Review Article

Retinal Prostheses for the Blind

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Abstract

Introduction: Using artificial means to treat extreme vision impairment has come closer to reality during the past few decades. The goal of this research has been to create an implantable medical device that provides useful vision for those patients who are left with no alternatives. Analogous to the cochlear implants for some forms of hearing loss, these devices could restore useful vision by converting visual information into patterns of electrical stimulation that excite the remaining viable inner retinal neurons in patients with retinitis pigmentosa or age-related macular degeneration. Methods: Data for this review were selected through a comprehensive literature search. Results: Advances in microtechnology have facilitated the development of a variety of prostheses that can be implanted in the visual cortex, around the optic nerve, or in the eye. Some of these approaches have shown the promise of providing useful visual input to patients with visual impairments. Conclusion: While the development of various retinal prostheses have shown promise in limited clinical trials, there are distinct advantages and disadvantages for each type of prosthesis. This review will focus primarily on the Epiretinal Intraocular Retinal Prosthesis, studied by our group, but will also briefly review other modalities: the subretinal prosthesis, cortical prosthesis, and optic nerve prosthesis.

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Introduction

Each year, thousands of people are afflicted with photoreceptor degenerative diseases that reduce vision to bare light perception or complete blindness.[1] Retinitis pigmentosa (RP) is the leading cause of inherited blindness with 1.5 million people worldwide affected and an incidence of 1/3500 live births. Also, age-related macular degeneration (AMD) is the leading cause of visual loss among adults older than 65, with 700,000 patients newly diagnosed annually in the United States, 10% of whom become legally blind each year.[2] Once photoreceptors are nearly completely lost, such as in end-stage RP or AMD, very few approaches can restore useful vision to blind patients. One possible avenue that has been explored is to use implantable microelectronics.[3-9] The different methods currently being pursued to electrically stimulate damaged areas of the visual system include electrical and neurotransmitter stimulation of the retina, as well as the use of light-sensitive nanoparticles,[10] and can be categorised by the sites of device implantation. Extraocular locations include the visual cortex, optic radiations and optic nerves[6-9] and intraocular sites include the epiretinal and subretinal surfaces.[3-5]

In this manuscript, we will review the history of artificial vision, including the first attempts at restoring sight. We will describe the various approaches that are currently under development, as well as discuss some of the advantages, disadvantages and challenges that remain.

Extraocular Approaches

Cortical Prostheses

Brindley and Dobelle pioneered the field of artificial vision, being the first to demonstrate the ability to evoke phosphenes and patterned perceptions by electrical stimulation of the occipital cortex via chronically implanted electrodes.[7,11-15] Arrays with over 50 electrodes were subdurally implanted over the occipital pole, providing evidence of the ability to return the sensation of vision to individuals who had injured or damaged the visual pathway anterior to the visual cortex. Dobelle's 64-channel platinum

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electrode surface stimulation prosthesis was shown to allow blind patients to recognise 6-inch characters at 5 feet (approximately 20/1200 visual acuity).[7] Difficulties encountered in these experiments included controlling the number of phosphenes induced by each electrode, interactions between phosphenes, the use of high currents and large electrodes that induced pain from meningeal stimulation, and occasional focal epileptic activity following electrical stimulation. Patients in these initial experiments complained of an inability to appreciate distinct phosphenes, but rather reported seeing "halos" surrounding each of these phosphenes.[11-15]

Intracortical stimulation was introduced in the hope of remedying the shortcomings of surface cortical stimulation via a lower current, higher fidelity system. These devices employed smaller electrodes closer to the target neurons, therefore requiring less current and resulting in a more localised stimulation. Initial studies, during which the intracortical prosthesis was implanted in humans for a trial period of 4 months, demonstrated the ability to produce phosphenes which exhibited colour.[16,17]

