Retinal Prostheses Development in Retinitis Pigmentosa Patients—Progress and Comparison

Alan Y. Chow, MD

Purpose: Since 2000, several groups have initiated chronic studies, implanting electronic retinal prostheses into the blind eyes of patients with retinitis pigmentosa to produce formed vision.

Design: A review and comparison of their techniques and results.

Methods: The 4 groups reviewed comprise 2 epiretinal and 2 subretinal groups. Visual function results reported in their publications during approximately the past 2 years are compared.

Results: Serious adverse effects occurred in both epiretinal groups but none in the 2 subretinal groups. Phosphenes with some similarity to the multielectrode stimulation pattern were induced by 1 group (EpiRet GmbH), and a somewhat higher phosphene pattern was created by another group (Second Sight). In 1 subretinal group (Retina Implant AG), an even higher phosphene pattern allowed recognition of letters and objects such as a cup or saucer. In the second subretinal group (Optobionics), besides perceived phosphenes, a neurotrophic rescue of visual function produced a marked improvement of visual acuity, color and contrast perception, visual field size, and improved darkness perception. In some subjects, recognition of facial features and household objects was restored.

Conclusions: Both epiretinal and subretinal prostheses created phosphene-type patterned vision in some subjects. The phosphene resolution of Retina Implant AG's subretinal device was substantially greater than both epiretinal devices. Of the 4 groups, only Optobionic's paracentrally placed subretinal Artificial Silicon Retina implant induced an unexpected neurotrophic rescue and return of lost visual function resulting in the greatest return of visual acuity, color and contrast perception, visual field enlargement, and darkness perception.

Key Words: retinitis pigmentosa, retinal prosthesis, epiretinal, subretinal

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Loss of vision from progressive degeneration of retinal cells is common and occurs in conditions such as age-related macular degeneration (AMD) and in retinal dystrophies collectively referred to as retinitis pigmentosa (RP).[1–3] Both groups of conditions are well known to be causes of significant and debilitating vision loss. Although intravitreal injections of anti–vascular endothelial growth factor agents such bevacizumab, ranibizumab, and aflibercept are now routinely used to treat vision loss from vessel leakage in wet AMD[4,5] and studies are now underway to investigate the possible benefits of gene therapy to treat Leber congenital amaurosis,[6] no generalized therapy is yet available that can treat the slow and relentless progression of vision loss in patients with generalized RP and dry AMD.

In the 1980s, one of the earliest vision restoration strategies for retinal dystrophies involved the transplantation of functional retinal tissue into damaged eyes.[7,8] Unfortunately, although anatomical success and preservation of transplanted tissue were achieved in some studies, none of the treatments achieved significant visual benefit in humans, and these efforts have now been largely abandoned. In the early 1990s, another strategy evolved, developed by several groups independently, to try to restore a level of vision by implanting retinal prostheses into the retina to electrically stimulate its cells.[9–19] Although the concept of a primitive prosthesis placed under the sclera to stimulate the retina had been described in a patent as early as the1950s,[20] nothing substantial developed, and the concept was lost to obscurity until reintroduced in the 1990s.

The groups recontemplating the prospect of retinal prostheses based their strategies on historically known findings. Retinal degeneration usually involves the progressive deterioration of photoreceptors function followed eventually by their death. The remaining retinal layers such as the bipolar cell layer, plexiform layers, and ganglion cell layer, however, can be partially spared, especially early in the course of the disease.[1–3] The investigators therefore reasoned that artificially stimulating the remaining retina electrically to create phosphenes, in a pattern resembling images, might restore some vision to affected patients.[9–19]

From earlier studies, it had been known that electrical stimulation applied to the eyeball surface can elicit repeatable visual sensations and patterns (phosphenes) in both normal subjects and RP patients that correlated to the location of stimulation.[21–26] These findings were corroborated by similar electrical stimulation experiments in the blind eyes of Royal College of Surgeons rats, which produce a downstream electrophysiological response recordable from their visual cortices.[27] In RP patients, phosphenes were perceived when electrical stimulation was initiated from inside the eye upon the retinal nerve fiber layer (RNFL) surface.[28] In vitro and in vivo animal studies also showed that evoked retinal and cortical potentials occur when the RNFL or the outer retina was stimulated.[10,11,29–31]

Based on these studies, 2 general approaches evolved to stimulate the retina depending on the location of the applied electrical stimuli,[9–19] either from the epiretinal nerve fiber layer surface accessed from the vitreous cavity (the epiretinal approach)[13–15,18,19,32–35] or from the subretinal space, stimulating photoreceptors or bipolar cells (the subretinal approach).[9–12,16,17,36–38] The animal studies and the preliminary short-term acute human studies from the 1980s and 1990s evolved into human studies with chronically implanted retinal prostheses. The first retinal prosthesis to enter clinical trials, a 5000-electrode microphotodiode chip, was implanted in a patient with RP by Chow and associates[12] in June 2000 (Artificial Silicon Retina [ASR], subretinal approach; Optobionics, Glen Ellyn, Ill), and the results of 6 study patients were reported in a 2004 publication. A long-term follow-up of greater than

From the Department of Ophthalmology, Rush University Medical Center, Chicago, IL.

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Dr Chow was an inventor in all the artificial silicon retina–related patents but owns none of them and receives no royalties from them. He is the owner of the "Optobionics" name and logo. The original Optobionics Corporation ceased operations in May 2007. Dr Chow was the founder and a former employee of Optobionics Corporation.

Reprints: Alan Y. Chow, MD, 191 Palamino Place, Wheaton, IL 60189. E-mail: alanykc@aol.com.

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7 years with additional patients was reported in 2010.[36] Subsequently, Humayun et al[13] implanted a 16-electrode epiretinal prosthesis in 2002 (Argus I, epiretinal approach; Second Sight Medical Products, Inc, Sylmar, Calif) and reported the study results in 2003, 2007,[14] and 2009.[32] In 2012, Humayun et al[33] published the results of their second-generation 60-electrode epiretinal prosthesis implantation study[34] (Argus II, epiretinal approach). Two additional groups have now published on chronically implanted retinal prosthetic devices. The group of Zrenner et al[37] (Active Subretinal Device based on the Optobionics ASR, subretinal approach; Retina Implant AG, Reutlingen, Germany) published 2 reports summarizing their implantation studies in 2011,[38] and Epi-Ret (Epi-Ret3, epiretinal approach; EpiRet GmbH, Gießen, Germany) also published study results in 2009[15] and 2011.[35]

MATERIALS AND METHODS

The status of human retinal prosthesis implant studies, over approximately the last 2 years as presented in peer-reviewed publications, is summarized in this review. Preoperative and postoperative vision status changes will be compared between the different devices and approaches as reported in those publications. Results from earlier publications and nonrefereed reports including earlier device failures and complications are not summarized other than if they were referred to again in the recent publications. Although many groups in countries around the world, other than the early groups mentioned previously, have now initiated preliminary animal and acute human stimulation studies and have presented in non–peer-reviewed formats such as meeting abstracts, this review is limited to covering studies of chronically implanted retinal devices (>1 day) in humans that have been reported in refereed journals. Study follow-up periods vary greatly and range from 4 weeks to 8 years. Because of this difference, the amount of information available for discussion regarding the various research groups will be different in this review. Also, as the enrollment vision criteria were different in the various studies, this should be taken into account in comparing the final postimplant vision achieved by the various devices. Related vision restoration investigations involving nonretinal electrical stimulation of visual cortex and optic nerve and early neurotransmitter-based stimulation studies and sensory substitution techniques such as pattern stimulation of the tongue and skin surfaces are not discussed. Please note that the author of this review was a primary investigator in the Optobionics studies. As of 2013, one of the prosthetic devices, the Argus II epiretinal implant, has received European Union CE Mark approval as well as American Food and Drug Administration (FDA) approval as a Humanitarian Device Exemption (HDE) product qualified for commercial sale.

RESULTS

Epiretinal Prostheses

EpiRet GmbH

A recent epiretinal group that has advanced to clinical trials in 6 patients is EpiRet GmbH based in Gießen, Germany, working with Philipps-University in Marburg, Germany, and the

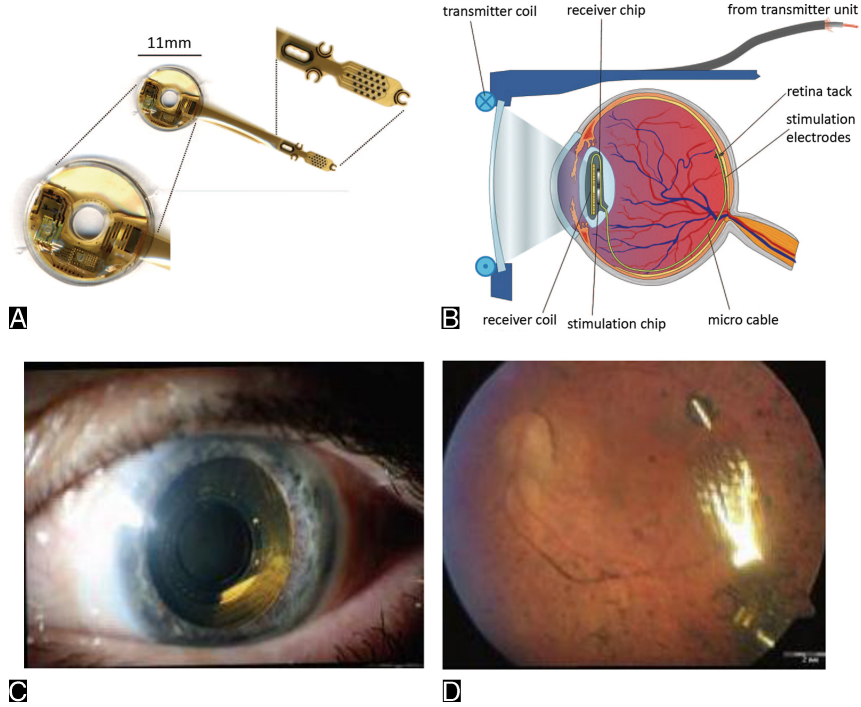

FIGURE 1. A, EpiRet GmbH—EPRET3 device with enlarged view of the receiver module attached to a polyimide base. Retinal tacks are placed through the C-shaped openings to secure the device to the retina. Length of the system: 40 mm.[15] B, EpiRet GmbH–EpiRet3 concept: a transmitter coil in the glasses sends data and energy pulses to the receiver unit located in the posterior chamber of the eye. The receiver unit powers 25 IrOx electrodes, located on a connected microcable, which stimulate the retina.[15] C, EpiRet GmbH—EpiRet3 receiver located in the posterior chamber of the eye.[15] D, EpiRet GmbH—EpiRet3 stimulating electrodes position on the retinal surface next to the macula.[15] Panels 1A and 1B have been reprinted, and panels 1C and 1D have been adapted by permission of The Association for Research in Vision and Ophthalmology from *Investigative Ophthalmology & Visual Science*, Roessler G, Laube T, Brockmann C, et al. Implantation and explantation of a wireless epiretinal retina implant device: observations during the EpiRet3 prospective clinical trial. *Invest Ophthalmol Vis Sci.* 2009;50:3003–3008.

