The Artificial Silicon Retina Microchip for the Treatment of Vision Loss From Retinitis Pigmentosa

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Objective: To determine the safety and efficacy of the artificial silicon retina (ASR) microchip implanted in the subretinal space to treat vision loss from retinitis pigmentosa.

Methods: The ASR microchip is a 2-mm-diameter silicon-based device that contains approximately 5000 microelectrode-tipped microphotodiodes and is powered by incident light. The right eyes of 6 patients with retinitis pigmentosa were implanted with the ASR microchip while the left eyes served as controls. Safety and visual function information was collected.

Results: During follow-up that ranged from 6 to 18 months, all ASRs functioned electrically. No patient showed signs of implant rejection, infection, inflammation, erosion, neovascularization, retinal detachment, or migration. Visual function improvements occurred in all patients and included unexpected improvements in retinal areas distant from the implant.

Main Outcome Measures: Subjective improvements included improved perception of brightness, contrast, color, movement, shape, resolution, and visual field size.

Conclusions: No significant safety-related adverse effects were observed. The observation of retinal visual improvement in areas far from the implant site suggests a possible generalized neurotrophic-type rescue effect on the damaged retina caused by the presence of the ASR. A larger clinical trial is indicated to further evaluate the safety and efficacy of a subretinally implanted ASR.

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RETINITIS PIGMENTOSA (RP) IS a prevalent and devastating cause of both central and peripheral vision loss.[1-3] This genetically diverse disease commonly affects both eyes and is progressive. No treatment is effective at restoring vision once it is lost. Although other patterns are observed, vision loss typically develops first in the midperiphery and then progresses to involve the peripheral and finally the central visual fields.

Retinitis pigmentosa results from outer retinal degeneration. This causes the outer portion of the inner anatomical retina (outer retina), composed primarily of photoreceptor outer and inner segments and their cell bodies, to become damaged, the inner portion (inner retina), comprising the remaining bipolar, horizontal, amacrine, and ganglion cells and nerve fiber layer, can be substantially spared.[4,5] The presence of these relatively intact remaining retinal layers has led investigators to study the effect of electrical stimulation on these structures to improve vision.

Electrical stimulation applied to external structures of the eye has produced visual sensations called phosphenes in healthy subjects[6-8] and blind patients with RP.[9] An electrophysiological correlate of this finding has been demonstrated in blind RCS [Royal College of Surgeons] rats, a model of photoreceptor degeneration in which extraocular electrical stimulation has produced visual evoked potentials.[10,11] Intraocular electrical stimulation of the retinal nerve fiber layer also produced phosphenes in patients with RP [12] and visual evoked potentials in animals.[13] In vitro and in vivo animal studies have shown that retinal and cortical electrical activity can be induced by electrical stimulation of the outer retinal area.[14,15]

As a result of these observations, we investigated in a pilot safety and feasibility study whether a subretinal prosthesis could produce electrical stimulation and phosphenes.[16-23] A 2-mm-diameter semiconductor microphotodiode array chip, 25 µm in thickness (artificial silicon retina [ASR] microchip), was designed for implantation into the subretinal space. This chip is composed of approximately 5000 independently functioning electrode-tipped microphotodiodes and is powered solely by incident light. The electrical charge produced by these microphotodiodes is designed to alter the membrane po-

tentials of contacting retinal neurons and to simulate how light would normally activate these cells to form retinotopic visual images. Because the implant would stimulate the outer retina at an early functional stage, subsequent visual signal processing by the remaining neuroretinal networks would theoretically be possible.

In the cat, pig, and rat models, placement of the solid ASR disc into the subretinal space produced a model of outer retinal degeneration that histologically resembled that of RP.[17,18,20,24,25] The immunohistochemistry of the overlying retina also showed an appearance similar to that seen in patients with hereditary retinal degeneration.[20] Additionally, ASR microchips functioned within the subretinal space[17-19] and demonstrated continued electrical activity for more than 3 years after implantation.[26] Functionally, ASR microchips induced retinal and possible cortical responses in the animal models.

Because of these findings in animal models and the substantial degeneration of the outer retina in patients with late-stage RP, we believed that the placement of a small ASR microchip in the subretinal space of a patient with late-stage RP would not cause further substantial injury to the retina. Furthermore, if the ASR microchip was placed in a midperipheral retinal location, the safety and efficacy of the device could be evaluated with a minimal risk of damaging the macular area.

To determine the safety and efficacy of the ASR microchip for possible human application, we conducted a pilot clinical trial, implanting the ASR into the right eyes of patients with RP and using the left eyes as controls.

METHODS

Between June 2000 and July 2001, Food and Drug Administration and institutional review board approval were obtained to enroll 6 patients into an ASR safety and feasibility clinical trial. Informed consent was obtained from all patients prior to entry. Eligible patients were aged 40 years and older, had RP, and were free of other significant eye or medical diseases such as uveitis, diabetes, glaucoma, or cardiac conditions. They had to have a Snellen visual acuity measurement of 20/800 OU or worse and/or 15° or less of the remaining central visual field as determined by Humphrey automatic visual field testing[27] (loss >10 dB, size III white static, and 31.5 apostilbs of background illumination). Finally, the patients had to be able to perceive electrically induced phosphenes produced by contact lens electrical stimulation. In this test, current and voltage were provided by 1 to 6 serially connected photodiodes, each illuminated by a 940-nm infrared light-emitting diode affixed above the photodiode and powered by 50-mA current. The voltage and current produced per photodiode were approximately 0.40 V and 200 μA with approximately 5 kΩ of measured impedance between the corneal contact lens electrode and the ipsilateral temple return electrode. Stimulation pulses consisted of 50% duty-cycle 5-Hz pulses with a polarity change every second and a total duration not exceeding 15 seconds. Thresholds for phosphene recognition in the 6 patients varied from 2 to 5 photodiodes electrically connected in series. The initial current generated varied depending on the impedance from approximately 200 μA for 1 photodiode to 600 μA for 5 photodiodes. Exclusion criteria included unrealistic expectations of the study, unstable personality, or other significant psychiatric conditions.

After enrollment, each patient provided a complete medical and ophthalmic history, and a complete medical examination was performed. As part of the ophthalmic history, a quality-of-life questionnaire was administered. To rule out cystoid macular edema, fundus photography and fluorescein angiography were performed unless contraindicated by allergy to fluorescein dye.