Current models of the intracortical prosthesis which are being studied include the Illinois Intracortical Visual Prosthesis project and the Utah Electrode Array.[6,16-17] The former device, consisting of 152 intracortical microelectrodes, has been chronically implanted in an animal model. Experiments have shown that receptive field mapping was also combined with eye-tracking to develop a reward-based training procedure. Further, the animal was trained to use electrically induced point-flash percepts, or phosphenes, in performing memory saccade tasks.[16,17] The Utah Electrode Array consists of multiple silicon spikes with a platinum electrode tip at each end, organised in a square grid measuring 4.2 by 4.2 mm.[6] A pneumatic system, which inserts 100 electrode devices into the cortex in less than 200 ms, is required for minimal trauma during insertion of this array.[6,16,17] The cortical visual prosthesis is advantageous over other approaches because it bypasses all diseased visual pathway neurons rostral to the primary visual cortex. As such, this approach has the potential to restore vision to the largest number of blind patients.

Optic Nerve Prostheses

The optic nerve is an interesting and appealing site for the implementation of a visual prosthesis as the entire visual field is represented in this small area. This region can be reached surgically, but there are several hurdles to overcome regarding this approach. First, the optic nerve is a dense neural structure with approximately 1.2 million axons confined within a 2-mm diameter cylinder. While this allows the entire visual field to be represented in a relatively small area, it remains difficult to achieve focal stimulation of neurons and to decipher the exact retinotopic distribution of the optic nerve. Surgical manipulation of this area requires dissection of the dura, creating possible harmful central nervous system effects, including infection and possible interruption of blood flow to the optic nerve.[18] In addition, intervention at this limited point within the optic pathway requires intact retinal ganglion cells and therefore is limited to the treatment of outer retinal (photoreceptor) degenerations.

Recently, Veraart et al[18] published the results of a study in which a volunteer, with retinitis pigmentosa and no residual vision, was chronically implanted with an optic nerve electrode connected to an implanted neurostimulator and antenna. An external controller with telemetry was used for electrical activation of the optic nerve that resulted in phosphene perception. The volunteer used a head-worn video camera to explore a projection screen and underwent performance evaluations during the course of a specifically designed training programme with 45 simple patterns. The results were encouraging in that the blind volunteer was able to adequately interact with the environment while demonstrating pattern recognition and a learning effect for processing time and orientation discrimination.

Intraocular Approaches

Epiretinal Prostheses

The epiretinal approach to the retinal prosthesis involves the capture and digitisation of images from the external world with a device such as a camera. These images are transformed into patterns of electrical stimulation, which are used to excite remaining, viable inner retinal neurons. Significant power and data telemetry mechanisms are required to drive this process. Several groups worldwide have developed different designs of epiretinal implants that vary in terms of the intraocular and external elements which constitute the devices and how they function to enable vision in patients. They are all guided by similar requirements, which include preserving as much of the normal anatomy/physiology of the eye as possible while minimising the amount of implanted electronics required to power the device.[19] Three such approaches are described below.

The Intraocular Retinal Prosthesis (IRP), developed by a team led by Dr Mark Humayun at the Doheny Eye Institute of the University of Southern California, working with a private company Second Sight Medical Products, Inc (Sylmar, CA) and engineers from other universities as well as the Department of Energy National Laboratories, consists of an extraocular unit, comprising small lightweight camera which is built into a pair glasses, an externally worn battery pack and a pager-sized visual processing unit (Fig. 1). This Model 1 device allows the externally mounted

camera to capture an image, which is then translated into a pixilated image by the custom software algorithms of the visual processing unit. This processed information, in the form of controlled patterns of electrical pulses, is then transmitted into the eye by magnetic coils and implanted in the temporal skull, which provide the inductive link telemetry system. The electrical stimulation pattern is delivered, via a transscleral (across eye wall) cable, to the intraocular portion of the prosthesis which consists of an array of a 16 platinum microelectrodes, ranging in size from 250 to 500 μm. The microelectrodes on the array use these pulses to stimulate any viable inner retinal neurons. The array is positioned just temporal to the fovea and is attached to the inner retinal surface using a single tack, which is inserted through the electrode array into the sclera[19,20] (Fig. 2).

