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VISUAL PROSTHESES

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■ **Abstract** The development of man-made systems to restore functional vision in the profoundly blind has recently undergone a renaissance that has been fueled by a combination of celebrity and government interest, advances in the field of bioengineering, and successes with existing neuroprosthetic systems. This chapter presents the underlying physiologic principles of artificial vision, discusses three contemporary approaches to restoring functional vision in the blind, and concludes by presenting several relevant questions to vision prostheses. While there has been significant progress in the individual components constituting an artificial vision system, the remaining challenge of integrating these components with each other and the nervous system does not lie strictly in the realm of neuroscience, medicine, or engineering but at the interface of all three. In spite of the apparent complexity of an artificial vision system, it is not unreasonable to be optimistic about its eventual success.

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INTRODUCTION

In the past several years, a revolution in biomedical engineering has begun around clinical applications to electrically stimulate the nervous system. Examples of clinical systems that have emerged from this revolution abound: cochlear implants to restore hearing, deep brain stimulators to alleviate symptoms of Parkinson's

disease, and vagal nerve stimulators to ameliorate the effects of epilepsy. A significantly more complex system likely to emerge in the next few years is one to restore functional vision in profoundly blind individuals by electrically stimulating the visual pathway.

The ultimate goal of artificial vision systems, also known as vision prostheses, is to artificially produce a visual perception in individuals with profound loss of vision due to disease or injury that can be used to perform activities for which current assistive technologies have severe limitations; such activities include reading text, recognizing faces, and negotiating unfamiliar spaces. In an intact visual system the ability to perform these tasks arises from a neural network with multiple structures processing information in parallel with feedback (1–3). When this system is damaged by disease or trauma, blindness can be the ultimate result; this is further exacerbated by the inability of the neural elements of the visual system to repair or regenerate. A vision prosthesis offers hope to these people with the prospect of bypassing the damaged elements of the visual pathway, interfacing to the remaining structures of the visual pathway, and artificially generating visual perception where none would otherwise exist. While a vision prostheses cannot hope to replace the complexity of the mammalian visual system, its goal is not to reproduce vision in all of its details (i.e. color, depth, textures), but to provide visual perception that is, admittedly, limited in scope but useful to the individual nonetheless.

This review presents our current understanding of the physiologic bases of artificial vision, discusses the advantages and disadvantages of the four current approaches to restoring vision, and discusses the status of various components that constitute an artificial vision system. Although there has been significant progress on many fronts since the first days of vision prostheses, this review concludes with a number of significant, unanswered questions. Certainly the next couple of years will see the initiation of experiments in humans to establish the fundamental physiologic principles of artificial vision, after which there is no doubt that clinical systems will begin to work their way through the various regulatory steps toward the market.

THE CASE FOR ARTIFICIAL VISION

The concept of artificially producing a visual sense in blind individuals is founded on our understanding of the structure of the mammalian visual system, its constituent processing elements, and the relationship between electrical stimulation of a part of the visual pathway and the resulting visual sensations. In this section, an overview of the anatomic and physiologic bases of artificial vision is provided to put the various approaches to restoring functional vision in blind individuals in context.

The function of the neural structures of the visual pathway is to transform incident photons from the world (light) into signals appropriate for the biologic nervous system, construct an accurate neural representation of the outside world, and then

extract relevant information from that representation. This is accomplished in a short time span (100 msec), by hierarchically processing the visual scene through successively more complex feature extractions using multiple neural subunits that are connected in a massively parallel fashion (3). Figure 1 is a schematic of the visual system highlighting the neural structures of the visual pathway most relevant to the development of a vision prosthesis. In the retina, light energy in the form of photons is transduced through biochemical processes in the 10 billion retinal pigment epithelial cells (RPE) into graded (analog) membrane voltage potentials and neurotransmitter release. These biological signals are subsequently filtered by the horizontal, bipolar, and amacrine cells of the retina to maintain overall sensitivity and enhance regions of high contrast (edges). These filtered analog signals are then converted into trains of action potentials, a form of digital signal, in the retinal ganglion cell for transmission out of the retina. The optic nerve is composed of axons from the retinal ganglion cells that go from the eye to the lateral geniculate nucleus (LGN) of the thalamus. From the LGN, the visual information passes through the optic radiations to the primary visual cortex (V1). The cells in V1, historically classified as simple and complex, tend to respond to more complex features of the visual information (e.g. binocularity, lines, velocity). From V1 the visual information passes to higher visual centers concerned with extracting specific features from the visual field (e.g. faces, movement, language). In going from the retinal pigment epithelial cells to higher cortical association areas, the neural representation of the world goes from light and color in a particular point in space to complex (e.g. faces) and, in some cases, abstract (in the case of art) perceptions. Thus, in a visual system not afflicted with blindness, light energy is the initiator of the cascade of processing in the different neural structures of the visual pathway that results in sight.

Fundamentally, blindness results from either an inability of the visual system to transduce light energy into biologic signals or a failure of the biologic signals to reach the brain. Regardless of which structures in the visual pathway have been damaged, vision prostheses use three physiologic principles of the visual pathway. The first principle is that electric current can be substituted for light to produce visual sensations. This was established with electric currents in humans by Penfield & Rasmussen (4) and later with significantly smaller current in primates (5). More significant are recent studies showing that electrical microstimulation of the retina (6, 7), optic nerve (8), and cortex (9–11) produces visual sensations (phosphenes) in blind subjects. These results reaffirm the second physiologic principle of a vision prosthesis, which is that most etiologies of blindness leave the upstream structures anatomically intact; that is to say, when RPE cells degenerate due to retinitis pigmentosa there is not a corresponding loss of neurons in the visual cortex. If the entire visual pathway degenerated with the loss of RPE cells, then the subjects tested by Humayun and collaborators would not have been able to perceive phosphenes. These principles and their supporting experimental evidence bolster the notion that a vision prosthesis that electrically stimulates the visual pathway can be used to produce visual sensations in blind individuals.

