperative SLO testing when she noticed a marked subjective improvement at 6 months. Objectively, her visual acuity improved from 20/800 preoperatively to 20/400 at 6 months, 20/250 at 9 months, and 20/160 at 12 months. No vision improvement occurred prior to 6 months. In contrast, the ETDRS visual acuity of the eye that was not operated on, which was tested at every follow-up examination, did not change during the testing period from the 20/400 preoperative value. The postoperative ETDRS visual acuity at 9 months was confirmed by SLO testing at an independent clinical center and measured 20/270 at a 40° field of view (**Figure 3**). The eye that was operated on contained 53 seeing and 37 nonseeing areas (Figure 3). There appeared to be some fixation at the nasal edge of the transplant bed, and there was a similar pattern of stability of fixation in both eyes. At 9 months, SLO testing of the eye that was not operated on measured the visual acuity at 20/369 (33 seeing and 37 nonseeing areas) (Figure 3), which was consistent with the visual acuity of 20/400 in the same eye by ETDRS testing.

The overlay of the SLO fixation and the photograph of the transplant show that the patient viewed the 20/270 letter (using 40° field of view testing) with a portion of the retina nasal to but at the edge of the transplant (**Figure 4**).The mfERG and mfVEP showed no clear signal preoperatively or postoperatively in any region of the retina.

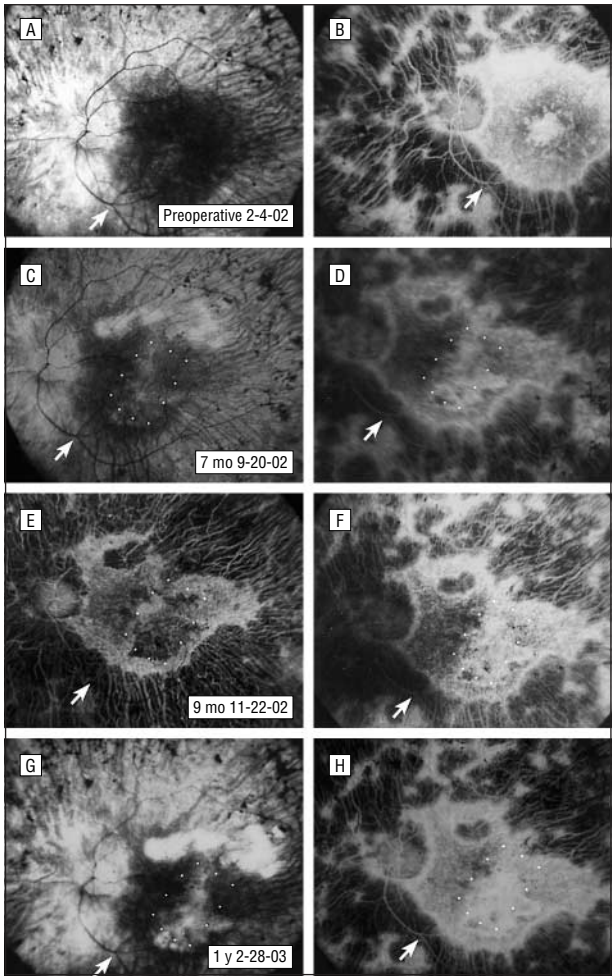

Figure 2. Fluorescein angiograms: Arrows indicate the same blood vessel landmark in all images (also shown in Figure 1). The images on the left show the early stages of fluorescein angiograms, and the images on the right show the late stages. The transplant area (which is the same area as in Figure 1B, C, and D) is outlined by white dots. A and B, Three weeks before transplantation. C and D, Seven months after transplantation. E and F, Nine months after transplantation. G and H, Twelve months after transplantation. There is no fluorescein leakage in the transplant area.