After it was demonstrated in several different animal models that epiretinal stimulation could reproducibly elicit neural responses in the retina, preliminary tests of acute (<3 hours) epiretinal stimulation were performed on humans in the operating room using hand-held electrodes as well as multielectrode arrays not affixed to the patients' retina. These patients perceived phosphenes in response to the electrical stimulation to the retina and were even able to detect motion as well as identify shapes, amounting to crude form vision.[21,22] Clinical trials testing chronic, long-term implantation of the IRP began in 2002 at the Doheny Retina Institute as part of a Food and Drug Administration (FDA) Investigational Device Exemption study. To date, 6 patients have received the 16-electrode, Model 1 implants manufactured by Second Sight Medical Products, Inc, (Sylmar, CA) (Figs. 3 and 4).

Patients described visual perceptions of retinotopically consistent phosphenes that were seen when local current was applied to the surface of the retina with the implanted electrodes. Not only were patients able to distinguish the direction of motion of objects,[22] but also their ability to discriminate between percepts created by different electrodes based on their locations demonstrate that retinotopic organisation is not lost when a patient loses sight.[23] Varying the stimulation level correspondingly enhanced the brightness or dimness of percepts seen as well.

During all postoperative follow-up periods, electrically evoked responses (EERs) from the visual cortex and psychophysical tests eliciting visual perceptions in patients have been recorded and provided quantitative and qualitative measures of visual perception in patients. These EERs and certain psychophysical tests have also been utilised preoperatively in potential patients not only for screening purposes but also for improved evaluation of critical parameters such as stimulation thresholds and current levels necessary for visual perception after the implant has been activated postoperatively.[24]

Histological examination of the effects of chronic stimulation to a retina implanted with an epiretinal prosthesis in both normal and retinal rod-cone degenerate (rcd1) dogs showed no indications of rejection in terms of any inflammatory reaction, neovascularisation, or encapsulation. The possibility that the affixed tack, in conjunction with the foreign material of the array as well as electrical impulses delivered to the implant, could possibly result in fibrous encapsulation of the tack, also exists. However, histological analysis of the mechanical effects of the tack after 2- to 3-month periods also shows minimal effect on the retinal layers upon epiretinal implantation.[25]

The next generation IRP Model 2 is currently undergoing development and we are awaiting FDA approval for human implantation. The Model 2 device will differ from its predecessor in several key ways. It consists of 60 electrodes and may incorporate MEMS components in order to allow for a better fit of a planar electrode array onto a curved inner retinal surface, which could result in closer contact to the retina and thereby lower stimulation currents. The image processor will remain extraocular but the information will be wirelessly transmitted to the Model 2 implant, which will convert the information to a pattern of electrical stimulation that will excite the viable inner retinal neurons. With the ever-increasing number of electrodes in future incarnations of the IRP, advances in microelectrode fabrication as well as its hermetic packaging requirements, power and data telemetry, and image processing capabilities will need to be achieved in order to reach the goal of implantation of a 1000-electrode epiretinal prosthesis.[19,23]

A second epiretinal prosthesis has been developed by Joseph Rizzo and John Wyatt at the Harvard Medical School. Their version of an implant is similar to that of the IRP group in that it consists of distinct intraocular and extraocular modalities. The intraocular components are composed of a photodiode panel and a stimulator chip that are affixed, away from the retinal surface, onto a modified intraocular lens. A flexible 10 μm thick polyimide electrode array is implanted onto the retina and attached to the epiretinal surface using a small gold weight and a viscoelastic made of hyaluronic acid.[26] The extraocular unit is composed of a charge coupled device (CCD) camera, a signal processing unit, as well as a laser, all mounted onto a pair of glasses. The battery back which powers the device is also located external to the eye. The photodiode panel acts to capture the processed signal from a laser pulse emitted from the glasses and the stimulator chip then delivers this information to the microelectrode array on the epiretinal surface of the eye.[27]

In order to study the acute effects of electrical stimulation

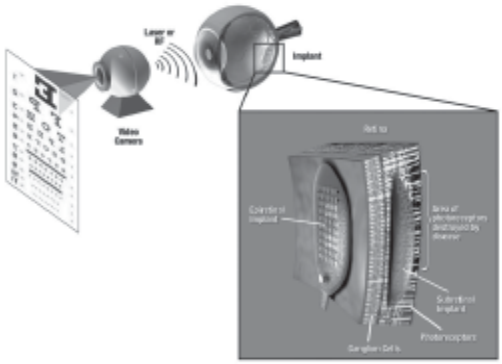

Fig. 1. Illustration of a functioning prosthesis with representation of epiretinal and subretinal implants.

