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CHAPTER 21

Artificial vision: needs, functioning, and testing of a retinal electronic prosthesis

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Abstract: Hundreds of thousands around the world have poor vision or no vision at all due to inherited retinal degenerations (RDs) like retinitis pigmentosa (RP). Similarly, millions suffer from vision loss due to age-related macular degeneration (AMD). In both of these allied diseases, the primary target for pathology is the retinal photoreceptor cells that dysfunction and die. Secondary neurons though are relatively spared. To replace photoreceptor cell function, an electronic prosthetic device can be used such that retinal secondary neurons receive a signal that simulates an external visual image. The composite device has a miniature video camera mounted on the patient's eyeglasses, which captures images and passes them to a microprocessor that converts the data to an electronic signal. This signal, in turn, is transmitted to an array of electrodes placed on the retinal surface, which transmits the patterned signal to the remaining viable secondary neurons. These neurons (ganglion, bipolar cells, etc.) begin processing the signal and pass it down the optic nerve to the brain for final integration into a visual image. Many groups in different countries have different versions of the device, including brain implants and retinal implants, the latter having epiretinal or subretinal placement. The device furthest along in development is an epiretinal implant sponsored by Second Sight Medical Products (SSMP). Their first-generation device had 16 electrodes with human testing in a Phase 1 clinical trial beginning in 2002. The second-generation device has 60+ electrodes and is currently in Phase 2/3 clinical trial. Increased numbers of electrodes are planned for future versions of the device. Testing of the device's efficacy is a challenge since patients admitted into the trial have little or no vision. Thus, methods must be developed that accurately and reproducibly record small improvements in visual function after implantation. Standard tests such as visual acuity, visual field, electroretinography, or even contrast sensitivity may not adequately capture some aspects of improvement that relate to a better quality of life (QOL). Because of this, some tests are now relying more on "real-world functional capacity" that better assesses possible improvement in aspects of everyday living. Thus, a new battery of tests have been suggested that include (1) standard psychophysical testing, (2) performance in tasks that are used in real-life situations such as object discrimination, mobility, etc., and (3) well-crafted questionnaires that assess the patient's own feelings as to the usefulness of the device. In the Phase 1 trial of the SSMP 16-electrode device, six subjects with severe RP were implanted with ongoing, continuing testing since then. First, it was evident that even limited sight restoration is a slow, learning process that takes months for improvement to become evident.

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However, light perception was restored in all six patients. Moreover, all subjects ultimately saw discrete phosphenes and could perform simple visual spatial and motion tasks. As mentioned above, a Phase 2/3 trial is now ongoing with a 60+ device. A 250+ device is on the drawing board, and one with over 1000 electrodes is being planned. Each has the possibility of significantly improving a patient's vision and QOL, being smaller and safer in design and lasting for the lifetime of the patient. From theoretical modeling, it is estimated that a device with approximately 1000 electrodes could give good functional vision, i.e., face recognition and reading ability. This could be a reality within 5–10 years from now. In summary, no treatments are currently available for severely affected patients with RP and dry AMD. An electrical prosthetic device appears to offer hope in replacing the function of degenerating or dead photoreceptor neurons. Devices with new, sophisticated designs and increasing numbers of electrodes could allow for long-term restoration of functional sight in patients with improvement in object recognition, mobility, independent living, and general QOL.

Keywords: neural retina; brain; retinal degeneration; electronic prosthetic devices; artificial vision; retinitis pigmentosa; age-related macular degeneration; visual performance; low vision; photoreceptor replacement

Retinal degenerative diseases: an overview

One of the most feared disabilities or diseases around the world is blindness, ranking close to cancer. Among sight-robbing conditions, some like cataract can be usually satisfactorily addressed through interventions like surgery. On the other hand, most of the intractable blinding conditions are of retinal origin, the most common type being the inherited retinal degenerations (RDs). These conditions form a broad, heterogeneous family of diseases that primarily affects retinal photoreceptor cells and thus might even better be called photoreceptor degenerations. These are all inherited diseases or at least have a strong genetic component. They broadly fall into two categories: (1) degenerations like retinitis pigmentosa (RP) that begin by primarily affecting rod photoreceptor cells; and (2) macular degenerations that mainly affect cone photoreceptors. An example of the latter is age-related macular degeneration (AMD), although retinal pigment epithelial (RPE) cells are also affected early in this disease process. Along with these specific disease entities, there are many more variations, usually spoken of as the rare RDs. These can be relatively cone specific (at least early on), as is Stargardt's disease, or rod specific, as are diseases such as Leber congenital amaurosis (LCA), Batten disease, or Usher syndrome.

The prevalence of the RP-like degenerations is estimated to be about 1:3500 around the world (Haim, 2002). This estimate is based on data obtained in a single country, Denmark, and awaits more global confirmation. Most evidence indicates that ethnic origin and geographic locale seem to play little or no role in the prevalence of RP. AMD, on the other hand, is much more prevalent than RP but has a more specific pattern of occurrence. Most AMD is seen in Europe, and in countries like the USA, Canada, and Australia that have mainly European-based populations. In the USA, for example, it is estimated that about 2 million Americans above the age of 55 have AMD, with another 7 million being ''presymptomatic,'' i.e., having no significant vision loss but exhibiting clinical signs of the disease such as the presence of drusen upon careful fundus examination. In RP and allied diseases, although the number of affected individuals around the world is relatively small, the disease usually is apparent at birth, in early childhood, or at least in the second or third decade of life. Thus, otherwise healthy individuals are severely affected socially and economically as well as often in need of substantial specialized care from governmental agencies for most of their lives. In contrast, AMD mainly affects those over 55 years of age but the large number affected and the effects on issues such as mobility, independent living, and injuries

such as falls related to poor vision make this a costly disease in terms of loss of quality of life (QOL) and economic costs to both the individual and the government.