The first two physiologic principles tell us how to generate visual perceptions in a damaged visual system without light; the last physiologic principle tells us how to position those phosphenes in visual space to generate a rational perception. Figure 1 is a representation of the visual system that has two adjacent points in visual space labeled "A" and "B". From the "retinotopic" organization of the visual pathway, light at these adjacent points in space will result in modulation of the visual cortex neurons in adjacent points in the primary visual cortex. The converse of retinotopy is that electrically stimulating the brain at the sites marked "A" and "B" will produce phosphenes in the visual field at the points "A" and "B". Understanding the retinotopic organization of the target neural structure, be it retina, optic nerve, or cortex, is necessary to determine the pattern of electrical stimulation necessary to faithfully reproduce the spatial structure visual scene.

In establishing the scientific justification for vision prostheses, we draw from our understanding of both the anatomy and physiology of the visual pathway. The anatomy of the visual pathway is such that there are three potential sites where electrical stimulation could be reasonably attempted to provide an artificially induced visual sensation: the retina, optic nerve, and brain. From the basic physiology of the visual pathways we know that: (*a*) The etiology of blindness does not destroy the entire visual pathway, (*b*) we can substitute electrons for photons to create visual perceptions, and (*c*) the retinotopy of the visual system tells us how to pattern our electrical stimulation to produce rational visual perceptions. A biomedical engineer working in the area of vision prostheses can use this information to determine where stimulation should be applied based on technological considerations and the reason for the blindness, how to stimulate (e.g., with pulses of electrical current), and the stimulation pattern necessary to faithfully reproduce the visual scene.

LESSONS LEARNED FROM VISION PROSTHESES

The desire to restore visual perceptions in blind individuals has a long history in biomedical engineering. Lessons learned from the first efforts to develop artificial vision systems have played an important role in the development of the current generation of these systems. The first efforts to provide a useful visual sense to blind individuals can be found in the early work of Brindley (10, 12–14) and his contemporary Dobelle (9, 15–19). For both of their systems, a large number of subdural stimulating electrodes (57 electrodes for Dobelle, 76 electrodes for Brindley) were placed over the occipital pole where high acuity vision is thought to be processed. Both Brindley and Dobelle were able to evoke phosphenes; Dobelle was able to effect patterned perceptions by electrically stimulating the brain through a subset of his implanted electrodes (20). Despite these successes, the use of surface electrodes has a number of significant issues. Because of the surface area through which the electrodes stimulate (1 mm^2), currents in the range of 1–3 mA were needed to generate phosphenes. To minimize interactions between electrodes caused by the spread of current in the brain tissue, electrodes were spaced

3 mm apart. Nevertheless, subjects still reported "seeing" halos that surrounded the individual phosphenes and joined them together (13, 20).

Despite early encouraging results, this approach to a vision prosthesis, surface stimulation of the primary visual cortex, did not yield a commercial device for several reasons. Although subjects reported small discrete phosphenes when individual electrodes were stimulated, simultaneous, multiple closely spaced phosphenes could not be achieved because of the spacing of the electrodes, nonlinear interactions between the electrodes, and the persistence of phosphenes. This inability to generate a dense phosphenes field severely constrained the system's capacity to convey visual information about faces and handwritten text, leading Brindley to comment "... I shall not judge that a strong case for the practical usefulness of vision prostheses has been made ..." (13). While the potential for surface stimulation in a vision prosthesis had seemed to run its course, other investigators began to suggest that intracortical microstimulation of the visual cortex would not have the same limitations (21). It would take technologies from the semiconductor manufacturing sector to make possible an array of electrodes suitable for microstimulating the human visual cortex.

The advent of silicon micromachining and micromanufacturing heralded the beginning of many new approaches to providing functional vision to blind individuals. Arrays of microelectrodes could be built with large numbers of electrodes and stimulating surfaces so small that only neurons in close proximity to the electrodes would be stimulated. With many options available for stimulating electrode arrays (22–26), researchers at the National Institutes of Health (NIH) set out to determine the feasibility of using intracortical microstimulation of human visual cortex to provide functional vision to the blind (11, 21). These experiments confirmed many of the proposed advantages of intracortical microstimulation over surface stimulation. It was found that punctate visual perceptions were generated at lower currents (microamps versus milliamps), the onset and offset of the percept was rapid, and electrodes could be spaced as close as 500 μm and generate distinct phosphenes. The advantages of electrically stimulating nervous tissue through penetrating microelectrodes to create phosphenes and the ability to manufacture arrays of microelectrodes using widely available silicon micromanufacturing techniques prompted researchers to begin investigating other options for vision prostheses outside of cortical stimulation.

CURRENT APPROACHES TO A VISUAL PROSTHESIS

The widespread availability of silicon micromanufacturing techniques to build silicon-based interfaces to the nervous system has, for the most part, driven the current push to develop a vision prosthesis. Interfaces can be constructed at the same scale as neurons (10–30 μm) with the capability to stimulate only a few neurons at a time to provide unprecedented phosphene densities. As a result of building novel interfaces to the nervous system, new concepts for vision prostheses have evolved to the point where, currently, four approaches to a vision prosthesis

are being actively pursued. This section details the current status of each approach, at least as much as is possible given the involvement of numerous companies in their development, and attempts to adequately identify the potential strengths and weaknesses of each.