TABLE 1. SAEs Comparison Between Implant Groups

SAEs, %	Second Sight 28 Patients of Epiretinal Argus II	EpiRet GmbH 6 Patients of Epiretinal EpiRet3	Retina Implant AG 11 Patients of Subretinal MPDA DS Array	Optobionics 6 Patients of Subretinal ASR Chip
Conjunctival dehiscence	3	0	0	0
Conjunctival erosion	2	0	0	0
Endophthalmitis—presumed	3	0	0	0
Hypotony	3	1	0	0
Reapplication of retinal tack	2	0	Not applicable	Not applicable
Tractional retinal detachment	2	0	0	0
Retinal rear	1	1	0	0
Inflammatory uveitis/ hypopyon	1	1	0	0

Fraunhofer Institute of Microelectronics circuits and Systems in Duisburg, Germany.[15,35] They developed a wireless epiretinal device called the EpiRet3 consisting of an extraocular portion and an intraocular portion (Fig. 1). The extraocular portion is a transmitter coil placed within a headset in front of the subject's eye, which produces power and signal pulses programmed from a computer. The pulses are received and processed by a receiver coil and stimulating electronics module located in the lens capsule or ciliary sulcus of the eye, which send the power and signal pulses via a metalized foil polyimide strip to 25 iridium oxide stimulation electrodes on an oval surface at the tip of the electrode strip. The foil is placed into the vitreous cavity inferiorly along the surface of the RNFL to rest adjacent to the macula. The electrode tip is secured with penetrating retinal tacks. The electrode array spans approximately 10 degrees on the nerve fiber layer surface. A major difference between the EpiRet3 and Second Sight's Argus II is that the receiving coil, stimulating electronics module, and the connected foil electrodes of the EpiRet3 are all implanted intraocularly compared with the more complicated separate extraocular and intraocular portions of the Argus II that require an open scleral track to connect the 2 components. The EpiRet3 implant remained in the eye for 28 days and was then extracted per the study protocol.

Serious adverse events (SAEs) were reported and were defined according to ISO 14155 as events that caused death, were life-threatening, caused permanent impairment of a body function or permanent damage to a body structure, required or prolonged a hospitalization, caused fetal injury or death, or required surgical intervention to preclude impairment or damage. Serious adverse events that occurred included hypotony with a flat anterior chamber in 1 patient that required sodium hyaluronate injection to reform the anterior chamber (Table 1). The same patient developed a retinal tear on device explantation that occurred during removal of the retinal tack and surrounding epiretinal membrane. In a second patient, inflammatory uveitis occurred that progressed into a sterile hypopyon that required anterior chamber tap and culturing (culture negative). This patient was treated with steroids and systemic antibiotics with clearing of the hypopyon in 5 days.

One-hour stimulation sessions were performed at 7, 14, and 27 days after surgery on each patient. Pulse currents were biphasic with the cathodic phase first and ranged from 3.2 to 100 μA. Pulse durations varied from 27 to 878 microseconds per full phase, and the current was delivered between selected pairs of electrodes. In the trials, all electrode pairs were activated randomly in succession. Subjects 1, 2, 5, and 6 reported visual percepts in all test sessions, whereas subjects 3 and 4 saw percepts in only 1 of 3 sessions (Table 2).

The visual sensations varied greatly between patients, with 3 subjects reporting seeing colors described as red, green, blue, and yellow. The percepts were generally bright phosphene patterns, but 2 subjects reported dark or black patterns. When 2 stimuli 900 μm apart were activated in a horizontal arrangement, subject 1 remarked seeing 2 stimulus patterns, one more nasally than the other. Subject 2 reported a percept in the corresponding upper visual field when 2 electrodes located at the lower edge of the electrode array were activated. When a lower left and an upper right electrode were stimulated, the same subject reported one percept as "higher" than the other. When an electrode pair at a separation distance of 3000 μm in a vertical arrangement was activated in subject 6, the patient reported seeing "2 points, 10 cm vertical distance, as if viewed at arm's length." The distance estimated between the induced percepts by this patient corresponded well with the retinal separation of the stimulating electrodes. Subjects 1, 2, and 3 correctly recognized the orientation of a linear arrangement of 2 to 4 activated electrodes including angles of 20 and 60 degrees and vertical. One patient, subject 3, perceived an oval electrode pattern of stimulation as a "line surrounded by a circle," "a circle and line," and "something oval like a rugby ball." The investigators reported that stimulation

TABLE 2. EpiRet GmbH–EpiRet3 Preoperative Vision and Postoperative Visual Percepts

EpiRet3 (Epiretinal) 25-Electrode Array EpiRet GmbH Patient—Study Duration	Preoperative Vision	Postoperative Visual Percepts With EpiRet3 Stimulation in 3 Sessions
#1, 4 wk	LP	+ Percepts in 3/3 sessions, some similarity to multielectrode pattern
#2, 4 wk	LP	+ Percepts in 3/3 sessions, some similarity to multielectrode pattern
#3, 4 wk	No LP	+ Percepts in 1/3 sessions, some similarity to multielectrode pattern
#4, 4 wk	LP	+ Percepts in 1/3 sessions, some correlation to electrode position
#5, 4 wk	Hand movements	+ Percepts in 3/3 sessions
#6, 4 wk	LP	+ Percepts in 3/3 sessions, some correlation to 2electrode position

success depended greatly on pulse duration rather than charge density. If the pulse duration was above a critical level for an individual, then current amplitude and thus charge density dropped to very low levels. The investigators recommended studying very long pulse durations of several hundred microseconds or even longer to decrease stimulation charge density thresholds.

Second Sight Medical Products

Although the first chronically implanted retinal prosthesis was the ASR subretinal device implanted by Chow and associates[12] in 2000 (Optobionics), Second Sight Medical Products (Second Sight) in Sylmar, Calif, was the first group to investigate a chronically implanted epiretinal device called the Argus I in a feasibility and safety study.[13,14,32] The Argus I was eventually implanted in 6 patients in a single-center study at the Doheny Eye Institute between 2002 and 2004 by Humayun et al[13] and consisted of a 16-platinum electrode device in a 4 × 4 array with electronics based on cochlear implant technology. The electrodes were either 520 μm (first 3 patients) or 260 μm (second 3 patients) in diameter and 0.8 mm apart and embedded in a thin silicone strip platform that was inserted through a scleral incision into the vitreous cavity. A single retinal tack pushed through a hole in the electrode tip, through the retina and into the sclera, was used to secure the electrode portion of the silicone strip to the nerve fiber layer surface. The electrodes were connected to 16 flexible conductors inside the strip that exited the sclera and orbit and ran in a channel drilled along the temporal bone of the skull to a stimulating electronics module embedded under the scalp by the ear. The internal module was powered by an external inductive wireless antenna link module that received power and signals from a computer that either generated the individual electrode signals or could process video signals from a glasses-mounted camera to power the 16 electrodes.

With this implant, the first 3 subjects were able to differentiate (although not recognize) common objects from each other such as a knife, plate, and cup and were able to detect the motion of a moving white bar (5 × 30 cm) against a black background. The vision of 1 patient who underwent implantation was tested with 4 orientations of square wave gratings and was reported to be better than chance at recognizing the grating orientation. The logarithm of the minimum angle of resolution acuity (logMAR) in that patient was determined to be ~ logMAR 2.5 (~20/6500). Interestingly, subjects did not perform consistently better in the testing when multiple electrodes were activated versus just a single electrode. Adverse events reported included conjunctival erosion over the external scleral portion of the implant and dislodgement of the retinal tack resulting in detachment of the implant electrode tip away from the retina, which required reinsertion of a retinal tack. Two subjects who underwent implantation in 2004 remain active in the study.

Between June 2007 and August 2009, Second Sight evaluated a second-generation Argus II retinal prosthesis (Figs. 2A, B) in a single-arm, prospective, multicenter international clinical trial at 10 clinical centers.[33,34] The results of this trial were published in April 2012[33] and in October 2012.[34]

Thirty subjects were enrolled in the study. The patients were at least 50 years old at most centers and 18 years or older at some sites. All were diagnosed with RP or a related outer retinal degeneration (1 subject was diagnosed with Leber congenital amaurosis and another with choroideremia). Vision in the enrolled subjects had to be worse than 2.9 logMAR (Snellen 20/15,900), which was generally light perception (LP) or worse. All were followed up for at least 6 months.

