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MAJOR REVIEW

Retinal Prosthesis for the Blind

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Abstract. Most of current concepts for a visual prosthesis are based on neuronal electrical stimulation at different locations along the visual pathways within the central nervous system. The different designs of visual prostheses are named according to their locations (i.e., cortical, optic nerve, subretinal, and epiretinal). Visual loss caused by outer retinal degeneration in diseases such as retinitis pigmentosa or age-related macular degeneration can be reversed by electrical stimulation of the retina or the optic nerve (retinal or optic nerve prostheses, respectively). On the other hand, visual loss caused by inner or whole thickness retinal diseases, eye loss, optic nerve diseases (tumors, ischemia, inflammatory processes etc.), or diseases of the central nervous system (not including diseases of the primary and secondary visual cortices) can be reversed by a cortical visual prosthesis. The intent of this article is to provide an overview of current and future concepts of retinal and optic nerve prostheses. This article will begin with general considerations that are related to all or most of visual prostheses and then concentrate on the retinal and optic nerve designs. The authors believe that the field has grown beyond the scope of a single article so cortical prostheses will be described only because of their direct effect on the concept and technical development of the other prostheses, and this will be done in a more general and historic perspective.. (**Surv Ophthalmol 47**:335–356, 2002.

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More than 1 million Americans are legally blind and approximately 10% have no light perception from all causes. Hereditary retinal degeneration and age-related macular degeneration are two examples of blinding retinopathies,[124] for which there are only a few ways to prevent or halt the development of blindness. Photodynamic or conventional laser therapy are two methods that can be effective in treating age-related macular degeneration,[13] and gene therapy and drug therapy are two examples of experimental approaches to prevent the development of blindness caused by retinal diseases.[10,135] There is also a limited number of experimental treatments, which can theoretically reverse visual loss: for example, gene therapy

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for retinal degeneration,[1] or retinal transplantation for different retinal diseases.[39] Visual prosthesis is another way with which several research groups hope to restore useful vision to blind patients.

One of the most important questions regarding visual prostheses is if an electrical stimulation of a small area of neuronal tissue in the visual pathways will create light perception that is comparable to that created by light stimulation of retinal photoreceptors. The visual cortex was the first target for the visual prosthesis engineering efforts. Foerster, a German neurosurgeon, noted that electrical stimulation of the visual cortex caused his subject to see a spot of light (phosphene). The spatial psychophysical location of the phosphene depended on the location of electrical stimulation spot over the cortex.[49] Others followed with similar results at different locations of the visual pathways, including the visual cortex, the optic nerve, and the retina (Table 1).[16,25,43,70,117,130,153] So, the answer to the first part of the question was yes, we can stimulate a small area of neuronal tissue and get a light perception, but the answer to second part was no, it is not comparable to light stimulation. The phosphene is seen usually as a white, round, or oval point of light, and it has different sizes. We describe these results in much more detail later in this article. Other important questions are related to whether a whole visual image can be created by stimulation of many small areas of neuronal tissue (pixels), how many pixels are required for such an image, and what are the electrical stimulus parameters (amplitude, duration, shape etc.) needed for each pixel to make it safe and effective.

I. General Considerations

A. EFFICACY OF A VISUAL PROSTHESIS

1. Psychophysical Experiments

There is a general consensus that electrical stimulation of the visual pathways via a small number of electrodes cannot be expected to provide unaided understanding of visual information. In an effort to define the minimum acceptable resolution for useful vision, several psychophysical experiments were performed. As early as 1965, it was suggested that 600 points of stimulation (pixels) would be sufficient for reading ordinary print.[14] Others suggested that 80–120 points are sufficient for large-print reading, while 200 points may allow recognition of simple obstacles.[139]

More recent studies of simulated pixelized vision showed that 625 points of stimulation is a better estimate for certain tasks.[26–28] These studies were conducted with a portable phosphene simulator, which consisted of a small head-mounted video camera and a monitor worn by a normally sighted human subject. To simulate a discrete phosphene field, an opaque perforated film masked the monitor. The visual angle subtended by images from the masked monitor was 1.7° or less, depending on the mask, and fell within the fovea of the subject. It was concluded that 625 electrodes implanted in a $1cm^2$ area near the foveal representation of the visual cortex could produce a phosphene image with a visual acuity of approximately 20/30. Such acuity could provide useful restoration of functional vision for the profoundly blind.[26]

In another experiment, using the same methods, the reading speed was measured in subjects viewing pixelized text. The results indicated that a 25×25 pixel array representing four letters of text is sufficient to provide reading rates near 170 words/minute with scrolled text, and near 100 words/minute with fixed text.[28]

The feasibility of achieving visually guided mobility was investigated with a similar device. Normally sighted human subjects were required to walk through a maze that included a series of obstacles. The results indicated again that 625 pixels provided useful visually guided mobility. Walking speed increased 5-fold during 3 weeks of training.[27]

To make a cortical electrode array of 600 or more channels, several methods were proposed. Consider-

TABLE 1

Experimental Results of Visual Stimulators That Were Implanted in Human Subjects at Different Locations of the Visual System

Reference	Type of Stimulation	Spatial Orientation	Patients	Reading Letters	Localization of an External Light Source	Time of Implant	Number of Electrodes
70,71	Epiretinal	+	Blind from RP and AMD	+		Acute	1–25
157	Epiretinal	+	Laser ablated retinas			Acute	1
153	Optic nerve	+	Blind from RP			Chronic	4
98	Subretinal	Not published	Blind from RP	Not published	Not published	Chronic	3,500

RP = retinitis pigmentosa; AMD = age-related macular degeneration.

ing the visual cortex's mean extent of 9.7 cm^2, the number of electrodes that can be inserted, using current technologies, can reach 10,000 or more, assuming that methods can be developed for electrode placement in cortical sulci and at the medial wall of the occipital hemispheres.[75]

Although these studies began to delineate the number of electrodes needed, the fact that all the pixels were projected on a very small area of the retina made it impractical to translate to a design of a retinal prosthesis, in which the electrodes would be spread over the entire macular region. Thus, a low vision enhancement system (LVES) has been modified to filter images on a head-mounted display in order to simulate pixelized prosthetic vision and to produce an array of dots. The results suggested that a fair level of visual function can be achieved for facial recognition and reading large-print text using pixelized vision parameters such as 25×25 grid in a 10° field, with high contrast imaging and 4 or more gray levels.[37]

It was reported recently that a blind volunteer with a 20-year-old electrode implant on the visual cortex surface is now able to navigate, perform simple tasks, count fingers and identify large print letters (corresponding to a visual acuity of approximately 20/1200). The implant includes 8×8 electrodes, many of them inactive. These abilities were acquired after a long period of training.[42] Early and current experiments with the cochlear implant demonstrated that electrical stimulation with only 4–8 input channels allows deaf patients to hear and even talk over the phone.[35,41,160] Perhaps a similar phenomenon (redundancy in visual information) and the plasticity of the visual system will permit fewer retinal or cortical stimulating electrodes (compared to the estimated number of 600 electrodes), to give blind patients some useful vision.

In spite of these interesting experiments, there are major issues on the way to predict the correct number of channels needed for functional vision. Some of them are related to the facts that visual prosthesis phosphenes may be of variable size, may show varying persistence, or may interact with each other. Also, there might be multiple phosphenes induced by the same electrode.[43,130] Most of these problems were encountered during cortical electrical stimulation, but that is most probably because more human experiments were performed at this anatomical location. However, it could be related to the fact that the higher one is at the visual pathway hierarchy, the less predictable the response becomes after bypassing several processing stations.

In the case of the cochlear prosthesis, psychophysical experiments have been of limited value in predicting the function of the cochlear implant. Until actual devices are implanted and tried extensively, one should suspect that the same might be true of the visual prosthesis.

2. Neuronal Electrical Excitation

a. Threshold Parameters for Electrical Stimulation

Hodgkin and Huxley used the voltage clamp technique in the squid axon to give the first complete description of the ionic mechanisms underlying the action potential of neurons.[67,68] According to the Hodgkin–Huxley model, an action potential involves the following sequence of events. A depolarization of the membrane causes Na+ channels to open rapidly resulting in an inward Na+ current (because of a higher concentration of this ion outside the cell membrane). This current, by discharging the membrane capacitance, causes further depolarization, thereby opening more Na+ channels, resulting in increased inward current. This regenerative process causes the action potential. The depolarization state of the action potential then limits the duration of the action potential in two ways: 1) it gradually inactivates the Na+ channels, and 2) it opens the voltage gated K+ channels with some delay. Consequently, the inward Na+ current is followed by an outward K+ current that tends to repolarize the membrane current (because of a higher concentration of this ion inside the cell membrane). Other conclusions from Hodgkin and Huxley experiments were the following: 1) the basic mechanism of action potential generation is the same in all neurons; 2) the nervous system expresses a large variety of voltage-gated ion channels (i.e., Ca+ channels); 3) gating of voltage-sensitive channels can be influenced by intracellular ion concentrations (i.e., Ca+ ions); 4) excitability properties vary among neurons mainly because of the variety of ion channels properties; and 5) excitability properties vary within regions of the neuron (i.e., axon vs. dendrites). The Hodgkin–Huxley model (equation) has been derived by fitting analytic curves to empirical data from the squid axon.