Patients answered questions regarding their visual function outside of the physician's office. They were asked to describe their visual perceptions for 7 aspects of visual function and to give a comparison rating of one eye relative to the other. These perceptions included brightness, contrast, color, shape, resolution, movement, and visual field size. Because the ASR was implanted in the right eye, patients were instructed to use their left eye as the basis for comparison, to assign a fixed rating value of 10 to the left eye, and then to compare the right eye with the left. For example, if the brightness of the 2 eyes was equal, both would receive a value of 10. If the brightness of the right eye was subjectively twice that of the left, the right eye would be rated a 20; if it was half that of the left eye, the right eye would be rated a 5. If the patient had no perception, a value of 0 was assigned. In the latter case, if the left eye had perception but the right eye did not, the left would be assigned a value of 10 and the right would receive a 0. Perceptions of the 2 eyes were again compared postoperatively and were also compared with their preoperative values when possible. For example, if the right eye developed subjective perception even though it previously had none, it would be compared with the left because a ratio comparison with a preoperative value of 0 in the right eye would not be possible.

Preoperative visual acuity testing was performed at least twice using standard back-illuminated charts from the Early Treatment Diabetic Retinopathy Study[28] (ETDRS) at 0.5 m, with the patient undergoing cycloplegia (1% cyclopentolate hydrochloride, 1% tropicamide, and 2.5% phenylephrine hydrochloride) and best-corrected visual acuity testing with a retinoscopic refraction at 0.5 m. Total ETDRS letters correctly identified were counted until 1 line (5 letters) was completely missed. If neither of the top 2 lines of ETDRS letters could be identified at 0.5 m, we recorded a visual acuity of counting fingers or hand motions (HM) at the associated distance as well as light perception (LP) in 9 visual field sectors.

Testing with the Humphrey Visual Field Analyzer II (Zeiss Humphrey Systems, Dublin, Calif) was conducted using the III and V white static spot sizes in the 30-2 (30° radius) and 60-4 (30°-60° radius) protocols, as well as a custom protocol with a 30° radius and a 4° spot separation, in both preoperative and postoperative test sessions.

Because Humphrey visual field testing was limited by the brightness of the instrument test target (10 000 apostilbs), additional visual field light-threshold testing was conducted in 9 visual field sectors in a 3×3 grid with less than 0.1 footcandle (ft-c) of background room illumination. This was accomplished by using a 0.5-in-diameter optical fiber halogen light source placed 10 cm from the patient's eye at the following 9 locations from the patient's perspective: right-upper, right-middle, right-lower, middle-upper, middle-middle, middle-lower, left-upper, left-middle, and left-lower. All positions except middle-middle were located approximately 45° from the optical axis (middle-middle position). Using stacked neutral-density filters in slide holders, illuminations from 300 ft-c down to 1 e-4 ft-c in 5-dB steps were used for threshold testing. The threshold was established in each sector by crossing it at least 3 times in an ascending and descending staircase paradigm. The testing was continued until all 9 sectors were completed. Both the implanted and control eyes were tested during the sessions. In patients 1, 2, and 3, this test was implemented by 4 to 6 months postoperatively and in patients 4, 5, and 6, by 2 months postoperatively. The test is referred to as the nine-sector test.

Electroretinograms and visual evoked potentials were performed preoperatively and postoperatively using an LKC (LKC