Compared with the Argus I, the Argus II consisted of a higher count 6 × 10, 60-electrode array (Fig. 3) that was connected via a

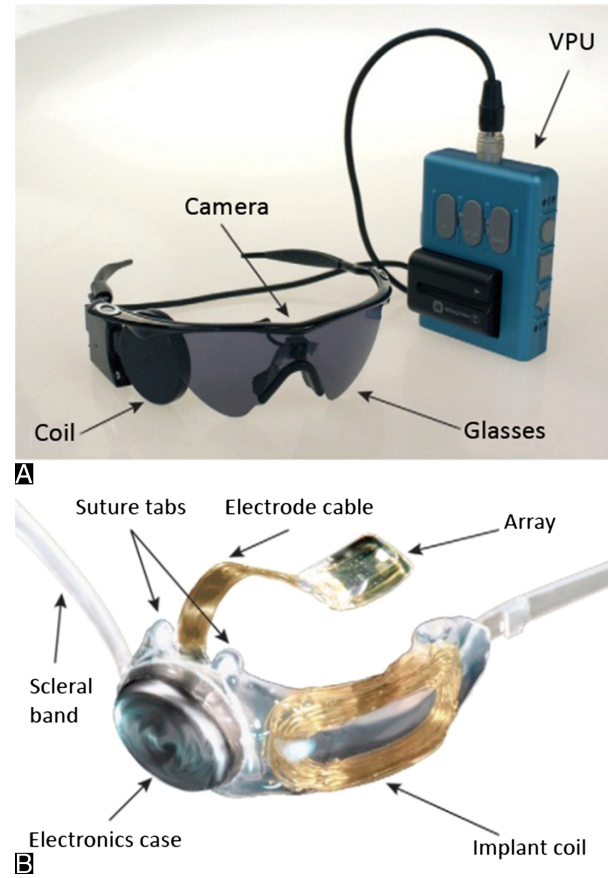

FIGURE 2. Second Sight—A, External components of the Argus II prosthesis system comprising the glasses-mounted video camera, radiofrequency (RF) transmitter coil, and battery-powered video processing unit (VPU). B, Implanted portion of Argus II prosthesis system comprising the 6 × 10 electrode array, electronics case, and implant receiver RF coil.[33] Reprinted by permission of Elsevier from *Ophthalmology*, Humayun MS, Dorn JD, da Cruz L, et al. Interim results from the international trial of Second Sight's Visual Prosthesis. *Ophthalmology*. 2012;119:779–788.

flexible metalized polymer ribbon that penetrated the sclera to attach to an electronics module secured with a band and sutured to the temporal surface of the eyeball (Fig. 2). A video camera mounted centrally on a pair of glasses sent imaged video signals to a processor module affixed to the temple piece of the glasses. The processor converted the video signals into power and signal pulses that were transmitted via a coil wirelessly to a coil embedded adjacent to the implanted scleral electronics module. The module converted the power and signal pulses into electrical stimuli that were routed to individual electrodes in the 6 × 10 array to create a pattern resembling the video images. The field of view of the camera was cropped to approximately match the 20-degree diagonal field of the stimulating electrode array.

As with the Argus I, the stimulating electrode-tipped ribbon strip was inserted into the vitreous cavity via a temporal pars plana sclerotomy and secured over or close to the macula with a single retinal tack. The investigators reported that as of July 30, 2010, 28 of the 30 subjects who underwent implantation were still being followed up. An implant was removed in 1 subject because of recurrent conjunctival erosion, and another

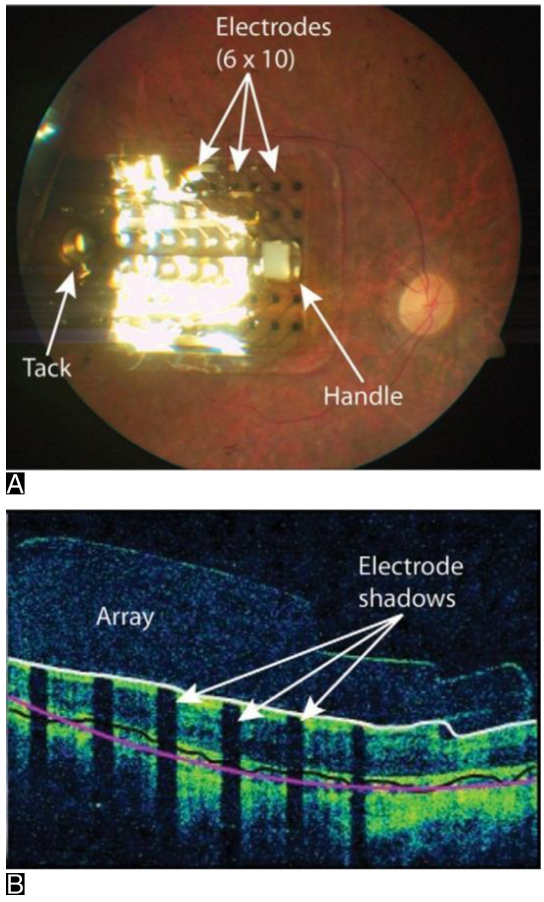

FIGURE 3. Second Sight—A, Fundus photograph of the Argus II 6 × 10 electrode array located over the macular region. The electrode array is secured to the retina with a penetrating retinal tack; the white square on the array is a section of tubing (the handle) used to position the array. B, Optical coherence tomography image of an implanted Argus II array. Shadows below the array (white arrows) are caused by blockage of the OCT light source by the metal electrodes.[33] Reprinted by permission of Elsevier from *Ophthalmology*, Humayun MS, Dorn JD, da Cruz L, et al. Interim results from the international trial of Second Sight's Visual Prosthesis. *Ophthalmology*. 2012;119:779–788.

patient became unavailable because of late institutional review board approval issues.

Clinical Safety and Device Reliability

Both SAEs and non-SAEs were reported in a number of patients who underwent implantation. There were 17 SAEs that were determined to be surgery or device related (Table 1). Most occurred within the first 6 months after implantation and were mostly in the first group of 15 patients who underwent implantation (13 SAEs in 7 patients).

The SAEs included conjunctival erosion and dehiscence over the extraocular portion of the implant sutured to the sclera, which together were the most common SAEs (17 SAEs). Culture-negative but presumed endophthalmitis occurred in 3 subjects but was successfully treated with intravitreal and systemic antibiotics. None of the implants in the presumptive endophthalmitis cases required removal. Three subjects developed hypotony, defined as a pressure of 5 mm Hg or less for 2 weeks or if associated with appositional choroidals or flat anterior chamber. One subject required implant removal, another the injection of silicone oil tamponade (which brought the intraocular pressure to 6–7 mm Hg), and in another the repair of an associated rhegmatogenous detachment. Two subjects developed retinal detachment (one with hypotony as described above) requiring surgical intervention and treatment. Two patients required additional surgery to retack the intraocular portion of the implant, which had become dislodged.

Non-SAEs included extensive conjunctival edema, inflammatory conjunctivitis, intraocular inflammation, suture irritation, ocular pain described mostly as foreign body sensation, corneal filaments, epiretinal membrane, elevated intraocular pressure, epiphora, mild vitreous hemorrhage, corneal abrasion, peripheral corneal vascularization, cystoid macular edema, decreased LP, dry eye, iris vessel engorgement, and scleritis. Transient headache, nausea, increased nystagmus, and vertigo were also reported.

Of the 60 electrodes per implant, approximately 94% of the electrodes remained active as of March 2010.

Visual Perceptions

In initial tests, all subjects were able to perceive some light with electrode stimulation. The perception of shape, however, was achievable by only a small number of subjects. In a white square over a black background localization test (Table 3A), 27 (96%) of 28 subjects were able to localize the square better with the Argus II system turned on than turned off.

In a preliminary motion detection test utilizing a white bar moving across a dark background, 16 (57%) of 28 subjects performed better with the system on than off.

In subsequent motion detection testing, utilizing a computer-generated, 1.4-inch-wide, high-contrast white bar moving across a dark 19-inch monitor (Table 3B), 15 subjects (54%) performed better with the prosthesis system turned on than with their residual vision. No difference was found in 11 subjects (39%), and 2 subjects (7%) performed better with their residual vision than with the Argus II system turned on.

Before surgery, the enrolled subjects all had been tested and showed a grating visual acuity of worse than 2.9 logMAR (Snellen 20/15,900), the lowest level tested. After surgery, none of the subjects scored reliably with the system turned off. With the system on, 7 (25%) of 28 subjects scored reliably between 2.9 and 1.8 logMAR (Snellen 20/1260) on a grating acuity test, whereas 21 (75%) of 28 subjects still showed vision worse than 2.9 logMAR (unable to score reliably) (Table 3C).

In orientation and mobility tasks, subjects were generally able to locate a doorway and follow a white stripe on the ground easier with the system turned on than off (Table 3D). The success rate for the doorway location task with the system off varied from 8% to 44% compared with a success rate of 52% to 60% with the system on. Similarly, subjects were able to follow a line on the floor more successfully with the system turned on (54%–82%) than off (15%–26%).

The conclusions of the authors were that the Argus II implant was generally able to restore some degree of useful artificial vision to a percentage of end-stage RP patients and that although significant SAEs were reported, the safety profile was not substantially worse than other forms of implants such as glaucoma filter devices.

Subretinal Prostheses

Retinal Implant AG

Of the subretinal prostheses being investigated, 2 devices have undergone clinical trials and have published results. The

TABLE 3. Second Sight–Argus II Comparison of System ''Turned-On Versus Turned-Off'' Patient Responses: Location of a White Square on a Black Background, Detection of a Moving Bar Across a Dark Screen, and Detection of a Doorway or White Strip on the Ground

A	
Argus II (Epiretinal) 60-electrode array	Significantly improved location of a white square on a black background with the Argus II turned on compared with off
Second Sight 36-mo study preoperative vision <2.9 logMAR	
Argus II—on	+ (96%) 27 of 28 subjects improved
Argus II—on	− (4%) 1 of 28 subjects not improved
B	
Argus II (Epiretinal) 60-electrode array	Significantly improved direction detection of 1.4-in moving white bar across a 19-in dark screen at 12-in distance with Argus II turned on compared with off
Second Sight 17- to 38-mo study preoperative vision <2.9 logMAR	
Argus II—on	+ (54%) 15 of 28 subjects improved
Argus II—on	− (39%) 11 of 28 subjects no difference
Argus II—off	− (7%) 2 of 28 subjects better with residual vision
C	
Argus II (Epiretinal) 60-electrode array	Able to score with a grating acuity of between 2.9 and 1.8 logMAR with Argus II turned on compared with worse than 2.9 logMAR with the system turned off
Second Sight 17- to 38-mo study preoperative vision <2.9 logMAR	
Argus II—on	+ (25%) 7 of 28 subjects able to score between 2.9 and 1.8 logMAR
Argus II—on	− (75%) 21 of 28 subjects not improved (<2.9 logMAR)
D	
Argus II (Epiretinal) 60-electrode array	Successful detection of doorway or successful following of a white strip on the ground with Argus II turned on compared with off
Second Sight From 3–24 mo postoperative, preoperative vision <2.9 logMAR	
Doorway detection—Argus II—on	52%–60% of subjects
Doorway detection—Argus II—off	8%–44% of subjects
White strip on ground detection—Argus II—on	54%–82% of subjects
White strip on ground detection—Argus II—off	15%–26% of subjects

first device is a collaborative effort from Retinal Implant AG working with the Universities of Tübingen and Regensburg, the NMI Natural and Medical Sciences Institute, and Klinikum Friedrichstadt, all in Germany, and Semmelweis University in Budapest, Hungary. This device evolved from a subretinal device that was patterned after the ASR developed by Chow following early collaboration discussions.

