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The Bionic Eye

A Quarter Century of Retinal Prosthesis Research and Development

Mark S. Humayun, MD, PhD,[1] *Eugene de Juan, Jr., MD,*[2] *Gislin Dagnelie, PhD*[3]

This article describes the history of visual prostheses, with emphasis on the development of the Argus II retinal prosthesis system (Second Sight Medical Products, Inc., Sylmar, CA). A brief overview of cortical electrical stimulation in the blind is provided, followed by an account of the design and development of retinal stimulation equipment at the Duke Eye Center in the late 1980s; the first human intraoperative tests there and the subsequent 8 years of tests at the Wilmer Eye Institute; the transfer of the project to the Doheny Eye Institute at the University of Southern California and the founding of Second Sight Medical Products; and the development and clinical trials of the Argus I and Argus II systems. In a series of vignettes, we pay tribute to the many colleagues and patient volunteers without whose help the work would not have been possible. *Ophthalmology 2016;123:S89-S97 © 2016 by the American Academy of Ophthalmology.*

Excellent reviews have covered the development of artificial vision,[1–4] yet the field is ever changing, characterized by many new developments.[5] Herein, we provide an overview of this field with emphasis on the Argus series retinal implants (Second Sight Medical Products, Inc. [SSMP], Sylmar, CA), those with which we are most familiar and that we have helped to develop over the past 25 years. In addition, we pay tribute to the contributions of many colleagues along the way and to the commitment of volunteer participants who underwent repeat testing and early implantation and without whom the development of an Argus implant would not have been possible.

Historical Background

Since ancient Greek times, visual percepts without light stimulation of the eye, called *phosphene*, have been known to arise when applying mechanical pressure to the eyeball.[6] Electrical stimulation of the nervous system to elicit phosphenes dates back to the 18th century. In 1775, LeRoy created light sensations in the blind by passing electrical currents around the head. Long-term visual cortical implants to restore sight to the blind started in the 1960s. Button and Puttnam[7] first implanted 4 occipital lobe electrodes with percutaneous connections in 3 blind patients. These electrodes received signals from cadmium-sulfide photocells whose output changed electrical stimulus amplitude and frequency based on the ambient illumination. Using these handheld photocells, the participants were able to scan their surroundings and roughly determine the location of illuminated objects. Brindley and Lewin[8] implanted a matrix of 80 stimulating electrodes onto the visual cortex of a 52-year-old blind person and showed that short electrical pulses were able to create phosphenes in the form of points, spots, and bars of colorless or colored light in specific visual field locations. Brindley[9] advanced the field of visual prosthetics by showing that electrical stimulation of the visual cortex could create spatial visual percepts, yet as of the writing of this article, the cortical visual prosthesis has not progressed to become an approved medical implant. This is in part the result of high morbidity and mortality associated with cortical implants in animals,[10,11] but mostly the significant advances in alternative approaches such as retinal artificial vision prostheses. In addition, because of the substantial signal processing that occurs in retina and midbrain and the complex structure of the occipital cortex, where different cortical areas are specialized for color, direction, motion, shapes, and binocular disparity and where most of the primary visual cortex is not readily accessible, it is more challenging to use cortical, compared with retinal, electrical stimulation to provide useful visual perception.

Over the past 25 years, the systematic exploration of retinal stimulation as a tool for prosthetic vision has blossomed at multiple locations. Shortly after our group reported the first results from acute retinal stimulation experiments in rabbits with chemically induced photoreceptor lesions (Humayun MS, et al. Invest Ophthalmol Visual Sci 1991;32:ARVO Abstract 2747), researchers at Harvard and the Massachusetts Institute of Technology (Rizzo JF, et al. Invest Ophthalmol Visual Sci 1994;35:ARVO Abstract 1311) and in Cologne, Germany (Szurmann P, et al. Invest

