Objective: To review progress toward an electronic retinal prosthesis for outer retinal degeneration.

Method: Literature review.

Results: Retinal degenerations such as retinitis pigmentosa result in a loss of photoreceptors. There is a secondary loss of inner retinal cells, but significant numbers of bipolar and ganglion cells remain for many years. Electrical stimulation can produce phosphenes in the eyes of individuals who are blind as a result of retinitis pigmentosa. Several research groups are trying to exploit this phenomenon to produce artificial vision with electronic retinal prostheses. Two groups, with private company sponsorship, have recently implanted first-generation devices in subjects with advanced retinitis pigmentosa. They have reported limited preliminary results. This article seeks to put these results in a broader context and review potential obstacles to successful prosthesis development. These include inner retinal cell viability, high thresholds, signal encoding, power requirements, biocompatibility, and device encapsulation.

Conclusion: There has been substantial progress toward an electronic retinal prosthesis, but fully functional, long-lasting devices are not on the immediate horizon.

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RETINAL DEGENERATIONS such as retinitis pigmentosa (RP) initially result in photoreceptor loss. Later in the course of the disease, there is secondary loss of inner retinal neurons. Postmortem studies demonstrate the presence of inner retinal cells even in eyes severely degenerated by RP (Figure 1). Counts of cells in the inner nuclear layer suggest that 40% to 88% are retained, whereas 20% to 48% are retained in the ganglion cell layer, depending on the severity of the degeneration and the retinal area sampled1-3 (Table 1).

The mechanism of damage and loss of inner retinal neurons in RP is unknown. The conventional explanation for the loss of inner retinal cells is transneuronal degeneration. Another hypothesis involves the action of retinal pigment epithelial cells that migrate to the inner retina. These cells may envelope, invade, and occlude retinal vessels. The resulting ischemia may cause loss of ganglion and bipolar cells.4 The proximity to the choroid enjoyed by the bipolar cell layer after loss of the outer retina may account for the relative preservation of these cells.

Because the genetic defects for numerous types of RP are now known, gene therapy for these conditions has been proposed.5 Although gene therapy may hold great promise for halting retinal degenerations, it does not seem likely that it could restore lost function. It is very difficult to insert genes into postmitotic cells.6 The numerous genetic subtypes of RP7 suggest that individually tailored approaches might be necessary for each mutation. In addition, many mutations have yet to be identified. Retinal or retinal pigment epithelial transplantations have been proposed as therapy.8 Thus far, extremely limited functional results have been obtained with these transplantations.6,9 Antiapoptotic treatment shows some promise but, again, results in animal models have so far shown limited success.6,9

Preservation of the inner retinal neurons in RP raises the possibility that appropriate stimulation of these cells may produce vision. The ganglion cells are the “output” cells of the retina. Driving them with suitable stimulation, electrical signals for example, may mimic their usual signals to the brain (Figure 2). In addition, the ganglion cells have a topo-
The concept of an electrical retinal prosthesis was introduced as early as 1956 by Tassiker in Melbourne, Australia. A variety of prosthetic designs have since been proposed. The simplest is a 1-piece subretinal device consisting of multiple small photodiodes (Figure 3A). When light is absorbed by a photodiode, it is converted to electricity. Each photodiode acts like an artificial photoreceptor, receiving ambient light and converting it to a graded electrical response. This electrical response may then act to stimulate adjacent nerve cells, such as bipolar cells. Since the ambient light arrives in a topographically appropriate distribution and also supplies power, this type of device is very simple in design. Epiretinal device designs typically are more complex because they rely on external imaging devices and power sources. Figure 3B is an example of one type of epiretinal device. An external television camera converts ambient light to an electrical signal. This signal is transmitted, along with additional electrical power, by an induction coil on the temple. A second coil on the scleral surface receives the power and signal and transmits these via a small cable to a microchip inside the eye. This chip contains electrical circuits that distribute the signal appropriately to small electrodes that contact the epiretinal surface. Other epiretinal device designs are illustrated in Figures 3C and D. Designs vary according to how much of the required electronic circuitry is contained in the intraocular device vs extraocular elements. Power and signal transmission may be accomplished by penetrating wires, induction coils, or lasers. Rizzo and Wyatt suggested placing the intraocular electronic components inside a modified intraocular lens, away from the retinal surface, and running a ribbon of electrodes from this device to the retinal surface.