Prospects for therapies available to RD patients

To date, patients with an inherited RD have had few possibilities for therapy. This is especially true for patients with RP and allied diseases where use of the nutritional supplement vitamin A has been the only possibility of treatment (Berson et al., 1993). However, the vitamin A regimen only helps a subset of RP, and even in these, it only slows the course of the disease. Dry AMD patients also have the possibility of nutritional therapy with the AREDS clinical trial, demonstrating that a combination of antioxidants can slow the disease process (AREDS Study Research Group, 2001). Here again though, the antioxidants are only recommended for a specific stage of the disease process and only slow the disease course. Wet AMD, the neovascular form of advanced AMD, does have some antineovascular drug options but it constitutes only about 10% of all AMD patients.

New treatments for the RDs, though, are on the horizon including the use of electronic devices that take the place of degenerating, dysfunctional, or dead photoreceptor cells. In fact, these electronic devices might be the best opportunity for therapy in most cases in comparison to other possibilities such as gene therapy, pharmaceutical therapy, nutritional therapy, and stem cell transplantation. If one considers the bulk of RP and dry AMD patients in relation to these five therapeutic options, they will fall into one of two categories: those patients with some viable photoreceptor cells remaining in their retinas and those in which most or all of the photoreceptor cells have died. For the former category, gene therapy is an appealing possibility for treatment since replacement of the defective gene theoretically can slow or even reverse the course of the disease (Hauswirth et al., 2004). In specific cases, long-term experiments on animal models of RP have been very successful (Acland et al., 2001). With only about 50% of the RD gene mutations known, however, a large number of patients would be excluded from treatment. In a similar vein, some genes are difficult to work with in vector applications due to large size, etc., limiting the patient pool even further. Moreover, safety issues yet remain with the general technique of gene therapy.

Pharmaceutical therapy is applicable only when a sufficient number of photoreceptors remain. It can be defined as the use of any agent (natural or synthetic) that prolongs the life of a photoreceptor cell — maybe even enhancing function and performance. A large number of such agents have now been identified (La Vail et al., 1992), including ciliary neurotrophic factor (CNTF), and successfully tested in animal models of RD. The half-life of such agents, though, is relatively short, necessitating frequent replenishment over a lifetime. Some can have serious side effects due to the multiplicity of their actions. The use of nutrients in slowing the disease process in inherited RDs has received widespread attention over the last few years, not only the AREDS work demonstrating some efficacy in slowing AMD but, more recently, the work showing positive results in slowing RP. Specifically, van Veen and Campochiaro with their respective groups have demonstrated that antioxidants slow photoreceptor cell death in a number of animal models of RP (Komeima et al., 2007; Sanz et al., 2007). As with the use of pharmaceutical agents though, more work needs to be done on both safety and efficacy issues as well as the issue of sufficient numbers of remaining photoreceptors to warrant using such treatment as anything other than a ''holding action'' while waiting for more effective treatments and cures.

When all photoreceptors are dead or otherwise not functioning (e.g., in advanced disease), two major tactics can be taken to replace the photoreceptors or at least their function. A direct route would be the use of photoreceptor cell transplantation and stem cell therapy. Despite substantial time and effort though, only modest results have been seen with photoreceptor cell transplantation from donor eyes into animal models of RP (Sagdullaev et al., 2003). Transplantation of stem cells to replace the dead photoreceptors is an attractive alternative to transplantation of retinal sheets or dispersed photoreceptor cells from donor

eyes. Stem cells have been found in adult mammalian tissues, e.g., retinal stem cells in the ciliary margin (Tropepe et al., 2000). Also, progress is being made in defining conditions in which stem cells assume a more adult photoreceptor morphology and function. Encouraging results from MacLaren et al. (2006) demonstrate some functional photoreceptor replacement in an animal model of RP but significant safety questions as well as questions of function need to be addressed before the technique can be deemed available for general RD therapy. The alternative to stem cell transplantation is the use of electronic prosthetic devices that are able to translate a photic image into an electrical response with the ultimate perception of a visual image. This could be by direct stimulation of remaining retinal cells (inner retinal layer) or by bypassing the eye completely and directly stimulating the brain. With the former, this affords artificial vision with an electronic implant functionally taking the place of the photoreceptor cells.

Electron prosthetic devices: general considerations

The most advanced prosthesis project is led by Dr. Mark Humayun at the Doheny Eye Institute, USC Medical School in conjunction with Second Sight Medical Products (SSMP). This is an effort initiated originally by Dr. Humayun with Dr. Eugene de Juan Jr. about two decades ago and is now in Phase 2 clinical trial. Early work in this area is summarized in Humayun (2001). Simply put, a retinal electronic prosthetic device takes the place of dead or nonfunctional photoreceptor cells. It translates outside photic images into electrical signals in the retina that can ultimately be perceived by the brain as visual images. Technically, a small camera is mounted behind the patient's eyeglasses, which captures an image, and in some models of the device, wirelessly sends the image to a microprocessor for conversion to an electronic signal (Fig. 1). This signal moves to a specialized receiver and then to the prosthetic microelectrode implant on the retina. The implant transmits the signal to the underlying retinal cells, which, after some preliminary processing, send the signal down the optic nerve for final processing in the brain and synthesis of a visual image.

Compelling arguments can be made for use of electronic prosthetic devices — both now and in the future. One reason for hope that a retinal prosthesis could be successful comes from the dramatic success of the cochlear implant (Jones et al., 2008). Even though fairly simple, its success in restoring hearing demonstrated that at least some secondary neurons were viable and functional, i.e., survivors of trans-synaptic degeneration, and are able to pass on sensory input from the implanted device. Of course, success of the ocular implant depends on the viability and functionality of secondary neurons of the retina. One way of noninvasively assessing at least the presence of viable inner retinal neurons if not their functionality is by optical coherence tomography (OCT). Matsuo and Morimoto (2007), for example, have examined the retinas of a number of subjects with RP using OCT and correlated visual acuity with retinal thickness. They conclude that OCT "may be used as a clinical test to assess the feasibility of retinal prostheses in the future."