Electrical stimulation elicits a neural response by opening the voltage-sensitive ion channels and bypassing the chemically gated channels in the stimulated cell. Once the membrane reaches a certain potential, a trigger mechanism is released and an action potential results (all-or-none mechanism). Many of the works studying models for electrical stimulation of neurons use the Hodgkin–Huxley equations.[8,99] These works studied the effect of different parameters on neuronal excitation threshold. The threshold is the minimum electrical stimulus amplitude and duration required for initiating an action potential. It is essential to determine the most efficient electrical stimulation parameters (i.e., pulse amplitude, pulse duration, pulse repetition, wave shape, pulse polarity, etc.—see below) and electrode

array properties for getting the lowest threshold possible. Such low stimulation threshold will enable an efficient design for any visual prosthesis, because these characteristics will determine how many channels of stimulation will be available, how much power will be necessary, and what mechanical properties will specify the device.

A number of factors can influence the efficacy of electrical stimulation. First, the threshold depends on the electrical properties and anatomy of the target neural elements, and what portion of the cell (dendrite, cell body, and axon) is stimulated. For example, myelinated axons are more easily stimulated then unmyelinated ones.[114] Consequently, one computational model of extracellular field stimulation of the retinal ganglion cell (RGC) has shown that even though the axon is closer to an epiretinal stimulating electrode, the extracellular stimulation threshold of the RGC soma is 58–73% lower than its axon.[55]

Second, the threshold is obviously affected by the distance from the electrodes to the target cell. Smaller distances from the target require less electrical energy for stimulation.[8] Third, the threshold during bipolar stimulation is also affected by the pulse duration.[54,136] Fourth, threshold can vary significantly due to the impedance of tissues and errors can be associated with the assumption that tissue electrical properties are the same in every stimulated compartment (homogenous and isotropic tissue properties), especially with bipolar electrical stimulation.[143]

Fifth, there is a well-defined relationship between the threshold current/charge and stimulus pulse duration required for neuronal activation.[11,58,158] As the pulse duration decreases, the threshold current increases. This relationship begins to break down at the extremes (i.e., a very short current pulse cannot activate a nerve regardless of the amplitude). Similarly, as the pulse duration increases, the threshold current approaches a minimum value called the rheobase, below which an action potential cannot be elicited regardless of pulse duration. This current level can be interpreted as a "leakage" current that can pass through the tissue without inducing depolarization. The chronaxie of a neuron is defined as a pulse width for which the threshold current is twice the rheobase current.[113] Charge, which accounts for both the pulse amplitude and pulse duration, is probably the most meaningful parameter for electrical stimulation because of damage considerations to electrodes and tissue (see section Threshold Parameters for Electrical Stimulation).[91,92,94] This is because electrode materials can withstand only certain charge density before irreversible toxic reactions occur at the electrode tissue interface. Charge and current have different minimum requirements during neuronal stimulation. A minimum charge is required for shorter pulse duration in contrast to current, which is minimized at longer pulse duration.[122] However, unlike electrical stimulation of other nervous system cells, the optimum pulse duration may not be short in the retina because graded potential cells have longer chronaxies than other excitable neurons.[54]

Sixth, in addition to current amplitude, charge, and pulse duration, investigators found that threshold is affected by the repetition rate of stimuli in the cortex and optic nerve.[130,153] In one of the cortical stimulation experiments the threshold was constant at frequencies of 150–200 Hz and increased 50% at 75Hz.[130] Furthermore, in the cortex, it was found that only those pulses delivered in the first 100 ms would determine the sensory response for trains of stimulus pulses at any specified set of parametric values.[64]

Seventh, the polarity of electrical stimulation is also an important factor. Neurons can be activated by cathodic threshold activation, anodic pulses and biphasic pulses.[53,118] In many neural systems, higher currents were required to reach threshold with anodic stimulation compared to cathodic stimulation, so cathodic stimulation is considered the preferred polarity for most of the visual prostheses.[113] Biphasic waveform can have either a cathodic or anodic wave first. However, for most applications, cathodic first biphasic pulses result in lower thresholds, presumably because they depolarize the cell membrane closest to the electrode.[82] The two phases of the biphasic pulse are used for charge balancing and thus avoiding irreversible reactions at the tissue electrode interface, which in its extensive form can result in electrolysis and significant pH changes as well as electrode metal deposition into tissue. The two phases can have equal amplitudes and pulse duration but can also be asymmetric with a phase having lower amplitude but longer duration in order to result in charge balance.[118] In a series of patients who underwent epiretinal electrical stimulation there was no difference between monopolar versus bipolar stimulation and cathodic versus anodic first stimulation.[70]

Eighth, another variable for threshold stimulation is the waveform. Two basic waveforms have been used frequently for neural stimulation: sinusoidal and pulsatile (square) waveforms. There are many variants of these basic waveforms that can be used for different purposes. The most frequently used is the pulsatile (square) waveform.[120]

Having reviewed the variables involved in electrical stimulation of neurons, we will now summarize the different threshold values found for electrical stimulation of several points along the visual pathways (not including the visual cortex). These values are presented in Tables 2 and 3. It should be noted that these studies were performed in different spe-

TABLE 2

Threshold Electrical Stimulation Parameters That Were Used by Different Groups During In Vivo Experiments

Reference	
Epiretinal stimulation parameters	
117	Rabbits, extradural recording, current threshold 105–720 μA, PD 100 μsec, electrode diameter 40 μm, charge density threshold 0.8–5.7 mC/cm^2. Determination of threshold was done by repeating the stimulation and recording at different anatomical positions.
71	**RP and AMD patients, current threshold 500 μA, PD 2 ms, charge density threshold 0.16–70 mC/cm^2, (1 μC/phase)[70]. Determination of threshold by counting the electrical stimuli with varying frequencies of stimulation.**
157	**Laser treated human retinas, current threshold 100–600 μA, charge threshold 0.1–0.6 μC, charge density threshold 0.8–4.8 mC/cm^2. Determination of threshold by counting the electrical stimuli with varying frequencies of stimulation.**
Subretinal stimulation parameters	
30	Normal rabbits cortical recordings), electrode surface area 0.36 cm^2, charge density threshold 2.8–100 nC/cm^2. Determination of threshold was done by reversing the input leads.
Optic nerve stimulation parameters	
153	**RP patient, current threshold 30 μA, PD 400 μsec, electrode area 0.2 mm^2, repetition rate 160 Hz charge density threshold 24 μC/cm^2/pulse. Determination of threshold by two-staircase limit method.**

RP = retinitis pigmentosa; AMD = age-related macular degeneration; PD = pulse duration.
Human Experiments Are Bolded

cies, at different electrophysiological sites, using different electrode sizes, and with different stimulus parameters (pulse repetition rate, pulse duration, waveforms, train lengths, etc.). The threshold was either measured by physiological methods (recording evoked potentials or single neuron responses from RGC) or by psychophysical responses (phosphene perception in humans). Thus, these results can only give an estimate of electrical stimulation threshold values of various locations along the visual system and only a few conclusions can be drawn as to optimal methods to be used during electrical stimulation. It is clear the in vitro electrophysiological threshold is lower than the in vivo electrophysiological and psychophysical thresholds.[59,65,69] This discrepancy is most probably due to the fact that the visual system cannot recognize the activity of a single or even a small number of neurons. If this is the case,

TABLE 3

Threshold Electrical Stimulation Parameters That Were Used by Different Groups During In Vitro Experiments

Reference	
Epiretinal stimulation parameters	
69	Charge density thresholds (using Pt electrodes): 2.98 μC/cm^2 (bullfrog), 8.92 μC/cm^2 (normal rabbit), 11.9 μC/cm^2 (chemically RD rabbit). Determination of threshold was not mentioned.
59	Rabbit isolated retina, electrode diameter 10 μm, PD 400 μsec, threshold current 0.06–1.8 μA, threhsold charge density 30–917 μC/cm^2. Determination of threshold was done by counting only response waveforms with ten or more sample points and by using synaptic transmission blockage.
Subretinal stimulation parameters	
141	Chick isolated retina, current threshold 35 μA, PD 0.4 ms, electrode surface area 0.01 mm^2, charge threshold 14 nC/phase, charge density threshold 178 μC/cm^2. Determination of threshold was not mentioned. Determination of threshold was done by control with light stimulation and by using synaptic transmission blockage.
140	Retinal degenerate rates (RCS) isolated retina, charge density threshold 500 μC/cm^2. Determination of threshold was not mentioned.