Cortical implants work in a manner analogous to epiretinal implants. An external miniature television camera sends its signal to an induction coil, which transmits the signal and power to a secondary coil buried under the scalp. Power and signal travel via wires to a microchip, which distributes electrical current to an array of electrodes that contact the primary visual cortex.

It has been known for many years that passing an electric current through the healthy eye can produce the sensation of light. Potts and Inoue demonstrated in 1969 that external electrical stimulation of the eye could elicit perception of light and a cortical response (electrically evoked response) in some subjects with RP, even when the visual evoked potential was essentially absent. These results seem to indicate that at least some retinal ganglion cells and more central elements of the visual system retain some function even in very advanced RP. A retinal prosthesis would depend on these remaining elements, limiting its use compared with a cortical prosthesis, which could potentially provide vision in instances where even the optic nerve has been destroyed. A cortical prosthesis might be able to help patients with blindness from diabetic retinopathy and glaucoma, 2 of the leading causes of blindness in the industrialized world, whereas a retinal prosthesis would be unsuccessful because of the loss of the ganglion cells that make up the optic nerve. A retinal prosthesis might also be useful in macular degeneration, where there is preservation of inner retinal elements. See Table 2 for a comparison of the major implant types.

Several groups in the United States, Germany, Japan, Australia, and Korea are actively pursuing research in visual prostheses for individuals with blindness. Pros-
theses have been suggested that electrically stimulate the retina, optic nerve, or visual cortex in an attempt to produce artificial vision. Two groups are designing devices based on the local release of glutamate. There is currently no device that fulfills the mission but incremental progress and success with cochlear implants for individuals with deafness provide the impetus to continue.

Chow et al and Humayun et al recently inserted prototype implants in human subjects with advanced RP. The inevitable publicity surrounding these events, and the inability of most media to convey a thorough context for it, prompted us to prepare this review to provide a balanced discussion of the current state of knowledge regarding retinal prostheses.

Major issues remain for prosthesis development. We will discuss problems with inner retinal cell viability, stimulus threshold, signal encoding, power requirements, biocompatibility, encapsulation, and testing of implant subjects.
INNER RETINAL CELL VIABILITY

As noted previously, a retinal prosthesis requires the presence of some viable retinal ganglion cells. The number, type, and location of viable ganglion cells that would be required for a useful prosthesis is unknown.

Although the studies cited previously show that numerous retinal ganglion cells remain even in advanced RP, the viability of these cells is unknown. Counts of ganglion cells are difficult and may be artifactually elevated by the presence of displaced amacrine cells. Counts of inner nuclear layer cells performed with standard histochemical stains include 5 cell types so the proportion of lost bipolar cells may be masked by preservation of other types.

The types of ganglion cells that remain are unknown. It is possible that selective loss of critical types may limit the results of electrical stimulation. In retinal areas where significant numbers of viable photoreceptors remain, it is doubtful that a prosthesis could improve existing vision. This is likely to limit prosthesis use to areas of severe degeneration.

It is not known whether the reduction in the number of ganglion cells in degenerated retinas is consistent with useful pattern vision. Some data from acute electrical stimulation experiments in humans with advanced RP that bear on this question are discussed later. Experience with cochlear implants suggests that these prostheses may be useful when only 10% of spiral ganglion cells remain. The relevance of this observation to the retina is uncertain.

The mechanism of ganglion cell loss in RP is unknown, as reviewed previously. Ganglion cell loss may continue in the presence of a prosthesis. There is no currently accepted method for noninvasively assessing the viability of retinal ganglion cells in the absence of photoreceptors. Two groups have used the electrically evoked response as a method to evaluate subjects who volunteered for intraocular stimulation experiments. Although there was a correlation between extraocular and intraocular thresholds in one small study, sufficient data are not available to rely on this test. Selection of the most appropriate candidates for a prosthesis will therefore be limited unless such a method is developed.