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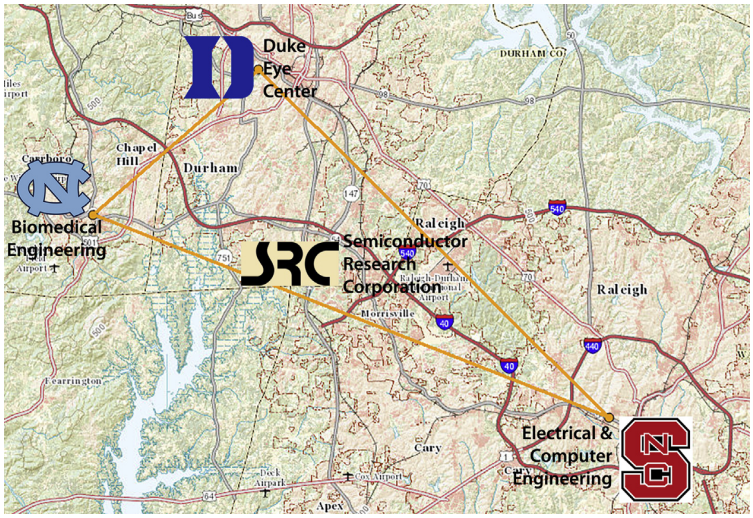
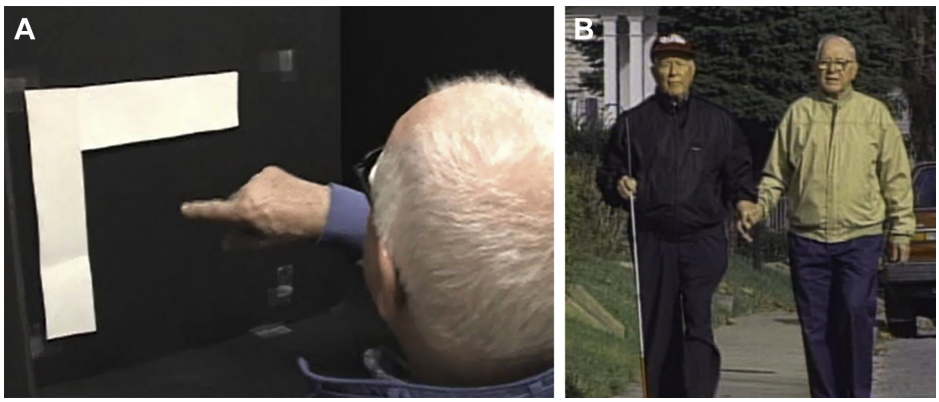


Creating the Concept. Diagram showing Research Triangle, North Carolina, where the concept was created. In 1987, 3 individuals came together and launched research into the development of a retinal prosthesis that eventually led to the current Argus II implant: Mark Humayun, who as a Duke medical student was struggling with his grandmother's vision loss resulting from diabetic retinopathy; Eugene de Juan, Jr., who at the Duke Eye Center had reassured the mother of a young girl losing her vision that "something is being done"; and Howard Phillips, a nuclear and electrical engineer who was Vice President of SRC, an advocacy group for the United States microelectronics industry. Their patent application in 1990 marks the formal start of the epiretinal prosthesis project. Initial animal studies at Duke were made possible by 2 experts who helped Humayun design a stimulator: Roy Propst, a biomedical and electrical engineering professor at the University of North Carolina, Chapel Hill, and Humayun's PhD advisor, and Wentai Lu, an electronics and computer engineering professor at North Carolina State University (Raleigh); other experts who helped were Ralph Cavin at SRC and Eric Javel, a cochlear implant researcher at Duke University.

Ophthalmol Vis Sci 1997;38:ARVO Abstract 185), began exploring the potential of using electrodes implanted in the eye to convey visual stimulation. A different approach was chosen by groups in Chicago (Chow AY. Invest Ophthalmol Vis Sci 1993;34:ARVO Abstract 660) and Tübingen, Germany (Troeger B, et al. Invest Ophthalmol Visual Sci 1997;38:ARVO Abstract 186), who advocated using photodiode arrays combined with microelectrodes as an integrated implant, placed subretinally. The Chicago group's effort eventually faltered because it failed to take into account the need for signal amplification and pulsed stimulation, but the approach by the Tübingen group led to the founding of the company Retina Implant AG (Reutlingen, Germany) and the introduction and European marketing approval of the Alpha IMS multiphotodiode array. The development of both externally driven electrode arrays and integrated photodiode arrays in Germany received a major boost through funding by the German Ministry of Research and Technology, spurred on in part by reports of our group's acute stimulation results presented at a meeting in Bonn, Germany, in 1994. Similar boosts of research activity in the field of visual prostheses through government support over the past 2 decades occurred in the United States (Department of Energy, Department of Defense, National Institutes of Health, and National Science Foundation), Australia, Japan, and Korea. The international cross-fertilization of ideas and developments in the field has been helped greatly by a series of conferences titled "The Eye and the Chip," organized by the Detroit Institute of Ophthalmology and held biennially since 2000.

Postmortem Morphometric Analysis of Retinas from Blind Patients

Concomitant with developing an engineering strategy to stimulate the retina in the late 1980s, we started to study the postmortem histologic results of donor retinas from patients who had the diagnosis of end-stage photoreceptor loss resulting from either retinitis pigmentosa or age-related macular degeneration.[12] The question we were asking was whether, despite near-total loss of the photoreceptors, the remaining inner retinal neurons remained present and viable; without such survival of inner retinal neurons, the implant would not have the ability to replace the damaged photoreceptor layer and stimulate the proximal visual pathway. The results of these studies showed that in retinitis pigmentosa (RP) postmortem eyes, despite near-total loss of the photoreceptors, approximately 80% of the inner nuclear layer and 30% of the ganglion cell layer survived in the macular region, as measured by nuclear counts.[13] Inner retinal cells also survived in the extramacular regions, but to a lesser extent.[14] Age-related macular degeneration (both neovascular and atrophic) showed an even greater preservation of nearly 90% of the inner retinal layers.[15,16] These results demonstrated that there were abundant remaining inner retinal neurons in these retinas with severe photoreceptor loss. But what was not known was how these neurons would respond to intraocular electrical stimulation. This question became the subject of even more debate after these initial studies