RP = retinitis pigmentosa; AMD = age-related macular degeneration; PD = pulse duration.

the exact number of stimulated neurons for in vivo psychophysical thresholds should be determined.

3. Electrodes

The electrodes' charge transfer efficiency will affect every subsystem of the prosthesis by influencing the power requirements and the electrode density.

Different materials were tested for the fabrication of electrode arrays. Even the precious metals (platinum, iridium, rhodium, gold, and palladium) corrode under certain conditions of electrical stimulation.[96] Platinum and its alloys with iridium are the most widely used for neural stimulating electrodes, due to its resistance to corrosion and considerable charge carrying capacity. The unavoidable dissolution of platinum under electrical stimulation decreases when a protein is included in the solution and with continuous stimulation.[119]

Iridium oxide (IrO_x) electrodes belong to a new category termed "valence change oxides." IrO_x has been used in research for nearly 20 years, but not commercially. IrO_x is exceptionally resistant to corrosion. The conservative charge density limit for chronic stimulation is 1 mC/cm^2 and it has a safe stimulation limit of 3 mC/cm^2 in vitro.[7] IrO_x electrodes have been proved to withstand more than 2 billion 10 mA current pulses without degradation.[169]

Recently, a titanium nitride (TiN) thin film electrode has demonstrated charge injection limits of 23 mC/cm^2, higher than both platinum and IrO_x.[73] Though TiN electrodes have better mechanical properties than IrO_x electrodes they seemed to have adverse effects on retinal cells' survival when in direct contact.[60] However, it was clear that no soluble factor is responsible for decreased cell survival and TiN is still used for fabricating electrode arrays in animal research.[171]

When calculating acceptable dimensions of electrodes, one should refer to safe charge density measurements. For example, as was discussed earlier, the conservative charge injection limits for platinum and IrO_x electrodes are 100 $\mu C/cm^2$ and 1mC/cm^2, respectively (see section Damage Caused by Electrical Current). Thus, the minimum sizes based on a 1 μC charge requirement for threshold intraocular stimulation of RP patients would be 0.01 cm^2 and 0.001 cm^2 for platinum and IrO_x, respectively. For disk electrodes, these values correspond to minimum disc radii of 0.56 mm for platinum and 0.18 mm for IrO_x.

Another possibility is to use capacitor electrodes. These electrodes operate without any faradaic reactions. A thin surface layer of dielectric material insulates the metal from the solution and prevents electrochemical reactions. The most practical material is anodized tantalum because of the small amount of direct current (DC) leakage. However, these electrodes have lower safe injectable charge density and charge storage ability than Pt, IrO_x, or TiN electrodes.[123]

The charge density limits are measured for uniform current distribution. However, due to certain geometric considerations, neural prosthesis electrodes are likely to have non-uniform current distributions, which can exceed the chemically reversible limits.[159] For example, it has been shown that disk electrodes create uneven current density with the highest densities or "hot spots" being near the edges of the disk. If the disks are recessed even to a small depth, the current density is more evenly distributed.[126]

Some general conclusions can be drawn from the discussion above. A stimulating electrode array must meet several requirements. These include a high number of densely packed electrodes to provide a high acuity image and individual electrodes that can safely inject a large amount of charge. Current electrode technology employed in neural prostheses uses hand-made electrode arrays with a small electrode count (up to 100). Micromachining technology has been used to fabricate electrodes of higher density for neural stimulation.[75] Some subretinal devices have much higher count of electrodes per device surface area (up to 7,600 electrodes in a three mm diameter device), because each electrode is part of a unit that contains a photodiode. This photodiode supplies the current necessary for electrical stimulation (see sections Power Supply and Subretinal Prostheses).

The global shape of the array, the shape of each electrode, the way to insert and attach it, and so forth, depends on the anatomical location of stimulation. If either IrO_x or TiN can be successfully incorporated into a visual stimulating array with smaller electrodes, then the potential advantages include more channels, higher image quality, and reduced power consumption.

4. Power Supply

Supplying adequate electrical power is a concern for any implantable electronic device. As mentioned above, the amount of power supply needed is dependent on electrical stimulus parameters and electrochemical properties of the electrode array. Some electrical stimulators for chronic pain treatment use a battery and rely on repeated surgery to replace it. Alternatively, it is possible to power implants without a physical connection (wirelessly) through an inductive link, in which current through a primary coil (metallic wire) driven by a signal and energy source, induces current in a secondary coil.[80] Some cardiac pacemakers and cochlear implants are inductively

powered. There are several parameters that can be adjusted when designing an inductive link.[84] These parameters include the diameter and number of turns of the primary and secondary coils, the relative position of the two coils and the frequency of the radio wave (typically over 1 MHz). Large primary and secondary coils may be undesirable for aesthetic reasons and anatomical constraints, respectively. Power transfer is maximized if the coils are coplanar. This is not practical for most implants and the coil planes are at least slightly offset decreasing efficiency for what is already an inefficient method for transferring power. Typical power transfer rates are approximately 2%. Nevertheless, a 5-mW power supply may be adequate to drive both the inductive link and the stimulator chip (for 100 electrodes). Mathematical estimates of millimeter size coils have estimated that up to 50 mW of power can be transmitted using a 9-cm diameter primary coil and a 1.5-mm secondary coil.[63] These calculations show that enough energy can be delivered into the secondary coil by this method. Alternatives have been proposed for delivering power to ocular implants, taking advantage of the transparent optical pathway. One conceptual device includes an infrared laser that would excite implanted photodiodes to produce electric current.[117] While this link would be more efficient than the inductive link, as the laser could be targeted, it raises safety concerns due to the presence of eye movements and the known deleterious effects of laser light on the retina.

One subretinal device (Artificial Silicon Retina [ASR]) does not have any external connections and is powered solely by incident light with wavelengths of 500–1,100 nm.[104] It contains approximately 3,500 microscopic solar cells called "microphotodiodes," each having its own stimulating electrode. These microphotodiodes are designed to convert the light energy from images into electrical impulses to stimulate the remaining functional cells of the retina in patients with AMD and RP types of conditions (see sections Retinal Prostheses and Subretinal Prostheses). When surgically implanted under the retina, in a location known as the subretinal space, the ASR is designed to produce visual signals similar to those produced by the photoreceptor layer. By converting light into electrochemical signals, the microscopic solar cells on the chip mimic the function of the photoreceptors to stimulate the remaining viable cells of the retina. This same principal method is used by another group that named the subretinal implant microphotodiode array (MPDA).[170,171] This group showed that the amount of incident visible light that can reach the subretinal device is limited and insufficient to generate enough current to activate a 200×200 μm^2 microphotodiode. Based on theoretical and empirical calculations of photodiode efficiencies and electrode impedance, the amount of visible light that is needed for this purpose is about 2000 W/m^2.[131,132] Empirically, this was shown by shining a spot of light (a laser beam) on the MPDA, and measuring the current at the surface of the MPDA intended to touch the subretinal space.[132] This range is far beyond the sunlight intensity on earth (fluorescent light 10 W/m^2, sunlight 100 W/m^2). To overcome this problem, additional energy in the near infrared light (NIR) was added to the spectrum of solar cells of the microphotodiode.[88,131] The infrared light is tolerated by the retina up to intensities of 2000 W/m^2, as opposed to the much lower tolerance of the retina to visible light. This is the key to boosting the stimulation power of the MPDA by a continuous NIR supply, which can easily be generated by standard light-emitting diodes.[131,132] The viability of the infrared enhancement of the stimulation power was proven, and pathways to further optimization are currently being searched.[131,132] Minimizing the stimulation electrodes surface area is another partial solution for this same problem.[31]

B. SAFETY OF ELECTRICAL STIMULATION

The biocompatibility of an implanted medical device in host tissue is one of the most important issues of visual as well as other prostheses.[167] Neuronal tissue can be affected by electrical current passing through, infection, and inflammation, which include acute and delayed types (foreign body) of immunologic reactions as well as idiosyncratic hypersensitivity reactions to polymers and metals that are usually well tolerated by most individuals. Implants can also include sources of carcinogens but evidence for such outcomes following implantation is rare.[62,97] Sources of toxic substances that can cause inflammation are antioxidants, catalysts, contaminants from fabrication equipment, and so on. Tissue reaction to implants can be classified as severe (sterile abscess), intermediate (a capsule, consisting of dense fibrous sheath without dead or necrotic cells), and mild (loose vascularized fibrous tissue).[161] Heat created by the electronic components can also impair neuronal tissues.