In summary, although significant numbers of cells remain in the inner nuclear and ganglion cell layers of the retina in advanced RP, we have little information about the types and subtypes of these cells. We do not have a method for noninvasive determination of the viability of these cells. Studies to identify the remaining cells and to noninvasively estimate their function are needed.

STIMULATION THRESHOLD

The amount of electric current that will be required to stimulate inner retinal cells and produce perception is a critical factor in implant design. First, the safety of any device will depend on keeping stimulus charge levels in a range that does not damage the retina. Second, the heat created by a device is primarily driven by its power consumption. The largest amount of power is consumed at the electrode-tissue interface because of its electrical resistance. Heat must be kept at levels that will not damage ocular tissues. Third, methods must be developed to deliver sufficient power to a device to allow suprathreshold stimulation of a sufficient number of electrodes to create useful vision. The stimulation threshold is a primary driving factor in determining these parameters.

Stimulation thresholds have been studied in a variety of models and species with very different methods, making direct comparisons difficult. The charge density required to produce a response is a critical variable. Many investigators do not calculate charge densities for their stimuli (or give sufficient data for the reader to do so), compounding the problem. A further difficulty is that the calculated charge density based on injected charge and electrode geometry does not take into account local “hot spots” (eg, at electrode edges) where the charge density may be considerably higher. Thresholds also vary significantly with stimulus conditions. For the purposes of this review, we present results obtained from intact animals and humans with fairly similar techniques in Table 3. In the rabbit studies presented in the table, either epiretinal- or subretinal-stimulating electrodes were placed. Recording electrodes were placed at the visual cortex. The smallest amount of electricity at the retina (given in coulombs [C] per centimeter squared of charge density) that would yield an evoked response at the visual cortex (electrically evoked potential) is given. In the human experiments, humans who were awake were tested. Either handheld intravitreal electrodes close to the retina or microfabricated electrode arrays in contact with the epiretinal surface were used. Electrode current and duration was varied until the subject reported a barely visible perception (usually a small spot of light). The human experiments are described further in the “Signal Encoding” section.

Thresholds have generally been lower for subretinal than epiretinal stimulation. In retinas with outer de-
generation, thresholds have been consistently higher. Unfortunately, data in humans have not been available for subretinal stimulation.

The explanation for higher thresholds in degenerate retinas is not clear. One possibility is that the remaining cells are abnormal in some way that elevates their thresholds. Another possibility is that a lower-threshold population of cells (most likely the photoreceptors) is destroyed by the degeneration and the remaining classes of cells (perhaps bipolar or ganglion cells) normally have higher thresholds. Greenberg measured latencies and chronaxies of responses to electrical retinal stimulation in frogs and in humans with RP. He concluded that for longer pulses, the bipolar cell is the most likely site of response to epiretinal stimulation in degenerated retinas. Ziv et al, working with isolated rabbit retinas, found evidence that brief pulses on the epiretinal surface stimulate retinal ganglion cells whereas longer pulses stimulate bipolar cells.

In summary, threshold measurements for perception have been obtained in humans with advanced RP by surface electrical stimulation. These thresholds are significantly higher than those from healthy humans or those for evoked potential recording in animals with outer retinal degeneration. Perceptual thresholds for subretinal stimulation in humans with advanced RP would be of great interest, but these have not been done.

Further consideration of the implications of these results is discussed in the “Biocompatibility” section.

SIGNAL ENCODING (ATTEMPTS TO CREATE PATTERN VISION)

Retinal prostheses are being designed to electrically stimulate cells that survive degeneration to produce artificial vision. Investigators must demonstrate that electrical stimulation excites visual cells in a predictable manner in order for a prosthesis to be reliable. Once stimulation parameters give reproducible visual effects, researchers must learn how to adjust these parameters to create useful vision.