Retinal Implant AG presently investigates an auxiliary powered subretinal device, which they call an MPDA DS array, a designation for a microphotodiode array–direct stimulation array (Figs. 4, 5).[37,38] The implant consists of an MPDA placed on a polyimide foil, on which is also fabricated a rectangular DS array of 4 × 4 hardwired titanium nitride compound electrodes, each of which can be activated independently. Each compound electrode is 120 × 120 μm and is composed of a 2 × 2 array of smaller electrodes, 50 × 50 μm each. The 16 compound electrodes of the DS array are spaced 280 μm apart or ~60 minutes of arc of visual angle and represent a minimum angle of resolution of logMAR 1.78 (Snellen 20/1200).

The MPDA portion of the implant (Figs. 4, 5) consists of a 38 × 40 pixel array of electric current–generating elements (1500 total), each with its own light-sensing microphotodiode, amplifier, and stimulation electrode. Each pixel element is 72 × 72-μm square with a 15 × 30-μm microphotodiode and a 50 × 50-μm titanium nitride electrode. Images focused by the eye upon the subretinal chip are captured in a pixelated pattern by the microphotodiodes several times per second and are converted into monophasic anodic voltage pulses at each electrode, which then stimulate contacting bipolar cells or remnant photoreceptors. The reference return electrode is located further back on the polyimide foil strip and is outside the eye. A silicon-coated cable that runs underneath the temporalis muscle connects the foil portion of the MPDA DS array to a connector plug, which exits the skin behind and beneath the ear. An external power supply and transmitter/receiver control unit worn by the patient are connected to the connector plug and power both the DS array and the MPDA array.

The amount of simulation current produced by each electrode is dependent on the brightness level sensed by its associated microphotodiode. The MPDA spans a visual angle in the subretinal space of approximately 11 × 11 degrees, with the angle between electrodes being 15 minutes of arc.

Eleven patients underwent implantation with the MPDA DS array. No SAEs were reported (Table 1). In 1 patient, a small circumscribed area of subretinal bleeding was observed, which completely reabsorbed within 10 days. The same patient also

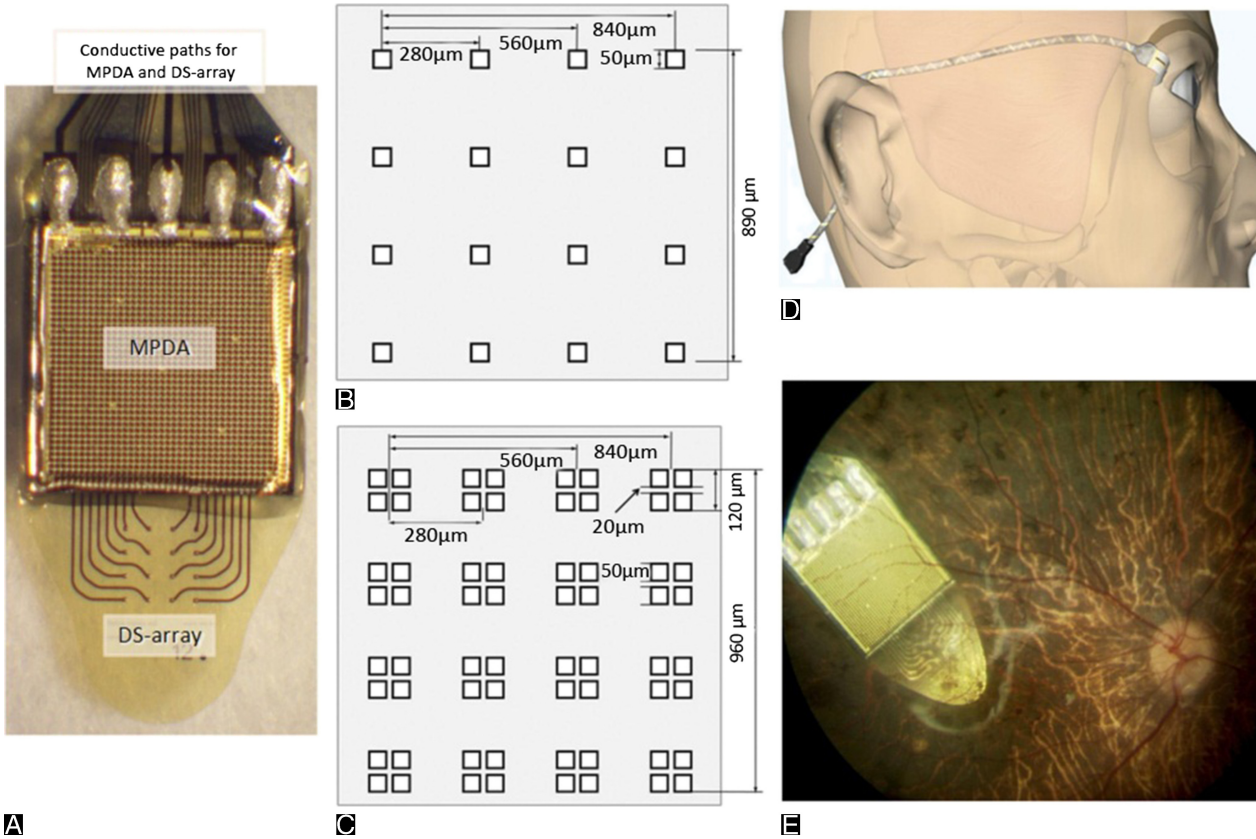

FIGURE 4. Retina Implant AG—MPDA with attached DS electrode array. A, MPDA fabricated on a polyimide strip containing gold conductors for the DS array and the MPDA. The 16 TiN electrodes of the DS array are located at the bottom portion of the implant. B, Configuration pattern of the first-generation DS array. The square electrodes are 50 × 50 μm with a grid separation of 280 μm. C, Compound electrode pattern of the second-generation DS array. Each compound electrode is composed of 4 smaller TiN electrodes grouped together to form the larger electrode. The smaller electrodes are separated by 20 μm, creating a compound electrode pattern of 120 × 120 μm. D, The external device interface is a percutaneous plug exiting the skin behind the lower ear. Under the skin, the plug is connected to a helical wire that courses to the orbital rim where it connects with the polyimide foil bending around the orbital rim. The reference return electrode is located on the polyimide foil at the orbital rim. E, Fundus photograph showing the MPDA DS array implanted subretinally in subject 10. Passing above the device are retinal vessels.[38] Reprinted by permission of The Association for Research in Vision and Ophthalmology from Wilke R, Gabel VP, Sachs H, et al. Spatial resolution and perception of patterns mediated by a subretinal 16-electrode array in patients blinded by hereditary retinal dystrophies. *Invest Ophthalmol Vis Sci.* 2011;52:5995–6003.

experienced a mild skin infection of the retroaurical cable exit after explantation of the device, which resolved after several days. Eight of 11 subjects had visual sensations on activation of the DS array electrodes (3 did not report any visual sensations). In 1 of the 3 subjects without visual sensation responses, technical hardware checks suggested failure of the implanted device. Six of the 11 participants had reliable perception of phosphenes when a single electrode of the 16-electrode DS array was activated (2 patients required multiple electrode activations to elicit phosphenes) (Table 4). In these 6 patients, the number of electrodes where thresholds could be obtained was determined. This number varied from 5/16 to 16/16. Four of the 6 subjects reported phosphenes as a single, round, yellowish spot, whereas 2 of the subjects described their phosphenes with an arc-like appearance. Five of the 6 subjects were able to discern different patterns such as lines or single letters when the pattern was created by a computer on the 16-electrode array. The perception of patterns created by the DS array suggested a best resolution of logMAR 1.78 (Snellen 20/1200), possibly limited by the 280-μm spacing of the ~60 minutes of arc of visual angle spacing of the array.

Visual results in 3 patients from MPDA array stimulation were reported (Table 4). Preoperative vision of the implanted eyes was LP in all 3 patients. The light-sensitive MPDA array was operated at a sampling frequency of 1 to 20 Hz with a 1- to 4-millisecond pulse duration.

Pupillary constriction reflexes were assessed using infrared light pupillography, which showed increased pupillary reactions to light with the MPDA chip turned on than off. It was noted that substantial pupillary light reaction still occurred with the chip turned off.

One of 3 patients, patient 2, was able to identify the direction of a moving dot pattern on a computer screen. The same patient was able to recognize the orientation of a black-and-white grating pattern (0.6-cm bright lines separated by 1.8-cm-wide black lines). Further testing was performed with this subject using Landolt C rings, and this patient was able to identify the opening of the ring corresponding to a best acuity of 1.69 logMAR (Snellen 20/1000). On other days of testing, his acuity varied from 1.75 to 1.94 logMAR.

Patient 2 was also able to reliably differentiate the letters L, I, T, and Z on a computer screen and recognize common lightly