Effects of the tissue on the implant include degradation and corrosion of polymers and metals, respectively;[74,119] mechanical dislocation of the implant by fibrous and glial tissue growth;[167] and possible damage to the electronic components of the implant by the surrounding ionic solution. Corrosion products can be determined by ultra violet (UV) spectroscopy of in vitro pulse solutions and extracts of stimulated tissue.[120] Corrosion effects on electrode surfaces are readily observed by scanning electron microscopy as well as other methods.

1. Damage Caused by Electrical Current

When applying electrical stimulation, neural damage limits need to be considered. Among the early studies that have had a significant impact on this field are the histopathological studies of long-term stimulation of the cerebral cortex with thin surface electrodes[110–112] and the electrochemical studies of the electrode-electrolyte interface.[19]

An early finding was that any net DC current could lead over time to irreversible electrolyte reactions. The relative safety of biphasic charge balanced waveforms compared with monophasic waveforms was demonstrated.[82] A biphasic current waveform consisting of two consecutive pulses of equal charge but opposite polarity has no DC component. A simple monophasic waveform is unacceptable for neural stimulation because it delivers DC and creates irreversible faradaic processes. Faradaic reactions involve electron transfer across the electrode-tissue interface and oxidation/reduction of chemicals.[20] It is necessary to know the chemical reversibility of reactions involving electrode materials in order to avoid tissue and device damage. Chemical reversibility requires that a pulse of opposite polarity will chemically reverse all processes occurring at an electrode subjected to an electrical pulse, and that H_2 and O_2 evolution as a result of electrical current will be prevented. Chemical reversibility can be examined by cyclic voltammetric analysis, direct observation of gas bubbles, UV spectroscopy, or atomic absorption spectrometry during in vitro stimulation.[6] Corrosion effects on electrode surfaces can be examined for example by scanning electron microscopy.

It was shown that electrical stimulation-induced neural injury is dependent on current amplitude and pulse repetition rate, but more importantly on charge density and charge per phase.[91,92,94] The charge per phase is defined as the integral of the stimulus current over half (one phase) of one cycle of the pulse duration. Charge density is defined as charge per phase divided by the electrochemically active surface area of the electrodes. From these definitions, it can be understood that very small electrodes can produce very low current thresholds, yet unacceptably high charge densities. Since charge density is responsible for the damage of tissue and electrodes, there is a theoretical limit to how small the electrodes can be.[18,146] Also, the total charge delivered to the tissue can not be ignored, even though the charge density can be within safe limits.[2,92]

Using simple waveforms, conservative charge density limits for chronic stimulation with Pt are 100 $\mu C/cm^2$.[91] For activated iridium oxide electrodes, the limit is 1 mC/cm^2.[7] Moreover, chronic stimulation can reduce the maximum charge density that is safely injectable.[156] Most of the studies that were done to determine these limits were performed with superficial cortical electrodes,[91,92] or intracortical microstimulation (see sections Surface Cortical Electrodes and Intracortical Microstimulation).[23,94] Other chronic stimulation locations were tested as well and it was found that auditory nerve electrical stimulation with a cochlear implant could be safe and have stable, effective long-term results. The cochlear implant allows complex speech perception that is now better than the average scores that profoundly deaf adults and children with some residual hearing obtain with a hearing aid.[34] Chronic electrical stimulation of the schiatic nerve showed growing stability of stimulation parameters particularly 8 weeks post implantation and on, suggesting that tissue encapsulation acted to stabilize chronically implanted electrodes.[57] It was also shown that transient changes in neural response properties, such as stimulation-induced depression of neuronal excitability, can be caused by electrical stimulation, but these have not been correlated to histologically detectable tissue damage.[2,93,94] In other studies, it was shown that repeated stimulation did not change the threshold amplitudes over time since implantation.[15,52,153]

Another important consideration regarding the safety of electrical stimulation is the design of the electrode array (in contrast to the design of each electrode). This array is in direct contact with biological tissue, thus, it has the potential to damage the tissue mechanically, and chemically, and vice versa.

Despite established safe limits for neural stimulation, long-term in vivo retinal stimulation must be performed before any conclusions regarding threshold stimulation parameters of the retina are drawn. The reason is that the threshold at which damage occurs cannot be freely extrapolated from one neural tissue to another.[95] We expect that with optimized electrode configurations and stimulus waveforms, effective stimulation below the safe limits can be achieved.

2. Infection and Inflammation

Despite the fact that the CNS and the eye have been described as immunologically privileged sites,[121,128] the course of inflammation is identical to that occurring elsewhere in the body once an incitement of inflammation has occurred.[103] Mere surgical manipulation, as well as infection, biodegradation, or the release of toxic substances from the implant, can provoke the inflammatory response, which includes all the components of the typical immunologic response of an organism. It is characterized by an outpouring of neutrophils from post-capillary venules into the affected area. Emigration of lymphocytes from the bloodstream is mediated by circulating an-

tigens and chemotactic factors. Macrophages are engaged in phagocytosis of injured cells, and plasma cells, which are involved in immunoglobulin mediated reactions. Bacterial infections are often delayed and appear to be due in part to the host's inability to respond properly to infections. Their origin is frequently distant infected sites in the body or skin flora.[46] Less often the origin is infected implants and surgical or nursing staff.[40] Attempts to avoid bacterial colonization on implants were accomplished by coating polymers with proteins, or antibiotics and strict sterilization.[129]

3. Heat Damage

Different components of the visual prostheses can produce excessive heat and cause damage to any neuronal tissue if not kept below a certain limit. Many of the studies regarding thermal exposure damage studied the effects of microwave and other electromagnetic field exposures. The safe limit is considered to be absorbed power of 0.08 or 0.4 W/Kg whole-body exposure for the general public and occupational exposures, respectively. These values have a safety factor of 10–50 compared to the value of 4 W/kg whole-body exposure that was found to disrupt a rat during a behavioral task (the animal stops performing a task and spread saliva on the tail, which is a thermoregulatory response in rats).[116] The retina's ability to dissipate and tolerate heat generated by an intraocular electronic heater was studied in 16 dogs.[105] It was shown that no more than 50 mW of power over a 1.4 mm^2 area can be applied directly onto the retina for more than one second. However, using the same heater, a power of 500 mW in the mid vitreous for 2 hours did not cause any histological damage. It was concluded that placing the electronics directly in contact with the retina, either epiretinally or subretinally, has a high risk of causing heat injury. Thus, any electronic component that produces relatively large amount of heat should be put as far away as possible from the retina.

4. Hermetic Sealing of the Electronics

All visual prostheses will consist of various electronic components. Most of the visual prosthesis designs will require implantation of these components in vivo. Implanted electronic elements such as data and power receivers and the stimulation processor must be hermetically sealed from the corrosive biological fluid.[169] However, this field of hermetic sealing requirement is still an area under investigation and is open to debate for the subretinal photodiode devices. If needed, the protective coating should last for several decades. The requirement of hermetically sealing a circuit in the case of neural stimulating devices is complicated by the demand that multiple conductors (feedthroughs) must penetrate the hermetic package so that the stimulation circuit can be electrically connected to each electrode site in the electrode array. These connections are the most vulnerable leakage points of the system.

The pacemaker industry has developed effective encapsulation using the hermetically sealed titanium can.[22] In addition to titanium, glass and ceramic packages have been proven hermetic. Integrated circuit electrodes and sensors require less bulky encapsulation. In the last few years, much attention has been focused on the development of miniature hermetic packages for microelectrode protection, though none provide a high number of reliable feedthroughs in a small volume.[61] Many types of welding or sealants tend to leak over time, are not biocompatible and are expensive.

Yet another hermetic packaging technique is based on electrostatic (anodic) bonding of glass to silicon. The process generates a high electric field at the glass-silicon interface and causes a permanent and irreversible fusion bond between silicon and glass.[154,163,169] Using a silicon substrate allows many micron scale feedthroughs to be micromachined into the hermetic package. Recently, a new technique of aluminum/silicon-to-glass solder bonding was developed. This technique provides more than 10 mega pascals bonding strength and a good hermetic sealing.[29] In summary, techniques for coating the electronics are a fundamental step to the future feasibility of any visual prosthesis, which has to clear the daunting hurdle of hermetically sealing a small electronic package with a high number of feedthroughs.