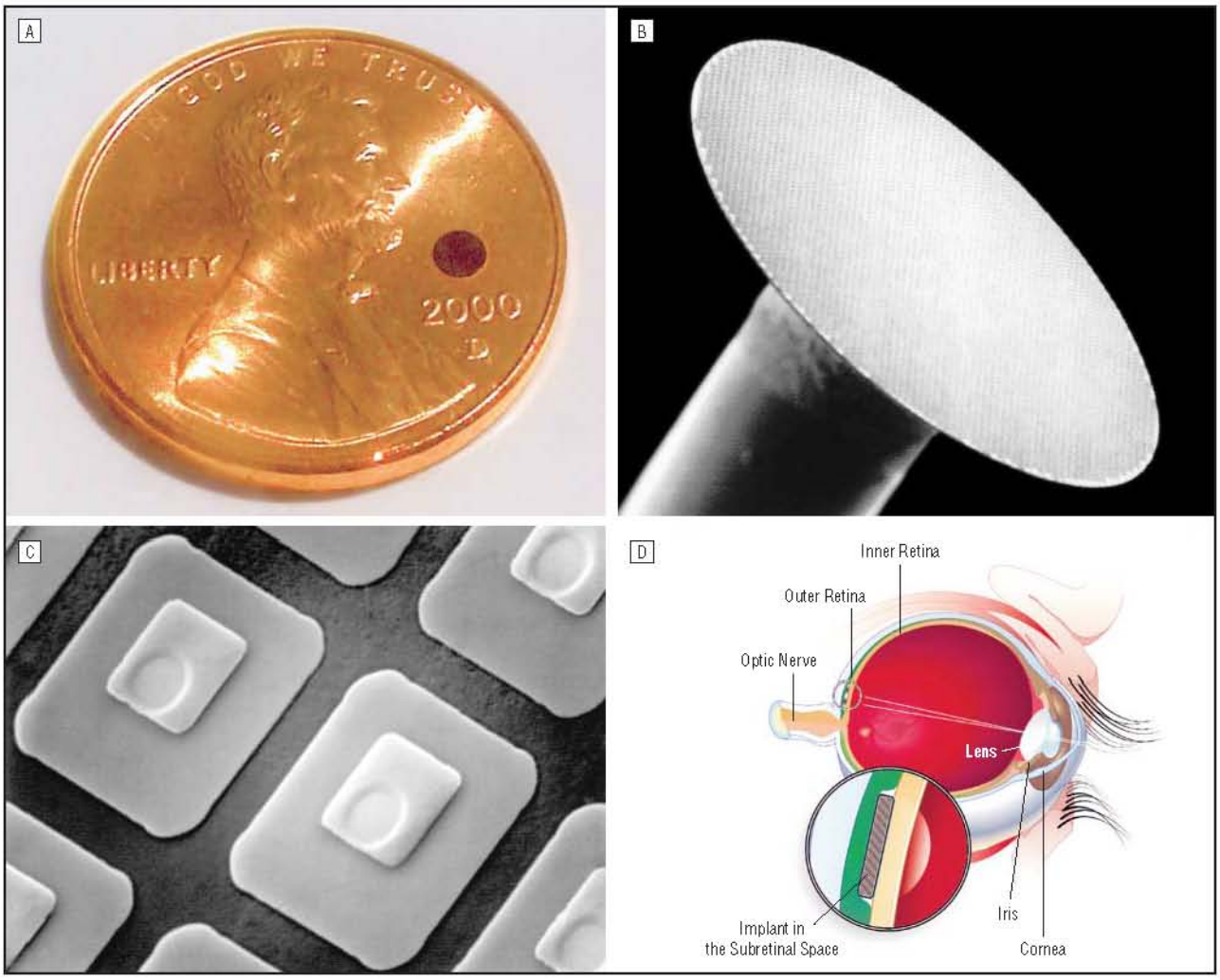

Figure 1. Artificial silicon retina (ASR). The model used here is 2 mm in diameter and 25 µm thick and contains approximately 5000 negative intrinsic layer–positive microphotodiode pixels electrically isolated from each other and separated by 5 µm. Each pixel is 20×20 µm square and is fabricated with a 9×9-µm iridium oxide electrode deposited and electrically bonded to each pixel. Pixel current was 8 to 12 nA with approximately 800 foot-candles of illumination. The ASR microchip was placed within a fabricated Teflon sleeve and secured intraoperatively to a saline-filled syringe injector; it was then deposited within the retina by fluid flow. A, The ASR's size relative to a penny. B, The ASR microchip (original magnification ×36). C, The ASR pixels (original magnification ×1400). D, Subretinal location of the implanted ASR microchip.

Technologies, Gaithersburg, Md) or Diagnosys Espion (Diagnosys LLC, Littleton, Mass) computer signal averaging system. White or infrared light (940 nm supplied by light-emitting diodes) was applied via handheld Ganzfeld stimulators (Optobionics Corporation, Naperville, Ill). The infrared handheld Ganzfeld stimulator allowed the determination of isolated implant electrical responses and patient perceptions to infrared light in the area of the implant.

The ASR (**Figure 1**) was implanted in the superior to superior temporal subretinal space (approximately 20° off axis from the macula) in the right eyes of all patients, who were given general anesthesia. A standard 3-port vitrectomy (irrigation cannula, light pipe, and aspiration vitreous cutter) was performed with pars plana lensectomy. A retinal bleb was created using a cannula and hydrostatic dissection. The retinotomy was extended to 2.5 mm using vitreoretinal scissors. The ASR was inserted through the retinotomy into the subretinal space, and air-fluid exchange was performed to flatten the retina. Laser or thermal cautery was not required in most patients. The scleral incisions were closed with absorbable sutures, and antibiotic steroid medication was applied. Postoperative follow-up examinations were conducted according to the study protocol. Patients visits were scheduled as follows: postoperative days 1, 2, and 4; weeks 1, 2, 4, 6, and 8; and months 3, 4, 6, 9, 12, 15, 18, 21, and 24. Fluorescein angiograms were performed at 6 months, and electroretinograms were done at multiple visits, including 1 year postoperatively.

RESULTS

Fifteen patients with RP were screened for our investigation. Thirteen patients were able to perceive phosphenes, and 6 were selected for ASR implantation. Patient 1 had isolated RP without a significant family history. Patient 2 had an extensive vertical autosomal dominant family history with multiple affected family members. Patient 3 had autosomal dominant RP with an affected brother and daughter. Patient 4 had type 2 Usher syndrome with no family history of this condition. Patients 5 and 6 were brothers who had autosomal dominant RP and a vertical family history.

In the immediate postoperative period, the most common adverse effect requiring intervention was elevation of the intraocular pressure (IOP) to higher than 25 mm Hg.

Visual Function After ASR Implantation*

Patient No./ Age, y	Follow-up, mo	Lens Type	Complications	ETDRS Visual Acuity Improvement	Subjective Improvement	Automated Visual Field Improvement	Nine-Sector Testing Improvement
1/66	18	PCIOL	None	NA	+	NA	+
2/45	18	Uncorrectedaphakia†	None	NA	+	NA	++
3/76	18	PCIOL	None	+	+	NA	+
4/73	6	Uncorrectedaphakia†	None	NA	+	NA	NA
5/59	6	ACIOL†	None	+	+	+	NA
6/59	6	ACIOL	None	+	+	NA	NA

Abbreviations: ACIOL, anterior chamber intraocular lens; ASR, artificial silicon retina; ETDRS, Early Treatment Diabetic Retinopathy Study[28]; NA, not applicable; PCIOL, posterior chamber intraocular lens; +, improvement measurable by the testing method; ++, improvement compared with a muscle light of the same illumination preoperatively.

*Patient 2 had a cataract, and patients 4 and 5 had lenticular opacities that diminished visualization of the ASR during surgery. Patient 5 complained about his eyeglasses correction for aphakia and received an ACIOL in a second operation. Patient 6 complained of movement in a previously placed PCIOL and was given an ACIOL in a second operation.

†Lensectomy was performed during ASR implantation in 3 patients.

This occurred in patients 1, 5, and 6. The IOP elevation generally occurred toward the end of the first week. This elevation was believed to be related to the steroid contained in the postoperative antibiotic steroid drops (dexamethasone with either tobramycin, neomycin sulfate, or polymyxin B sulfate) because the IOP decreased rapidly when treatment with the drops was stopped but increased when their administration was restarted. Elevated IOP was treated with IOP-lowering medication and steroid tapering. After approximately 3 weeks, when the steroid antibiotic drops regimen was stopped, the IOP returned to preoperative values. Scratchiness in the eye that was operated on was noted by several patients and resolved after approximately 6 weeks when the external absorbable sutures dissolved. Patient 5 noted aniseikonia between his aphakic ASR-implanted eye and his unoperated on eye when using glasses. A subsequent anterior chamber intraocular lens relieved those symptoms. Another patient noted syneresis of images seen from the implanted eye, which was believed to be related to syneresis of a previously implanted posterior chamber intraocular lens. These symptoms substantially improved after replacement of the syneretic posterior chamber intraocular lens with a stable anterior chamber intraocular lens.

No patient experienced infection, prolonged inflammation or discomfort, undesirable visual symptoms, intraocular or retinal hemorrhage, neovascularization, implant rejection, migration, or erosion through the retina.