Tissue Typing of Donor and Recipient

Donor HLA Antigen Typing	Recipient HLA Antigen Typing
HLA-A1	HLA-A2
HLA-A30	HLA-A3
HLA-B13	HLA-B14
HLA-BW4	HLA-BW6
HLA-B14	HLA-B27
HLA-BW6	HLA-BW4
HLA-DR17	HLA-DR1
HLA-DR7	HLA-DR13

Immediately after surgery, the patient required ventilation for pulmonary edema following general anesthesia. This development did not appear to be related to the instrument or fetal tissue retinal implant in her eye used during the retinal transplantation. Appropriate notification was made of this adverse event to the FDA and institutional review board. The result of this event was that

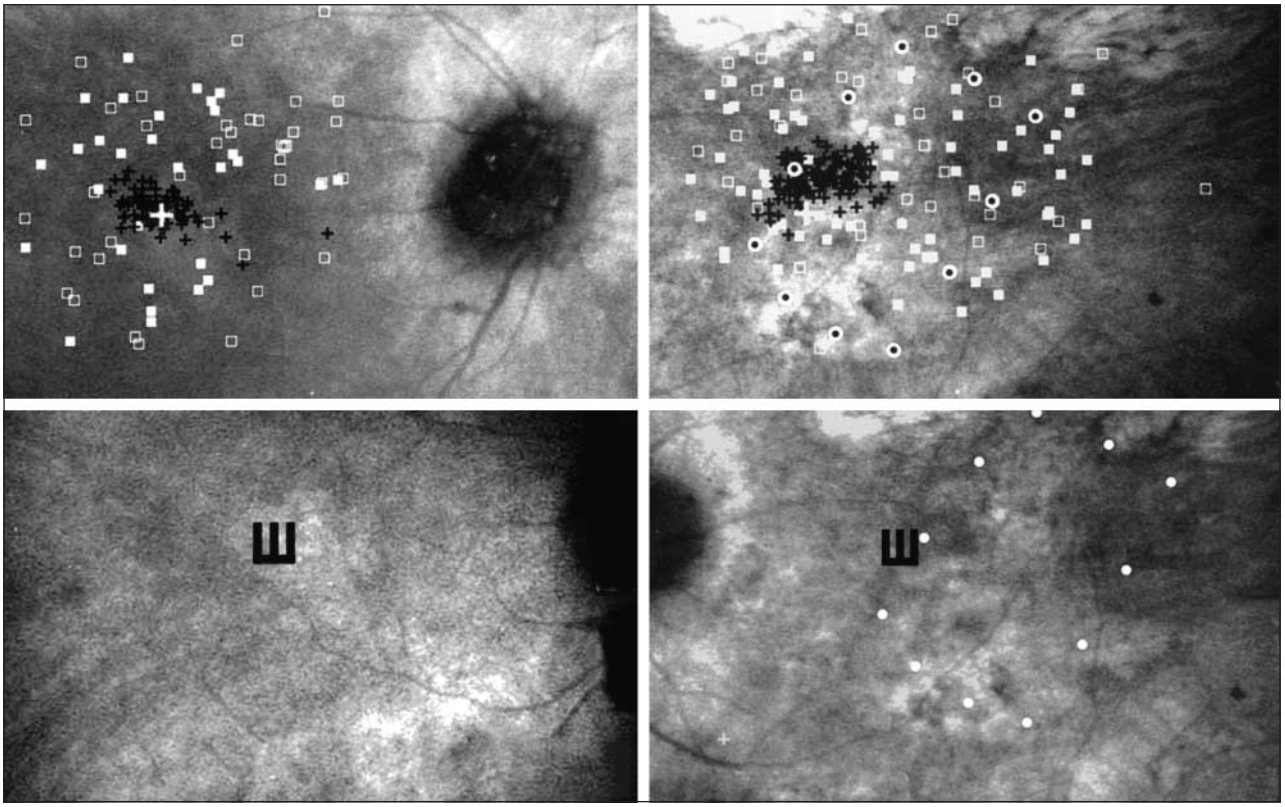

Figure 3. Scanning laser ophthalmoscope: The top row shows microperimetry of the eye that was not operated on (left) and of the eye that was operated on (right). Seeing areas are indicated as filled white squares and nonseeing areas as open white squares; fixation points are indicated by black crosses. The microperimetry data indicate that fixation is not stable and sometimes involves retina over the transplant area as well as retina adjacent to the transplant. The transplant area is outlined by black-on-white dots. The eye that was operated on contained 53 seeing and 37 nonseeing areas. In contrast, the eye that was not operated on contained 33 seeing and 37 nonseeing areas. The bottom row shows fixation of a large, horizontal black *E* in the eye that was not operated on (left) and in the eye that was operated on (right). The patient fixated on a large, horizontal black *E* at the nasal edge of the transplant but outside of the area of the transplant. The patient could not consistently see the *E* in this location. Potential acuity meter 20/369 OD (40° field of view); potential acuity meter 20/270 OS (40° field of view).

the patient had increased oxygen saturation levels for 5 days postoperatively in the range of 96.7% to 98.9% as measured by blood gases and oximeter readings, which had been supplemented from a baseline of 92% saturation preoperatively.