II. Cortical Prosthesis

A. SURFACE CORTICAL ELECTRODES

One of the earliest experiments included three blind patients, two of whom were able to locate a light source by scanning the visual field with a photocell. The photocell output electrically stimulated the cortex via electrodes in a wire passing through the scalp and skull and penetrating the visual cortex.[25]

Brindley and Lewin performed key experiments in this field by implanting devices consisting of 80 electrodes on the visual cortex of blind patients (Fig. 1). Wires through a burr hole connected each electrode to a radio receiver screwed to the outer bony surface of the skull. An oscillator coil was placed above a given receiver in order to activate the receiver via radio frequency and stimulate the cortex. With this system, the patients were able to see phosphenes at different positions of the visual field, demonstrating that many of the implanted electrodes were functional. This experiment showed that a chronically activated electrical stimulation multichannel device was possible.[15,17] The field of the cor-

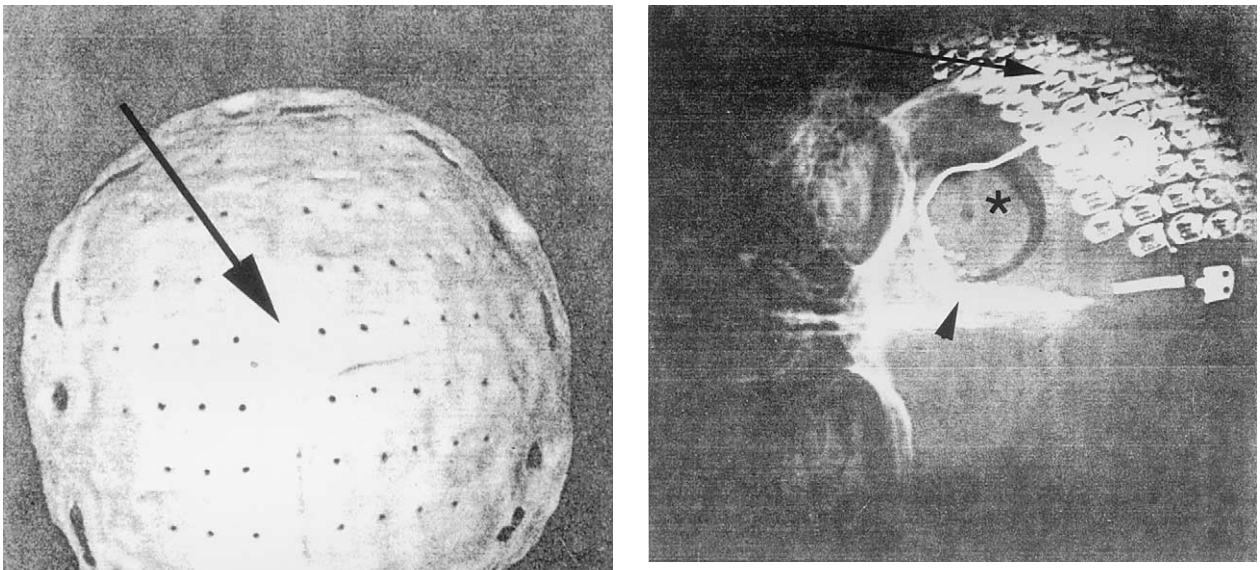

Fig. 1. Left: The first chronic cortical visual prosthesis before implantation. The arrowhead points to the electrode array and the arrow to the "array" of radio receivers. *Right:* X-rays of the same device after implantation. The electrode array (arrow head) is connected to the radio receivers (arrow) through a burr hole (asterisk). (Modified with permission of *Journal of Physiology.*[15])

tical visual prosthesis was reviewed in 1975[77] and also as part of a very recent review.[89]

Some of the difficulties of these early experiments included interactions between phosphenes, multiple phosphenes induced by the same electrode, inconsistency of phosphenes, and usage of high currents and large electrodes.[43,130] Occasionally, pain was caused by meningeal stimulation, and possible focal epileptic activity was induced following electrical stimulation.[106]

Later, efforts continued and 64 channel platinum disk electrode arrays were implanted by Dobelle and his colleagues on the surface of the occipital cortex of blind patients.[44,48,52,64] These electrodes were interfaced with a camera consisting of a 100 × 100 charge-coupled phototransistor array. Random letters were used to stimulate the camera, which in turn used to stimulate only 6 out of the 64 electrodes. The prosthesis allowed these blind patients to recognize 6-inch characters at 5 feet (approximately 20/1200 visual acuity).[42,44] It was also found that phosphene brightness was a logarithmic function of stimulating current amplitude.[48]

B. INTRACORTICAL MICROSTIMULATION

Smaller electrodes have higher impedance but require less current to stimulate more localized cortical tissue.[120] This localized stimulation can theoretically reduce interactions between phosphenes, induction of multiple phosphenes by the same electrode, and inconsistency of phosphenes, which were observed with large surface electrode stimulation. As a result, the development of intracortical electrodes came about.[5,76,90,101,102,130,150] One group inserted 37.5 μm diameter iridium microelectrodes into the occipital cortex of patients who were submitted to craniotomies under local anesthesia for excision of epileptic foci. Stimulation was performed with both surface and intracortical electrodes. Both methods elicited phosphenes, but the stimulus current threshold for intracortical microstimulation was 10–100 times lower than that for stimulation using surface electrodes.[5] The same group developed a system with 38 microelectrodes that were implanted in an area of 40.8 × 19.2 mm in the visual cortex of a 42-year-old patient totally blind for 22 years secondary to glaucoma. The electrodes were implanted for a period of 4 months and this experiment showed that despite being blind for many years, the subject was able to perceive phosphenes at a predictable and reproducible location of the visual space.[130] It was also demonstrated that simple patterned perceptions could be evoked by electrical stimulation via small groups of these microelectrodes. Electrodes spaced as close as

500 μm apart generated separate phosphenes, and at levels near threshold, the phosphenes usually had colors.[5]

Undoubtedly, the lower current threshold of the intracortical microstimulation, the predictable forms of generated phosphenes, the absence of flicker phenomena, reduction of phosphene interactions, the opportunity to increase the number of electrodes, and the reduced power requirement and current per microelectrode are the main advantages of the intracortical microstimulation approach over surface cortical stimulation.[5,130] Because of these advantages all major efforts investigating the development of a visual cortical prosthesis have abandoned the use of surface electrodes and are developing intracortical microelectrodes.

One of the groups has focused on the use of doped silicon penetrating electrode array for a cortical implant.[102] The tips of the 1.5/1.0-mm long electrodes are covered with platinum. The array typically looks like a nail bed and consists of 100 penetrating electrodes. The diameter of each electrode at its base is 80–100 μm and 2–3 μm at the tip. Tissue reaction to chronic implantation of this electrode array varied from no reaction at all or a thin capsule around each electrode track, to gliosis, buildup of fibrotic tissue between the array and the meninges, array displacement, and bleeding.[102] Thin capsules around electrode tracks and tissue accumulation on pulsed CNS electrodes were also reported by others.[2,94,156] Nevertheless, tissue encapsulation does not always preclude effective stimulation.[56,156]

The preferable fixation site of the intracortical microstimulation arrays is probably the cortex itself and not the skull because of the constant movement of the brain in relation to the skull. The cortical arrays are currently inserted either by manual insertion of individual or groups of 2–3 electrodes normal to the cortical surface to a depth of 2 mm[130] or by a pneumatic system that inserts 100-electrode arrays into the cortex in about 200 msec.[125]

Another electrode technology for cortical stimulation uses silicon micromachining to fabricate multichannel arrays for neural prostheses applications. Microfabricated silicon electrodes were initially conceived in the early 1970s.[162] In subsequent years, the dimensions of these electrodes have been decreased utilizing the concurrent advances in the microelectronics industry. Today, micromachined silicon electrodes with conducting lines of 2 μm or less are standard.[9,66,81,149] These fabrication processes have been advanced by the microelectronics industry and therefore allow the integration of microelectronics and the electrode array into a monolithic device. The primary reason for the inclusion of on-chip electronics in such a device is to minimize the number of external leads required between the electrode sites and the outside world. Recording/stimulating sites are located along the silicone probe substrate. These probes are capable of extracellular recording/stimulating of many cells in neural tissue simultaneously on a spatially distributed basis.[3,100,144,163] Chronic implantation and in vitro testing have demonstrated the ability of silicon devices to maintain electrical characteristics during long-term implantation.[156]

The biocompatibility of various chronic intracortical stimulating arrays was examined. Preliminary experiments of chronic implantation of stimulating devices over the cortex revealed a fibrous membrane covering the surface of every implant that was examined 6 weeks or more after insertion. These membranes had little effect on threshold for stimulation.[15] There was only one report on the need to remove a chronic device from the cortical surface of a patient because of a blood-borne infection.[42]

There are advantages and disadvantages that are associated with the cortical stimulation approach in general. The skull will protect both the electronics and the electrode array and a visual cortical prosthesis will bypass all diseased neurons distal to the primary visual cortex. By doing so, it has the potential to restore vision to the largest number of blind patients. However, spatial organization is more complex at the cortical level, and two adjacent cortical loci do not necessarily map out to two adjacent areas in space, so that patterned electrical stimulation may not produce patterned perception. In addition, every small area of the cortex, even at the level of the primary visual cortex, is highly specialized for color, motion, eye preference, and other parameters of visual stimuli. Thus, it is unlikely to get simple perceptions even when stimulating few hundreds of neurons in the case of intracortical microstimulation. Moreover, the convoluted cortical surface makes it difficult for implantation, and surgical complications can have devastating results (including death) on generally healthy subjects.