Patients 1, 3, and 6 were pseudophakic before ASR implantation. Preoperatively, patient 2, who had bare to no LP, had a 3+ posterior subcapsular cataract (<20/200 view in the affected eye). Patient 4, who had a visual acuity of HM at 1 ft, had a 1+ anterior subcapsular cataract, 1+ nuclear sclerosis, and 1+ posterior subcapsular cataract (20/30 view in the affected eye). Patient 5, who had a visual acuity of counting fingers at 1 to 2 ft, had a 1 to 2+ anterior subcapsular cataract, 1+ posterior cortical cataract, and 0 to 1+ nuclear sclerosis cataract (20/30 view in the affected eye). To facilitate viewing of the implant during the procedure, the cataracts were removed from patients 2, 4, and 5 during the ASR operation. Patients 2 and 4 were left aphakic, and patient 5 underwent secondary anterior chamber intraocular lens implantation approximately 1 month after ASR implantation.

CLINICAL CHARACTERISTICS

The **Table** summarizes the clinical characteristics and results. At the last follow-up visit, there were no ASR-related complications. The retina overlying the implant remained clear with patent vessels (**Figure 2**). Fluorescein angiograms showed no signs of neovascularization, vascular dropout, disruption, or leakage. In all patients, the anterior and posterior segments of the eye appeared quiet. All devices were functioning electrically, as demonstrated by electroretinographic recordings of ASR electrical spikes to infrared stimuli (**Figure 3**A).

Before implantation, only 2 (patients 5 and 6) of 6 patients were able to read ETDRS letters in either eye at 0.5 m. Preoperatively, patient 5 read 16 to 25 letters OD and 24 to 28 letters OS, and patient 6 read 0 letters OD and 0 to 3 letters OS. These 2 patients demonstrated postoperative improvements in the total number of ETDRS letters read (Figure 3B) that were consistent with their subjective impression of improved central perception of contrast, shape, and resolution. Six months after implantation surgery, patient 5 read 35 to 41 letters OD and 21 to 28 letters OS, and patient 6 read 25 to 29 letters OD and 0 letters OS. The smallest letters read in the right eye improved from a Snellen equivalent of approximately 20/800 to 20/200 OD for patient 5 and from worse than 20/1600 (no letters read) to approximately 20/400 OD for patient 6. Patient 3 was unable to read any of the ETDRS letters preoperatively (<20/1600) in either eye but postoperatively was able to see some of the largest letters with the right eye only (approximately 20/1280-20/1600 OD) at 12 to 18 months (Figure 3B). On multiple tests, positive responses from preoperative central Humphrey visual field testing with the size V white static target could be obtained consistently only for patients 5 and 6. Postoperatively, only patient 5 demonstrated improved central and paracentral visual fields (30-2) in the right eye on multiple tests (**Figure 4**).

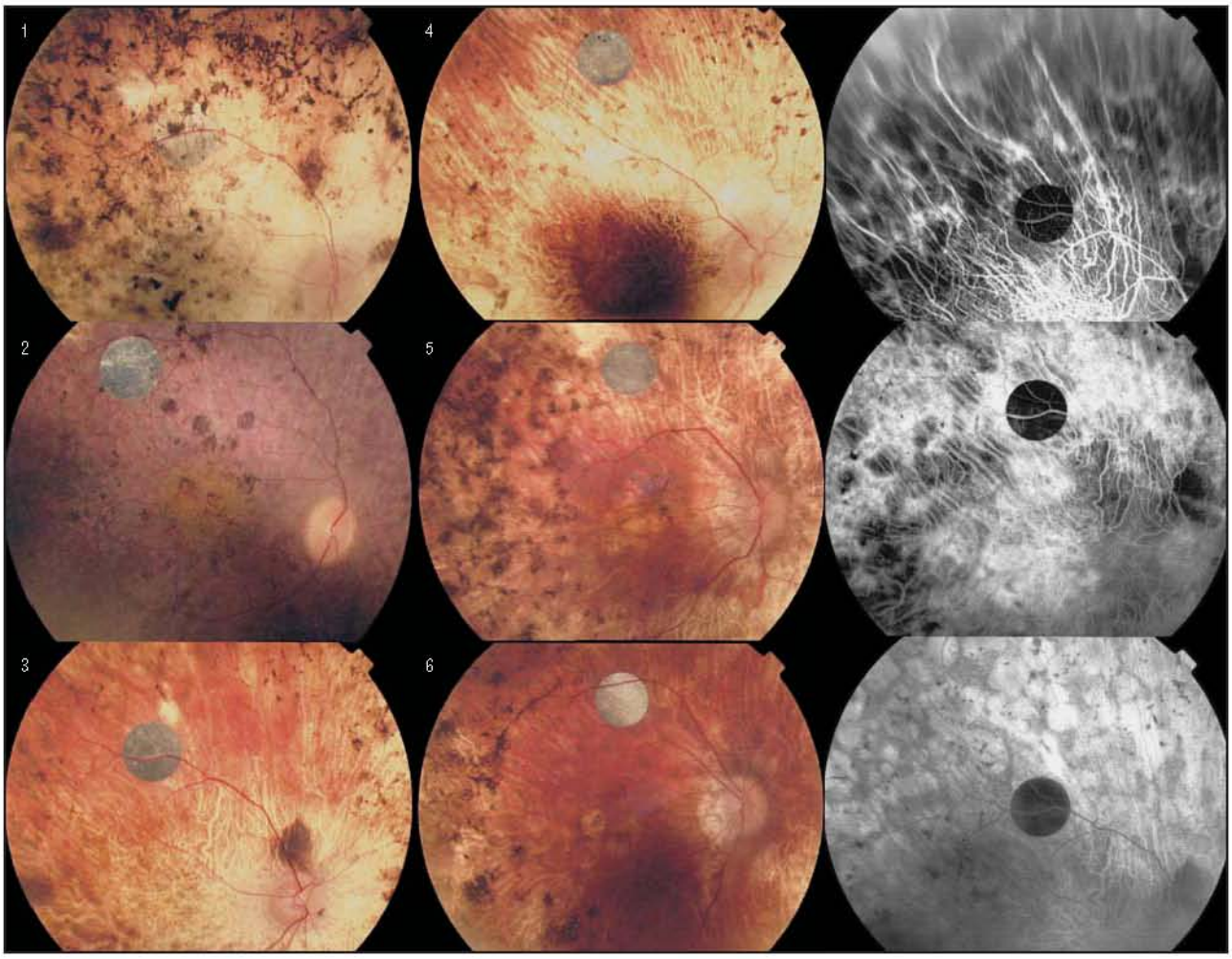

Figure 2. Fundus photographs and fluorescein angiograms of an implanted artificial silicon retina microchip in the superior temporal retina. Photograph number indicates the patient number; the fluorescein angiogram (right) is from patient 3. Top to bottom: early, middle, and late phases.