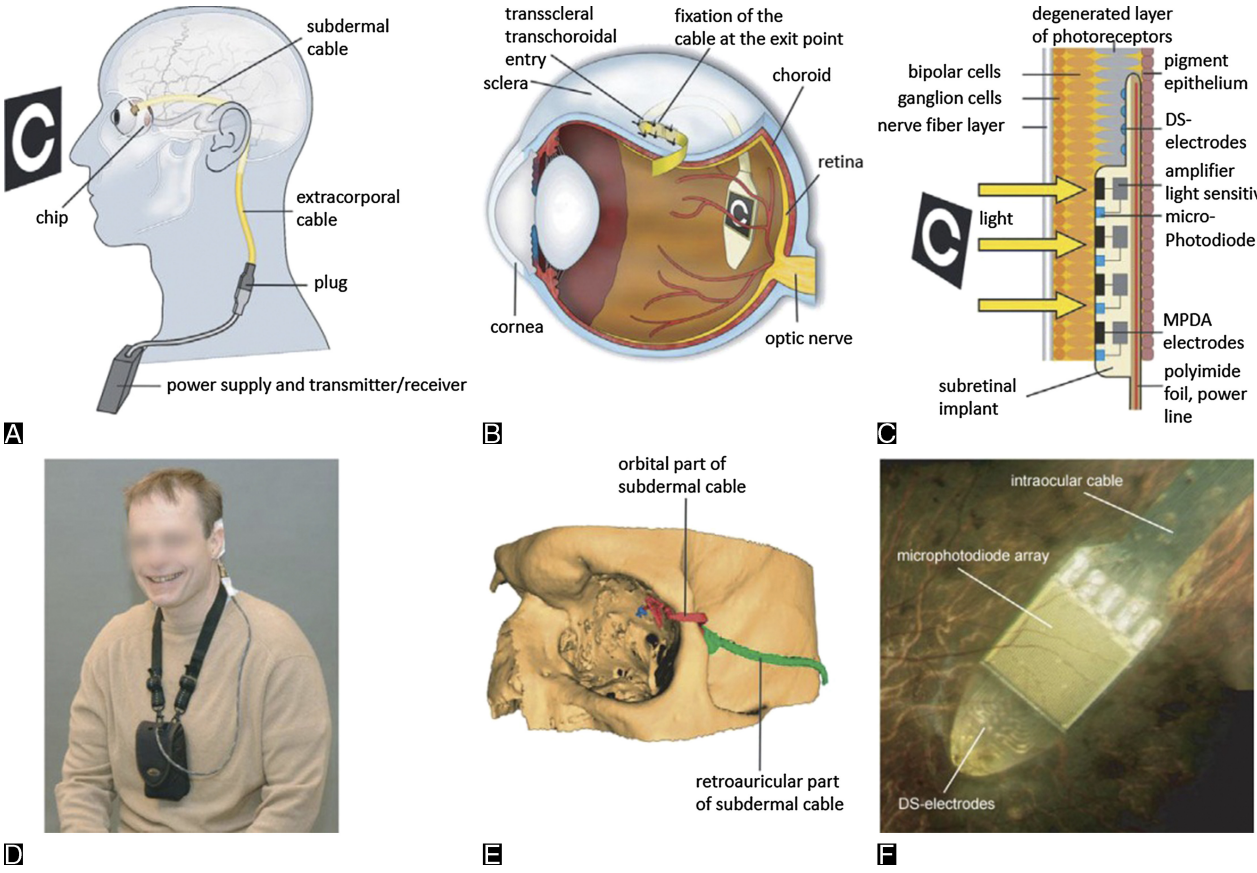

FIGURE 5. Retina Implant AG—Implant components in the body. A, The cable from the MPDA DS array in the eye courses under the temporalis muscle to the exit behind the lower ear and connects with a wirelessly controlled power unit. B, Position of the implant in the subretinal space. C, Position of MPDA photodiodes, amplifiers, and electrodes relative to retinal cells and pigment epithelium. D, Patient wearing the wirelessly controlled power unit. E, Course of the polyimide foil (red) around the orbital rim and the connecting cable (green) under the temporalis muscle in a 3-dimensional reconstruction of CT scans. F, Fundus photograph of the subretinal implant at the posterior pole of the subject's eye.[37] Adapted from Zrenner E, Bartz-Schmidt KU, Benav H, et al. Subretinal electronic chips allow blind patients to read letters and combine them to words. *Proc R Soc.* 2011;278:1489–1497.

shaded objects lying on a dark table cloth such as a cup, saucer, knife, spoon, square, triangle, and circle (Table 4). Patient 2 was also able to distinguish between 16 different letters (5–8 cm high, Tahoma font) cut out of white paper and placed on a black table cloth. He read correctly the letters composing words (LOVE, MOUSE, SUOMI) and noted spelling mistakes in his name, MIIKKA, saying that 1 "I" and 1 "K" were missing from the spelling arrangement that the investigators had presented to him. This same subject was also tested with a computer-generated clock face (6 × 1.5-cm white bar for hours and 12 × 1.5-cm white bar for minutes on a dark circular clock face) and was able to correctly recognize 11 of 12 settings at full-quarter hours. He was also able to distinguish 7 of 9 contrast differences of 15% among 9 neighboring cards (10 × 10 cm in a 2AFC mode, $P = 0.07$). Patients 1 and 3 recognized fewer objects and to a much lesser extent.

Optobionics

The second subretinal group involved in clinical trials, Optobionics, has implanted their device, the ASR, in 42 patients and has follow-ups of up to 8 years. Optobionics was founded by the author who proposed the concept of subretinal prostheses in patents beginning in 1991.[9] This was followed by the report in 1997 of the successful short-term subretinal electrical stimulation of the retina in an animal model that produced cortical responses.[10] After approximately 8 years of animal investigations, the first human clinical trial of a retinal prosthesis began in 2000 as an FDA-approved feasibility and safety pilot study.[12]

In the pilot study, 6 RP patients with severe bilateral vision loss were implanted with the ASR chip in a paracentral location outside the macula, all in the right eye (Fig. 6). The ASR device was a custom-designed silicon chip 2 mm in diameter and 25 μm thick (Figs. 5A–D). On its light-facing surface was fabricated ~5000 individually isolated P-N junction microphotodiodes in an N-i-P configuration. This meant that the surface electrode of each microphotodiode pixel that was in contact with the overlying residual photoreceptor and bipolar cells was the negative cathode, whereas the common ground-return electrode (for all the microphotodiodes) on the backside of the ASR was the anode. Each microphotodiode pixel was 20 × 20-μm square with a 9 × 9-μm iridium oxide electrode and was separated from its adjacent pixels by a 5-μm-wide electrically insulating channel stop.

The concept was that when placed into the subretinal space, incident light focused through the retina would stimulate the ASR microphotodiodes to produce an electrical charge concentrated on their electrodes. This electrical charge would be

TABLE 4. Retina Implant AG—16-Electrode DS Array and MPDA Patient Responses: Phosphene Perception, Sequential Stimulation-Induced Approximate Visual Acuity, Black/White Strip Orientation—Landolt C Ring Acuity—Letter Differentiation, Recognition of Common Objects

DS Array (Subretinal) 16-Electrode Array; MPDA 1500 Elements. Retinal Implant AG, Patient–Study Duration; Preoperative Vision	DS Array Individual Electrode Stimulation, Phosphene Perception; Number of Individual Electrodes Responding	DS Array Pattern Stimulation; Perception Obtained With Sequential Stimulation of 15 Electrodes; Approximate Visual Acuity	MPDA, Black and White Strip Orientation; Landolt C Ring Acuity; Letters L, I, T, Z Differentiation	MPDA, Some Recognition of Common Objects on a Table–Cup, Saucer, Square, Triangle, Circle, Spoon, Knife
#S1, 4 wk LP	+ 14/16	+ ~20/1200	—	
#S2, 4 wk LP	+ multielectrodes required	—	—	
#S4, 4 wk LP	—	—	—	
#S5, 4 wk LP	—	—	—	
#S6, 4 wk LP	+ multielectrodes required	+ ~20/1200	—	
#S7, 4 wk LP	+ 10/16	+ ~20/1200	—	
#S8, 4 wk LP	+ 5/ 16	+ ~20/1200	—	
#S9, 4 mo LP	—	—	—	
#S10, 4 mo LP	+ 16/16	+ ~20/1200	—	Patient #1 ++
#S11, 4 mo LP	+ 15/16	+ ~20/1200	+ Black/white strip orientation 4AFC	Patient #3 +
#S12, 4 mo LP	+ 15/16	+ ~20/1200	+ Black-and-white strip orientation 4AFC + Landolt C ~20/1000 + L, I, T, Z differentiated	Patient #2 ++++

hyperpolarizing in light and a depolarizing in darkness, which would stimulate the overlying remnant photoreceptor and/or bipolar cells to produce the corresponding visual sensation of light and darkness. Because the remaining outer plexiform, amacrine cell, inner plexiform, ganglion cell, and nerve fiber layers are relatively spared in RP, especially early in the disease course, the resulting analog retinal signal might be processed by the remaining retinal cells into a retinotopically correct pattern of digital signals representing the incident image. In the development of the ASR chip, it was important to recognize that vision is a combination of seeing both light and darkness caused by the hyperpolarization and depolarization, respectively, of the photoreceptors. Because of this need, the iridium oxide electrode of the ASR chip was constructed to be able to hyperpolarize in light and depolarize in darkness, thus producing the necessary polarity for the electrical stimulus.

In a largely conventional operation, the ASR chip was implanted through an enlarged pars plana sclerotomy. After a complete vitrectomy, a subretinal bleb was created in the retina superior and temporal to the macula with a 39-gauge subretinal cannula and balanced salt solution. The bleb was then opened with vitreoretinal scissors, and the ASR chip was brought into the subretinal space with a custom inserter and placed in a paracentral location just outside the macula area. A fluid-air exchange flattened the bleb, and there was no need for a retinal tack or other means to stabilize the implant or seal the retina. The sclerotomy was closed with absorbable sutures, and no protruding wires or cables exited from the eye. The implantation procedure typically took approximately 45 minutes.

In June 2000 and July 2001, 6 RP patients with 20/800 or worse vision OU underwent implantation with the ASR chip in the right eye just outside the macula. The results were reported in 2004 after a follow-up period of 18 months for patients 1, 2, and 3 and 6 months for patients 4, 5, and 6 (Fig. 7).[12] In the follow-up period, no SAEs occurred (Table 1). Specifically, there were no occurrences of infection, inflammation, rejection, discomfort, retinal detachment, erosion of the implant through the retina or any ocular structures, reoperation, systemic adverse effects, or vision loss compared with before surgery. All patients experienced unexpected vision improvement in areas both close to the implant and away from the implant. These vision changes consisted of subjective and objective improvement of complex visual function such as visual acuity, color and contrast perception, and improved darkness of the visual field background at night. Visual field enlargement was also noted in 3 patients. The greatest improvement occurred in patients with the least severe and least advanced RP.

In 2 of the 6 patients, preoperative vision was good enough to allow ETDRS letters to be read at half meter. After ASR implantation, improved letter reading performance in the implanted eye was noted in these 2 patients. Patient 5, who read 16 to 25 letters preoperatively in the preimplanted eye, improved to 35 to 41 letters 6 months after surgery, whereas the unimplanted eye remained unchanged at 21 to 28 letters. Patient 6 improved from 0 letters preoperatively to 25 to 29 letters at 6 months in the implant eye, whereas the unimplanted eye was 0 to 3 letters preoperatively and 0 letters at 6 months. Visual field enlargement postoperatively was demonstrated in 3 of the 6 patients (Fig. 8).

Although direct infrared light stimulation of the implant was able to elicit phosphene responses in 4 of the 6 patients, the complex nature of the vision improvement, which took from 1 week to 2 months to develop, suggested that a generalized neurotrophic effect may have resulted from ASR stimulation.