There are currently many groups around the world that are working on visual prosthetic devices and each has its own approaches and technologies. Some of these approaches bypass the eye completely and, after electronic processing of a video camera image, send the visual signal directly to the brain. One of the first to test for direct electrical stimulation of the brain in blind patients was Brindley and Lewin (1968). After stimulation of the occipital pole of the right cerebral hemisphere by "an array of radio receivers," the patient was "caused to experience sensations of light (phosphenes) in the left half of the visual field." Dobelle (2000) has also been a pioneer in this effort, trying to connect a television camera to the visual cortex. More basic work on a cortical visual prosthesis has demonstrated that sensory percepts can indeed be elicited by "modest levels of electrical currents passed into the cortex" by the Utah electrode array (Normann et al., 1999). Similarly, work on a sophisticated cortical implant by Troyk et al. (2005) has progressed to the point where there is hope for a future clinical trial.

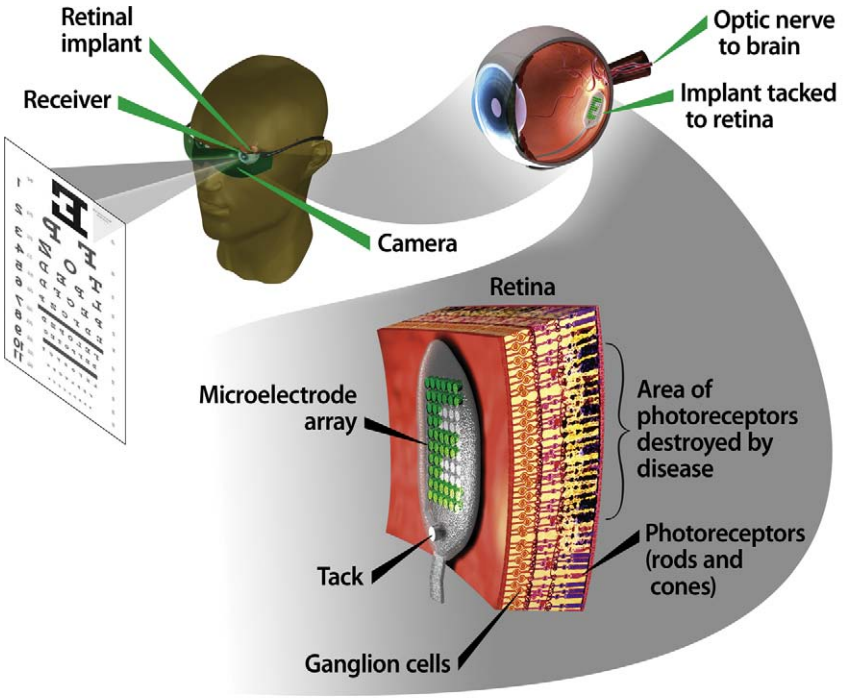

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Fig. 1. Components of the retinal electronic prosthesis. (Left top) External images such as from an eye chart are captured by a miniature camera mounted behind the eyeglasses of the patient. (Right top) These signals are sent to a microprocessor that converts the data into an electronic signal, then to a receiver in the eye, and finally to a microelectrode implant tacked to the retina. The array stimulates underlying retinal cells and this biological signal is sent through the optic nerve to the brain for the creation of a visual image. (Bottom) The enlarged area of the retina shows a theoretical microelectrode array tacked to the front, vitreal (ganglion cell) side of the retina. (Adapted with permission from the Department of Energy newsletter, 5 January 2008.)

Most groups, though, focus on the eye and employ an intraocular implant. Some designs for the implant are quite new, for example, employing an optoelectronic system that theoretically could give a stimulating pixel density of up to 2500 pix/mm^2 (Palanker et al., 2005). Others have taken novel surgical approaches. In this regard, Tokuda et al. (2007) have implanted a multichip stimulator into a scleral pocket to achieve suprachoroidal transretinal stimulation. They were able to elicit electrically evoked potentials (EEPs) in the visual cortex using this device. The use of localized chemical release (e.g., neurotransmitters) from the implanted device has been proposed (Peterman et al., 2004) as well as a neural interface that utilizes vertically aligned multiwalled carbon nanotube pillars as microelectrodes (Wang et al., 2006). Many other approaches from groups in different countries are under investigation but a summary of these activities is outside the scope of the present article. Most groups of researchers, however, have taken a more direct approach with the implantation of more conventional electrodes directly on the retina using a subretinal or epiretinal approach. In the subretinal approach, the electronic implant is placed in the subretinal space between the pigment epithelial cells and the dead/dying photoreceptors. In the epiretinal approach, the implant is placed on the front surface of the retina, i.e., the ganglion cell layer. Applicability of such approaches has been reviewed in several publications including Zrenner (2002); Weiland et al. (2005), Winter et al. (2007) and the recent book by Humayun et al. (2007).