COMMENT

The approach used in this patient with RP was to transplant an intact sheet of fetal neural retina and RPE. A specialized instrument and method have been developed to transplant sheets of fetal neural retina and RPE into the subretinal space between the neurosensory retina and RPE. This approach has significant advantages over other techniques because it maintains the correct orientation of the retinal sheets,[6,11] and the minimal trauma associated with the procedure reduces the possibility of rosette formation or rupture of the Bruch membrane.

To date, no effective treatment has been developed for the recovery of visual loss from RP, but the following 3 treatments are being investigated: (1) Oral vitamin A therapy has been demonstrated to be safe and effective in slowing the rate of electroretinogram loss in RP but shows no effectiveness in the recovery of lost vision.[12] (2) Gene therapy and pharmacologic therapy are underway but are still under development and not in use in clinical trials at this time, although a clinical trial of gene therapy in Leber congenital amaurosis will probably be initiated in 1 to 3 years.[13] (3) Development and use of a visual prosthesis is actively being pursued in many centers but the visual potential of existing devices is not known.[14-16]

In this patient, by 1 year postoperatively, no graft encapsulation, tissue destruction, or macular edema indicating rejection was seen clinically or with fluorescein angiography. However, one cannot exclude the presence of more subtle graft rejection without histological data. Previous reports of human transplantation have varied in the incidence of rejection depending on whether the transplantation involved patches of RPE cells or dissociated cells and whether the patients had exudative or nonexudative manifestations of age-related macular degeneration.[12,17-19] The observed pigment loss of the transplant might have been due to the death of the RPE cells (ie, graft failure) or to the fact that the pigment production of the cells could not keep up with the growth of the cells. Based on clinical experience, depigmented RPE cells do not necessarily function normally. Pigment loss has also been observed in cografts of rat fetal retina with RPE although the donor RPE cells could still be identified by bromodeoxyuridine label.[11] However, it cannot be excluded that slow rejection was occurring. Perhaps there was a mild rejection response first manifested as a loss of pigment. Nevertheless, fluorescein angiography