Pioneers, Take 1. The first patient pioneers: (**A**) H.C. performing a shape recognition task at Doheny Eye Institute at the University of Southern California and (**B**) the Churchey brothers (NBC Nightly News, December 7, 1993; image courtesy NBC Universal). Among the many intrepid volunteers who agreed to undergo retinal stimulation in the operating room under local anesthesia so they could report what they saw and so others eventually might see again, H.C. stands out. Devoutly religious, born and raised in a tight-knit community in rural Western Maryland, a long-term participant in a natural history study of retinitis pigmentosa (RP) at the Wilmer Eye Institute, and losing his last useful vision by approximately 1980, he became the first subject to be stimulated at Duke Eye Center, a 5-hour drive from home by his wife. His twin brother, who also had RP, also underwent stimulation, both at Duke and at Wilmer. H.C. volunteered for 2 additional stimulation surgeries at Wilmer and became the first patient to receive an Argus I implant, for which he flew to the University of Southern California. He and his wife stayed for months at a time in Los Angeles, far from family and friends. The commitment of such early volunteers enabled us to study the surgical and mechanical aspects of the procedure and, most important, to explore which stimulation patterns were most effective in providing useful visual input.

detailed morphometric analysis showing that the remaining retinal neurons develop aberrant connections that severely disrupt the well-stratified neural and highly specialized local networks of the native retina.[17,18]

Early Intraocular Studies: Handheld Electrodes

In 1956, Tassicker patented a method of implanting a light-sensitive selenium photodiode under the retina to restore light sensation, although he never tested the actual feasibility of the procedure. Starting in 1987, our group began using intraocular electrical stimulation as a means to restore sight. Early preclinical studies with custom-built stimulation equipment and electrodes showed that controlled electrical stimuli could elicit retinal responses in animals with severe retinal degeneration.[19,20] From 1992 through 1994, the first human tests were conducted by our group, initially at the Duke Eye Center and later at the Wilmer Eye Institute at Johns Hopkins, to evaluate focal epiretinal electrical stimulation and its effects.[21,22] We performed intraoperative acute stimulation in 5 blind (little or no light perception) volunteers under local anesthesia using probes with different diameters (50, 100, and 200 μm) and shapes to stimulate the retina electrically. All patients were able to perceive transient phosphenes of different sizes and appearances. Three participants had late-stage RP, 1 had lost vision in both eyes from a massive subretinal hemorrhage as a rare complication of macular degeneration, and 1 had blindness caused by early onset retinal dysfunction of unknown cause.[21] In 4 of 5 participants, electrical stimulation of the macula in 4 quadrants was perceived as a phosphene whose location corresponded to the retinotopic area of stimulation. The participant who did not reliably detect the stimulation was the one who was blind since birth, presumably because of poor development of retinotopic organization. In follow-up experiments by our group, patients were tested with an electrode that had a linear footprint along the retina and with a probe with 2 electrodes placed less than 1 mm apart. One of the test participants perceived these stimulations as either an elongated linear phosphene or 2 separate phosphenes. Using a probe with 3 electrodes at the tip, another participant was able to resolve 3 separate phosphenes at 1.75 degrees center-to-center distance, corresponding to a visual acuity of 4/400, or 2 logarithm of the minimum angle of resolution (logMAR) units.[22]

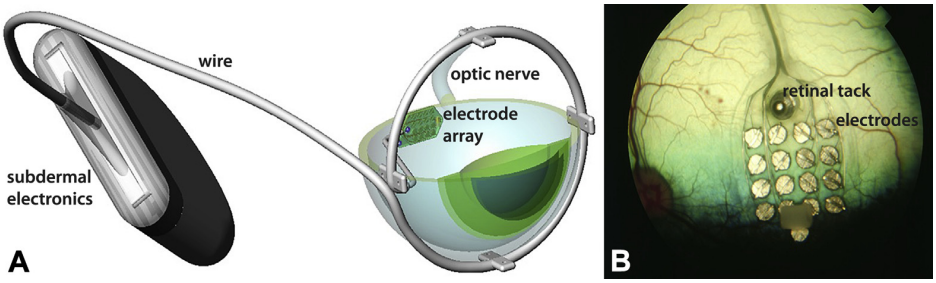
Our group further studied short-term retinal electrical stimulation using multielectrode arrays in 2 blind patients with RP.[21,22] Electrodes 400 μm in diameter were embedded in a silicon matrix with a 200-μm interelectrode distance. One patient was tested with a 3×3 spatial arrangement and another patient received a 5×5 square array. The first patient was able to describe a "box with an empty center" when the 8 outer electrodes forming the perimeter were stimulated. The second patient perceived continuous vertical and horizontal lines when a column or a row of electrodes was activated, instead of linear dots, suggesting that visual percepts that were close to each other seemed to merge into a single phosphene. Letter shapes (U and H) also were perceived when pattern stimulation was used with the 5×5 array, indicating that a multielectrode array potentially could impart visual function.[22] These short-term human results established the proof of principle and, combined with preclinical tests, led to the design and development of the first long-term retinal implant for human use, the Argus I (also called Argus 16).