Optobionics was the first company to attempt a government-approved clinical trial in the USA by using a subretinal implantation approach with a semiconductor-based microphotodiode array (Peachey and Chow, 1999). The subretinal space is perhaps theoretically the most logical place for implanting the array since it places the prosthetic device juxtaposed to the dying or dead photoreceptor cells. However, this is a surgically more challenging route compared to others like the sclera pocket route or the epiretinal route (described below), leading to the possibility of more severe surgical complications. The Optobionics device also apparently suffered from the fact that the current it generated was only from light energy, i.e., it is passive with no external power supply. In spite of these problems, initial reports were that this Artificial Silicone Retina (ASR) was both safe and efficacious (Chow et al., 2004). In fact, all implanted RP patients demonstrated unexpected improvements in visual function. Interestingly, this improvement included areas relatively far from the implants, suggesting a "possible generalized neurotrophic-like rescue effect on the damaged retina caused by the presence of the ASR" (Chow et al., 2004). The fact that a number of neuron-survival agents, normally found in the retina, can prolong photoreceptor cell life and function is well known (La Vail et al., 1992). Subsequent studies on the ASR in the RCS rat model of RD confirmed this hypothesis in that implantation of either active or inactive ASR chips resulted in photoreceptor rescue (Pardue et al., 2005). Since Optobionics did not meet the endpoints in the human trial, the company is now defunct.

A more successful version of a subretinal prosthetic device is seen in the implant developed by Retina Implant GmbH in Germany, which also contains light-sensing microelectrodes. This device has received extensive animal testing (Gekeler et al., 2007) and has been implanted in human subjects. Dr. E. Zrenner, University of Tuebingen Eye Clinic, heads the research effort and clinical testing, which, to date, has included eight patients for a 30-day period of time. This implant contains an array of 1500 light-sensitive microphotodiodes in the subretinal space, but unlike the Optobionics device, it has an external power source. The microphotodiodes serve to adjust the strength of the stimulus pulse based on the intensity of light incident on the photodiode. This experimental device has a percutaneous cable through which stimulus pulses and control signals are applied. Because of packaging though, the device cannot be used for long periods each day but only turned on for a few hours. The group hopes to have a permanent implant in the near future. A long-time leader in implant science has also been the Boston Retinal Implant Project led by Drs. Joseph Rizzo and John Wyatt Jr. They have developed novel strategies in engineering, surgical approaches, functional neuroimaging, and human testing, for example, studying the perceptual efficacy of array stimulation in short-term surgical trials in humans (Rizzo et al., 2003).

The alternative to a subretinal implantation approach is an epiretinal approach where the implant is placed on the vitreal (front) side of the retina. Here, there is close juxtaposition to the retinal ganglion cells, although the specific cell/cells stimulated by this approach is/are not known. Attention, however, is being given to possibly localizing the electrically stimulated cells through the use of techniques such as mathematical modeling (Ziv et al., 2005). Specifically for epiretinal implants though, three major efforts have progressed to the point of clinical testing. One is with IIP-Technologies GmbH, which has an implant called the Learning Retina Implant designed such that the patients can optimize their visual perceptions in a computer-mediated dialog. Human work has started in this arena with implantation studies on legally blind patients (Feucht et al., 2005). There has also been a demonstration in cats that activation of the cortex is achieved by epiretinal stimulation (Walter et al., 2005). Another effort has been called the EPI-RET project. This implant has a "learning neural computer" called a Retina Encoder, which works interactively with the user to achieve the best image possible. After implantation in two rabbits, Gerding et al. (2007) stated that "Retinal implant areas in contact to implanted devices presented a severe structural damage and disorganization." A report from the University Eye Hospital in

Aachen, Germany, states that six subjects have been implanted with the 25-electrode device that is relatively large and includes a part that replaces the ocular lens as well. The third effort, the USC-SSMP consortium is, as mentioned above, probably the most advanced with a government-approved clinical trial starting in 2002. Results from this work are given in more detail in the section A clinical trial and testing of an epiretinal prosthetic device.

Morphological and neuronal bases for implantation of a retinal prosthesis

The morphological basis that demonstrates the feasibility of a retinal implant was established in publications designed to determine if suitable numbers of inner retinal neurons remained in RP and AMD patients after photoreceptor degeneration and death to act as a ''platform'' for the prosthetic implant. In RP, it was indeed found that there was significant preservation of the inner retinal layers well after onset of the disease process. For example, Stone et al. (1992) reported that, in the macular regions of donor eyes from patients with different types of RP, there was indeed ganglion cell loss but that a significant number of cells remained at increasing eccentricities. Santos et al. (1997) found that, in the macular region of the retina, 30% of the ganglion cells were ''histologically intact'' along with ''78% and 88% of the inner nuclear layer cells ….in groups of patients with severe and moderate RP respectively.'' Subsequent morphometric analyses of the extramacular retina demonstrated less preservation in the inner nuclear layer and ganglion cell layer (Humayun, 1999). Parallel work on the macular region in patients with AMD demonstrated that the ganglion cell layer and the inner nuclear layers of patients with geographic atrophy (GA) (Kim et al., 2002a) and disciform AMD (Kim et al., 2002b) are relatively well preserved compared to the outer nuclear layer.

Even though morphometry shows significant numbers of cells remaining in the inner retina, marked abnormalities can be found in most of the remaining cell types of the retina in more advanced cases of RD. Studying retinas of donor patients with RP, Fariss et al. (2000), for example, found that remaining rod, amacrine, and horizontal cells demonstrate neurite sprouting. Many of these abnormal neurites were seen to contact the surfaces of GFAP-positive Muller glia. Other aspects of ''neural remodeling'' have now been reported in animal models of RD (Marc et al., 2003). Along with neurite sprouting, the formation of cryptic connections, and self-signaling, there is movement of amacrine and horizontal cells into the ganglion cell layer. Significantly, Muller cells also increase intermediate filament synthesis with the formation of a dense fibrotic layer in the subretinal space, effectively sealing the retina from the choroid. All of these pathological changes have ramifications for the ultimate success of retinal prosthetic implants. It would seem, however, from studies described below on CNS connections, that enough inner retinal neurons (e.g., ganglion cells) do remain such that they can pass a visual signal down the optic nerve to the brain. Similarly, neurite sprouting and inappropriate connections between neurons and neurons, and neurons and glia, can diminish the passage of proper signals, but again, human studies in patients with advanced RP, which have been cited below, demonstrate that at least some signals get through. Also, there is the possibility that, with neuronal plasticity, the imposition of a visual signal from the implant might lead to realignment of the connections in retina and/or brain to a more normal configuration. Finally, the formation of a gliotic seal at the level of the edge of the degenerating photoreceptor cells could be a significant impediment to restoration of function by prostheses placed in the subretinal space but would probably have little impact on epiretinal placement of the prosthetic device.