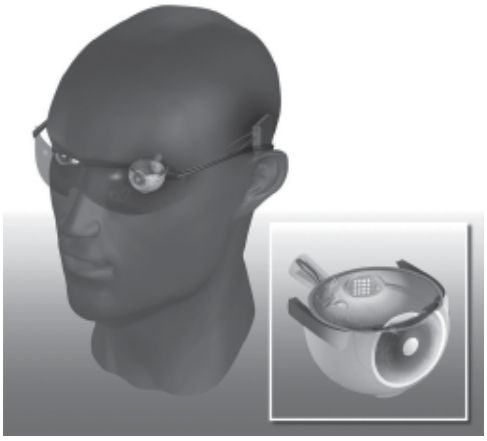

Fig. 2. Schematic representation of the Second Sight TM, Model 1 Intraocular Retinal Prosthesis (IRP) apparatus, including camera, connector cable and microelectrode array.

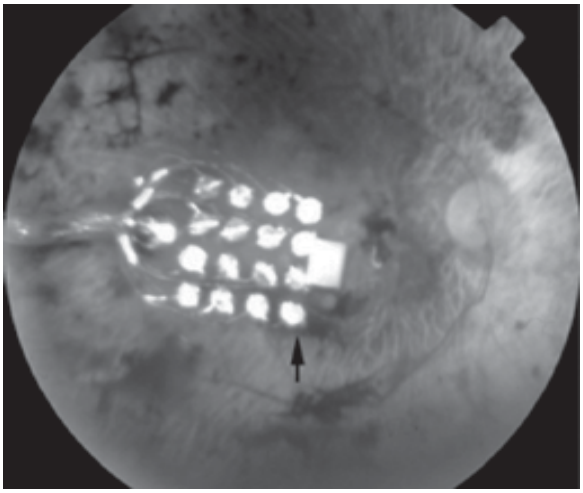

Fig. 3. Fundus photograph of the Second Sight Model 1 epiretinal microelectrode array in a patient with long-standing retinitis pigmentosa. Arrow denotes placement of array in the macula.

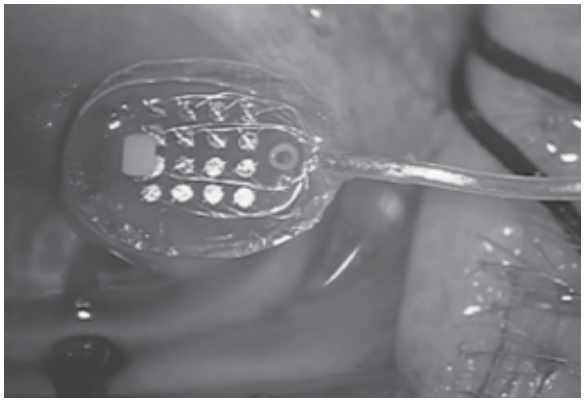

Fig. 4. Photograph of the Second Sight Model 1 epiretinal microelectrode array prior to insertion into the vitreous cavity in a patient with longstanding retinitis pigmentosa.

on visual perception, Rizzo and Wyatt implanted their device in 5 blind patients with RP and 1 normal-sighted patient who was scheduled for enucleation due to orbital cancer. Three different types of electrode arrays, varying in the number, size and spacing of the peripheral electrodes, were tested. Similar to the results found by the IRP group, they observed that higher charge densities were required to stimulate the retinas in patients with worse vision. No apparent damage as a result of electrical stimulation of the retina was evident in histological specimens from the retina of the enucleated eye of the normal-sighted patient.

This group used a series of psychophysical experiments to study several of the fundamental questions regarding the elicitation of visual perception that the IRP group had attempted to answer in their animal and human studies. Would blind subjects report a single percept after stimulation of a single electrode at or slightly above threshold? Could pattern vision be achieved when multielectrode stimulation was given? When stimulating the same electrode at different times, would the percept seen be the same?