III. Retinal Prostheses

During the early seventies it became clear that blind humans can also perceive electrically elicited phosphenes in response to ocular stimulation, with a contact lens as a stimulating electrode.[107–109] When obtainable, these electrically elicited responses indicated the presence of at least some functioning inner retinal cells. Because a number of blinding retinal diseases are due predominantly to outer retinal (in particular photoreceptor) degeneration,[72,127,142] the idea of stimulating the remaining inner retinal cells came about. Early experiments showed that inner retinal layers can be electrically stimulated and elicit an electrical-evoked response (EER).[78,79,147]

Two of the more common outer retinal degenerative diseases are RP and AMD. The incidence of RP is 1/3,500 live births and there are approximately 1.5 million people affected worldwide. It is the leading cause of inherited blindness.[24] Age-related macular degeneration is the main cause of visual loss among adults older than 65 in western countries. Annually, there are approximately 700,000 new patients in the United States who lose vision due to this illness and 10% of these who have the disease become legally blind each year.[36]

Postmortem morphometric analysis of the retina of RP patients revealed that many more inner nuclear layer cells (bipolar cells and others [78.4%]) are retained compared to outer nuclear layer (photoreceptors [4.9%]) and ganglion cell layer (29.7%).[72,127,142] Similar results were obtained from AMD patients (Kim et al: Morphometric analysis of the macula in eyes with disciform age-related macular degeneration. Under submission). Given that there is limited transynaptic neuronal degeneration, it is feasible to stimulate the remaining retinal neurons.

The exact retinal target cell for electrical stimulation is not trivial to identify because many of the studies designed to explore this target cell were based on extracellular recording of neuronal action potentials. However, it should be noted that in the retina, there are neurons (photoreceptor, bipolar, and horizontal cells) that when excited do not generate action potentials but only graded potentials.[45] In these neurons, electrical stimulation can evoke a graded potential that can be very difficult to document with extracellular recordings.

The retinal prosthesis has actually developed in two different directions. One is called the epiretinal approach, in which the device is implanted into the vitreous cavity and attached to the inner retinal surface so the electrical stimulation meets the inner retina first. The second approach uses a potential space between the neurosensory retinal and the retinal pigment epithelium into which the device is implanted, so the electrical stimulation meets the outer retina first (Fig. 2).

There are advantages and disadvantages for the retinal stimulation approaches. The advantages include the ability to use existing physiological optics and retinotopic organization of the eye in addition to the natural processing ability along the proximal visual pathways. Furthermore, the vitreous cavity fluid can be utilized as a heat sink and the prosthesis could be visualized by dilating the pupil in an outpatient setting. Less surgical morbidity and mortality are expected in comparison to any of the cortical prostheses implantation methods.

The disadvantages of the retinal stimulation approach include the following:

1. There is non-focal widespread stimulation due to activation of ganglion cell axons along their path to the optic nerve, because axons from different retinal locations are passing within short distances from each other. Because of obvious anatomical considerations, ganglion cell axons should be less affected by the subretinal prosthesis compared to the epiretinal prosthesis.
2. Possible difficulties in chronic attachment of a device to the retina. This is a main concern for the epiretinal design. In contrast, the subretinal prosthesis is supported by the natural adherence forces that exist between the RPE and the sensory retina.[168]
3. Bipolar and ganglion cells encode many proper-

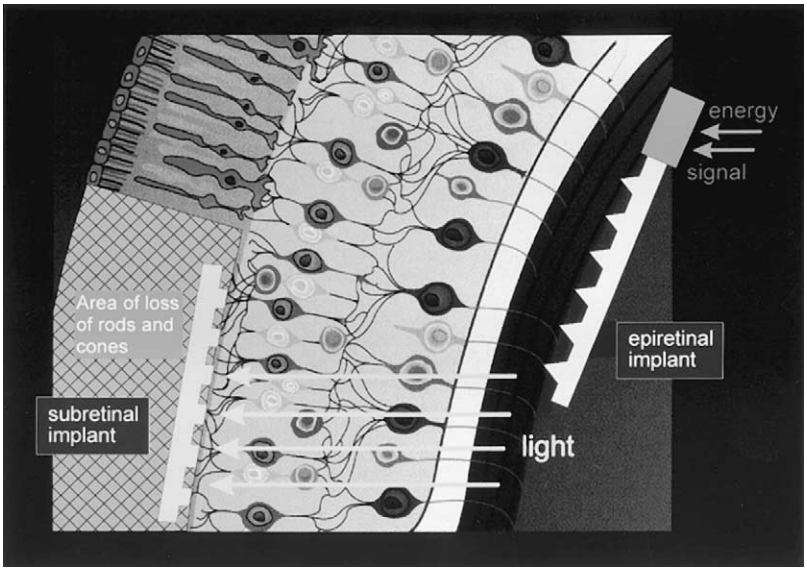

Fig. 2. The epiretinal and subretinal concepts. The epiretinal electrode array is located on the surface of the inner retina. The subretinal electrode array is located in the subretinal space, between the sensory retina and the retinal pigment epithelium. Both electrode arrays are shown without any additional necessary components such as the stimulating chip, receivers, photodiodes, and so forth to simplify the concept (Courtesy of Professor E. Zrenner.)

ties of the visible light (color, intensity, etc.) and the question is which property will be encoded during electrical stimulation if many bipolar and ganglion cells are activated simultaneously.

4. This approach is limited to outer retinal pathologies.

A. EPIRETINAL PROSTHESES

Progress in the field of neural prostheses has converged with advances in retinal surgery to enable the development of an implantable retinal prosthesis. Currently, several groups have been developing epiretinal prostheses.[38,47,69,70,164]

Recently, intraocular acute (6–8 hours) epiretinal stimulation studies to examine the effects of electric stimulation were performed in primates.[51] Functionality of the prosthesis was confirmed by cortical EER recording.

Similarly, blind RP and AMD patients were examined acutely (~1 hour) to see if retinal electrical stimulation can evoke visual sensations.[71] Prior to the surgical procedure, patients had to pass a screening test, which grossly tested the inner retinal function. They had to perceive light in response to electrical stimuli delivered by a contact lens. The surgery involved a three-port pars plana vitreoretinal procedure with subconjunctival anesthesia placed only over the sclerotomies in order to avoid disruptions of the optic nerve function. Different types of stimulating electrodes were handheld on the retinal surface. The patients were then asked to tell the surgeons about their visual perceptions. Focal electrical stimulation elicited phosphenes in all patients and 4 out of 5 patients were able to describe spatial and temporal aspects of the stimuli. The resolution could be estimated as 4.5/200, a crude ambulatory vision.

Epiretinal electric stimulation was tested again in nine other RP and AMD patients.[70] Two patients were tested with an electrode array consisting of 3×3, 5×5 or 3×7 electrodes (Fig. 3). Seven other subjects were tested with simple devices consisting of 3 platinum electrodes packaged as a surgical instrument in a hand-piece. The study showed that electrical stimulation threshold was dependent on the electrode's location (i.e., the macular region required lower threshold currents than the peripheral retina to elicit visual perceptions). Also, patients with less advanced RP or AMD required lower thresholds currents than those with more advanced disease. These findings are important because lower thresholds would allow for smaller electrodes and greater resolution.