Central connections in retinal degeneration and prosthesis implantation

Given that enough inner retinal cells are present in cases of RD on which the microelectrode device can be implanted, a key question is whether the brain, in fact, can ''see'' an appropriate visual

image. Specifically, can the brain receive the visual signal from the remaining retinal inner layers and interpret it as a fair representation of the image input from the video camera? It is possible that central connections are damaged in the degenerative process or degenerate in response to disuse (i.e., lack of visual input) over years of effective blindness. To at least partially answer this question, Humayun et al. (1996) evaluated the direct stimulation of the retinal surface of RP subjects who had little or no light perception. Focal electrical stimulation was effected using monopolar and bipolar conductors in a controlled manner. The results demonstrated that the electrical stimulation did elicit visual perception, viewed by the subjects as discrete spots of light (phosphenes). Some subjects could track movement of the stimulating electrode and perceive two phosphenes in response to the stimulation of two independent electrodes. Importantly, the phosphenes were perceived in the appropriate stimulated area of the inner retina. In follow-up studies, Humayun et al. (1999) again examined pattern stimulation of the human retina in subjects with end-stage RP or AMD. These studies confirmed that the subjects could indeed see phosphenes in response to the electrodes and yielded valuable information as to the amplitude of current needed to elicit a percept, the need for close proximity of the electrode to the retina, and threshold differences between macular and extramacular areas of the retina. Taken together, all these studies show that the brain can respond to retinal stimulation, even after long years of little or no formed sight or even light perception. The effects of visual deprivation and the relative plasticity of the visual system have been recently reviewed (Fine, 2007).

In a parallel set of experiments, Weiland et al. (1999) examined the possible retinal site(s) of electrically elicited visual perception. In this case, eyes from two normal subjects were subjected to laser damage, thus creating an area of retinal ''degeneration'' surrounded by normal retina. These areas were then tested with a hand-held stimulating device placed within the eye over the damaged or normal portions of the retina. The tested eyes had been scheduled for exenteration due to cancer near the eye. The laser procedure was performed a few days before the exenteration surgery, and the stimulation procedure was performed prior to surgery. It was found that a variety of percepts could be seen by the subjects treated with krypton red laser, which ablated the outer retina but left the inner retinal cells relatively intact. No percepts were perceived, though, in areas treated with the argon green laser, which damaged both the outer and inner nuclear layers. This suggests that electrical stimulation can be effective in the damaged retina, that the site of such stimulation is the inner retinal neurons, and that the signal can be transmitted to the brain. More recently, Schiefer and Grill (2006) studied the retinal sites of excitation after epiretinal electrical stimulation. They found that stimulation was highly dependent on the physical geometry between the electrode and the underlying ganglion cells. Thresholds were lowest when the electrode was placed close to the characteristic 90° bend in the ganglion cell axon, perhaps explaining why epiretinal stimulation ''results in the production of punctuate rather than diffuse or streaky phosphenes.''

Visual perception: measurements in low vision and brain processing after therapeutic intervention

Along with establishing the morphological basis for prosthesis implantation in the retina as well as whether functional central connections yet remain, the problem of reliable and reproducible testing for small improvements in vision in subjects with advanced RD must be overcome. As defined by Dagnelie (2008) in a recent review, vision loss to RP patients is not a ''simple, discrete variable'' with ''normal vision, low vision and blindness.'' Rather, it is a ''near endless gradation of ever decreasing vision levels.'' This continuum then determines to a great extent the level of activity, performance, independence, QOL, etc. of the affected individual. Thus, sight restoration through an electronic prosthetic device must be considered in this continuum for each individual — starting with the most severely impaired (totally blind) patients but hopefully applicable to

the partially sighted — both RP and AMD patients. Testing of patients with retinal implants is similarly complex in that it must also be individualized depending on the initial level of impairment and the level of sight restoration. However, this is not an insoluble problem. In his review, Dagnelie defines three basic approaches to measuring visual function in very low vision patients. These are simple light detection, light localization, and the perception of movement, usually of a specific light source. There are also features of vision, even very low vision, that are measurable. In Table 1, Dagnelie provides us with a hierarchy of functions, from light perception to stereoacuity. Each of these has a definable performance from simple orientation to relatively complex threading. Thus, simple tasks can be designed such that each of the eight separate levels of function can be assessed and therefore provide a good measure of visual function.

Simulations of prosthetic vision have also been made in subjects with full or partial vision to estimate the performance level that might be expected with actual patients using the prosthetic device (Walter et al., 2007). In this way, information can be gained not only on performance and the effects of learning on the measurement of low vision but also on the usefulness of simple experimental paradigms such as the use of checkerboard square patterns in testing implanted patients.

Table 1. Examples of measurable aspects of vision

Measurable aspects of vision	
Function	Performance
Light	Orienting
Projection	Pointing
Movement	Following
Color	Selecting
Shape/pattern	Classifying
3-D structure	Navigating/manipulating
Hyperacuity	Aligning
Stereoacuity	Threading

Note: The examples are ordered from simplest to most complex. Each line in the left column (''Function'') lists a specific visual function. To the right of it is a corresponding visual task (''Performance'') for which the function is a prerequisite. (Reprinted, with permission, from the *Annual Review of Biomedical Engineering*, Volume 10 © 2008 by Annual Reviews www.annualreviews.org).