Wilmer Wonder Years. Three-electrode coaxial probe allowing bipolar and resolution tests during intraoperative stimulation. In late 1991, Eugene de Juan moved to Wilmer, and so did the intraoperative tests; Mark Humayun, and the animal studies, joined after he completed his residency at Duke. This started an intensive period of animal experiments, surgical technique development, intraoperative patient tests, and simulation studies of prosthetic vision. Surgical instruments, electrode arrays, and techniques for animal studies were developed in the Intraocular Retinal Prosthesis laboratory. Three new collaborators joined the project: Gislin Dagnelie for his knowledge of psychophysics and simulation studies, MD-PhD student Robert Greenberg (whose advisor was Eugene de Juan) to perform animal and modeling studies; and postdoctoral researcher James Weiland from the University of Michigan for his expertise in electrode materials and neural stimulation.

Argus I and II Retinal Prosthesis Systems

Two generations of devices, the Argus I and Argus II, have been developed by SSMP. Argus I is a first-generation epiretinal prosthesis approved for a phase I clinical trial by the United States Food and Drug Administration (FDA) aimed primarily at establishing safety. Studies with the Argus I demonstrated the safety of long-term stimulation, motivating the development of the more advanced Argus II retinal implant, which received European Union approval (CE Mark) in 2011 and FDA approval for clinical use in 2013. Although the Argus I was a modified cochlear implant and strictly an experimental device implanted only at the University of Southern California by a single surgeon (M.S.H.), the Argus II was designed and built to become a periocular and intraocular retinal prosthesis intended for commercial use.

The basic operations of the Argus series systems have many similarities. Both consist of a miniature camera mounted on a pair of glasses, an external video processing unit (VPU) worn by the user, and extraocular and intraocular components that are connected via a transscleral multilead cable. The camera captures visual scenes and sends the information to the VPU to reduce resolution and convert local image properties into individual electrode settings that then are multiplexed onto a radio frequency (RF) carrier signal for wireless transmission by an antenna on the glasses frame. The extraocular electronics, along with a transceiver coil, receive and convert the RF signal to the electrical pulses for the electrodes, using the RF energy to power the implant. The stimulation pulses are delivered via the cable to the intraocular electrode array that is attached to the retina using a scleral tack. The extraocular component of Argus I was implanted surgically in the temporal bone and the intraocular array contained 16 electrodes in a 4×4 arrangement, with a center-to-center separation of 800 μm. Two electrode diameters, 250 and 500 μm, were used to determine how size would affect impedance and perceptual threshold. Clinical studies using arrays with alternating sizes



Cochlear Cousins. **A**, Diagram of the Argus I extraocular electronics clearly showing the subcutaneous 16-channel cochlear implant receiver. **B**, Photograph showing the intraocular 16-electrode array of the Argus I. The cochlear implant has had an indelible impact on our work. Mark S. Humayun carried out a project in Javel's cochlear implant laboratory at Duke. A cochlear implant engineer built several probes for intraoperative human tests at Wilmer. The idea to use cochlear implant electronics to accelerate Food and Drug Administration approval of the Argus I implantable device exemption stemmed from Eugene de Juan's visit to the Royal Victorian Eye and Ear infirmary in Melbourne around 1997. Entrepreneur Al Mann and cochlear implant pioneer Joe Schulman, following earlier discussions with Mark S. Humayun and Eugene de Juan, hired Robert Greenberg to help lead the Al Mann Foundation in early 1998. Mann and Greenberg founded Second Sight Medical Products (SSMP) later that year, with Eugene de Juan's patient Sam Williams and others. Dr. Greenberg was appointed President and CEO. SSMP greatly benefited from Joe Schulman's 30 years of experience in implantable electronics.

showed that for these large electrodes, size was not as important as other factors, such as stimulation amplitude and frequency, and that thresholds were low enough to allow a further reduction in electrode size.[23] As a result, a reduced electrode diameter was used for Argus II, allowing for a higher number of electrodes on the array. The intraocular electrode array of Argus II contains 6×10 electrodes with a diameter of 200 μm, separated by 525 μm. Moreover, unlike Argus I, the extraocular electronics of the Argus II implant, packaged in a metal case, are sutured to the episclera between the rectus muscles in the superotemporal quadrant and are held in place by a scleral band.