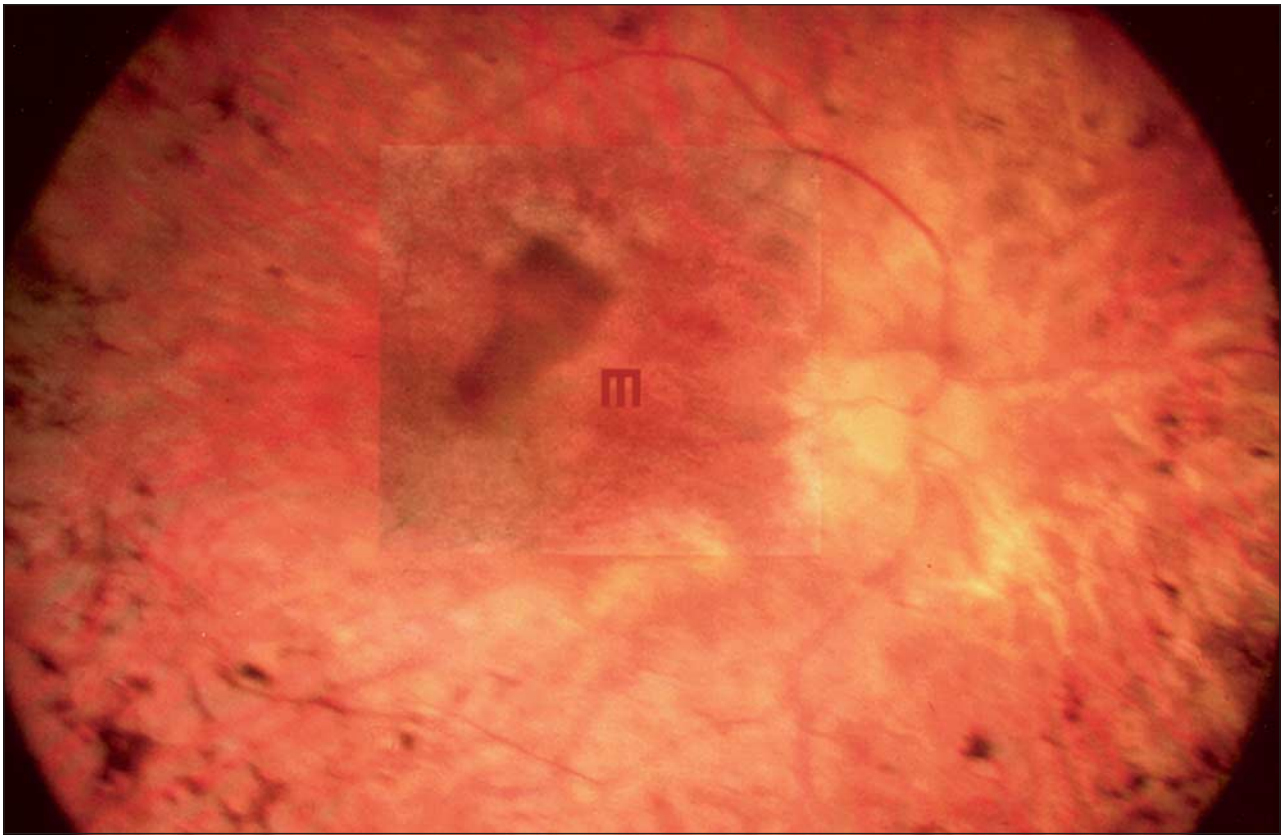

Figure 4. Overlay of scanning laser ophthalmoscope fixation image and fundus photograph of the transplant at 2 weeks postoperatively. Vascular landmarks were used to superimpose the 2 images accurately. This shows that the patient used retina nasal to the nasal edge of the transplant to view the 20/270 letter.

showed no dye leakage in the area of the transplant at 6 to 12 months.

The patient showed a general increase of major histocompatibility complex class I antibodies at 3 months after transplantation, which indicates that some event stimulated the patient's immune system to produce antibodies. Whether the transplant or some other stimulus (eg, an illness) was responsible is unclear but it shows a nonspecific immunologic response as opposed to a graft-specific response. No new antibodies to graft-specific antigens developed as would be expected in the presence of graft rejection. Also, the loss of pigment in the graft occurred gradually across the 3- to 6-month period, and the beginning of the loss of pigment in the transplant was seen well before the titer increase of the anti–class I antibody.

Taken together, our data indicate that changes in recipient antibody production were not initiated by graft recognition and that graft-specific sensitization and thus rejection had not occurred in the observed time frame.

Because of the "immune privilege" of the subretinal space, retinal allografts do not elicit a classic immune response.[20-22] Allogeneic subretinal transplants of postnatal mouse retina (cell aggregates) contain microglial cells expressing major histocompatibility complex class I and II antigens at 35 days posttransplantation.[21] Most microglial cells are associated with blood vessels and migrate into the retina postnatal in rats[23] and beginning at 16 weeks' gestation in humans.[24] Since the number of microglial cells in fetal rat retina is much lower than in postnatal retina,[25] fetal retina, which still lacks inner retinal vessels, may be less immunogenic than postnatal rat retina. In an animal model using allografts of Long-Evans or August Copenhagen Irish rat donors into Sprague-Dawley or Royal College of Surgeons rat recipients, stable transplants were seen in rats 6 to 10 months after surgery,[6] indicating that allogeneic retinal sheet transplants can be tolerated in the subretinal space of rats with retinal degeneration. However, this does not necessarily prove that no rejection occurred in the patient since results in animals cannot be directly extrapolated to humans.

The subjective and objective visual acuity improvement appeared concurrently at 6 to 7 months after surgery. The patient's report of vision improvement was corroborated by ETDRS visual acuity testing. The SLO testing indicated a similar result as the corresponding ETDRS protocol for visual acuity testing. However, since there was no preoperative testing, any improvement could not be confirmed by SLO.