Compared with the unoperated on eye, 2 eyes (patients 1 and 3) with the ASR showed improvement on the 9-sector test at 6 months to 1 year after surgery. In patient 1, threshold sensitivity improved by approximately 1000% to 1500% in all sectors and was consistent with the patient's impression that his entire visual field was brighter in the eye with the implant compared with the same eye before surgery as well as the unoperated on eye (**Figure 5**). In patient 3, threshold sensitivities in the right-middle, right-lower, and middle-lower sectors of the 9-sector test improved at 18 months by approximately 5000% to 10 000% (Figure 5). These visual field areas of improvement on the 9-sector test were consistent with the patient's subjective impression that his best vision for objects directly in front of him was achieved when he elevated his chin and used his inferior visual fields to look straight ahead. Patient 2 showed consistent LP in multiple sectors of the operated eye on the nine-sector test compared with her subjective bare to no LP in those same sectors preoperatively. These perceptions were in keeping with the patient's postoperative impression that she developed consistent LP in the right eye and noticed shadows of people given the proper lighting conditions. This patient's 9-sector thresholds did not improve further beyond 1 year after surgery.

No patient was able to perceive or discriminate color on preoperative pseudoisochromatic plate color testing. Postoperatively, patient 5 reported substantial improved color perception of his environment such as seeing the green and white of highway signs, red and white of stop signs, red and white checks on a tablecloth, green grass, and multiple colors in his environment. These perceptions were consistent with his ability to correctly identify the blue and orange dots of the control isochromatic plate and the red and green dots of the test plate using the operated on eye. The unoperated on control eye was never able to perceive colors in the pseudoisochromatic plates.

COMPARATIVE SUBJECTIVE VISUAL FUNCTION CHANGES AFTER ASR IMPLANTATION

In the first group of 3 patients, at 18 months after surgery, their impressions were that visual function improvements had stabilized. In the second group of 3 patients, at 6 months after surgery, the impressions of 2 patients (patients 5 and 6) were that their visual function changes had generally stabilized, but patient 4 reported continuing improvement.

Patient 1 had LP in both eyes before surgery. The preoperative right-left self-reported comparison ratio for

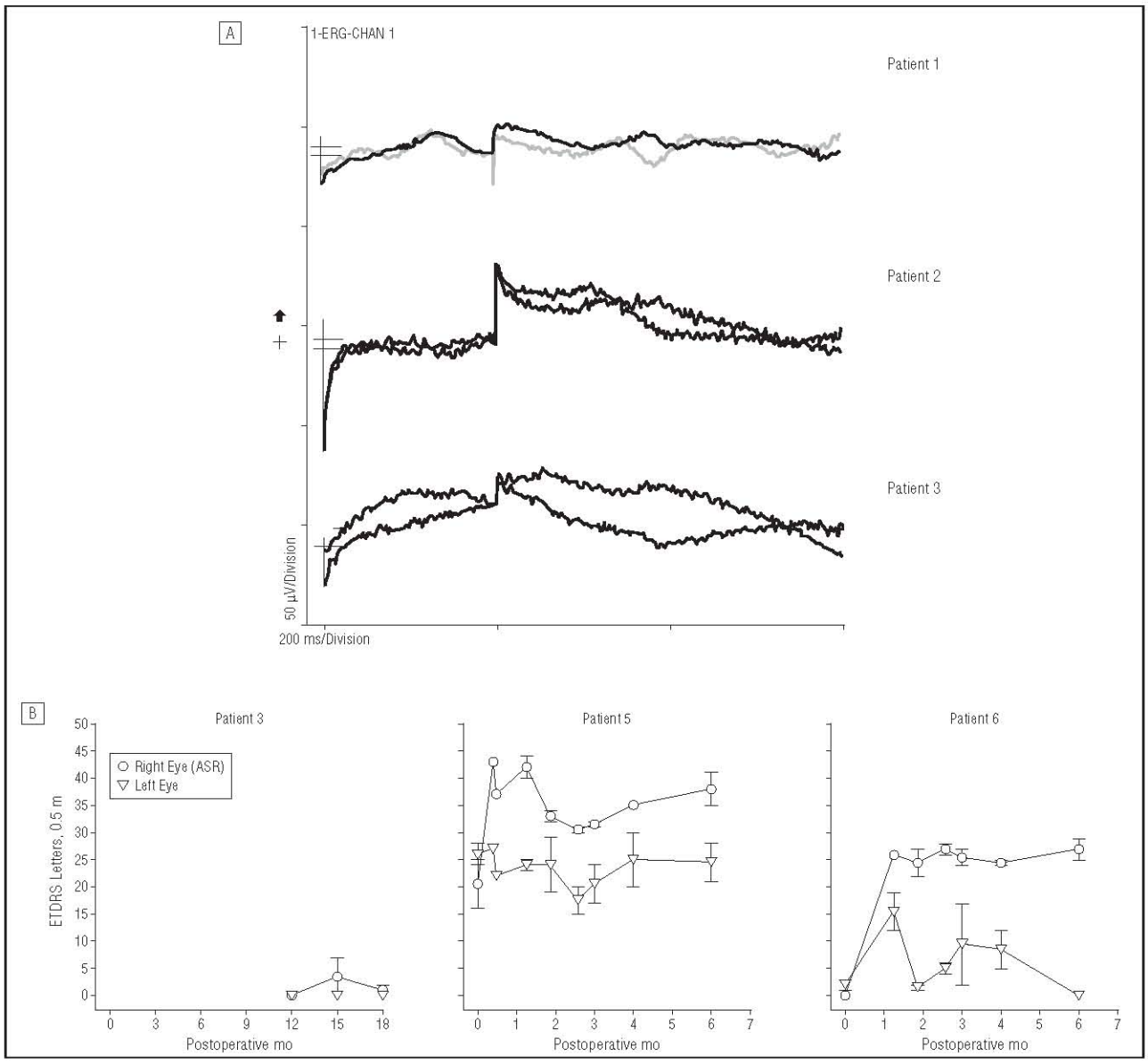

Figure 3. A, Electroretinograms from patients 1, 2, and 3 at 1 year after implantation, showing persistent electrical activity of the artificial silicon retina (ASR) microchip. B, Early Treatment Diabetic Retinopathy Study (ETDRS) chart visual acuity measurements at 0.5 m in 3 patients. Patients 3, 5, and 6 demonstrated improvement in their ETDRS visual acuity in the ASR-implanted right eye. Patient 3 read no letters preoperatively but at 12 to 18 months was able to read several letters.

brightness was 5:10, and for visual fields it was 2:10. Postoperatively, the ratios stabilized at 7:10 and 15:10, respectively, at 18 months. The visual field size in the right eye was subjectively about 750% larger compared with the same visual field before surgery. Functionally, the patient reports not having to turn his head to see light coming from the right side.