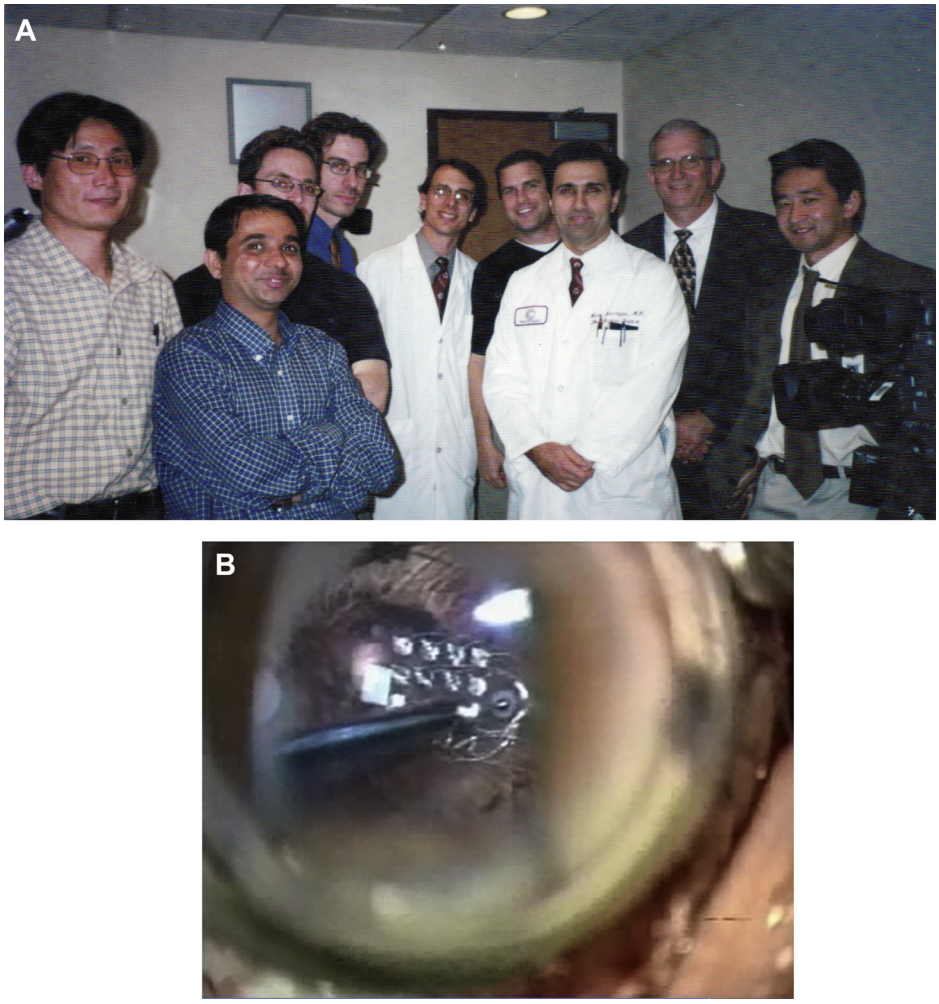
Argus I was implanted monocularly in 6 participants blinded by RP.[23–26] All participants perceived light when the device was activated and could perform visual spatial and motion tasks after a short period of training. Safety was observed with all devices, although 1 participant had the device explanted for unrelated health reasons. The early and interim results, collected up to 4 years after implantation, presented several important findings. Participants described phosphenes as being round, oval, and elongated.[23,27] Phosphene brightness increased as a function of stimulation amplitude and frequency, but phosphene size exhibited much greater dependence on amplitude than on frequency.[23,28] Perceptual thresholds stayed well below the safe limit (charge density, 0.35 mC/cm^2 per pulse) established for platinum electrodes, allowing safe and chronic suprathreshold stimulation.[23,25] The distance between the retinal surface and the electrode is a critical determinant of the efficiency of stimulation, underscoring the importance of keeping the array in close proximity to the retina.[23,25] Synchronized stimulation at different retinal locations was able to produce visual percepts at an acuity level that matched the spacing of electrodes in the array.[28,29] Additionally, these studies found no evidence of tissue damage or electrode corrosion. Even longer-term (10 years) safety and effectiveness of Argus I was reported in 1 participant.[30] Optical coherence tomography and other ophthalmic images show a stable physical retina–implant interface. Although similar perceptual thresholds were initially obtained at the 250- and 500-μm electrodes, the larger 500-μm electrodes exhibited significantly lower thresholds 10 years after surgery.[30]