The results from their short-term studies in 5 patients were mixed and inconclusive. By stimulating a single electrode above threshold levels, multiple phosphenes were often perceived by the blind subjects. Simple pattern vision was not achieved by either the blind or the normal-sighted patients when multielectrode patterns of electrode stimulation were applied in trials with multiple electrodes. On average, 3 of the 5 blind RP patients accurately described the percepts that corresponded to the correct stimulation pattern only 32% of the time, compared to 43% for the normal-sighted patient. Driving the same electrode with the same stimulus parameters at different times showed relatively good reproducibility, which was achieved 66% of the time in the 5 patients.[26,27]

Despite the short-term nature of their study and the relatively fewer number of trials than is generally necessary for most psychophysical studies, the investigators pointed to the 66% reproducibility level in test-retest trials as well as the fact that 1 of 40 control tests produced a false image to validate their data.[27] The 3 aims of their acute study were to show that blind patients could report basic form perception with epiretinal stimulation, to demonstrate perceptual differences between the normal-sighted volunteer and blind subjects, and to illustrate the perceptual effects of various stimulus parameters.

They attempted to explain some their inconsistent results from a methodological perspective. Rizzo and Wyatt noted that the hand-held technique in which electrodes were held above the retinal surface, as performed by Humayun et al, allow for better scanning of the retinal surface for areas which require less stimulation, thus eliciting more consistent phosphenes in patients. They attributed some of their unexpected results to their inexperience with stimulation paradigms rather than retinal degeneration alone. They also pointed to the short-term nature of their study, which did not allow for the same learning effects or neural plasticity that chronic studies afford, as another possible cause of inconsistent results. Though they could not explain many of the disparities between what they hypothesised and what was observed, the future direction of their studies include obtaining a more thorough understanding of stimulation paradigms necessary for future acute and chronic studies of epiretinal implantation.[26,27] Recently, due to the inability of getting good or consistent results with epiretinal stimulation, Rizzo and Wyatt have abandoned the epiretinal approach and are now developing a subretinal approach very similar in nature to the Zrenner group (see below).

The Learning Retina Implant has been under development by a consortium of 14 expert groups in Germany directed by Rolf Eckmiller since 1995. Like the previous 2 epiretinal prostheses, their implant also consists of intraocular and extraocular components. The retina encoder (RE), which approximates the typical receptive field properties of retinal ganglion cells, replaces the visual processing capabilities of the retina by means of 100 to 1000 individually tunable spatiotemporal filters. The RE is to be situated in the frame of a pair of glasses and in future models of that prosthesis, embedded in a contact lens. The processing of visual information that occurs in the RE simulates the filtering operations performed by individual ganglion cells. The RE output is then encoded and transmitted via a wireless signal and energy transmission system to the implanted retina stimulator (RS). The RS is a ring-shaped, soft microcontact foil centered about the fovea that is affixed to the epiretinal surface and must be in contact with a sufficient number of retinal ganglion cells/fibres to elicit electrical spikes. Visual patterns are mapped onto spike trains for the contacted ganglion cells through the REs. The REs not only simulate the complex mapping operation of parts of the neural retina, but also provide an iterative, perception-based dialogue between the RE and human subject. The purpose of this dialogue is to tune the various receptive field filter properties with information "expected" by the central visual system to generate optimal ganglion cell codes for epiretinal stimulation.[28]

Eckmiller and his group have successfully tested their retina encoder/stimulator in several different animal models as well as normally sighted subjects.[29,30] While there have been significant advances in the manufacturing and testing of the microcontact foils as well as wireless signaling and energy transfer mechanisms, thus far, they have taken a cautious approach towards implanting their device in blind patients.[31,32] In tackling the problem of developing an intelligent man-machine interface for the blind, they have chosen to focus their efforts on understanding the information processing requirements of both the retinal prosthesis and the brain in terms of a dialogue-based RE tuning. In order to optimise the dialog between the retina encoder and the central visual system, proper stimulation coding of electrically induced neural signals for the retinal ganglion cells in contact with the RS needs to be determined. In order for a desired visual percept to be generated by the central visual system, significant information in the form of electrically induced neural signals must not only be provided by the RE/RS system but also be clear or unambiguous for interpretation by the brain.[33,34] As the thrust of the German effort thus far has been on the retinal encoder, clinical trials, primarily focusing on testing of the learning implant and dialogue-based RE tuning, are just being initiated.