Patient 2 had bare to no LP in the right eye with LP in the left eye before surgery. Preoperatively, only the left eye had subjective perceptions of brightness, contrast, shape, and visual field size. Postoperatively, she is still unable to read any letters on the ETDRS chart. However, she subjectively reports substantial visual function improvement in the right eye, particularly in the inferior nasal visual field, that has persisted at 18 months. The self-reported postoperative right-left ratios were as follows: brightness, 8:10; contrast, 10:10; shape, 10:10; and visual field size, 8:10. Functionally, this patient reports being able to see shadows of people with her right eye

Patient 3 had a visual acuity of HM to LP OU before surgery. At 18 months after surgery, the patient noted that preoperatively the right-left ratios had been 7:10 for brightness and 10:10 for shape, resolution, movement, and visual field size. He indicated that postoperatively these ratios were 30:10, 35:10, 50:10, 50:10, 50:10, and 50:10, respectively. Functionally, the patient reports regaining the ability to use nightlights for navigation at night and can now see movement on television.

Patient 4 had a visual acuity of HM OU before surgery. Preoperatively, the self-reported right-left ratios were 10:10 for brightness, contrast, shape, and visual field size. Postoperatively, the ratios were variable but improved in the right eye compared with the left: 15:10, 17:15, 17:

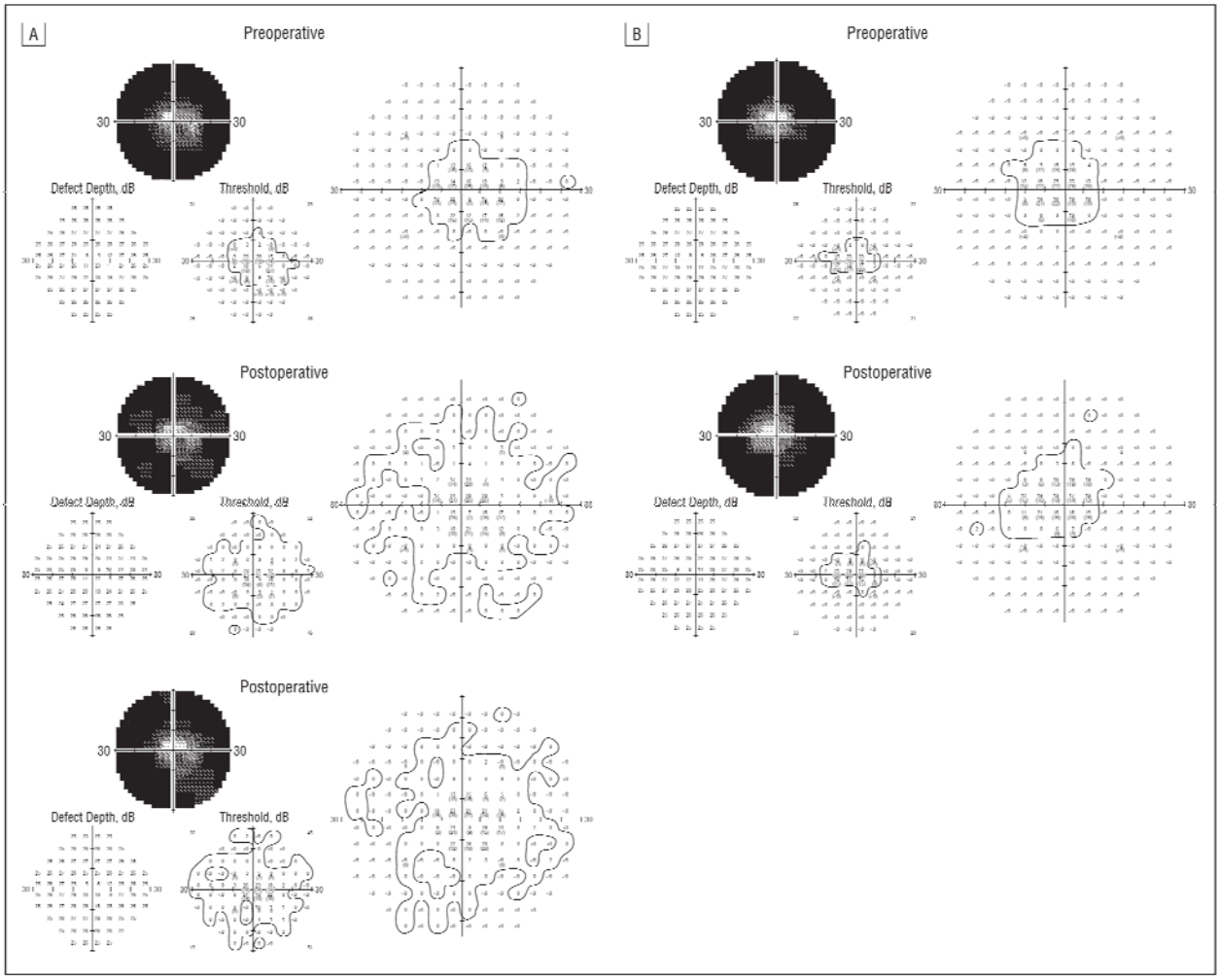

Figure 4. Results of Humphrey central visual field tests with the V white static spot size for patient 5, demonstrating consistently improved central and paracentral visual fields in the right eye postoperatively compared with the preoperative measurements. Whereas almost all of the visual field outside the 15° radius in both eyes was preoperatively less than a 0-dB threshold (unrecordable with threshold sensitivity >10 000 apostilbs) (A, top, and B, top), large portions of the visual field in the right eye were recordable postoperatively at 0 dB or better (A, middle and bottom). The Humphrey visual field test results of the unoperated on left eye were substantially unchanged (B, middle).

10, and 13:10, respectively, for brightness, contrast, shape, and visual field size. Postoperative perception of movement was noted to be 2:10 relative to what the patient remembered from his youth. Subjectively, this patient indicates that when both eyes are used, his overall visual function is substantially improved from a rating of 10 preoperatively to approximately 25 after surgery. Functionally, the patient reports now being able to navigate his yard without a cane and that he can readily tell which lights are on at night in his house.