Subretinal Prosthesis

Retinitis pigmentosa is a progressive degenerative disease of the eye characterized by the gradual loss of retinal pigment epithelial cells. Vision loss progresses to blindness as these cells die off and the capacity of the retina to transduce light into biologic signals is diminished. In what could be considered a bio-based approach to vision prostheses, consortia in the United States (27) and Germany (28) are determined to replace the lost RPE cells with ones of a man-made origin. In this approach, a silicon micromanufactured device called a microphotodiode array (MPD) or semiconductor microphotodiode array (SMA) is placed behind the retina between the sclera and the bipolar cells where incident light is transformed into graded electrical potentials that stimulate the bipolar cells to form a visual sensation. There are a number of requirements that a subretinal vision prosthesis must satisfy in order be a viable option for a vision prosthesis: (*a*) It must be possible to manufacture the devices in a sufficiently dense configuration to provide closely spaced phosphenes; (*b*) the devices should, ideally, have a dynamic range that is behaviorally relevant in humans; (*c*) the microphotodiodes must generate enough current to stimulate remnant bipolar cells to produce detectable phosphenes; and (*d*) the biocompatibility of the device should be such that the materials, implantation procedures, and device design contribute to long-term functionality. Encouraging progress has been reported in each of these areas.

The manufacture of subretinal stimulating arrays is easily achieved with current silicon micromanufacturing techniques. MPD arrays are routinely made, where each detecting/stimulating unit measures 20 μm $\times$ 20 μm and adjacent units are separated by 10 μm (29, 30). The individual sensor/stimulator elements can be manufactured to produce positive or negative voltages in response to light to simulate depolarizing and hyperpolarizing events corresponding to on/off cell behavior. These elements are also manufactured to be sensitive to light in the 500–1100 nm wavelengths, which generally corresponds to the visible spectrum (400–700 nm). The use of traditional micromanufacturing techniques means that many thousands of these devices can be placed on a single structure 3 mm in diameter and 50–100 μm thick with a density of $\sim$1100 devices/mm^2, or approximately the same density as the RPE cells that they are replacing. Further, these devices can be made to exhibit many of the same electrophysiologic behaviors as healthy RPE cells (29, 30).

A persistent question with the subretinal approach is that the passive nature and low quantum efficiency of photodiodes necessitates the use of unrealistically bright lights in order to generate the necessary voltages and currents needed to stimulate bipolar cells. The amount of ambient light expected under normal circumstances

is approximately 8 lux, which is below the 70 klux used by Zrenner et al (28) and 12 klux used by Chow & Chow (31) to generate sufficient energy to stimulate the bipolar cells. Although the development of higher efficiency semiconducting diodes would certainly decrease the overall amount of light needed to produce sufficient currents for stimulation, it is likely that active electronics will be necessary in order for this approach to operate under normal lighting conditions. Unfortunately, because active devices require external power and transmission systems, this will complicate the design of devices using photodiodes considerably.

The mechanical and material biocompatibility of the devices is another persistent area of concern with the subretinal approach. The reported evidence suggests that implanting these structures in the subretinal space is possible without causing permanent damage to the retina. However, histological evaluation of the retina over the implant site reveals that there is an ongoing degenerative process indicated by a decrease in the cellular density of the inner retina (30), expression of glial fibrolytic acidic protein (GFAP) in Müller glia (28), and the presence of macrophages in the implant site (30). The reason for these changes is not clear at this time. Zrenner and colleagues maintain that the changes in the retina are not the result of soluble toxins coming off the implant and this is likely to be the case given the demonstrated biocompatibility of silicon, silicon nitride, and silicon oxide in nervous tissue (32, 33). Zrenner et al point out that the flat, rigid nature of the implant is likely to mechanically damage the compliant, curved retina. In addition, there is the possibility that in animals that do not have epi- or intraretinal vasculature, obstructing the flow of nutrients from and the removal of waste to the choroid could be the causative agent in the degeneration. For these reasons, the next generation of MPD arrays are likely to be constructed on flexible substrates that have perforations to permit the unobstructed flow of materials through the array (28). Although flexible substrate microelectrode arrays have been demonstrated elsewhere (34), there is no current information on the application of this technology to a subretinal vision prosthesis.

The concept of using a high-density array of phototransducing devices to stimulate the remnant retinal structures has an inherent appeal in that it attempts to provide functional vision by simply substituting man-made RPE-like devices for the damaged natural ones. Further progress in this approach will involve: (*a*) moving to flexible substrates to accommodate the delicate nature of the retina, (*b*) going from passive to active devices to reduce the necessary light intensity, (*c*) adopting standard metals for neurostimulating electrodes such as IrO in case TiN forms toxic byproducts under bias, and (*d*) establishing the functionality of the restored visual sense in behaving animal models.

Epiretinal Prosthesis

An alternative approach to stimulating the retina from "behind," as is the case with the subretinal implants, is to use an array mounted to the "front" of the retina. In contrast to the subretinal approach, where the stimulating device was placed in

the outer retina between the sclera and the bipolar cells, the epiretinal approach places the stimulating device on the inner retina between the vitria and the retinal ganglion cells (RGC) (35, 36). Based on recently published models of extracellular stimulation of the human retina (37, 38), the epiretinal implant will likely stimulate both RGC cell bodies and passing axons from RGC located on the periphery. This approach bypasses the damaged or missing photoreceptors as well as any remnant retinal circuitry (amacrine, bipolar, and horizontal cells) and directly stimulates the output layer of the retina. To date, a number of experiments performed in sighted and blind human subjects demonstrate the potential for epiretinal electrical stimulation to provide patterned visual perception (6, 7, 39, 40). Further experiments have shown that arrays of disk electrodes can be used to evoke neural activity in an isolated retina (41) and that passive devices seem to be exceedingly well tolerated by the retina (42).