Compared with the Argus I, the Argus II array not only contains a higher electrode (pixel) density for increased spatial resolution, but also covers a larger retinal area to accommodate a greater visual field. A single electrode of Argus II subtends a visual angle of approximately 0.7° and the entire array of approximately 20°, because 270 μm on the retina approximates 1° in visual field. Between 2007 and 2009, a total of 30 participants (29 with RP and 1 with choroideremia) received the Argus II implant in the United States and Europe.[31] Among these 30 devices, 29 remain implanted and functional; only 1 was explanted because of recurrent conjunctival erosion, rather than device failure. All participants were able to perceive light during electrical stimulation.[32] Since the CE Mark (2011) and FDA Humanitarian Device Exemption (2013), close to 150 additional patients have received an Argus II implant, most of them in Western Europe and Saudi Arabia.

Psychophysical Assessment

The level of vision afforded by today's retinal prosthetic devices is very limited. Some participants accomplish remarkable feats of object and shape recognition, yet "moving shadows" is the most accurate description of the images perceived by Argus II wearers, especially when they first experience retinal prosthetic stimulation; similar reports have come from clinical trials with other retinal implants. For this reason, standard test tools such as letter charts and automated perimeters are of little use in assessing visual function. This has hampered market approval by regulatory bodies; in particular, FDA guidelines equate proof of efficacy with measurable benefits according to standardized outcomes: letter visual acuity and contrast sensitivity, static and kinetic visual fields, and widely used self-report instruments such as the National Eye Institute Visual Function Questionnaire. The inability of Argus II users to score measurable improvements on such outcomes does not mean that they have no benefit from the implant; it simply means that the instruments used are improper for the measurement task at hand. This becomes clearer when comparing Argus II users with patients with ultra-low vision (ULV), defined as hand movements, light projection, or light perception; these patients do not have measurable outcomes on standardized visual function tests, yet an inventory of visual activities in focus groups yielded a list of 760 distinct activities that can benefit from ULV (Dagnelie G, et al; Invest Ophthalmol Vis Sci 2013;54:ARVO E-abstract 2784).

The visual function tests used in the Argus II feasibility study (clinicaltrials.gov identifier, NCT00407602) and post-approval study (clinicaltrials.gov identifier, NCT01860092) include target localization, motion direction discrimination, and grating visual acuity (Luo YHL, et al; Invest Ophthalmol Vis Sci 2014;55:ARVO E-abstract 1834).[33] Target localization requires the participants to scan the visual scene and point to a white square that appeared on a black screen at random locations. The recently published 3-year results indicate that with the system on, 89% of the 28 participants were able to localize the target with a higher accuracy than with the system off.[31] Motion direction discrimination examines a participant's ability to detect sequential activation of electrodes in the array. It relies on retinotopic preservation and temporal processing of the remaining visual pathway. With the system on, 56% of the 27 participants were better at identifying the direction of a white bar moving across the black screen at a random angle.[31] Grating visual acuity, developed for a clinical trial of a subretinal photodiode array,[34] measures a participant's ability to differentiate the orientation of black and white gratings of varying spatial frequencies.[35] No participant scored on the scale in this test with the system off, whereas 48% and 33% of the participants scored 2.9 logMAR or more with the system on at years 1 and 3 after implantation, respectively. The average acuity value at both time points was 2.5 logMAR (Snellen equivalent, 20/6250), and the best acuity obtained so far is 1.8 logMAR (Snellen equivalent, 20/1250).[31,36] High-contrast orientation and mobility tasks in more realistic settings, such as finding a door



Doheny Days. A, The Doheny–Second Sight Medical Products, Inc., team involved in the initial Argus I implantation: (left to right) Ron-Ching Dai, Manjunatha Mahadevappa, Richard Williamson, Robert Greenberg, James Weiland, Brian Mech, Mark Humayun, James Little, and Gildo Fujii. **B**, Intraoperative photograph showing placement of the tack to fixate the initial Argus I implant over the macula. Several members of the team, including Jim Weiland, Mark Humayun, and Eugene de Juan, Jr., moved to the Doheny Eye Institute at the University of Southern California in the summer of 2001. This move had the benefit of placing the academic team and fledgling company Second Sight in the same city, which greatly improved collaboration. Shortly after that move, pioneer patient H.C. received the first 16-electrode Argus I retinal prosthesis, in February 2002. In the next 2 years, 5 more Argus I implantations were performed. From these implantees, we learned that long-term stimulation of the retina was well tolerated and generally safe, and that patients learned to use the limited information to perform simple tasks.

on the wall and following a line on the floor, offer further evidence that the implant provides functional vision and thus is of long-term benefit to the test participants.[35]

Besides the standard clinical tests, laboratory-based exploration of Argus II-produced prosthetic vision was carried out in subsets of the participants. Notably, Arsiero et al (Invest Ophthalmol Visual Sci 2011;52:ARVO E-abstract 4951) demonstrated in 11 participants that their ability to identify high-contrast shapes was improved significantly by the implant. da Cruz et al[37] divided the alphabet into 3 subsets of increasing complexity and reported letter recognition ability by 21 participants with the system on. Six participants were able to consistently identify letters of reduced sizes, the smallest measuring 0.9 cm at a 30-cm distance for the easy subset (L, T, E, J, F, H, I, and U). Four were able to identify simple 2- to 4-letter words correctly. These studies offer compelling evidence that Argus II users can discriminate forms.