Retinal ganglion and bipolar cells are topographically arranged in an orderly distribution across most of the field of vision. This has led to the simple concept that an array of electrodes can be placed against the retina, with rows and columns like lights on a scoreboard, and that activation of electrodes in the array in a given shape might yield perception of a similar shape. In several respects, this concept is an oversimplification. There are many types of retinal ganglion and bipolar cells, which are small and closely spaced. Electrodes in a prosthesis will have to be large to avoid exceeding safe charge-injection limits. Each electrode is likely to stimulate many cell types indiscriminately. These cell outputs would then be very different than the normal physiologic situation in which there is a different orchestration of responses. Even worse is the possibility that focal stimulation might activate ganglion cell axons representing many cells across a broad area of the retina. This is likely to produce diffuse rather than focal perceptions. Work in animals and humans has therefore been undertaken to investigate the physiologic and perceptual consequences of electrical stimulation.

Animal experiments have shown that subretinal or epiretinal electrical stimulation in isolated retina and eyebud preparations influences ganglion cell activity. The patterns recorded from ganglion cells in response to focal electrical stimulation in some experiments seem comparable with those evoked by focal spots of light. Retinas from animals with degenerated, chemically inactivated, or chemically decoupled photoreceptors still show ganglion cell responses to focal electrical stimulation.

Cortical evoked potentials have been recorded in a variety of animals in response to focal epiretinal and subretinal stimulation. The cortical evoked response waveforms and amplitudes are also comparable with those evoked by focal spots of light. Although these results are encouraging, they are a long way from demonstrating the production of useful pattern vision from electrical stimulation of the retina. It should be remembered that a complex visual evoked response can be recorded in humans with stimulation by a diffuse flash of white light alone, showing that the evoked potentials in animals are not necessarily indicators of pattern vision.

Because of the limitations of animal experiments, 3 groups have undertaken epiretinal electrical stimulation of the retina in human volunteers. Most experiments were done in volunteers with advanced retinal degeneration, although 2 volunteers had healthy retinas and orbital cancer. Two others were undergoing vitrectomy for other conditions.

The first human tests were done with epiretinal stimulation and handheld intravitreal electrodes. Subjects reported small spots of light in response to electrical stimulation. Two-point discrimination was also reported using multiple electrodes. Correlation of the length of perception with the duration of the stimulus convinced the investigators that operating lights were not the cause of perception. These results were very encouraging.

Later experiments by others aimed at eliciting form perception showed results that conflicted with these early reports. One group, using handheld electrodes, showed that subjects could distinguish a vertical from a horizontal line, a few letters, or a square shape. Another group found that a subject was able to perceive a shadow from a handheld electrode, even when no current was delivered. The later investigators felt this approach could lead to false-positive perceptions. Additional experiments were done with electrode arrays in contact with the retina. With this device, subjects sometimes reported single round percepts to electrical stimulation with a single round electrode. Frequently, however, they reported multiple percepts to single-electrode stimulation (which did not occur in a subject with normal sight). Stimulation of multiple electrodes, in contrast, did not always produce multiple percepts. The percept reported from stimulation of the same electrode(s) with the same electrical parameters did not always produce the same percept. Results in the subjects with retinal degeneration were reproducible 66% of the time and in the healthy subject, 82% of the time. Clear-form perception as obtained by others was not obtained, even in the subject with normal sight. This group therefore determined whether perceptions met a “reasonable expec-
cation” based on the configuration of stimulated electrodes. This expectation was met for the subjects with RP 48% and 32% of the time for single- and multiple-electrode trials, respectively. For the subject with normal sight, this expectation was met 57% of the time. Two-point discrimination could not be obtained in all subjects.