There are, however, three issues relevant to the epiretinal approach. The first is that an epiretinal device needs to be firmly affixed in place in order to efficiently stimulate the retina as well as provide a consistent visual perception. A number of mechanisms present themselves for affixing the device ranging from tacks into the sclera to exotic fibrin-based adhesives. Although the use of tacks has been shown to satisfy the criteria for fixation in 2–3 month periods (42), there is a possibility that the tack, in conjunction with the foreign materials and electrical stimulation could result in a fibrous encapsulation response, but this effect has yet to be seen. Another issue of concern is the viability of the tissues under the implant. Majji et al report the complete absence of gross indicators of rejection of the implant (e.g. inflammation, neovascularization, and encapsulation) and that the retina under the implant appears perfectly normal and well perfused. However, their assessment of retinal viability did not differentially compare the tissue under the array with unimplanted tissues. Although unlikely given the histological evaluation, it is possible that the function of retina under the implant has been adversely affected while appearing morphologically healthy. The need for pulsed currents to stimulate the RGCs means that an epiretinal implant will be an active rather than passive device. As is the case with any active implanted electronics, power will dissipate into the surrounding tissues. Although the epiretinal approach benefits from having the vitria in which to dissipate heat, the effect that temperature will have on the overall biocompatibility of the device is unclear.

Further development of an epiretinal vision prosthesis will involve research activities in three principal areas. The results cited in this section pertain to disk electrodes and surface stimulation; as with cortical prostheses, a penetrating microelectrode array could use smaller stimulation currents for more discrete stimulation and better control over phosphene generation. However, using an array of penetrating microelectrodes could introduce biocompatibility issues because relative micromotion between the array and the retina might provoke a vigorous encapsulation response. There has been considerable research into the effects of chronic electrical stimulation of peripheral nerves (43), spinal cord (44), and cortex (45–48); the effects of chronic electrical stimulation on the retina are still not

known. Although the results of Humayun with passive implants are promising, it is possible that the stimulation paradigm that is most effective at stimulating retinal ganglion cell bodies also results in long-term damage to the tissues. The ability to produce phosphenes by electrically stimulating the retinas of blind individuals on an acute basis does not permit evaluation of other behavioral characteristics of the evoked visual capacity. Prior to initiating long-term studies in human volunteers, behavioral studies in animals are warranted to demonstrate the stability of the evoked visual capacity and the viability of the implanted stimulating system over extended periods of time. Nevertheless, epiretinal implants appear to be a potentially viable approach for restoring functional vision in blind individuals.

Optic Nerve Stimulation

One issue with electrically stimulating the retina or visual cortex is that the visual field is represented over a relatively large area, making coverage of the entire visual field nearly impossible with current electrode array technologies. In the visual pathway, the optic nerve is one place where the entire visual field is represented in a relatively small area. In a fairly novel approach to a vision prosthesis, it has been proposed that spiral cuff electrodes similar to those used in functional neuromuscular stimulation (49–52) could be used to electrically stimulate the optic nerve and produce visual perceptions. The objective is to place multielectrode cuff electrodes around the optic nerve and, by using complex patterns of electrical stimulation, selectively stimulate subsets of axons, or even individual axons, in the optic nerve (53, 54). In a proof-of-concept experiment performed in a blind human volunteer, the ability to safely interface to the optic nerve and evoke multiple phosphenes covering the entire visual space could be produced from a single cuff by varying the stimulation parameters (8).

Two significant issues present themselves with respect to the application of cuff electrodes as an interface to the optic nerve in a vision prosthesis. The first concerns the retinotopic organization of the optic nerve. Although there appears to be coarse structure to the receptive fields within the nerve (8), a fine organization has not been reported in other mammals using tracing techniques (55). The second is that selectively and simultaneously stimulating multiple subsets of axons using cuff electrodes could require cuffs with prohibitively large numbers of contacts (56–60), which increases the risk of the cuff electrode damaging the nerve (61).

Although only in the initial stages of investigation, electrical stimulation of the optic nerve may benefit from the use of intraneural microelectrode arrays, perhaps similar to one proposed by Branner & Normann (62), rather than surface stimulation. Intraneural microstimulation has the advantage of using small stimulating currents, which permits a high degree of selectivity and functional independence between the electrodes. A significant proof-of-concept milestone will be overcome when this technique is able to demonstrate selective and simultaneous activation of multiple discrete phosphenes.

ICMS of Visual Cortex

The final approach currently being investigated for a vision prosthesis brings us full circle to electrical stimulation of the primary visual cortex. Since the days of Brindley and Dobelle, progress in intracortical microstimulation (ICMS) of the visual cortex has concentrated on establishing the safety, long-term biocompatibility, and functionality of penetrating microelectrode arrays in the brain (63, 64). Once these requirements have been satisfied in animal preparations, it will be appropriate to begin investigations in humans to establish whether, as in the retina, patterned electrical microstimulation of the visual cortex results in patterned perceptions.

The Utah Electrode Array has 100 microelectrodes, each 1.0–1.5 mm long, arranged in a square grid contained in a package 4.2 mm by 4.2 mm. The only way that a structure such as this can be implanted into brain tissue is through the process of pneumatic insertion, which uses an expanding bolus of high pressure air to push the array into the tissues in less than 100 μsec (65). Hundreds of Utah Electrode Arrays and arrays manufactured by the Huntington Medical Research Institute have been implanted using this technique, which, when properly executed, effectively implants the electrodes without causing observable damage. Further, in three acute experiments in humans, 100 electrode arrays were implanted and removed after 30 minutes without incident. Based on evidence from animal experiments and a small number of human implants, we believe that implanting arrays with large numbers of microelectrodes impose no significant additional risks.

A number of studies have looked at the biocompatibility and the functionality of arrays of electrodes implanted in the brain (23, 47, 66–68). In all cases, a thin sheath forms around the electrodes, encapsulating and isolating them from the surrounding tissues. Except in isolated cases reported by Rousche, this sheath does not proliferate and explant the array from the tissues nor does it inhibit a response to the implant. In fact, other researchers have shown that there are numerous active ongoing processes around implanted silicon microelectrodes (69–71). However, the fact that chronic single unit recordings can be obtained in primates for periods of years (72, 73) suggests that a reexamination of the relationship between the presence of glial and astrocyte responses and the functionality of the implant is warranted. The capacity of the penetrating microelectorode arrays to stimulate cortex and evoked sensory behaviors has been evaluated in cat primary auditory cortex (74) and the dorsal cochlear nucleus (75). In Rousche & Normann's experiments, the threshold to evoke an auditory-detection behavior by stimulating a single microelectrode in the array remained stable around 10 nC/phase for periods of 100 days (which is equivalent to 20 μA for 100 Hz stimulation). In human brainstem implants, subjects were able to perceive and comprehend evoked auditory sensations for at least 3 months.