Subretinal Prostheses

The subretinal approach to restore vision by means of a prosthestic device involves the implantation of a microphotodiode array between the bipolar cell layer and the retinal pigment epithelium. Surgically, this involves gaining access to the subretinal space either ab externo (scleral incision) or ab interno (through the vitreous cavity and retina). This approach was first described by Alan and Vincent Chow of Optobionics Corp, who believed that a subretinal implant could function as a simple solar cell without the need for a power or input source of any type.[35-37] Their Artificial Silicon Retina (ASR) Microchip is powered entirely by light entering the eye, without batteries or other ancillary devices. Two millimeters in diameter, the ASR contains approximately 5000 microelectrode-tipped microphotodiodes which convert incident light into electrical signals similar to those normally produced by the retina's own photoreceptors. These electrical impulses, in turn, stimulate any viable retinal neurons, which then process and send these signals to the visual processing

centres in the brain via the optic nerve. As part of a safety and feasibility study, the ASR Microchip was implanted in 6 patients, with a follow-up of 6 to 18 months. Chow et al[38] reported gains in visual function in all patients as well as unexpected improvements in retinal areas distal to the implantation site. They noted that a larger clinical trial would be necessary to further demonstrate the safety of the ASR Microchip, as well as to further validate their results.

It has been demonstrated that the idea behind this simple approach was not feasible because it lacks a source of viable power.[39] In fact, Chow et al have abandoned the notion that their ASR Microchip is efficacious as a prosthetic device and now believe that the low levels of current delivered from the implant, although insufficient to electrically activate any remaining retinal neurons in a retina with damaged photoreceptors, may be therapeutic as well as neuroprotective to otherwise dying retinal photoreceptors. Studies by Pardue et al are ongoing to determine whether these effects are indeed neuroprotective as well as if they are persisting and reproducible.[40,41] In addition, studies are also ongoing to determine whether an electronically inactive implant can have similar effects. Hence, this type of an implant works through a "growth factor" that then rescues the remaining photoreceptors. Thus, this device is not a true retinal prosthesis but is best classified as a therapeutic device.

Another design for a subretinal implant has been under development since 1996 by a consortium of research universities in Germany under the guidance of Eberhart Zrenner. Their implant consists of a microphotodiode array (MPDA) which contains approximately 7000 micro-electrodes in a checker-board pattern configuration. It measures 3 millimeters in diameter and 50 microns in thickness. Each MPDA, with an area of 400 μm^2, was made of biocompatible silicon and silicon oxide.,and designed to be both insulating and permeable to light.[42-46] Zrenner et al have demonstrated in various animal models with comparable retinal degenerations that subretinal stimulation elicits neuronal activity in retinal ganglion cells. They defined parameters necessary for successful electric stimulation and then incorporated these data into the development of their photodiode arrays. Implantating their prosthesis in rabbits, cats, and pigs, they attempted to detect electrically stimulated activity in the visual cortex as a result of retinal stimulation as well as investigate the long-term biocompatibility and stability of these implants in the subretinal space.[47-49] Cortical evoked potentials were recorded with chronically implanted epidural electrodes during stimulation with light flashes as well as during electrical stimulation in the subretinal space. It was shown that in nearly half the animals tested, no cortical activation was detected subsequent to implantation. This was explained to some extent by the fact that subretinal fluid was observed during examination after implantation, potentially interfering between the electrodes and the neuronal architecture. After 14 months, angiography and histological findings of the retina adjacent to and in the vicinity of the implant site revealed no significant foreign tissue rejection reactions or occurences of inflammation.[50,51]

Having identified that the subretinal approach to a retinal prosthesis is not practical without an additional source of energy to power the implant, the feasibility of polyimide film electrodes in a cat model was demonstrated and further exploration of film-bound electrical stimulation was planned.[52] Prototypes of their subretinal device have an external power source that supplies energy to the subretinal implant by means of very fine wires that are run outside of the eye. Future implementations of this source of energy into their implant may include transpupillary infrared illumination of receivers close to the chip and electro-magnetic transfer. With these prototypes both designed and manufactured, Zrenner and the consortium are planning to conduct a clinical pilot study limited to 30 days and to 8 completely blind RP patients in 2005 (http://www.eye-chip.com).