These disparities between the groups may be due to differences in methods or subjects. It is surprising that microfabricated electrodes in direct contact with the retina would yield results that were seemingly less satisfactory than those obtained by handheld electrodes. It is also difficult to explain the disparities based on subject selection because Humayun et al.16,35 had many subjects with severely reduced vision, some of whom had no light perception. Although results obtained by Rizzo et al.37,26,57 in the subject with normal sight were superior to those they obtained in their subjects with RP, they still did not obtain perceptions that consistently matched the stimulation patterns. This suggests that the stimulation methods, rather than the severity of the retinal degeneration, may be responsible. Eckmiller et al.61 have suggested that the stimulus that will be required to produce pattern vision by epiretinal devices is likely to be very complex. They have designed a method to optimize stimulus parameters using a learning neural network approach. It is likely that this device could only be tested in a chronic implantation, not an acute experiment. In a preliminary report of 2 acute human tests, Eckmiller et al. apparently did not use this approach, although they did use careful physiophysical methods with control subjects. Their report (to date) concentrated on the technology and methods and did not report results of attempts to produce pattern vision.

Proponents of subretinal stimulation argue that this approach will provide pattern vision with much simpler stimuli because it takes advantage of any remaining processing capability in the middle layers of the retina. It would be of great importance to test this hypothesis with an active subretinal device. Safety and technical considerations have precluded doing this type of testing in an acute experiment. (See “Testing of Implant Subjects” section for discussion of preliminary results in subjects with chronic subretinal implants.)

In summary, visual cells can be excited in a predictable manner by electrical stimulation. Cortical evoked responses have been obtained in several species by direct electrical stimulation of healthy and damaged retinas. Perception of light has been demonstrated in numerous human volunteers with advanced RP to intravitreal and surface electrical stimulation. Efforts to produce pattern vision in human subjects have yielded conflicting results.

**POWER REQUIREMENTS**

Most current subretinal device designs consist only of an array of subretinal microphotodiodes. Although the simplicity and similarity to the natural situation are conceptually attractive, experiments show that such devices do not generate sufficient current from ambient light alone to stimulate inner retinal elements in animal eyes.68,59 Recent work by Gabel et al.59 showed that cortical activation secondary to retinal stimulation with such a device required brightness comparable to 2 to 3 times sunlight levels. Simple photodiodes will also not produce charge-balanced pulses, which are the safest form of electrical stimulation of nerve tissue.61 Across time, pulses that are not charge balanced will lead to dissolution of metal with toxicity to neural tissue and loss of electrode function. Methods to amplify these signals and produce charge-balanced pulses are proposed but these add significant complexity.60

It is not practical to use an intraocular battery to deliver power to a visual prosthesis for several reasons. Repeated intraocular surgery to replace batteries poses unacceptable risks. Potential toxicity of chemicals in batteries is unacceptable. Finally, the weight of batteries is likely to be prohibitive. Power will therefore have to be transmitted from outside the eye. Because there are severe limits on the amount of power that can be delivered this way, the power requirements of a prosthesis are critical.

The power requirement for a retinal prosthesis depends primarily on the threshold charge needed for perception and the number of electrodes in the stimulating array. As noted in the “Stimulation Thresholds” section, we have some measurements of epiretinal thresholds in subjects with advanced RP. These show considerable variability. Although it seems reasonable to assume that subretinal thresholds will be lower, we do not yet have these numbers. The number of electrodes needed to achieve form perception, if this indeed can be accomplished, is unknown. Simulations of prosthetic vision have been attempted in human subjects with normal vision.62,63 These studies suggest that a 4×4 array (with 16 electrodes) is unlikely to allow vision better than crude localization. A 6×10 array (with 60 electrodes) might allow spot reading and object recognition. The relevance of these simulations is uncertain because they were carried out in subjects with normal visual systems. It is likely, however, that at least this many electrodes would be required in diseased retinas.

Using thresholds obtained from acute human trials, Caulfield et al.64 estimated the number of electrodes that could be driven by epiretinal devices. One device would use an external laser to deliver power to an intraocular receiver. They estimated from a model that 15 mW could be delivered and that this would be sufficient for 208 electrodes. Using a device with power transmission via induction coils, up to 3.4 mW could be delivered, sufficient to drive 47 electrodes. Power transmission via induction coils would be simpler and more reliable than transmission with a laser. The latter requires precise alignment of the laser with an intraocular target and clear media.