The animal work conducted so far demonstrating the biocompatibility and functionality of the Utah Electrode Array lays a foundation on which more experiments

need to be performed. An issue with these biocompatibility studies has been the choice of animal models; cats are a convenient model for cortical anatomy but the results of these studies need to be replicated in primates where the brains are considerably larger and the dura significantly tougher. Further development in a cortically based prosthesis requires: (*a*) a better understanding of the biocompatibility of these structures in primates and includes determining the nature of pial proliferation reported by Rousche & Normann (68, 74), and Maynard et al (67), (*b*) behavioral experiments in primates to determine the stability of the stimulation thresholds and evoked visual perceptions, and (*c*) short-term experiments in human volunteers to replicate the results of Schmidt et al (11) evaluating stimulation parameters for optimal phosphene generation. Experiments in human subjects can also be used to evaluate the crux of the cortical vision prosthesis proof-of-concept: patterned perceptions from patterned electrical stimulation.

Engineering a Vision Prosthesis

Despite the differences in the approaches, all vision prostheses share a common set of components; the most significant differences are in the interface to the nervous system. These components, illustrated in Figure 2, are: a camera to convert light into electrical signals, a means of transforming visual space to the retinotopic organization of the target structure, a way to transmit power and control signals to implanted electronics, a way to stimulate multiple electrodes to generate the phosphenes, and an interface to the nervous system. In some cases, the component is implicit in the design of the prosthesis; passive subretinal implants do not need a camera, but in most cases, the component requires the development of highly integrated electronic circuitry. In all cases, the ultimate design principle for the component is that it should mimic the function of the biologic element it is replacing as closely as possible.

The component of a vision prosthesis requiring the least amount of engineering effort will be the front-end camera. It is likely that existing digital camera technologies will be easily adaptable to the needs of a vision prosthesis in aesthetics, dynamic range, sensitivity, and depth of field. Commentaries on these features can be found in a number of review articles about artificial vision (35, 64). The mapping of visual space onto the retinotopy of the target neural structure will be complicated by the uniqueness of this map to individuals, the presence of plasticity in the visual pathway, and the sheer number of electrodes/phosphenes likely to be involved. Although this laborious process can be performed by hand (6, 9, 10), automatic systems for coregistering the visual space to the perceptual space have been proposed (76). These systems use a neural net that has a running "dialog" with the user in which the user's responses to sequences of electrical stimulation are used to optimize both the generation of phosphenes and the resulting visual perception. If the plasticity of the visual pathway turns out to be limited with respect to electrical stimulation, this system could be crucial to the eventual success of all vision prostheses. All of the components up to this

point are likely to be integrated into a single device resembling a set of eyeglasses; from this point on the components are likely to reside wholly inside the body.

The next step is to get information about the current visual scene from the outside world to the implant. This changes radically depending on whether the implant stimulates the retina or later sites in the visual pathway. Two methods for transmitting signals through the skin are percutaneous connectors (63, 77) and radio frequency (RF) telemetry (13, 78–81). Percutaneous connectors have the advantage that they are generally robust and can be designed so that implanted electronics such as demultiplexers are not necessary. The downside of percutaneous connectors is that they are prone to cause chronic infections, which can be exacerbated by large connectors needed for implants with hundreds of electrodes. In retinal implants, the percutaneous connector could take the form of a fine ribbon cable that passes from the inside of the eye, through the sclera, to the outside of the eye (35, 82). In the other implants, the percutaneous connector would most likely be affixed to the skull in an unobtrusive area behind the ear such as are used with cochlear implants. Telemetry offers the potential to pass both power and control signals without breaking the skin. In the retinal prostheses, this is even simpler as the lens offers an optically transparent communication path to the retina. A laser mounted on glasses would be used to transmit both power and information to the implanted circuits used to stimulate the target cells (35).

The next parts of the system are the multichannel stimulators necessary to simultaneously pass current through many electrodes in a manner that will evoke consistent phosphenes. These stimulators need to be "smart" in that they must be able to determine if an electrode has failed. In addition, safety concerns require that there be a guaranteed voltage compliance to avoid tissue damage caused by breaking down water at the electrode interface. There is an engineering trade-off; putting smarts on the chip increases the amount of power dissipated by circuits and decreases the capacity for upgrades, but greatly lowers the bandwidth necessary to communicate with the chip. In addition, more complicated chips have more potential failure modes, which could be catastrophic in an implant that cannot be repaired in situ.

The last technological item in a vision prosthesis is the actual interface to the nervous system where electrical stimulation takes place. There has been significant progress in the past few years in understanding the electrochemical processes that occur at the electrode-tissue interface and designing optimal interfaces to the nervous system (83–85). Surface electrodes are used extensively in cochlear implants because they are simple to put into position, and they preserve the integrity of the epithelial cell layer. These advantages come at the cost of not being able to selectively stimulate the desired neural elements that evoke the desired visual perception. Microelectrode arrays come in many different architectures (23, 25, 26, 86, 87) but the long-term biocompatibility of these devices is still the subject of active research. Figure 3 is a typical Utah Electrode Array shown against a penny to provide a sense of scale. Figure 4 is a modification of the Utah

Figure 3 A typical Utah Electrode Array.