Wilke et al. (2007) point out that the use of artificial vision devices (AVDs) could yield results quite different from normal vision and that ''novel test strategies'' might be needed to adequately assess visual performance with these devices. Certainly, the most widely used tests for visual function are those for visual acuity and visual field but these are insufficient measures when confronted with very low vision as in bare light perception and with the small changes that might be encountered with at least the first generation of visual prosthetic devices. Similarly, electroretinography (ERG) and pattern ERG are often used to assess outer and inner retinal function, respectively, but again, these may not be of sufficient resolution to detect small improvements in vision with the help of the implanted devices. To minimize these problems, Wilke and colleagues propose a battery of tests based on a three-pillar approach such that ''sufficient information'' is gained about the ''efficacy of an AVD in severely visually impaired patients as well as information needed for further development.'' The first pillar consists of standardized psychophysical tests that might be applicable to the visual condition but, as pointed out by the authors, these tests are probably the least relevant to the real-life conditions faced by the patient in their daily living. The second pillar consists of tests related to the day-to-day activities of the patient, such as mobility and navigational skills. These may be the most relevant in assessing the helpfulness of the retinal prosthesis but can be less objective than the standard testing unless carefully monitored and controlled. The third pillar is the most subjective in that it solicits the patient's own evaluation and impressions as to the usefulness of the AVD in the format of a carefully crafted questionnaire. Taken together though, these three, very different testing methods could give the best evaluation possible of even a marginal or incremental improvement in vision with use of the device. Overall, what is needed is an accurate and reproducible method to link visual testing with real-world functional capacity in individual patients with very low vision.

In spite of these barriers, a number of psychophysical tests have been devised in animals

that are important in preclinical testing of the prosthetic device and other treatment strategies and also might be applicable to human subjects. Optokinetic testing of visual acuity, for example, which, by inference, gives information about brain function (Thomas et al., 2004b). Also, direct responses can be measured from the superior colliculus after a therapeutic intervention in rats with RD (Thomas et al., 2004a). Smirnakis et al. (2005) used fMRI to see if there were changes in area V1 of the monkey brain after binocular retinal lesioning. They showed that the cortical topography was unchanged. Eckhorn et al. (2006) have measured cortical responses to prosthetic stimulation of the cat retina and determined that the resultant temporal and spatial resolutions are "sufficient for useful object recognition and visuomotor behavior." Indeed, the ultimate testing in vision must be done in the brain rather than in the retina as even robust retinal signals do not guarantee a coherent cortical visual image. In fact, much evidence points to loss of neural function over long-term blindness in a "use or lose" scenario. Also troublesome is the possibility that those affected very early in development with severe photoreceptor dysfunction or dysplasia, i.e., the loss of afferent input, might not even form the initial proper visual pathways between retina and brain since functional signals are never perceived by the retina. Although the latter situation has yet to be directly assessed in situations such as the early blindness seen in human LCA, it is clear from animal experiments that some measure of vision is possible. For example, sight restoration (both rod and cone function) through gene replacement therapy has been observed in a dog LCA model of retinal dysfunction. These are RPE65 mutants, in which photoreceptors remain relatively intact morphologically but lose function (Acland et al., 2005). This restoration of vision implies that there is rescue of already formed connections or that there is the formation of new, functional synaptic connections once the perception of the signal (i.e., light) is restored after successful gene transfer. Aguirre et al. (2007) explored visual processing in these mutant dogs using functional MRI (fMRI). They found that, before therapy, minimal cortical response could be detected in the primary visual areas of the lateral gyrus. Following therapy, though, cortical responses were markedly improved.

In parallel, human subjects with LCA were studied with structural MRI by Aguirre and collaborators and were found to have "preserved visual pathway anatomy and detectable cortical activation despite limited visual experience." Similarly, central visual pathways were found to be intact in a second model of LCA, the CEP290 mouse mutant (Cideciyan et al., 2007). Schoth et al. (2006) have used diffusion tensor imaging (DTI) to assess the level of organization of the optic radiation in subjects with acquired blindness compared with normally sighted subjects. DTI evaluates the integrity of large fiber tracts such as the optic radiation. The investigators found that both the visual fiber and pyramidal tracts appeared to be normal in the blind subjects with no axonal degeneration of the optic radiation observed. Taken together, all these data indicate that imposition of a visual signal even on the long-term blind patient with an electronic prosthetic device could result not only in restoration of retinal function but also in brain recognition and processing of the signal, yielding a visual image.

A clinical trial and testing of an epiretinal prosthetic device

As mentioned above, the prosthetic device furthest along in development at this time is that engineered and in current clinical testing by SSMP as originally conceived by Dr. Mark Humayun with Dr. Eugene de Juan, Jr. at Duke University. This work was continued by Dr. Humayun with Dr. James Weiland, Dr. Robert Greenberg (now with SSMP), and others at Johns Hopkins University and currently at the Doheny Eye Institute, USC School of Medicine. The first-generation design of the prosthetic implant was simple; a silicone–platinum array with 16 electrodes (4×4 array) touching or at least close to the retina. A schematic view is shown in Fig. 1. A small tack secures the array to the retina. As outlined above, an external camera and an image-processing chip are mounted on the eyeglasses

of the patient. These capture the visual image, pixelize it, and send the signal through a telemetry link to the electronic retinal implant. The implant produces a pattern of small electrical currents that approximate the initial visual image. Appropriate underlying retinal neurons are activated, resulting in a dot pattern at each point of stimulation. Taken together, they theoretically yield an image akin to that formed by a dot-matrix printer. Although it is not yet known which cells of the retina (e.g., ganglion, bipolar, both, etc.) are active in accepting the signal, it is presumed that these remaining cells process the signal in as normal a manner as possible (based on the individual's severity of disease) and pass it down the optic nerve for final brain processing and the putative perception of a specific image.