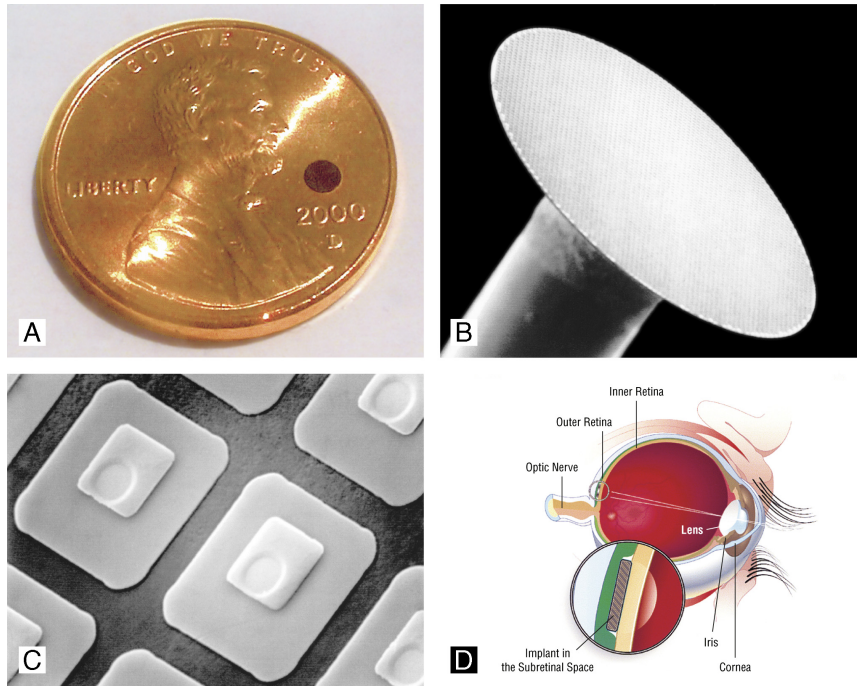

FIGURE 6. Optobionics—(A) Size of the ASR chip compared with a penny. B, Low-power scanning electron microscope photograph of the ASR chip (26×). C, Individual ASR pixels on the chip's surface (1150×). D, ASR chip location in the subretinal space.[12] Reprinted by permission of the American Medical Association from *Archives of Ophthalmology*, Chow AY, Chow VY, Packo KH, et al. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. *Arch Ophthalmol.* 2004;122:460–469.

This was supported by several subsequent animal studies where RCS rats with progressive retinal degeneration also experienced anatomical and functional retinal rescue after ASR chip implantation. A study of growth and neurotrophic factor expression, in RCS rats implanted with the ASR, showed marked up-regulation and expression of Fgf2 compared with controls.

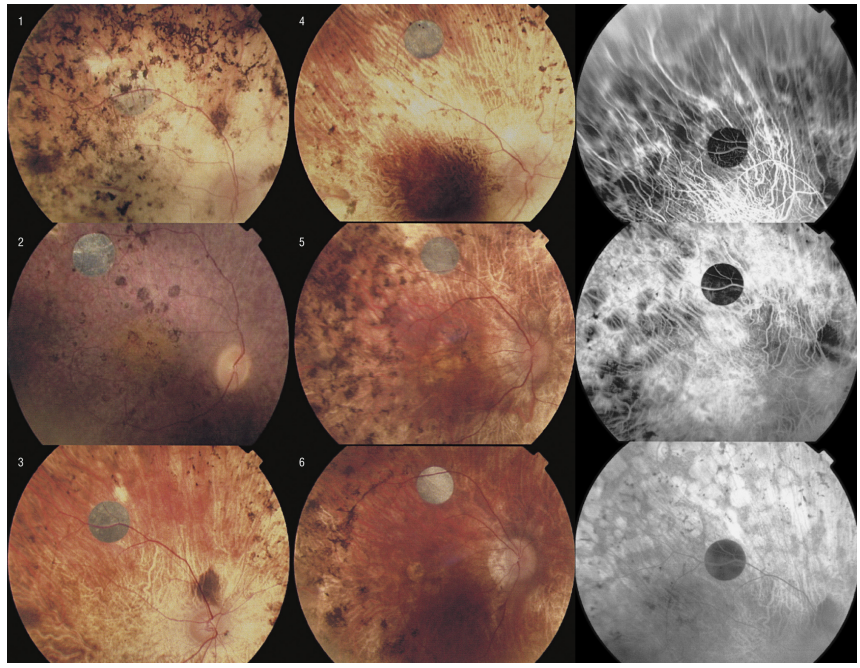

FIGURE 7. Optobionics—Fundus photographs showing ASR chips implanted subretinally in patients 1 through 6 with fluorescein angiograms of patient 3.[12] Reprinted by permission of the American Medical Association from *Archives of Ophthalmology*, Chow AY, Chow VY, Packo KH, et al. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. *Arch Ophthalmol.* 2004;122:460–469.

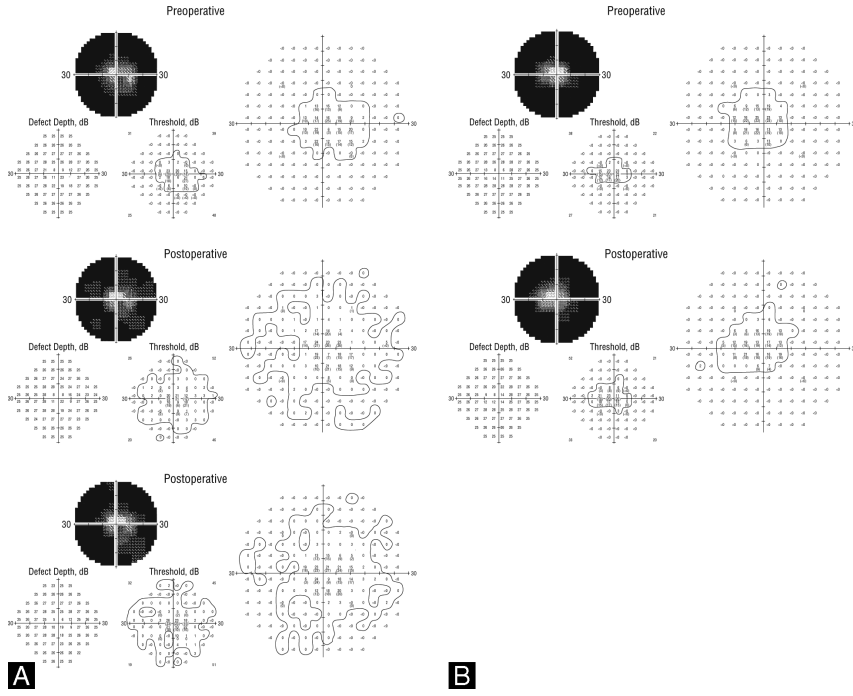

FIGURE 8. Optobionics—Automated visual field testing of patient 5 showing enlargement of the central visual field in the implanted OD (A) and no change in the unimplanted OS (B) within 6 months postoperatively.[12] Reprinted by permission of the American Medical Association from *Archives of Ophthalmology*, Chow AY, Chow VY, Packo KH, et al. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. *Arch Ophthalmol.* 2004;122:460–469.

No significant up-regulation or expression occurred for other growth/neurotrophic factors such as Cntf, Fgf1, Igf, and Gdnf.

In view of the results, it was clear that the most significant effect of the ASR chip was not its action as a retinal prosthesis (producing phosphenes) but rather its neurotrophic influence on the retina, including the macula—to restore a level of vision of the type that was lost. Therefore, although ASR prosthetic chips with auxiliary power had been conceived and designed by the author to produce brighter phosphenes if needed, the emphasis of Optobionics changed from developing a vision prosthesis to elicit phosphenes, to that of refining a therapeutic device capable of rescuing retinal function and restoring vision of the type that was lost in retinal dystrophies. It was also decided that the ASR chip would not be placed under the macula, as would be considered for a prosthesis but rather in a paramacular location. A paramacula location for ASR implantation would avoid insertional injury to the macula and allow for neurotrophic rescue of its function.

Subsequently, the phase I pilot FDA feasibility and safety study expanded to a phase II multicenter trial that performed implantation on 42 patients, with the longest implantation now being approximately 12 years. Interim results showed persistent neurotrophic restoration of visual function. An American Ophthalmological Society Transactions thesis detailing the long-term vision improvements in 6 patients, who had vision in the range testable by ETDRS charts and a custom grating acuity test, was published in 2010.[36] This is the most current refereed publication on patients who underwent ASR implantation and will be summarized.

In the American Ophthalmological Society study, 4 additional patients who underwent ASR implantation with vision recordable by ETDRS letters or grating acuity testing were added to the 2 reported in the pilot study and followed up for 4.5 to 8 years. All 6 patients tolerated the ASR well with no SAEs (Table 1). Visual acuity was assessed with ETDRS charts and a newly developed 4-Alternative-Forced-Choice (4AFC) Chow Grating Acuity Test (CGAT). The CGAT was developed to assess visual acuity that was lower than the lower limit recordable by ETDRS charts at half meter (20/1600).

The results showed that improvement and/or slowing of vision loss occurred in all 6 patients in the implanted eye compared with before surgery (Figs. 9A–F) (Table 5). ETDRS chart testing showed fewer to the same number of letters recognized preoperatively by the preimplanted right eyes compared with the unoperated control left eyes. Postoperatively, 4 of 6 patients had higher mean ETDRS letters recognized (sometimes substantially higher) in the implanted eyes compared with the unoperated eyes. In the remaining 2 of 6 patients, the number of ETDRS letters recognized in both eyes was too close to zero for this test to be helpful in differentiating visual acuity between the eyes.

At 2.5 to 3.5 years postoperatively, CGAT was added to the ETDRS charts, which extended the lower-acuity range that could be tested by logMAR 0.6. The CGAT showed that the mean CGAT acuity for all 6 patients who underwent ASR implantations at their latest test session was higher in the implanted eye than in the unoperated control eye (Figs. 9A–F) (Table 5). All patients noted substantially improved subjective vision in their implanted eye compared with the unoperated eye.