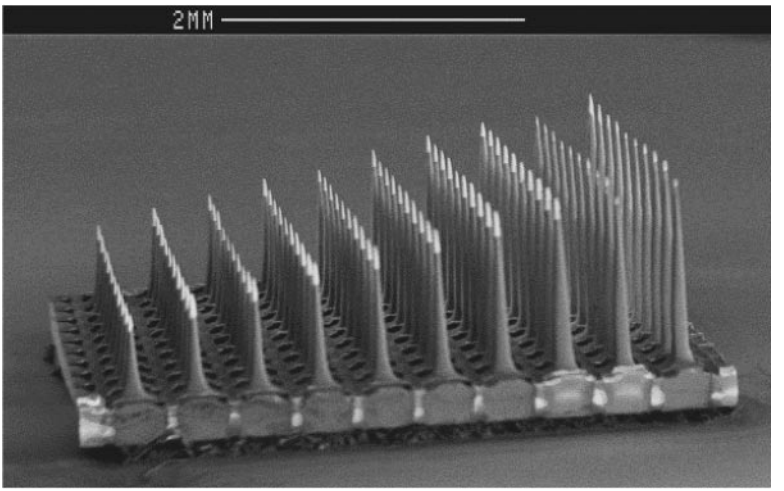

Figure 4 A modification of the Utah Electrode Array in which the length of the electrodes is uniformly graded.

Electrode Array in which the length of the electrodes is uniformly graded. This structure permits accessing information that is processed in the horizontal and vertical directions.

CURRENT ISSUES IN VISION PROSTHESES

Despite the progress made in developing vision prostheses, significant materials, engineering, physiologic, and behavioral questions must be addressed before clinical systems become a reality. These questions are common to all of the approaches taken toward realizing a vision prosthesis. Unfortunately, though many of these questions can be answered in animal models, at some point, these experiments must be performed on humans to answer some of the more subtle questions concerning patterned perception from patterned electrical stimulation. Some of these questions are discussed below.

The first question relates to the biocompatibility of implanted materials and structures for chronic electrical stimulation of nervous tissues. Traditionally, biocompatibility assessments have been performed with Nissel-type stains that are simple to perform and useful for determining cellular densities around implanted electrodes (67, 88). These stains, however, are not specific to a cell line (neurons, glia, astrocytes), nor do they reveal information about the status of the cell (normal, pathologic, degenerating); thus, these stains are generally most useful for evaluating the extent of the encapsulation response and determining whether cells from the immune system are present. Recently, many labs have begun to use stains for GFAP to evaluate the biocompatibility of implanted tissues, evaluating positive stains as indicative of negative biocompatibility. Zrenner et al point out that in degenerate retinal preparations, Müller cells overexpress GFAP regardless of whether an implant is present or not (28). Likewise, the researchers at the University of Utah have seen instances in cortex where implant sites have had significant GFAP responses and single unit recordings for periods of months. This points to a fundamental question regarding implanted neurostimulating devices: Should biocompatibility be defined from a primarily functional standpoint or are there specific changes that can be revealed by histologic preparations that more closely correlate with traditional definitions of biocompatibility? I believe that the answer to this lies within the field of molecular biology where researchers routinely use state-of-the-art confocal microscopy and immunohistochemistry not only to identify cell types, but to find out what they are doing. In contrast to the traditional Nissel-type stains, using immunohistochemistry to evaluate implanted tissues may allow us not only to identify cells in the neighborhood of the electrode, but also to determine their viability as well.

Included in the issue of biocompatibility is the effect of chronic electrical stimulation on nervous tissues. Research in the peripheral nervous system and spinal cord shows that chronic electrical stimulation can cause significant changes

in the morphology of cells and fibers in proximity to the stimulating electrode (45–48, 66, 88–92). This issue is paramount for vision prostheses as the implanted tissue could routinely be stimulated at very high rates for eight hours per day, every day, for an implant lifetime of decades. For both subretinal and epiretinal prostheses, there is a striking lack of experimental evidence as to the effects of long-term electrical stimulation of the retina. Although the optic nerve systems are nascent, experimental results in the peripheral nervous system using cuffs should be applicable. In the cortical vision systems, not only are there concerns about the direct effects of electrical stimulation on the cells themselves, but also whether the neural network could develop pathologic conditions (e.g. epilepsy) from repetitive electrical stimulation (11).

There are also many questions about the relationship between patterned electrical stimulation of the visual system and the resulting perceptions. For instance, will plasticity in the visual system be a major or minor factor in the capacity of the user to make sense of the stimulation? While it is impossible to pick the location of phosphenes a priori to implantation, is it possible to "retrain" the visual system by presenting highly organized patterns of stimulation that will adjust the neural representation of space to conform to the geometry of the prosthesis? Will automatic systems such as proposed by Eckmeller et al (76) need to be retuned each day or will the maps remain stable indefinitely? It is apparent that plasticity in the visual system might be what makes vision prostheses work, but it could also cause many problems.

For a vision prosthesis to provide functional vision, the user must be able to interpret the patterns of electrical stimulation. These patterns of electrical stimulation need to reflect both the spatial and temporal patterns present in the visual scene. We still do not know how the brain will interpret the patterns of stimulation resulting from many hundreds or thousands of electrodes. Thus the question remains, does patterned electrical stimulation of the visual pathway result in a patterned visual perception? Despite the studies of Schmidt et al (11) in human visual cortex, we still do not understand how closely spaced electrodes in either the retina or the cortex will interact to produce lines and more complex shapes from multiple phosphenes. In addition, prototype systems will not provide additional features of visual sensation (color, texture, depth) but there is hope that, as we begin to understand how the visual system represents these abstractions, we can incorporate them into the electrical stimulation.