In 2002, Phase 1 of an FDA-approved clinical trial began with the 16-electrode device (Argus-1, A-16). Ultimately, six patients with advanced RP who had little or no remaining light perception received the implant. Although this safety phase of the trial has been successfully completed, testing of these patients has continued as much as possible to the present time. Importantly, safety has been seen with all the implanted devices with no major sequelae, although one device was removed because of unrelated health problems. Surprisingly, some efficacy was also observed in the implanted patients. All patients had restoration of light perception and all saw discrete phosphenes. After a period of time, they also could perform visual spatial and motion tasks. The remaining patients are currently using their devices at home with continuing success. The first publication on an implanted patient reported on the initial 10 weeks of testing (Humayun et al., 2003). The patient had X-linked RP with no light perception in his implanted, right eye (50 years) and bare light perception in his control, left eye. Subsequent to a training period, this patient could describe the relative location of phosphenes generated by the activation of selected individual electrodes under laboratory, double-masked test conditions. For example, in a two-alternative forced-choice test, the patient was highly successful in distinguishing between pairs of vertically or horizontally aligned activated electrodes. Cortical-evoked potentials were also evoked by retinal stimulation through the device. The relative locations of the percepts were found to correspond to the position of the particular electrode(s) activated. Also, there was a good correlation found between percept brightness and stimulation level, demonstrating that, along with simple light perception, the ability to discern between different light levels can also be restored. Finally, testing of the use of the camera unit in conjunction with the retinal implant was also successful along with the tests described above when the electrodes were directly activated. With the camera unit activated, the presence or absence of ambient light could be ascertained as well as the direction of motion of test objects. One of the important lessons from this initial testing was that sight restoration is a learning process that takes time. Specifically, the ability to locate phosphenes in the correct visual field was markedly enhanced with use. Similarly, the learning effect was observed with increased use of the camera unit.

Mahadevappa et al. (2005) expanded the initial report on a single patient to longer-term results on three implanted patients. Specifically, threshold and impedance values were investigated in an attempt to gain critical information as to the charge needed to induce a percept without causing damage to the delicate underlying retinal tissue. Previous short-term studies on human subjects (Humayun et al., 1999) had indicated that a relatively high level of current was needed to induce a phosphene, one that, with the implantation of a permanent device, might cause retinal damage over a period of time. For these studies, the retinal array was connected to a stimulator that gave precise control of each individual electrode in the array. Concurrently, OCT measurements were made to determine the distance between the array and the retina as this geometry certainly could play a role in the current requirements. It was found that thresholds varied greatly between the three subjects (24–702 μA with a 1 ms pulse). However, these values were lower than those seen in the original, short-term studies, i.e., those values needed to elicit a percept. Thresholds were found to increase with time. This could be due to a

number of factors, most likely to the lifting off of the array from the retinal surface. Variability was also seen in the impedance values. As with the thresholds, this is probably due to differences in the distance between the array and the retina in the different subjects and to changes with time. The studies underscore the importance of controlling the distance between the implant and the underlying tissue. If the array is within 0.5 mm of the retina, no correlation is seen between this gap distance and either threshold or impedance. As one might expect, at greater distances, higher thresholds and lower impedance values were observed. The underlying message from these studies, however, is that the relatively low threshold values observed permit the continuation of testing in a safe manner.

As outlined in section Visual perception: measurements in low vision and brain processing after therapeutic intervention, the ultimate test of efficacy of the retinal device is improved performance. Assuming that the implanted patients start with very low vision or none at all, this can be best assessed through the scoring of simple tasks that are relevant to everyday living. Yani et al. (2007) have done this with three subjects with RP who had the Argus 1 implant, i.e., the 16-electrode array. Because of the design of the device, the implant could be controlled either by the head-worn video camera or by an independent computer. Threshold and impedance values were measured to be able to correlate these values with the level of task performance. To assess the operation of the device, preliminary tests were performed with the electrode implant controlled by a computer operated by an investigator. In this way, several areas of function could be assessed: discrimination between individual electrodes, sequential activation of paired electrodes, and subject discrimination of activated rows versus columns of four electrodes. In all these activities, the patients scored significantly better than chance. Subsequent to this, a series of simple tasks were designed to be performed by the patient using the video camera. These were similar to those theoretically outlined by Dagnelie (2008) in Table 1. Table 2 summarizes these tasks. Operationally, white bars or other objects (with a black background) were passed in front of the video camera under conditions of ambient room lighting. On the whole, the patients scored well in multiple iterations of most tasks. In the motion discrimination task though, the patients were asked to keep their head motionless such that the perception of motion was not confounded. Under these conditions, they did not do as well. This was probably due to the small field of vision afforded by the camera (15° of visual angle). In cases where head scanning was permitted (other tasks listed in Table 2), all patients scored above the level of chance. Particularly compelling were results from the object discrimination task in which patients were asked to discriminate between a plate, knife, or cup placed before them on a dark background. Repeated testing gave scores well above chance — 67%, 73%, and 63% with $P < 0.001$. Thus, on the whole, patients performed reliably better with the implant, although differences were seen between the patients. Such variation might be expected though due to many reasons such as differences in age, disease type/stage/severity, implant placement, patient attention, etc. That any positive results were obtained with the three end-stage RP patients and the initial low-resolution device, though, is heartening and bodes well for possible success in further studies with improved models of the device. As the authors conclude — ''the results do suggest that a low-resolution epiretinal prosthesis can provide visual information that can be used to accomplish simple visual tasks that are impossible with the subject's natural light perception vision.''