Patient 5, preoperatively, had acuities of ~20/800 in both eyes. At 6 months after surgery, the implanted OD tested at ~20/200, whereas the control OS was ~20/320. At 3.5 years, the vision OD was 20/223, and OS was 20/360. At 8 years, the vision OD was 20/165, and OS was 20/225 (Fig. 9A). This patient was again able to recognize people again by their faces and his own face in the mirror and noted general improvement of color and

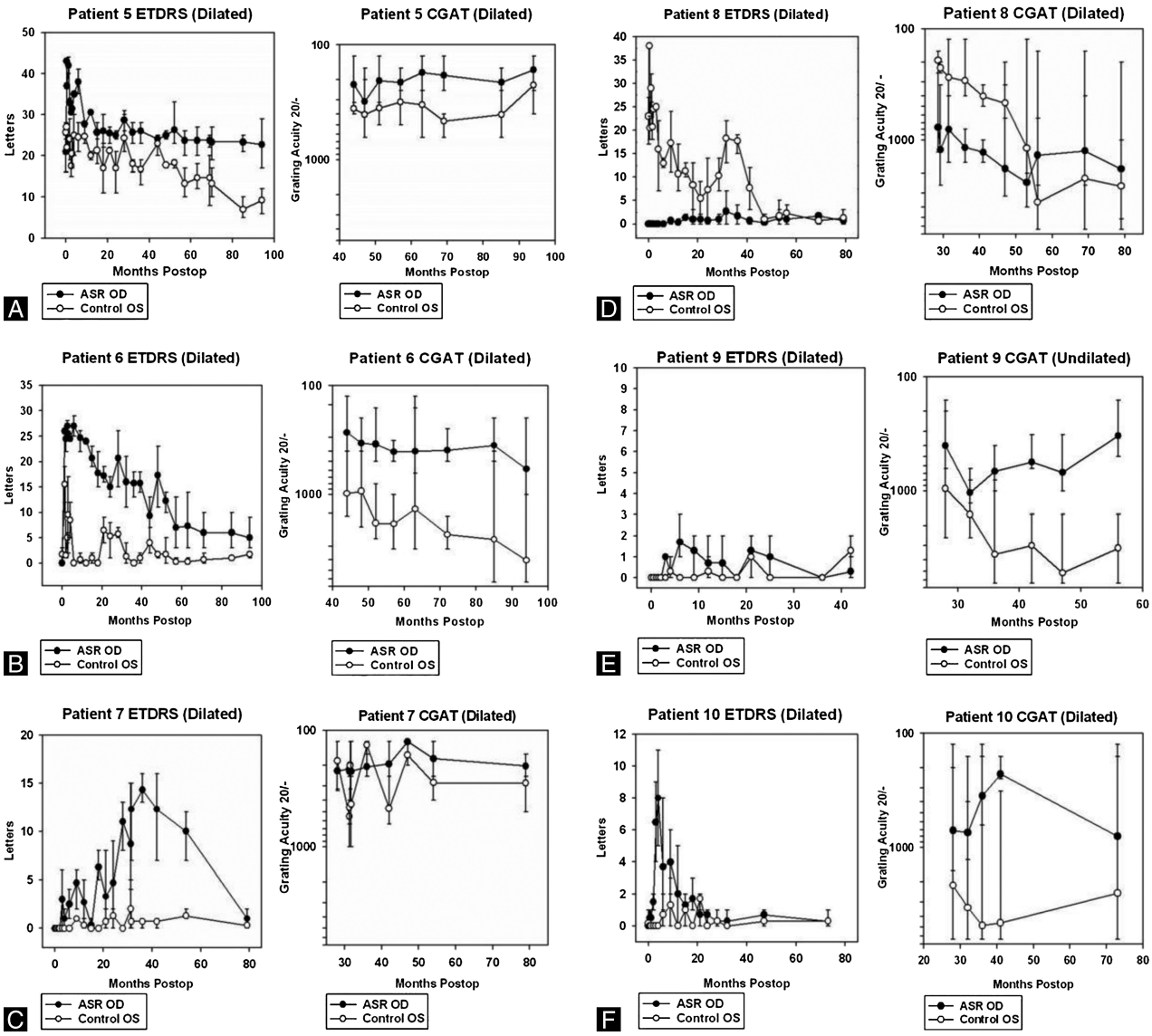

FIGURE 9. A, Optobionics—Postoperative ETDRS (left) and CGAT (right) visual acuities for patient 5. Error bars show the full range of responses.[36] B, Optobionics—Postoperative ETDRS (left) and CGAT (right) visual acuities for patient 6. Error bars show the full range of responses.[36] C, Optobionics—Postoperative ETDRS (left) and CGAT (right) visual acuities for patient 7. Error bars show the full range of responses.[36] D, Optobionics—Postoperative ETDRS (left) and CGAT (right) visual acuities for patient 8. Error bars show the full range of responses.[36] E, Optobionics—Postoperative ETDRS (left) and CGAT (right) visual acuities for patient 9. Error bars show the full range of responses.[36] F, Optobionics—Postoperative ETDRS (left) and CGAT (right) visual acuities for patient 10. Error bars show the full range of responses.[36] Reprinted from Chow AY, Bittner AK, Pardue MT. The artificial silicon retina in retinitis pigmentosa patients (An American Ophthalmological Association Thesis). *Trans Am Ophthalmol Soc.* 2010;108:120–154.

contrast perception. He remarked that he never realized that a table cloth that was on his kitchen table for years was red-and-white checkered and noted seeing the green color of the grass and highway signs again.

Patient 6 had preoperative vision of less than 20/1600 in the implanted OD and barely 20/1600 in the control OS. At 3.5 years postoperatively, the vision OD was 20/271, and OS was 20/980. At 8 years postoperatively, vision OD was 20/585, whereas OS was 20/4050 (Fig. 9B). Postoperatively, this patient was able to identify features of persons and differentiate the color of traffic lights with his implanted eye. He commented that he was able to see his food well enough again to eat with a fork instead of having to feel for the location of the food with his fingers. He was also able to locate his coffee cup without searching for it in the same way.

Patient 7 had preoperative vision of less than 20/1600 OU. At 3.5 years postoperatively, the vision in the implanted OD was 20/194, and OS was 20/470. At 7 years postoperatively, vision OD was 20/203, whereas OS was 20/285 (Fig. 9C). Postoperatively, this patient noted improvement of vision in both eyes, but greater on the implant side. He remarked that he could see himself better in the mirror, commenting on how his gray hair used to be black the last time he remembered seeing himself in the mirror years ago.

Patient 8 had preoperative vision of less than 20/1600 OD and 20/800 OS. At 2.5 years postoperatively, vision in the

TABLE 5. Optobionics—Comparison of Preoperative and Postoperative Visual Acuities in ASR Implanted (OD) and Nonimplanted (OS) Eyes

ASR Chip (Subretinal) 5000 Microphotodiode Array	ASR Chip Implanted OD	Nonimplanted OS Control
Optobionics 4.5- to 8-y Study Patient, Study Duration	Visual Acuity Change, Preoperative and at Follow-up Times (ETDRS Letters and Grating Acuity)	Visual Acuity Change, Preoperative and at Follow-up Times (ETDRS Letters and Grating Acuity)
#5 Preoperative—3.5–8 y	~20/800—20/223—20/165	~20/800—20/360—20/225
#6 Preoperative—3.5–8 y	<20/1600—20/271—20/585	20/1600—20/980—20/4050
#7 Preoperative—3.5–7 y	<20/1600—20/194—20/203	<20/1600—20/470—20/285
#8 Preoperative—2.5–6.5 y	<20/1600(HM 1.5ft)—20/770—20/1830	~20/800—20/193—20/2600
#9 Preoperative—2.5–4.5 y	<20/1600—20/400—20/328	<20/1600—20/952—20/3140
#10 Preoperative—2.5–6 y	<20/1600—20/711—20/796	<20/1600—20/2150—20/2503

implanted OD was 20/770 and OS 20/193. By 6.5 years after surgery, vision OD was 20/1830, whereas vision in OS had dropped to 20/2600 (Fig. 9D). This patient now uses predominately his implanted eye to navigate around the house, whereas preoperatively his OS was his dominant eye. With the implanted eye, postoperatively, he is able to see objects such as the burners on his stove and dishes in his china cabinet. He commented that, after surgery, darkness perception had improved and that nights were much darker compared with before surgery. Preoperatively, his visual field would remain bright at night despite the absence of light.

Patient 9 had preoperative vision of less than 20/1600 OU. At 2.5 years postoperatively, vision in the implanted OD was 20/400 and OS 20/952. At 4.5 years after surgery, vision OD was 20/328, and OS was 20/3140 (Fig. 9E). After surgery, this patient noted being able to see again Christmas tree lights and their colors and the lights on the dashboard of her car. She was able to again see her son play basketball along with other members of his school team.

Patient 10 had preoperative vision of less than 20/1600 OU. At 2.5 years postoperatively, vision in the ASR-implanted OD was 20/711 and OS 20/2150. At 6 years after surgery, vision OD was 20/796, and OS was 20/2503 (Fig. 9F). This patient also noted increased darkness perception at night compared with before surgery when it remained bright in his visual field despite the absence of light. He was able to again see colors in his environment, household objects, and his children in the house. He remarked that before surgery he would have to feel around the floor with his hands and kick with his feet to locate the vacuum cleaner if he lost track of it. After surgery, he is able to successfully find the vacuum cleaner with his vision only.

DISCUSSION

During approximately the past 2 years, 4 groups have refereed publications reporting longer-term human clinical studies with retinal prostheses. Two groups (Epi Ret GmbH, Second Sight) reported on epiretinal devices,[13–15,32–35] whereas 2 other groups (Retinal Implant AG, Optobionics) reported on subretinal devices.[12,36–38] The patient entry vision criteria between the groups were different, which should be kept in mind when evaluating the level of postoperative vision recovery. The preoperative vision for the Argus II patients was limited to LP or worse, that is, no LP. For the EpiRet3, it was hand motions (HMs) to LP; for the DS array/MPDA, it was LP; and for the ASR, it was HM to 20/800.

An analysis of reported SAEs shows that SAEs were reported only in epiretinal subjects. The types of SAEs included conjunctival dehiscence and erosion over the extrascleral portion of the implant, presumed endophthalmitis, hypotony, need for reapplication of a retinal tack, tractional retinal detachment, retinal tear, and inflammatory uveitis. Conjunctival dehiscence and erosion occurred only with the Argus II device because the EpiRet3 was implanted entirely intraocularly. Retinal tears and inflammatory uveitis, however, occurred with both epiretinal devices. The lack of device-related retinal tears and inflammatory uveitis with subretinal devices may be due to their subretinal location, which would isolate them from vitreous shearing forces during eyeball movement. Such forces could theoretically move and shift epiretinal retinal devices, which may have caused the observed retinal tears and inflammation. Also, as subretinal devices do not require retinal tacks to secure their location, there would be no retinal tacks to become dislodged. In the articles published during the 2-year period of this review, subretinal devices appear to be associated with fewer SAEs than epiretinal devices.