A third type of subretinal prosthesis has recently been developed by Rizzo and Wyatt (see comment above). Though their Retinal Implant Project is still in its early stages of development, they have reported that biocompatibility studies examining the effects of a foreign material in the subretinal space as well as surgical methods to implant their device have been extensively evaluated in rabbits, pigs, and dogs. Minimally invasive surgical techniques utilising a posterior, ab externo approach to implant the prosthesis and to insert the stimulating electrode array in the subretinal space, have been tested. While their results have been encouraging to date, further studies regarding the long-term biocompatibility of materials in the subretinal space as well as methods to protect the retina upon insertion of the prosthesis during surgery will need to be performed before a clinical trial is conducted to determine the safety and efficacy of their implant in blind patients.[52]

The subretinal prosthesis approach, like other methods of artificial vision, has its distinct advantages and disadvantages. One advantage is that the microphotodiodes of a subretinal prosthesis directly replace the functions of the damaged photoreceptor cells while the retina's remaining intact neural network is still capable of processing electrical signals. Placement of the subretinal prosthesis in closer proximity to any remaining viable inner retinal neurons in the visual pathway may be advantageous in possibly decreasing currents required for effective stimulation. In addition to the relative ease in positioning and fixing the microphotodiodes in the subretinal space, the lack of

mechanical fixation allows for less surgically induced trauma upon implantation. Unlike the epiretinal prostheses, external cameras or image processing units are not required and the patients' eye movements can still be used to locate objects.

However, the limited area of the subretinal space which will contain the microelectronics predisposes the contacted retinal neurons to an increased likelihood of thermal injury resulting from heat dissipation. Additionally, if the subretinal implant is composed only of an electrode array with the electronics outside the eye, the prosthesis must have a cable piercing the sclera leading to potential tethering on the cable. The tethering effect on the electrode array in the subretinal space leading to possible movement after implantation as well as the more invasive transchoroidal incision that can lead to extensive subretinal bleeding are some of the major disadvantages to the subretinal approach. Thus far, the greatest deficiency of current subretinal prostheses has been the lack of an external source of energy for the microphotodiodes. Levels of ambient light are not sufficient for the current generated by a single microphotodiode, to stimulate adjacent retinal neurons. Only with an additional source of energy can light from a normal environment be adequate for the modulation of the stimulating current at each individual microphotodiode as is necessary for a retinotopically accurate transfer of stimulating current to retinal neurons.

Future research by all groups will need to address the long-term biocompatibility of microelectronics in the saline environment of the eye in terms of hermetic packaging of the microfabricated electrode arrays as well as minimisation of the heat generated and dissipated with its use. Also included in these biocompatibility issues is the unknown effect of chronic electrical stimulation on the retina. In addition to this, significant attention needs to be given to the manner in which visual images will be encoded and delivered in patterns of electrical stimulation to the retina. Plasticity of the visual system in response to electrical stimulation as well as how the brain interprets a pattern of stimulation resulting from 16, or in the future, thousands of, electrodes is still not understood but will be crucial in the evolution of prosthetic design.

Although many advances have been made, the field of artificial vision is relatively young. With ongoing advances in technology, surgical techniques and treatment options, there has been significant advancement towards restoring some vision to patients suffering from AMD and RP. Finally, hope for these projects ultimately lies in the feedback from patients with the implants. It is our hope that within the next decade, patients with these diseases will be able to receive a retinal prosthesis, suitable to their needs, and possess vision allowing them to possibly perform crude operations and even see faces they have not seen in many years.

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