Table 2. Examples of measurable specific tasks

Measurable task	
Task	Example
Motion discrimination	White bar movement
Spatial detection	Placement of white bar
Object counting	Detection of 0–3 objects
Form discrimination	Angle discrimination of white bars
Object identification	Identification of common objects

Note: Tasks are designed to reliably measure specific functions of everyday living and are described more fully in the text. (Modified from Yani et al., 2007.)

Future studies

Since publication of these encouraging results, progress has been made in improving the USC-SSMP retinal prosthetic device and in clinical testing of other prosthetic devices by many of the other excellent groups working in this field. For example, basic studies on the functioning of the implant continue in patients receiving the SSMP Argus 1 (16 electrode) device. de Balthasar et al. (2008) investigated the relationship between perceptual thresholds, electrical impedance, electrode size, and distance between the device and the retina in six RP patients who had received the implant. Distance between the retina and the implant was measured by OCT. Interestingly, the investigators found a strong correlation between stimulation thresholds and the distance between the retina and the electronic implant but not with the other parameters. These data reinforce the importance of ''maintaining close proximity between the electrode array and the retinal surface…'' In a related study, Wang et al. (2008) investigated the effects of implantation of the device in different areas of the retina on pursuit eye movements in normally sighted subjects with normal vision and in those using a simulated prosthetic device. As expected, pursuit movements using the device were slower and less smooth than in normal vision but yet ''functional, even if the prosthesis is implanted in the peripheral retina.'' In a rat model of RD, Kent et al. (2008) investigated the possible protective effects of neurotrophic agents that could be used in conjunction with the implantation of a retinal prosthesis. They found that retinal sensitivity was higher in eyes treated

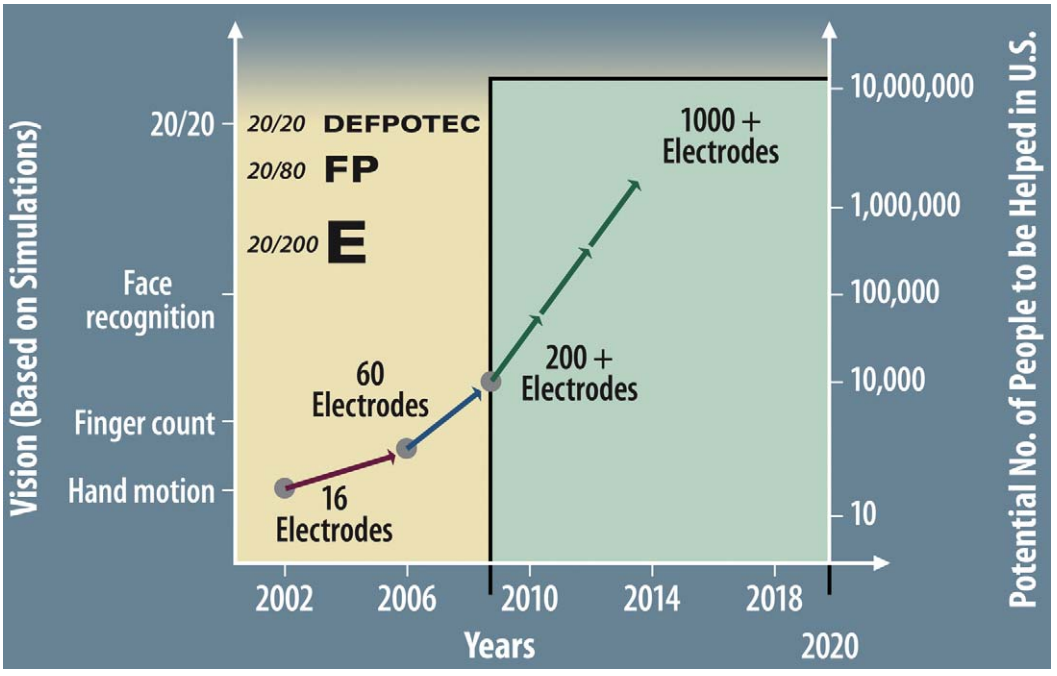

Fig. 2. Timeline for progress of the artificial retina. Progress started with the installation of the first 16-electrode device in 2002, which restored light perception and the ability to perform simple visual spatial and motion tasks (hand motion level). Theoretically, there is improvement with 60 and 200+ electrode implants (finger count level) with the possibility of face recognition and reading ability with a 1000+ electrode device. (Left scale) Progression in vision from bare hand motion to face recognition. At 20/200 visual acuity, large letters can be recognized. At 20/20, small letters can be seen with good reading ability. (Right scale) Number of patients potentially helped with the different generations of prosthetic devices. (Adapted with permission from the Department of Energy newsletter, 5 January 2008.)

with CNTF. Thus, agents such as CNTF might not only protect against apoptosis but help to maintain thresholds at lower levels in implant patients. It is interesting to point out that Caffe et al. (2001) have found that the combination of two neurotrophic agents (CNTF+BDNF) is even better than just one in rescuing photoreceptor cells in an animal model of RD. One can thus expect that improvements in implant design (e.g., numbers of electrodes), implant testing (e.g., better low vision assessment), as well as innovative ways of improving function of the implant (e.g., use of multiple neurotrophic agents) will continue to increase the overall performance and usefulness of the prosthetic device.

Figure 2 outlines the progress of the Artificial Retina Program. In 2002, the first of six patients received the 16-electrode implant (Argus I), which, besides safety, demonstrated the surprising results of restoring light perception and rudimentary vision. Currently, a 60-electrode device (Argus II) is being tested in Phase 2 of a clinical trial sponsored by SSMP. A device with 200+ electrodes is being planned. If all goes well, a 1000+ device can be envisioned that should restore a patient's ability to recognize faces and read large letters. This would allow fairly normal functioning of the patients in society with a marked improvement in their QOL. To achieve this though, there needs to be proper functioning of the two parts of the central nervous system, the brain and the neural retina, brought together in this case by a retinal electronic prosthesis.

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