In summary, the total power required for a retinal prosthesis is currently unknown because we have only a few threshold measurements from epiretinal electrodes in humans with RP and we do not know how many electrodes must be driven to produce useful vision. Using induction coils for power transmission, the best current estimates suggest that there will be barely enough power. A laser delivery system can provide more power but will be more difficult to develop and use. Simple subretinal devices consisting only of microphotodiodes are unlikely to produce sufficient power.
**BIOCOMPATIBILITY**

The ideal implant material would be nontoxic to the retina and would not elicit rejection, inflammation, or fibrosis from the host. For an electronic implant, 3 factors must be considered: (1) chemical, biophysical, and immunological reaction to the implant materials and surgery, (2) reaction to electrical stimulation, and (3) heating of the tissue. These elements cannot be entirely separated because reaction to electrical stimulation depends in part on the material that the electrodes are composed of, whereas heating depends on power consumption, materials used, and implant location.

**Tissue Reaction to Materials**

A variety of materials that might be used for implants have been tested in rat retinal cell cultures.\(^6\) Cell survival on these materials was poor. Coating of the materials with poly-D-lysine, poly-L-lysine, or laminin greatly improved cell survival on all materials except titanium nitride. Chronic, inactive implants have been observed for 8 months. A careful histochemical study suggested that these materials was poor. Coating of the materials with biocompatibility in animal eyes. Epiretinal implants\(^66,67\) did not dislocate, and histologic changes around them were minimal. Electroretinogram results and visual evoked potentials remained normal in these eyes. Subretinal implants\(^52,58,68\) also did not dislocate. These eyes, however, show marked loss of outer retinal cells, with fibrosis and/or retinal pigment epithelial changes in many cases. Exploration of electrically active devices with gold electrodes from animal eyes showed dissolution of the gold after 8 months. A careful histochemical study suggested that the outer retinal degeneration across subretinal implants in cats with normal vision resembles naturally occurring degeneration in Abyssinian cats.\(^69\)

In summary, epiretinal devices secured with tacks over normal retinas show little histologic change in the underlying retina, although the extent to which these arrays actually contact the retina is not obvious. The functional integrity of the underlying retina has not been determined. Subretinal devices implanted under normal retinas cause severe degeneration of the outer layers and a variable degree of changes in the inner retina. Modification of the subretinal devices with perforations may decrease the degree of overlying degeneration. Histologic features have not been studied after chronic placement of a subretinal device in a retina with preexisting outer degeneration, which is the clinically relevant situation.

**Tissue Reaction to Electrical Stimulation**

Charge injection into tissue may be accomplished by faradaic or capacitive mechanisms. The capacitive mechanism is ideal because it allows charge transfer without transfer of electrons, which will cause potential damage to the host tissue or the electrode. Unfortunately, the amount of charge that can be delivered per unit area (ie, charge density) is too low for the purposes of a retinal prosthesis. In faradaic injection, electron transfer occurs across the electrode-tissue interface and chemical species are oxidized or reduced. Faradaic charge injection may be irreversible or reversible. Irreversible injection results in new chemical species being introduced into tissue, with the potential for toxicity. It also leads to electrode corrosion. Reversible faradaic injection relies on charge-balanced current pulses to minimize or eliminate this problem. Completely reversible faradaic injection is, for several reasons, not obtainable. Hence, some degree of potentially destructive chemical reactions will occur. The goal is to minimize these reactions. Judicious selection of electrode materials, electrode geometry, and stimulus parameters can reduce the amount of charge that is injected into the tissue.