Perhaps the most important result of this study was associated with form recognition. Patients were able to identify crude forms such as letters or a box

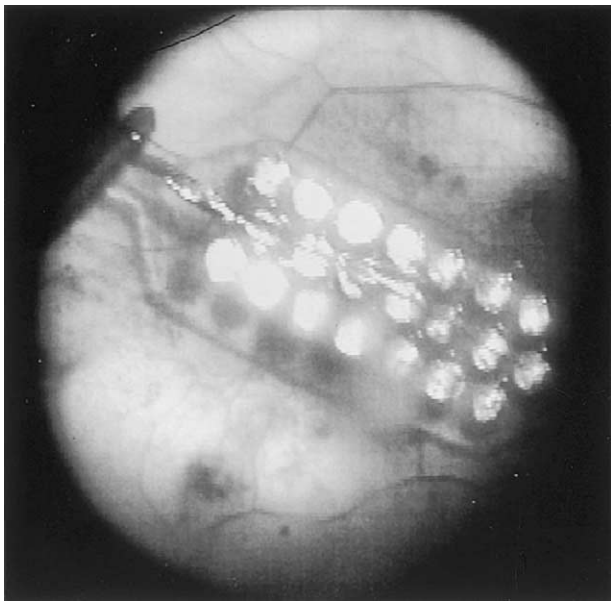

Fig. 3. Acute epiretinal electrical stimulation in a RP human patient with 3×7 electrode array.

shape during the short period of electrical stimulation testing. When the electrical stimulation ended, there was no persistence of the image. Other important psychophysical perceptions in this study included flicker fusion (at a repetition rate of 40–50 Hz) and different color perceptions.[70]

As discussed earlier, epiretinal prostheses will be exposed to ocular rotational movements that can reach a speed of more than 400 degrees/second.[4] Bioadhesives, retinal tacks, and magnets were some of the methods examined for epiretinal attachment. In one study, the retinal tacks and the electrode array remained firmly affixed to the retina for up to 1 year of follow-up with no significant clinical or histological side effects.[85] Similar results were shown in rabbits.[155] In another study, nine commercially available compounds were examined for their suitability as intraocular adhesives in rabbits. One type of adhesive (SS-PEG hydrogel, Shearwater Polymers Inc.) proved to be strongly adherent and non-toxic to the retina.[86]

Another disadvantage of the epiretinal prosthesis is the relative distance from its target cells. The thickness of the nerve fiber and ganglion cell layers is at least 20–200 and 20–40 μm, respectively. Since there is a 3-dB rise in threshold for every 250 μm in distance (up to 1 mm) from a stimulating electrode (400-μm diameter platinum electrode),[54] more current will be theoretically necessary for electrical stimulation than if the electrodes were in close contact to their target cells. Some of the charge density threshold values (0.16–70 mC/cm^2) for acute epiretinal stimulation of patients blind from RP, were well

above the safe threshold for Pt electrodes chronic stimulation (see section In Vivo Characterization of Epiretinal Excitation).[71] These values are affected by the fact that many times the stimulating electrodes in acute experiments were as far as 0.5 mm from the retinal surface. Nevertheless, these are diseased retinas that require increased charge for stimulation.[71] In order to reduce the charge density and keep it within safe limits for long-term stimulation, one should use either larger electrodes and thus lose resolution, or get closer to the target cells, that is, penetrate into the retina.

The cell bodies (somas) of these ganglion cells are mapped over the retinal surface in locations that approximate the projection of the visual world onto the same surface. However, at any particular location on the retinal surface, axons from peripheral sites overlay the individual ganglion cell bodies. If these superficial passing axons were preferentially stimulated, groups of ganglion cells from large areas of the retina would be excited. One might expect the visual perception of such a stimulus to appear as a wedge or arc because of the characteristic course of the ganglion cell axons in the nerve fiber layer. On the other hand, if the ganglion cell bodies or deeper retinal cells were stimulated, one would expect the visual perceptions to be focal spots.[71] When RP and AMD patients' retinas were stimulated with 50–200 μm diameter platinum disk electrodes, the patients reported of spots of light and not wedges.[70,71] This would implicate that the electrodes did not preferentially stimulate the RGC axons.

Stimulating the bipolar cells will allow more of the natural retinal processing to take place. Stimulating the ganglion cells, which are closer to the epiretinal electrode array, may require less current but would require more image processing and complex stimulation patterns to account for the lost retinal processing. Recently, latency and strength-duration experiments that were conducted in isolated frog retinas suggested that higher currents stimulate RGC directly while lower currents activate other cells (photoreceptors, bipolar cells).[54] Another finding was that the target cells of shorter pulse duration (< 0.5 msec) were RGC cells/axons whereas a deeper cellular elements were the target for longer pulse duration (> 0.5 msec).[54] This is consistent with the finding that deeper retinal cells have unusually long chronaxies compared to RGC.[54] Thus, there are several lines of evidence to suggest that epiretinal electrical stimulation of the retina can result in well-defined retinotopic visual percepts, and that RGCs and RGC axons stimulation can be avoided by using long pulse duration in excess of 0.5 msec. More in vitro and in vivo data should be collected to verify these results in the future.

Different aspects of the safety of the epiretinal prosthesis were examined in several experiments. Some experiments used only sham devices with no electrical stimulation in order to examine mechanical biocompatibility. In one such study, performed in 4 dogs, no retinal detachment occurred and only RPE changes were noted near the retinal tacks, which were used for fixation of the epiretinal implant.[85] In another study it was reported that 9 out of 10 rabbits were implanted with an epiretinal device without serious complications. The implant was stable at its original fixation area and no change in retinal architecture underneath the implant was found by light microscopy. In three cases, mild cataract formation was observed, and in one case, a total retinal detachment was found after 6 months of follow up.[155]

Epiretinal implantation has the advantage of keeping most of the electronics off the retinal surface (Fig. 4), in the vitreous cavity, a naturally existing and fluid filled space, which greatly helps in dissipating the heat generated by the electronics.[105] Previously, the epiretinal intraocular prosthetic chip including a photosensor, processor and a stimulus-driving chip was developed.[83] However, it became apparent that an improvement could be achieved in having photosensing[47] or video capture performed extraocularly, allowing for enhanced video processing, more custom control over the video signal, and less hardware to be implanted into the eye.[84] The two units can be connected either by infrared laser,[117] or by inductive link telemetry (Fig. 4),[63,84,148] allowing the intraocular unit to derive both power and data signals from the extraocular unit. The extraocular unit includes a video camera and a video processing board, a telemetry encoder chip, a radio frequency amplifier, and primary coil (or laser source). The intraocular unit consists of a secondary coil (or a photovoltaic receiver), a rectifier and regulator, a retinal stimulator with a telemetry protocol decoder, a stimulus signal generator and an electrode array.

1. In Vitro Characterization of Epiretinal Excitation

Several in vitro experiments with isolated retina preparations have shown that neuronal activity can be evoked by electrical stimulation. Early experiments showed that secondary slow-wave retinal potentials have been induced by trans-retinal electrical stimulation of an amphibian eye cup preparation.[78,79] Such experiments allow us to delineate electrode shapes and pulse parameters in controlled settings. In vitro experiments to define threshold currents for retinal electrical stimulation were performed in different preparations. Threshold parameters during various in vitro electrical stimulation experiments are shown in Table 3.

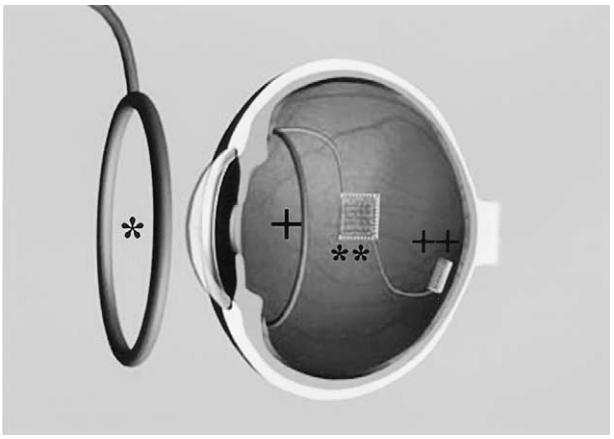

Fig. 4. A sketch of an epiretinal implant shown with extraocular primary coil (*) and an intraocular secondary coil in the sulcus of the ciliary body (+). The receiver and the stimulating chips are located in the mid-vitreous (**) and connected to the epiretinal electrode array (++).