From a vision restoration perspective, both epiretinal devices were able to induce phosphenes in the vicinity of the implant electrodes in most but not all subjects. In 1 of 6 patients who underwent EpiRet3 implantation, the epiretinal prosthesis was able to create line orientations and visual patterns that bore similarity to the pattern of its stimulating electrodes.[35] Subjectively, the EpiRet3 patient described stimulation from a vertical arrangement of activated electrodes as a "line, like a half moon, or a semicircle" and a diagonal arrangement of activated electrodes as an "arc, yellow arc." The most notable visual result was when the electrodes were activated in an oval pattern, the patient noted a "line surrounded by a circle," "a circle and a line," and "something oval like a rugby ball." Higher degrees of visual function did not occur, and subjective return of formed vision that affected daily activities was not reported by any patient. The EpiRet3 demonstrated that in at least 1 of the study patients some degree of pattern recognition could result from its stimulation.

The Argus II device was implanted into many more patients than the EpiRet3 device. In their study,[33] Second Sight showed that most subjects (96%) were able to more accurately locate a bright square on a black background with the system turned on than off. The system, however, was less successful in allowing patients to detect the direction of a moving bar of light on a computer screen. In this test, 56% of patients performed better with the system turned on than off, compared with 46% who did

not perform better. In real-world tests such as the detection of doorways, subjects generally performed better with the system turned on than off (52%–60% successful with the system on vs 8%–31% with system off). Higher levels of visual function such as object recognition did not occur. Thus, similar to the EpiRet3, the epiretinal Argus II implant was able to confer some degree of visual perception that included motion detection.

Regarding the image accuracy created by epiretinal devices, some subjects reported perceptions that did not correspond to the pattern of electrical stimulation,[35] for example, "a line and a circle" when stimulated with an oval electrode pattern. These reports may be because in addition to the targeted ganglion cells being stimulated, the intervening RNFL may be receiving electrical stimulation from epiretinal stimulation. If this did occur, the perception of phosphenes in locations other than the specific areas of stimulation (ie, the origin of the nerve axon) could be explained. Also, epiretinal stimulating electrodes were not in direct contact with the targeted ganglion cells due to the intervening RNFL (the electrodes were even farther away from the bipolar cells if they were also targeted). The noncontact arrangement of epiretinal electrodes in the Argus II and the EpiRet3, relative to their targeted cells may have affected the devices' ability to reproduce stimulation patterns that corresponded accurately with the electrode pattern.

Retina Implant AG's hybrid 16-electrode DS array/MPDA produced phosphene patterns with the 16-electrode DS array either as an orientation of lines or as multiple orientations of the figure "C" through sequential electrode activation.[37,38] The device produced phosphene visual acuities of ~20/1200 in 7 of 11 patients who underwent implantations. When the microphotodiode array portion of the implants was tested with a pattern of black-and-white gratings, and Landolt "C" rings were presented on a computer screen, 1 of the 11 patients tested achieved a visual acuity of 20/1000. This 1 patient was also able to differentiate the letters L, I, Z, and T and recognize some common objects such a cup, knife, and spoon. One other patient was able to localize and differentiate a saucer from a cup and a square shape on a table. Another patient was able to differentiate just a saucer from a plate on the same table. Overall, the resolution performance of the subretinal DS array/MPDA appeared higher than for the Argus II and EpiRet3. It is possible that the retinotopic similarity of the photoreceptor/bipolar target cell arrangement to projected images on the retina, along with the close target cell proximity to the stimulating electrodes of the subretinal device, produced greater resolution potential in the DS array/MPDA compared with the epiretinal devices.

Forty-two patients have now been implanted with Optobionics' ASR (Table 6). The most recent study summarizes the results of 6 of the patients who underwent the longest implantations with almost 8 years of follow-up.[36] The most important finding was that of consistently better long-term ETDRS and CGAT visual acuity in the implanted eyes compared with before surgery and also compared with the opposite control eye. The results suggest a persistence neurotrophic effect in the implanted eyes even 8 years after surgery. Final visual acuity in 1 patient was 20/165 compared with ~20/800 preoperatively. In the remaining 5 patients, with preoperative visual acuities of HM at 1.5 ft to <20/1600, final acuities were 20/585, 20/203, 20/1830, 20/328, and 20/796. Because the mechanism of vision improvement of the subretinal ASR device is likely different than the other prosthesis groups, comparison of vision recovery between the ASR and the other devices is difficult. The vision enrollment criteria for the ASR studies were also higher than those for the other devices.

The nature of recovered vision in patients who underwent ASR implantation was noteworthy. As opposed to the patterned phosphenes produced by either epiretinal or subretinal prosthesis summarized in this article, the vision recovered in patients who underwent ASR implantation was of the type of vision that was lost. Specifically, there was recovery of complex visual function including visual acuity, contrast and color perception, visual field

TABLE 6. Optobionics—Preoperative Vision and Postoperative Subjective Observations of Patients After ASR Chip Implantation

Preoperative Vision and Subjective Observations of Patients 5 Through 10 After ASR Chip Implantation (Optobionics)		
Patient	**Vision Preoperative of Implanted OD**	**Selected Subjective Vision Changes Postoperatively**
5	CF at 1–2 ft	Recognizes people again by their faces and also his own face in the mirror. Improvement of color and contrast perception. Sees table cloth on kitchen table as red-and-white checkered squares for the first time. Sees the green color of grass and highway signs again. Recognizes paper money denomination again.
6	HM at 4–5 ft	Able to identify features of persons and differentiate traffic light colors. Sees food well enough to eat with a fork instead of having to feel the food with his fingers. Able to locate coffee cup without searching with hands. No longer embarrassed to eat with others.
7	HM at 2–3 ft	Improved vision in both eyes, but greater on the implant side. Sees himself better in the mirror, commenting on how his gray hair was black the last time he saw himself in the mirror years ago.
8	HM at 1–2 ft	Uses implant eye to navigate around the house instead of the control eye, which was the better eye preoperatively. Sees objects like the burners on the stove and dishes in his china cabinet. Darkness perception improved—nights much darker postoperatively compared with before surgery. Preoperative visual field remained bright at night despite the absence of light.
9	HM at 5–6 ft	Sees again the lights and their colors on a Christmas tree and on the dashboard of the car. Able to see her son along with other players as they played basketball for the school team. Able to read the time on the oven LED clock.
10	HM at 5 ft	Improved darkness perception at night compared with before surgery. Preoperatively, it remained bright in his visual field despite the absence of light. Sees again colors in environment, household objects, and his children in the house. Before surgery, would have to feel the floor with hands and kick with his feet to locate the vacuum cleaner if he lost track of it. After surgery, able to find the vacuum cleaner with his vision only.

CF, count fingers visual acuity.

size (some patients), and most interestingly improved darkness perception. The recovery of darkness perception after surgery was a surprise when patients began reporting seeing darker nights, compared with a chronically bright environment regardless of whether it was night or day. It became apparent that the recovery of darkness perception was important for contrast perception, which is the ability to see both light and dark areas simultaneously in the same field.

In development of the ASR implant, although the basic concepts and advantages of subretinal prostheses were first proposed and espoused by the author, the discovery of a possible neurotrophic rescue effect on visual function in RP subjects who underwent ASR implantation meant that, rather than a prosthesis effect, an even more important potentially therapeutic effect was discovered.[12,36] In addition, as the genotypes of the first patients who underwent ASR implantation were quite varied, the finding of a potential therapeutic benefit in almost all patients, despite their genotype differences, suggests that interruption of a common degeneration pathway may be occurring. The discovery of a positive ASR-induced therapeutic effect on the electroretinogram and histology of a degenerated mammalian retina have now been reported in the RCS rat model of retinal degeneration. This effect is associated with an up-regulation of fibroblast growth factor 2.[36]

Recovery of subjective visual function in patients who underwent ASR implantation created interesting situations for some patients. One patient remarked that before surgery he felt embarrassed eating meals with others as he had to feel with his fingers to locate his food. Postoperatively, this was no longer the case as he was able see well enough to eat with a fork again. Another patient told of how, preoperatively, it was difficult to discipline his young children when they misbehaved as they would hide from him in the house simply by being very quiet. Postoperatively, locating his children as well as objects around the house was possible. Finally, a patient was happy to be able to recognize the faces of his friends and children again but was distraught at how old he now looked in the mirror. Despite these personal observations, one should be cautious. Although the recovery of vision to a level that allows the performance of daily activities is notable, subjective recovery of visual function in nonmasked studies can be influenced by a placebo effect. Nevertheless, the recovery of vision to a level where familiar everyday activities can again be performed by subjects who underwent implantation bears further investigation as a means to evaluate implant response whether it be from a prosthetic or neurotrophic basis.

The discovery of a potential neurotrophic rescue of visual function in RP patients who underwent ASR implantation does raise questions. First, would it be beneficial to implant the ASR earlier in the disease to preserve as much visual function as possible? Would implanting more than 1 device achieve a greater neurotrophic response? Would ASR implantation be beneficial in conditions similar to RP such as dry AMD? Finally, should ASR implantation be considered before the implantation of a retinal prosthesis, especially a subretinal macula device that could block choroidal nourishment and possibly damage a retina that could be rescued?

As of early 2013, only Second Sight's Argus II epiretinal implant has received the American FDA HDE approval and the European Union CE Mark approval. As such it is the only device that is available for implantation by physicians outside an approved investigational study. Second Sight currently receives private and governmental funding. Optobionics' ASR successfully completed the phase I and the phase II multicenter phase FDA clinical trials and received approval to conduct the final phase III Premarket Approval (PMA) study. However, because of the large size and duration of the required FDA PMA study, sufficient funds (~US $200 million) were unavailable, and the study ended when Optobionics ceased operations. A restarted Optobionics (by the author) is endeavoring to raise funds for a less expensive (compared with the PMA) FDA HDE approval process for the ASR. Retina Implant AG continues operations, funded by the German government and private investors, and is in clinical trials of sits subretinal DS array/MPDA implant. EpiRet GmbH receives funding from investors and the German government. The current status of clinical studies for its EpiRet3 implant is not publicly known.

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"I know not all that may be coming, but be it what it will, I'll go to it laughing."
— ***Herman Melville, Moby Dick***