Experiments to determine safe charge-injection limits for a variety of materials have been performed in neural tissue. For platinum, a limit of \(10^{-4}\) C/cm\(^2\) has been proposed.\(^59\) Oxidized iridium has a significantly higher limit (1-2 \(\times\) \(10^{-3}\) C/cm\(^2\)).\(^64,71\) The most recent evidence, however, is that the product of charge density and charge per phase determines the safe charge-injection level.\(^59\) Safe charge-injection limit determinations have been made primarily in brain tissue, and although it seems reasonable to use them as estimates for the retina, actual charge-density safe limits for the retina are unknown. In addition, the stimulus paradigms used to determine safe limits (typically experiments were performed across several hours on 1 day) do not closely mimic what the retina would be exposed to with long-term stimulation by a prosthesis. Weiland et al\(^73\) recently reported results of long-term epiretinal stimulation in dogs. Using 90 or 180 \(\mu\)A, 1-ms biphasic pulses, they stimulated the retina through an array of 16 electrodes, each 500 \(\mu\)m in diameter. The stimulation was done for 10 to 12 hours per day for up to 60 days. Seven of the dogs had normal retinas, and 2 had retinal degeneration. Clinical examination, fluorescein angiography, and histologic study results of some eyes showed no damage attributable to the electrical stimulation. As noted in the “Stimulation Thresholds” section, acute experiments in humans with RP show thresholds between 2.8 \(\times\) \(10^{-3}\) to 2.8 \(\times\) \(10^{-4}\) C/cm\(^2\) with an epiretinal microelectrode array directly on the retinal surface.\(^37\)

In summary, with present materials and stimulus paradigms, long-term epiretinal stimulation requires charge levels close to or higher than the established safe limits for neural tissue. Further experiments such as those reported by Weiland et al\(^73\) are needed to determine safe levels that are specific to the retina, particularly with conditions that more closely resemble what the retina would be exposed to with an implanted prosthesis. We do not know whether safe charge levels for subretinal stimulation would differ from those for epiretinal stimulation. Thresholds for subretinal stimulation in humans with RP have yet to be determined.

**Tissue Reaction to Heating**

A prosthetic device that consumes electrical power will create heat. The creation of heat will elevate temperature proportional to the amount of heat created per unit of time and the ability of the local structures to conduct away the heat. In most prostheses designs, the major areas of power consumption are in the microelectronic chip (if any) and at the electrode-tissue interface.

Liu et al\(^74\) developed a computational model to assess the heating effects of prototype prostheses and con-
cluded that the power dissipated by the implanted chip (vs at the electrode-tissue interface) would have the greatest effect on temperature increases in the eye. These results suggest that a microelectronic chip may have to be located away from the retina to avoid damage by heating. Locating such a chip in a modified intraocular lens or platform is one possible design, as mentioned previously. Caulfield et al64 suggest that most power will be dissipated at the electrode-tissue interface, creating the most heat at this site. According to this model, there would be less advantage in avoiding damage from heat by locating the microelectronics away from the retina.

The degree of temperature elevation that the retina can tolerate over the long-term, however, is unknown. Piyathaisere et al75 examined the histologic features after heating dog retina. With the heat probe on the retinal surface, dissipation of power of 50 mW or greater for 1 second damaged the retina acutely. If the same parameters were used but the animal was allowed 4 weeks to recover, damage was not found by standard histochromic analysis. Twenty milliwatts for 1 second in this location did not cause changes, whereas 100 mW showed damage immediately and at 4 weeks. Placing the probe in the midvitreous did not produce damage even at power levels of 500 mW for 2 hours. Accordingly, the safe limit for power consumption at the electrode-retina interface may be between 20 and 50 mW. It is therefore possible that the number of electrodes that can be stimulated at one time may be severely limited by the potential of damage from heating.

In summary, heat can damage the retina. The heat produced by a prosthesis depends on its power consumption, which in turn depends on the stimulus current needed for each electrode, the number of electrodes, and the operation of microelectronics that drive the electrodes. Compromises may have to be made between the desire for resolution with as many electrodes as possible and complex microelectronics vs the need for safety.