Prosthetic Vision Rehabilitation

In 2012, after obtaining the CE Mark for clinical implantation in Europe, and more recently after Humanitarian Device Exemption approval by the FDA, the Argus II has moved from an experimental device to a clinical treatment method. With this came the responsibility for SSMP and the implant teams to provide follow-up to the implant wearers,

Pioneers, Take 2. Photograph showing patient T.B. donning his Argus I glasses. The Argus I pilot study called for a new cohort of brave volunteers, this time willing to undergo surgery that included placement of subcutaneous wiring to an occipital antenna coil. Five new volunteers joined H.C. in undergoing the surgery, and among these, T.B. stands out. Living in the Los Angeles area and the last to receive an Argus I, he spent countless hours in the laboratory to help us understand the effects of the implant and of the stimulation, which then enabled the development of the Argus II. When the Argus II became available, T.B. once again volunteered, but this meant implanting the Argus II in his remaining eye, and the Food and Drug Administration would not allow a second-eye implant until more was known about its safety record. As of this writing, T.B. has had the Argus I functioning for well over 10 years in one eye and has had an Argus II for almost 1 year in his second eye, making him the only person in the world to have bilateral retinal implants. He continues on a weekly basis to help us compare the 2 devices and improve the Argus implants.

beyond postoperative care and so-called device fitting, that is, setting threshold, timing, and gain parameters for all 60 electrodes. Only after this fitting procedure, after the camera is turned on and the patient begins the arduous task of learning to interpret the unfamiliar visual percepts, does it become clear that being a successful Argus II user requires determination from the patient and also specific guidance from rehabilitation experts. For this reason, SSMP has developed a rehabilitation kit with various shapes on a contrasting background that can be felt as well as visually explored, along with several hand-eye coordination and scanning tasks. Experienced occupational therapists, orientation and mobility instructors, and certified low-vision therapists receive additional training targeted at helping Argus II patients gain experience in controlling the VPU settings (inverse video, filters for glare and low-contrast conditions, etc.) and improving their skills for orientation, object localization, and identification. We have found that the range of skill and motivation among Argus II users can be considerable, and thus it takes a highly experienced and creative therapist to optimize training for a given patient.

Evaluating the progress made by a patient requires the development of assessment tools. As argued previously, standard visual performance measures, like standard visual function tests, are not capable of measuring prosthetic vision

Recent Recognition. Photograph taken on May 19, 2016, at a White House ceremony showing President Obama with Mark Humayun, who received the National Medal for Technology and Innovation, the nation's highest engineering award, for his work in bioelectronics in medicine as exemplified by the Argus II.

and ULV. During the Argus II feasibility study, the lack of appropriate outcomes was addressed through the development of the Functional Low-Vision Observer-Rated Assessment.[38] The strengths of this instrument are the assessment of the user in the home environment, the combination of subjective (user and rater) and objective (task performance) factors, and the evaluation by 2 independent experts. The weakness is that the measures are not standardized because all activities involve familiar surroundings and objects in users' homes. Therefore, an instrument such as the Functional Low-Vision Observer-Rated Assessment is unlikely to be accepted by regulatory bodies.

Calibrated performance measures and self-reported outcomes through standardized questionnaires are much more likely to gain acceptance as standards by regulatory bodies, but until now, no such instruments have been available that are capable of assessing prosthetic vision. A targeted visual functioning questionnaire for individuals with ULV recently was developed, (Dagnelie G, et al; Invest Ophthalmol Vis Sci 2014;55:ARVO E-abstract 2150) and Argus II users have measurable outcomes on this self-report instrument and on a set of standardized activities that were derived from items in this questionnaire (Dagnelie G, et al. Optom Vision Sci E-abstract 155252, 2015). These instruments currently are being validated in a larger population of ULV patients and retinal implant users and can be expected to play a role in future clinical trials of retinal prostheses and other novel sight-restoring treatments.

Adverse Events in Argus II Recipients

In the course of the feasibility study and in the context of the Humanitarian Device Exemption application to the FDA, several reports have been compiled and published about adverse events experienced by Argus II recipients.[31,36] Most of the adverse events occurred in a relatively small subset of patients in the early postoperative period and were treated effectively. Data on adverse events in the 100+ patients who have received an Argus II since the system was approved for clinical implantation in Europe and the United States are awaiting publication. In general, adverse events

were similar in nature, but substantially lower in number and severity, than during the Argus II feasibility study (Greenberg RJ, personal communication, 2016).