Patient 5 had a visual acuity before surgery of approximately counting fingers at 1 to 2 ft OU, with the smallest ETDRS letters recognized translating to a Snellen equivalent of approximately 20/800 OU. He noted equal visual function in both eyes in all perceptions (10:10) preoperatively. Postoperatively, the right-left ratios were as follows: brightness, 17:10; contrast, 30:12; color, 17:10; shape, 15:10; resolution, 35:10; movement, 13:10; and visual field size, 11:10. Functionally, the patient reports that he can more easily discern denominations of paper money, sees well enough to use eating utensils, and recognizes faces again, something he has not been able to do for approximately 10 years.

Patient 6 had a preoperative visual acuity of HM OU and noted equal visual function in both eyes in all perceptions (10:10) before surgery. Preoperatively, he recognized no ETDRS letters with the right eye (<20/1600 OD) and a maximum of 3 letters with the left (20/1600 OS). Postoperatively, the right-left ratios were variable between days but appeared to maximize as follows: brightness, 20:10; contrast, 25:10; color, 20:10; shape, 20:10; resolution, 20:10; movement, 20:10; and visual field size, 18:10. Functionally, the patient reports that he can sometimes recognize denominations of paper money. At times, he is able to differentiate the color of traffic lights. He also sees well enough to locate cars in the street and to find his coffee cup at meals.

COMMENT

This pilot clinical trial supports the hypothesis that ASR retinal prosthetic chips can be safely and consistently

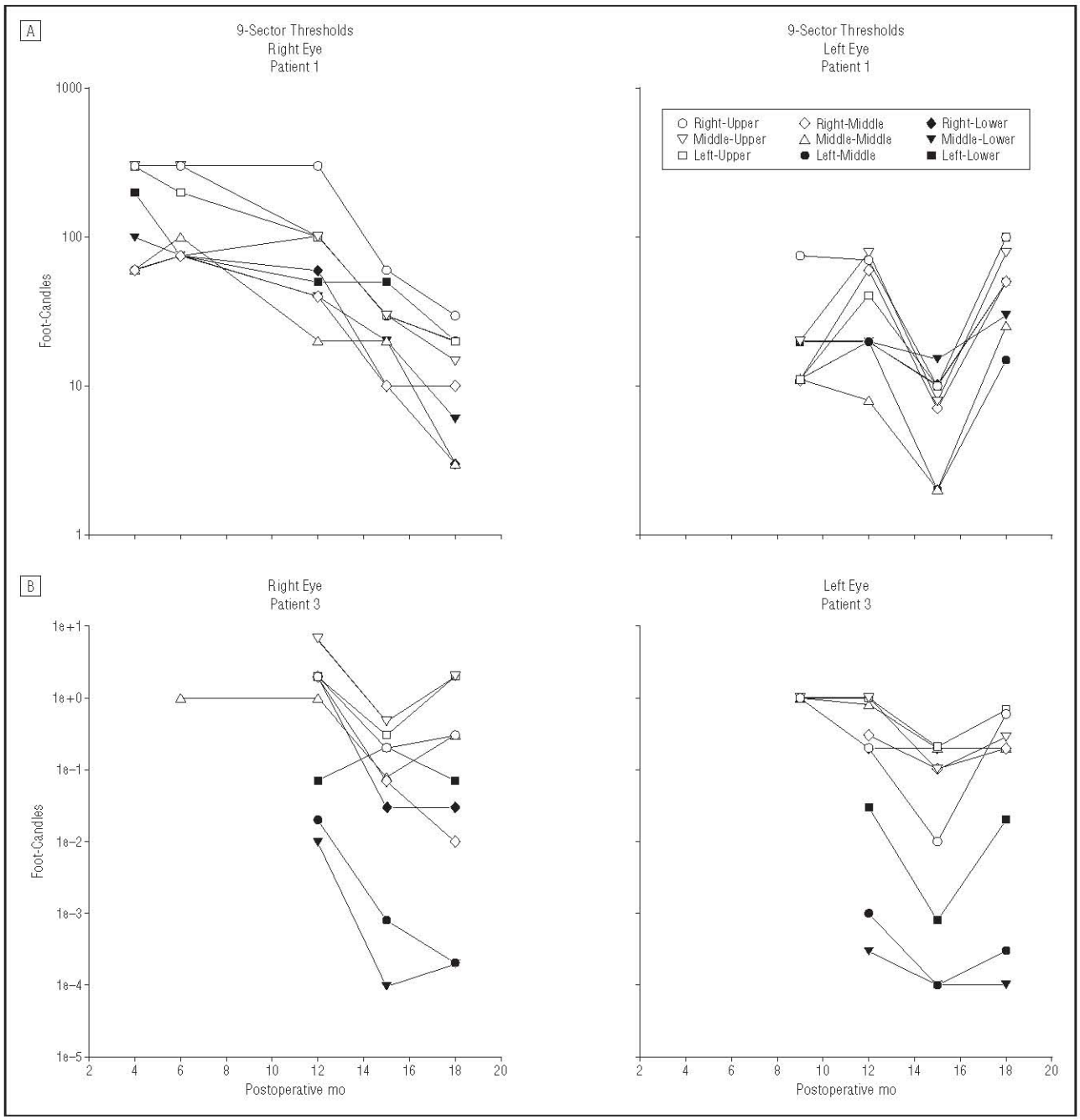

Figure 5. Results of 9-sector testing. A, The right eye of patient 1 showed improvement in light thresholds of 1000% to 1500% in all sectors. No persistent changes were noted in the control (left) eye. B, The right eye of patient 3 demonstrated an improvement in light thresholds of 5000% to 10 000% in the right-middle, right-lower, and middle-lower sectors. No persistent changes were noted in the control (left) eye. The threshold improvements in the indicated sectors of the right eye in patient 3 were consistent with this patient's subjective impressions.

implanted into the subretinal spaces of patients with RP. The microchips were well tolerated without discomfort, and patients showed no signs of rejection, infection, inflammation, neovascularization, vessel disruption, retinal detachment, migration, or erosion of the implant through the retina. These results are consistent with previously reported findings from animal studies showing similar biocompatibility of the implant materials (silicon, silicon oxide, titanium, and iridium oxide).[17-20] The continued electrical activity of the ASR microchip is also consistent with similar observations from animal studies.[26]

Regarding subjective responses, 4 of 6 patients (patients 2, 3, 4, and 5) indicated perception of light sensation to infrared light in the projected visual field of the implant during testing. Typically, the first test of a session resulted in perception of light but not subsequent tests. This response may be associated with an electrical capacitive block in the retina that results from the initial monophasic electrical stimulus, which prevents repeated acute responses (the repetitive light flashes observed by all patients preoperatively as a result of external contact lens electrical stimulation were caused by biphasic stimulation, which would prevent a capacitive block).