ENCAPSULATION

Just as implant materials may harm the eye, the saline environment of the eye may lead to corrosion of implant materials. A surface coating of an encapsulant that is resistant to the saline environment will therefore be required.76 Encapsulant materials are hydrophobic, preventing entry of water molecules.77 The presence of even minute amounts of water inside a microelectronic device will eventually lead to failure.78 Biocompatibility, on the other hand, generally requires hydrophilic materials because proteins will denature on contact with hydrophobic materials. Implants thus will probably require a hydrophilic, biocompatible coating over a hydrophobic encapsulant.

Hammerle et al79 studied the stability of microphotodiode arrays based on silicon-oxide substrates. Devices placed in phosphate-buffered saline for up to 21 months were undamaged when examined by scanning electron microscopy and energy dispersive x-ray analysis. When the same type of device was implanted in the subretinal space in animal eyes, the silicon-oxide layer was completely dissolved within 6 to 12 months. This study highlights the need for encapsulation with suitable materials. It also shows that in vivo testing of materials is essential. Encapsulation of intraocular devices for long-term implantation remains a major challenge.

TESTING OF IMPLANT SUBJECTS

The first retinal implants have appropriately been placed in subjects with very advanced RP and very poor vision. These early implants are probably not capable of very high resolution. It is thus not possible to simply test preimplant and postimplant Snellen acuity to assess the results of implantation. In addition, there is now considerable experience from clinical trials that indicates the significant subjectivity of measurements of visual function. Subjects in trials therefore routinely have baseline and periodic postintervention visual function measurements performed in a standardized manner, after a protocol-driven refraction, by a masked examiner. While the specific methods used in most ophthalmic clinical trials are not appropriate for subjects undergoing implantation, the general principles should be followed. This important experience from previous trials has not yet been applied to the testing of subjects undergoing implantation.

Humayun et al31 presented brief findings from a single subject implanted with a chronic, epiretinal device (Second Sight, Valencia, Calif) with 16 electrodes. Preoperatively, the subject had no light perception vision from retinitis pigmentosa. Postoperatively, the authors demonstrated that the subject could perceive light in response to electrode stimulation. The subject perceived individual spots in response to stimulation of each of 16 electrodes. The size and brightness of the spots varied with electrode position and stimulus current. In general, the location of the perceived spot corresponded to the retinal position of the stimulating electrode. With a camera connected to the implant, the subject could detect room light and locate a flashlight. The subject could perceive motion. Form perception was not reported. Chow et al30 recently reported results from chronic implantation of a 2-mm-diameter subretinal array of microphotodiodes (Optobionics Company, Chicago, Ill) in the superotemporal retina of 6 subjects with advanced RP. The results were given mainly via videotaped interviews of the subjects by Alan Chow, MD. Some visual acuity and field data were reported. Subjects reported increases in vision, central visual fields, and color vision that did not correspond to the retinal area over the implanted device.

Many groups have contributed to the effort to produce a retinal electronic prosthesis during the last decade. We now know that at least some perception can be obtained in individuals with nearly blind eyes with RP by epiretinal electrical stimulation. The quality of the perception that can ultimately be obtained is unknown. Small devices can probably safely be placed on the retinal surface for extended periods. Heat-producing components will have to consume very little power or be located away
from the retina. The optimal arrangement, fixation, and connection of components of a prosthesis have yet to be determined. Sufficient power can probably be delivered to an intraocular device by appropriately placed induction coils or by a laser. Subretinal devices can be placed and remain in a stable location. The long-term biocompatibility of subretinal devices must be demonstrated, but there is promise that improvements can be made in this area. Encapsulation of a device to protect it from the saline environment of the eye remains a challenge. Stimulation thresholds may be sufficiently high that new electrode materials and/or configurations will have to be developed.

To date, psychophysical evaluation of subjects pre-implantation and postimplantation has not been sufficiently quantitative or objective. We would encourage the development of a standard, psychophysically rigorous protocol for the preoperative and postoperative testing of subjects who have retinal prostheses. This will allow more reliable presentation and interpretation of data by the ophthalmic community.

We can thus tell our patients with outer retinal degenerations that there is progress toward an electronic retinal prosthesis but fully functional, long-lasting devices are not on the immediate horizon.

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