Recent and Anticipated Developments

Interestingly, although the Argus II was not designed to produce color percepts, it has been reported that up to 9 different colors can be elicited, depending on the stimulation parameters. The most prominent colors are white, yellow, and blue (Stanga PE, et al. Invest Ophthalmol Vis Sci 2011;52:ARVO E-abstract 4949). Different colors were elicited from the same retinal area by varying stimulation parameters. Additionally, the participants simultaneously could perceive 2 distinct colors at separate retinal sites (Stanga PE, et al. Invest Ophthalmol Vis Sci 2012;53:ARVO E-abstract 6952). Although far from generating controlled color vision, these results demonstrated, for the first time, the possibility of using electrical stimulation to control the color of phosphenes.

In 2015, surgeons in Manchester, United Kingdom, performed the first Argus II implantation in a patient with dry age-related macular degeneration, as part of a phase I clinical trial aimed at evaluating the safety and usefulness of Argus II in late-stage age-related macular degeneration. The patient, at the age of 80 years, had completely lost central vision and relied entirely on his peripheral vision before the surgery. Peer-reviewed publication of the study results is pending (initial results were presented at the 2016 meeting of the Association for Research in Vision and Ophthalmology [Stanga PE, et al. Invest Ophthalmol Vis Sci 57:ARVO E-abstract 3733, 2016]).

For the time being, the Argus II remains the only retinal implant approved for clinical implantation in the United States and Europe. The subretinal Alpha AMS implant has a CE Mark and may seek approval in the United States soon, and at least 2 other implant types are in clinical feasibility testing at present. Research teams in Australia and Japan have placed electrode arrays in the suprachoroidal space,[39,40] and an infrared-sensitive subretinal array with a corresponding head-worn imaging system, developed at Stanford University,[41] may enter clinical testing in the near future.

Future implants, and future versions of the Argus series, are likely to have more (smaller) electrodes, but that by itself may have only a limited benefit: The Alpha IMS has 25 times as many electrodes as the Argus II, spaced at roughly 80 μm (vs. 525 μm in the Argus II), yet its highest observed resolution is 1.5 times that of the Argus II, rather than 6.5 times, as might be expected.[42] The most likely reasons for the limited resolution of the Alpha IMS are the relatively large distance between the subretinal stimulating electrodes and the inner retinal target cells and the extensive rewiring of the inner retina after degeneration of the photoreceptors that is thought to cause spontaneous activity throughout the inner retina as well as reverberation in response to (crude) electrical stimulation.[18] In intraoperative epiretinal testing with dual electrodes preceding the development of the Argus series, we observed 2-dot resolution corresponding to 20/1000 visual acuity.[21] An epiretinal implant in perfect apposition to the inner limiting membrane, with 100- to 200-μm electrode spacing, could achieve visual acuities in the 20/400 range, but this may depend on the extent to which reverberations in the inner retina can be controlled. Including a variable digital zoom factor up to 4 to 8 times in the VPU would make the resolution similar to what patients with geographic atrophy or Stargardt disease can accomplish with standard low-vision aids, in central rather than eccentric viewing. Thus, a functional visual acuity level may be feasible with increased electrode density and numbers, but without fundamental changes from existing technology.

Acknowledgments. Some colleagues who contributed ideas, time, and effort to the conceptual and material development of retinal prostheses are being acknowledged elsewhere in this article, but we pay tribute to dozens more who allowed the project to progress. The article also highlights 2 outstanding examples of volunteers, but all 50+ participants in our studies have demonstrated great altruism and risked their own well-being for the future of prosthetic vision. Without their commitment, the creation of Argus retinal implants would not have been possible.

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[1] USC Roski Eye Institute and USC Institute for Biomedical Therapeutics, University of Southern California, Los Angeles, California.
[2] ForSight Labs, Menlo Park, California.
[3] Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.

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Conception and design: Humayun, de Juan, Dagnelie

Analysis and interpretation: Humayun, de Juan, Dagnelie

Data collection: Humayun, de Juan, Dagnelie

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Abbreviations and Acronyms:
FDA = Food and Drug Administration; **logMAR** = logarithm of the minimum angle of resolution; **RF** = radio frequency; **RP** = retinitis pigmentosa; **SSMP** = Second Sight Medical Products, Inc.; **ULV** = ultra-low vision; **VPU** = video processing unit.

Correspondence:
Gislin Dagnelie, PhD, JHU Lions Vision Center, Wilmer Woods 358, Johns Hopkins Hospital, 1800 Orleans Street, Baltimore, MD 21287. E-mail: gdagnelie@jhmi.edu.