Questions that remain persist in the realm of engineering. The early work of Cha et al (93–95) suggests that 625 grayscale pixels could provide functional vision suitable for reading text and negotiating unfamiliar spaces. Two significant issues with these experiments are that the pixels were in a strict rectilinear organization and of a uniform size. Based on the organization of receptive fields in the retina, optic nerve, and cortex (96), it is not likely that such structured spatial organization will be achieved with stimulating arrays. Figure 5 is a high-resolution receptive field map of cat visual cortex obtained with simultaneous recordings from a Utah Electrode Array. For each neuron recorded, a box was constructed indicating the

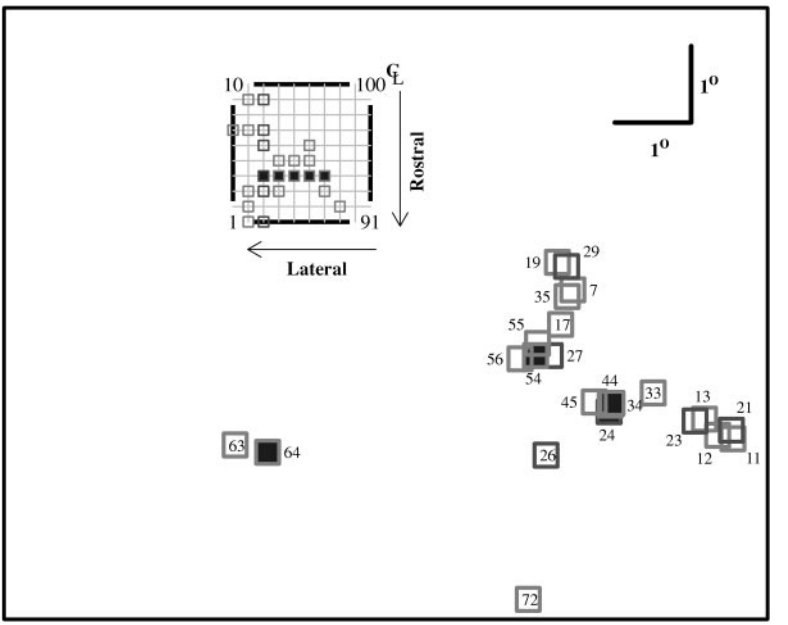

Figure 5 A receptive field map of cat visual cortex obtained with simultaneous recordings from a Utah Electrode Array. The boxes show the likely position of phosphenes generated by stimulating electrodes in a row and column of the array.

location and size of the region of visual space monitored by that neuron. Figure 6 shows a representation of the conformality of the receptive field map. The measured receptive fields are shown as square boxes. Black lines go from the receptive field to the corresponding position on the electrode array. In a highly conformal map, there would be a rational structure to the lines; in the data shown, this is certainly not the case. Thus, it would be prudent to reinvestigate the number of pixels needed while varying the size of the receptive fields and altering the spatial relationship between receptive fields to go from highly conformal to completely random. This would yield significant insight into the number of electrodes likely to be needed to provide functional vision. These experiments could be based on the systems designed to aid individuals with low vision (97–100) and could be used to generate accurate simulations of functional vision in real-time.

Another engineering issue associated with vision prostheses is the dissipation of power in living tissues. Many researchers in this field propose using active electronics that are implanted inside the body. These electronics consist of telemetry systems, microstimulators, or multiplexing subsystems, all of which will dissipate power. Significantly increasing the local temperature around the implant can have significant consequences on its biocompatibility. Simulations of epiretinal

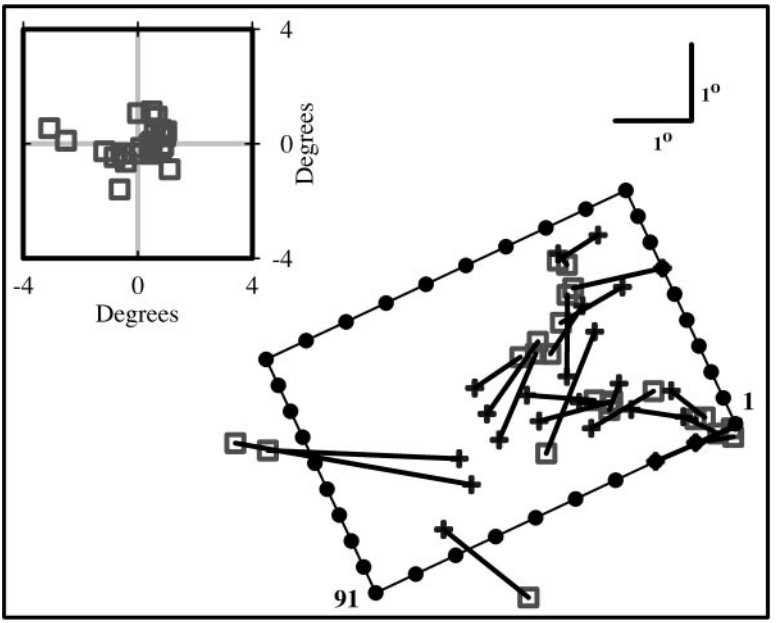

Figure 6 A representation of the conformality of the receptive field map. The measured receptive fields are shown as square boxes. Lines go from the receptive field to the corresponding position on the electrode array.

vision prostheses suggest that implanted systems would only slightly increase in the temperature in the eye (Humayun presentation, Detroit, 1999); however, these simulations were performed on an incomplete understanding of the final design of the retinal implant. If more electrodes are needed to provide useful vision, the power requirements could increase significantly. The question of power dissipation is more acute in the subretinal space where the vitria cannot act as a large heat sink. Cortical implants may benefit from the presence of the rapidly circulating cerebral spinal fluid that could efficiently remove heat from the implant area. In all cases, we do not understand how changing the temperature in the vicinity of the implant could adversely affect the biocompatibility of the implant.

The last question that needs addressing for a successful vision prosthesis is how electrodes and microelectronics can be insulated from the biologic medium for extended periods of time under electrical bias. Many materials have been used to insulate microelectrodes, with Parylene showing the most promise (101, 102). However, polymeric coatings for implanted electronic devices have proven problematic as electronics implanted in vivo have inevitably failed after short periods of time (103, 104). A number of designs for hermetically sealed packages

have been demonstrated, but these have yet to be transferred to relatively large implant systems consisting of multiple electrodes and electronics modules. Until it is possible to protect these high-speed transistor-based electronics from ion contamination from the biologic medium, progress toward a vision prosthesis will be severely hindered.