Substantial and persistent visual function improvements were noted in all patients who underwent implantation with the ASR. These improvements spanned subjective impressions, lifestyle and quality-of-life changes, task performance, ETDRS letter recognition, color recognition, Humphrey visual field testing,[27] and the custom 9-sector test of visual fields. The retinal areas and levels of improvement, however, were greater than those expected from a small ASR chip implanted in the superior to superior temporal retina and stimulating a small portion of the retina. Although phosphenes were perceived in the visual fields corresponding to the ASR in 4 of 6 patients, improvements in visual function also occurred in retinal visual fields distant from the implant, including the macular region. These improvements were first noted about 1 week to 2 months after surgery and continued until approximately 6 to 12 months postoperatively.

The mechanism of visual function improvement in the retinal areas distant from the implant is unlikely to be caused by direct ASR electrical stimulation from the pixels to the retinal cells. The improved perceptions of contrast, color, resolution, movement, and visual field size are too great and too complex to be explained by a direct electrical effect of the implant. A possible explanation of this improvement may be that it is due to an indirect, generalized neurotrophic effect on the retina from ASR electrical stimulation.

Consistent with this theory is the observation that visual function improvements did not appear immediately. Improvements began from 1 week to 2 months after ASR implantation and continued for approximately 1 year. Patients 3 and 5 complained of worsened vision during the first month after surgery before improvement was noted. Patient 2, who had no subjective LP before surgery, noted inconsistent LP during the first week after surgery and then a "quarter-size" light at several feet in the projected visual field of the implant. In the succeeding weeks, the spot of light increased to a vertical oval that covered the left and middle visual fields.

Data from other studies have suggested growth and neurotrophic effects from electrical stimulation. The application of electrical currents to a variety of organ systems may promote and maintain certain cellular functions. These functions include bone growth,[29,30] spinal cord growth,[31] and cochlear spiral ganglion cell preservation.[32,33] Recently, deep brain electrical stimulation of the subthalamic nucleus and globus pallidus interna in patients with Parkinson disease significantly relieved tremors and spasticity in these patients.[34] The mechanism of improvement has been hypothesized to involve improved neurotransmitter balance and the up-regulation of a variety of growth and neurotrophic factors.[35,36]

Neurotrophic factors have been widely reported to promote and maintain retinal cellular functions. Brain-derived neurotrophic factor, neurotrophin 4, neurotrophin 5, fibroblastic growth factor, and glial cell line–derived neurotrophic factor have been shown to enhance neurite outgrowth of retinal ganglion cells and to increase their survival in cell cultures.[37] Glial cell line–derived neurotrophic factor has been shown to preserve rod photoreceptors in an animal model of retinal degeneration,[38] and ciliary neurotrophic factor has slowed photoreceptor degeneration in mice with retinal degeneration, and the Q344ter rhodopsin mutation with photoreceptor degeneration.[39] Nerve growth factor injected into the intraocular space of the C3H mouse with retinal degeneration results in a temporary rescue of photoreceptor cells compared with controls.[40,41]

Mechanical injury stimuli, such as a penetrating wound of the sclera and retina, up-regulate messenger RNA expression of basic fibroblast growth factor and ciliary neurotrophic factor and are accompanied by a transient increase in fibroblast growth factor receptors. These factors are hypothesized to exert photoreceptor-protective and rescue effects after injury.[42] We hypothesize that chronic low-level electrical stimulation to a partially degenerated retina with RP induces a similar up-regulation of protective neurotrophic survival factors that improve the function of remaining but inadequately functioning photoreceptors.

Some limitations of this pilot study should be addressed. Our study involved only limited controls and validation of the newly developed 9-sector test. This consisted primarily of using 1 main examiner (A.Y.C.) to perform almost all of the 9-sector examinations, with assistants recording the results. A few evaluations were performed by other examiners but generally with the supervision and guidance of the main examiner. All examinations of the eye with the implant were accompanied by evaluations of the unoperated on control eye to help reveal potential intersession variability and placebo effects. Although multiple preoperative repetition of the 9-sector test was performed on some of the later-enrolled patients to establish a preoperative baseline, repetition was not universally performed with the earlier patients.

Caution is appropriate in interpreting patients' subjective comparisons of visual function between their two eyes preoperatively and postoperatively; these perceptions could be affected by their belief in whether a surgical intervention (ie, ASR implantation) would help them. Nevertheless, we felt that the comparison of this type of information with data obtained from other visual function tests would be useful.

Finally, 3 of the 6 patients who underwent implantation had cataracts of varying severities, which were subsequently removed during ASR surgery. Although removal of mild cataracts may improve visual acuity at higher spatial frequencies in normally sighted individuals, it is generally acknowledged that the removal of mild cataracts (20/30 view in the affected eye) would unlikely affect visual acuity in the range of patient 5 (20/200 to 20/800) or patient 4 (HM). In addition, removal of a 3+ posterior subcapsular cataract probably would not improve vision from subjective no-LP to LP with form recognition in a patient with retinal injury.

Questions for future research include the following: Can similar safety results and efficacy responses be obtained from a larger group of rigorously tested preoperative and postoperative patients? If so, can more optimal ASR stimulation parameters be used (eg, voltage, current, duration, charge, phase, and chronicity of stimulation)? Would the implantation of multiple devices be more effective than a single device? If ASR im-

plantation exerts a neurotrophic effect, would earlier implantation in specific types of retinal degenerative disease be more effective? Finally, would patients with other forms of outer retinal degeneration, such as age-related macular degeneration, also benefit?

In summary, ASR microchips containing approximately 5000 microelectrode-tipped microphotodiodes were implanted into 6 eyes of 6 patients in a pilot safety and feasibility study. After 6 to 18 months of follow-up, all ASRs functioned electrically, and no patient showed signs of implant rejection, infection, inflammation, erosion, neovascularization, retinal detachment, or migration. Visual function improvements occurred in all patients and included unexpected vision improvements in retinal areas distant from the implant. Further study is required to verify these findings, to assess the optimal settings for ASR stimulation, and to determine the groups of patients most likely to benefit from ASR implantation.

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Dr A. Chow has full access to all of 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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