The SLO testing showed that fixation was unsteady and involved the nasal edge of the transplant as well as the retina nasal and immediately adjacent to the transplant. Viewing of the 20/270 letter was done with the retina at the nasal edge of the transplant.

There are 2 mechanisms that may explain the visual improvement: a trophic effect of the transplant on host cones[26,27] or local synaptic connections between the transplant and host. Basic fibroblastic growth factor[28-30] and various cytokines and neurotrophic factors[31] have been shown to protect against photoreceptor degenera-

tion due to continuous light exposure or genetic defects.[32,33] These growth factors likely act indirectly on photoreceptors via Mueller cells.[34] It has also been suggested that transplanted normal rod photoreceptor cells release soluble factor(s) to enhance cone survival in primary rod photoreceptor dystrophies[35] without the need for specific synapse formation.

An alternative or additional mechanism by which the transplant may have improved the vision in this patient is by local synaptic connectivity between the transplant and host. However, this is uncertain in this case since the patient fixated only on the edge of the graft. In Royal College of Surgeons rats and transgenic rats with retinal degeneration, transplants of fetal retinal sheets can restore visual responses in an area of the superior colliculus that topographically corresponds to the placement of the transplants in the retina.[36,37] Preliminary studies suggest synaptic connections between subretinal transplants and host retina by a trans-synaptic virus tracing from the host brain to the transplant[38] (M.J.S., unpublished data, March 1999-June 2002). At the present time, however, there is no published experimental evidence that transplanted fetal neurosensory retina can reestablish appropriate synaptic connections with the residual host neural network.

The failure of the mfERG to reveal improvement was not contradictory to our conclusion of improved vision but rather indicative of an inability to extract any clear signal from the considerable recording noise (ie, a very low signal-noise ratio). Because of the nature of the multifocal technique, any movement of the stimulus on the retina due to lack of good fixation will smear the stimulation and response of functional areas of retina with adjacent nonfunctional areas. This effect will diminish any signal that may be present. The mfERG is additionally complicated by the issue of whether the waveform recorded focally from the region of the transplant will resemble waveforms characteristic of normal retinas.[7] The waveform is likely to be affected by the types of connections made between the donor and host and precludes reliance on standardized templates in the analysis. Although no new tissue has been introduced to the visual cortex, waveforms composing the normal mfVEP vary considerably across the visual field because of the convolutions of the primary visual cortex and individual variability. In patients, it is possible that transplant-induced changes in input and activity of the visual cortex after many years of their absence may result in neural plasticity that produces waveforms uncharacteristic of normal mfVEPs. The approval of the FDA to perform this procedure in patients with better visual acuity (up to 20/400) and with less nystagmus will provide our future studies with greater potential for showing improved function with mfERG and mfVEP testing.

The effect of the patient's exposure to oxygen saturation levels at 96.7% to 98.9% for 5 days postoperatively on the transplant is unknown.

Diseases that affect the RPE and photoreceptor cells of the retina (eg, RP, age-related macular degeneration, rod-cone dystrophy, and Stargardt disease) might conceivably benefit from this type of transplantation in the future.

An additional improvement has been seen in the patient presented in this article since the time the manuscript was submitted. The patient was tested with follow-up ETDRS and SLO. The last SLO data presented in the article were at 9 months after surgery. At 1 year 3 months after transplantation, SLO testing showed a visual acuity of 20/260 in the eye that was operated on and 20/330 in the eye that was not operated on with a 40° field of view. At 2 years 3 months after surgery, SLO testing showed improved visual acuity in both eyes: 20/84 in the eye that was operated on and 20/139 in the eye that was not operated on. The fixation was similar over the transplant in both tests. At 2 years 2 months, ETDRS testing showed a visual acuity of 20/200 in the eye that was operated on, whereas the visual acuity of the other eye remained unchanged at 20/400. Subjective improvement also occurred. At 2 years 2 months after the surgery, the patient noted that she could definitely see better with the eye that was operated on. The vision in that eye was less cloudy than that of the other eye. She could also read the large-print *Reader's Digest* and print on the computer with the eye that was operated on that she could not read with the other eye.

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Dr Radtke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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