SUMMARY AND CONCLUSIONS

This review presents some of the anatomic and physiologic bases for artificial vision, discusses the status of four approaches to restoring functional vision in the blind, describes some of the engineering issues facing developers of these systems, and presents some of the remaining questions relevant to artificial vision. In general, the four approaches to artificial vision demonstrate at some level that it is possible to manufacture an interface to the target neural structure, implant the stimulating device, and evoke visual sensation via passing electric currents. In some cases, there is histological evidence as to the biocompatibility of the stimulating devices, and in other cases, there is evidence as to the long-term functionality of the implant system. Although many of the obstacles facing developers of vision prostheses are engineering-related (miniaturization, power, functionality), there still are a number of questions that lie squarely in the realm of biologists (foreign body reaction), psychophysicists (pixelized vision), and bioengineers (novel interfaces to the nervous system).

In addition to many scientific justifications for continuing to research artificial vision, there are emotional and economic reasons as well. The potential emotional effects of regained independence from an artificial vision system defies valuation. However, any system capable of providing a rudimentary visual capacity to the blind would have profound effects not only on the users of the system, but on the economy as well. Despite the numerous assistive technologies available to the blind, the lack of visual capability remains a significant sensory deficit that impacts everything from daily living to competing in the workplace. Currently, there are 1.1 million people in the United States who are considered legally blind, and this number will only increase as the population ages. Although injuries to the eyes do account for a small number of cases of blindness, the vast majority results from eye diseases such as retinitis pigmentosa, age-related macular degeneration, and retinal damage secondary to diabetes. In addition to its psychological and emotional costs, blindness has been estimated to cost the federal government alone $4 billion a year; this number does not include the costs to states or private organizations. Although an artificial vision system cannot be expected to restore the fullness of visual perception, being able to read large text and negotiate unfamiliar surroundings would be of great assistance to these people.

Despite the great promise of vision prostheses as a near-term assistive technology for blind individuals, it is important to remember that artificial vision is only a work-around and that molecular biologists or geneticists may be able to devise ways of preventing diseases of the retina or transplanting cells that have been lost

and getting them to reintegrate into the remnant neural network. Nevertheless, progress in these areas has been slow and depends on our further understanding of the complexities of forming tissues from groups of cells. Vision prostheses, on the other hand, may, in the end, be a more manageable case of straight-forward engineering.

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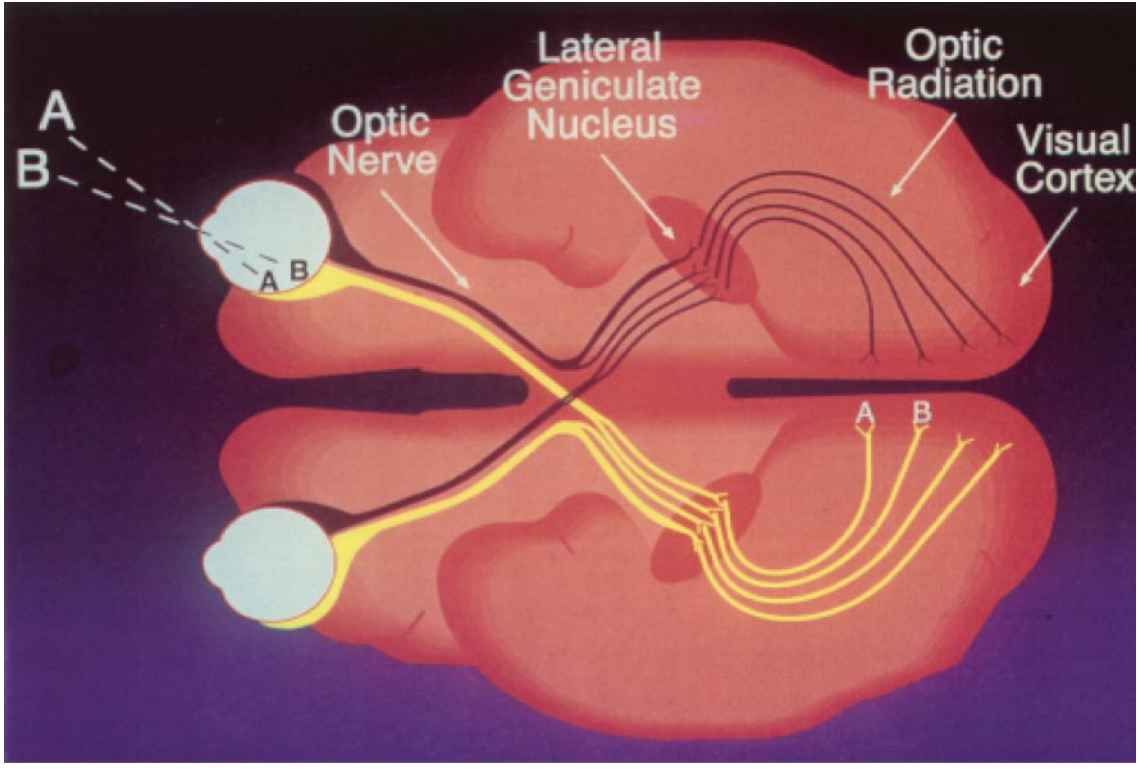

Figure 1 A schematic of the visual system highlighting the neural structures of the visual pathway most relevant to the development of a vision prosthesis.

Figure 2 The components of a vision prosthesis must include a camera to convert light into electrical signals, a means of transforming visual space to the retinotopic organization of the target structure, a way to transmit power and control signals to implanted electronics, a way to stimulate multiple electrodes to generate the phosphenes, and an interface to the nervous system.

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