One study of normal retinal stimulation was performed in bullfrog eyecups and reported a charge density threshold of 2.98 $\mu C/cm^2$.[69] Another study was performed with rabbit isolated retinas. Charge density threshold values were between 30 $\mu C/cm^2$ and 917 $\mu C/cm^2$.[59] These results were similar to findings in isolated human retina, concluding that rabbits are a good model to study retinal electrical stimulation.[59]

2. In Vivo Characterization of Epiretinal Excitation

Because many of the experiments to develop a safe and effective implantation in humans have been and will be performed in animals, indirect methods of recording the function of the central visual system have been developed. Threshold parameters during various in vivo electrical stimulation experiments are shown in Table 2.

Several experiments using scalp and subdermal electrodes positioned over the visual cortex were performed to demonstrate that EER can be recorded after external electrical stimulation of the eye.[38,54,107–109,138,147]

Penetrating electrodes within the cortical tissue have the potential to record single neuron activity in addition to multi-unit activity recorded by epidural electrodes.[90,137] Other invasive methods for recording visually evoked potentials or EERs were tested. An epiretinal microfilm electrode array was used to stimulate the retina in normal cats.[65] The evoked potentials were recorded with epidural recording electrodes positioned over the visual cortex. The charge balanced threshold value was 178 $\mu C/cm^2$. Recently, subdural electrodes were compared to subdermal electrodes in recording visual and electrical-evoked potentials in dogs.[87] Electrical stimuli of 1 msec 6 mA elicited an 87.3 μV amplitude response that was recorded with subdural electrodes vs. 1.1 μV that was recorded with subdermal electrodes (in the same animal). In addition, the amplitude of the VEP recorded with subdural electrodes was higher than the one recorded with sub-dermal electrodes (159.5 vs. 9.9 μV, respectively).

B. SUBRETINAL PROSTHESES

Several groups have been developing subretinal prostheses.[31,171] The subretinal space is obviously a good location to stimulate the bipolar cells because of its physical proximity to the inner nuclear layer (Fig. 5).

The artificial silicon retina (ASR) is a subretinal prosthetic device comprised of subunits measuring 20×20 μm.[31] Every subunit is a combination of a silicon microphotodiode and a stimulating electrode. The density of the subunits is 1100 subunits/mm^2. These subunits are designed to convert the light energy from images into electrical impulses to stimulate the remaining functional cells of the retina in patients with AMD and RP types of conditions. The ASR is powered solely by incident light and does not require the use of external wires or batteries. By converting light into electrochemical signals, the microscopic solar cells on the chip mimic the function of the photoreceptors to stimulate the remaining viable cells of the retina. These solar cells, in turn, activate the adjacent electrode in the subunit and thus create an electrical current, which stimulate adjacent retinal tissue. This translates into a relatively simple intraocular operation and array activation. The surgical procedure can be performed extraocularly through the sclera (ab externo) or intraocularly through a retinotomy site after a standard vitrectomy

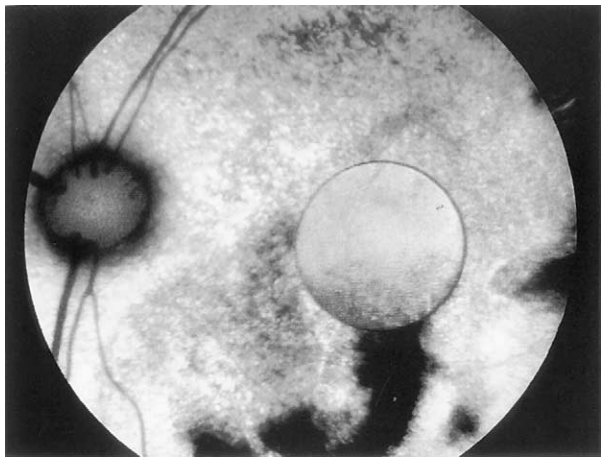

Fig. 5. Fundus photograph of a cat taken approximately 3 months after a subretinal implantation of a microphotodiode array in a cat. (Reprinted with permission of Martin Dunitz, Ltd.[33])

procedure (ab interno). The ab externo procedure is performed by preparing a scleral flap 6 mm from the limbus. Intraocular pressure is reduced by paracenthesis. Then the choroid is incised and a custom-made implantation tool is used to insert the device into the subretinal space.[171] The subretinal approach takes advantage of the adherence forces between the sensory retina and the retinal pigment epithelium to keep the array in place. In some occasions though, the array can be displaced after implantation.[104]

Recently, phase I clinical trials (IDE) of subretinal visual prosthesis implantation in three human subjects were announced. The retinal prosthesis, measuring 2 mm in diameter and 25 μm of thickness, contained 3,500 solar cells that generate power from light received by the eye.[98] Later, the same group implanted silicon chip artificial retinas into the eyes of three additional patients blinded by retinal diseases, continuing a first-of-its-kind safety, feasibility, and efficacy study to restore visual function.[32] The implantation takes about 1.5–2 hours to complete. The patients were all discharged from the hospital 1 day later and recovered at home. The subretinal positioning of the retinal prosthesis has the advantage of placing the stimulating electrodes closer to the bipolar cells, which may also permit lower stimulus thresholds.[30,31,60,104,145,171]

Several biocompatibilty issues of the subretinal approach have been studied. These include limitation of the implant power generation by size requirements,[104] and creation of a mechanical barrier between the retina and the choroid, which provides nourishment to the outer layers of the retina.[171]

Modern-day photovoltaic or solar cells are relatively inefficient compared to the natural photoreceptors of the eye. In order to activate neurons, solar cells need to provide electrical energy many orders of magnitude higher than the amount of current produced under typical retinal illumination. This translates, based on empirical and theoretical calculations, into using a very bright image intensifier (20 suns or 2000 W/m^2) in order for the stimulator chip to generate the level of currents that have resulted in visual perceptions in the blind. This, however, can be overcome by adding more energy in the near infrared light spectrum of solar cells and minimizing the electrode surface area. These concepts are investigated and partially proven by subretinal prosthesis groups and further improvements are anticipated in this area (see section Power Supply).[31,131,132]

A mechanical barrier between the retina and the choroid might be responsible to patches of fibrosis and RPE changes that were found after chronic subretinal implantation. The histology of the retina showed declining inner nuclear and ganglion cell layer densities, but no inflammatory response.[104] Another report showed that there was irregular glial proliferation above the electrode array.[171] However, in another study, three rabbits were implanted with an electrode array in the subretinal space. No side effects were reported.[30] Similarly, micropigs were sacrificed after an implantation period of 14 months.[50] The outer retina degenerated but the inner retina remained intact with no Müller cell proliferation. To prevent a possible barrier effect, one of the groups incorporated porous electrode array structures to facilitate nutritional exchange between the retina and the underlying choroid.[131]

1. In Vitro Characterization of Subretinal Excitation

Several groups examined the threshold for subretinal electrical stimulation. These studies were performed by stimulation from the photoreceptor side of the retina. Human testing has shown that stimulation threshold vary greatly depending on the health of the retina. Thus, it is important from the standpoint of developing a retinal prosthesis to compare electrical stimulation experiments of normal to degenerated isolated retina.

The charge density threshold values of one of these studies were in the range of similar epiretinal in vitro experiments (178 $\mu C/cm^2$).[141] This study was performed on isolated normal chicken retina. The results also demonstrated that spatially organized electrical stimulation could produce spatially discernible responses in retinal output. Another study, performed on isolated retinas from retinal degenerate rats (RCS), reported of a threshold charge density of 500 $\mu C/cm^2$.[140] These studies were done with the "sandwich preparation," that is, stimulating with a micro-electrode array from one side of the retina and recording with a patch electrode placed on the cell bodies of the RGC from the other side of the retina.[50,141] Similar to epiretinal human experiments, we can see that a much higher charge density threshold is required to stimulate diseased retinas. One possible explanation for this phenomenon is that photoreceptors have the lowest thresholds and since degenerated retinas lack photoreceptors, much higher charge density values are required to activate the remaining cells.

2. In Vivo Characterization of Subretinal Excitation

The ability to electrically stimulate the retina with a subretinal device and record central nervous responses were demonstrated in several experiments. In one experiment, subretinal electrodes connected to extraocular photodiodes were implanted in three rabbits and tested acutely.[29] Aside from incident light stimuli, no external power source was used. Flash stimuli were provided with a Grass PS-22 pho-

tostimulator. Cortical potentials were recorded from subdermal electrode placed at the occiput. Cortical responses were recorded from all three rabbits and maintained even when the stimulation polarity was reversed (this is a well-known method to examine if the elicited response from electrical stimulation of neuronal tissue is an electrophysiological response or an artifact. If the response has the same polarity after the stimulation polarity is reversed, then it is considered a real electrophysiological response. If, instead, the polarity of the response changes after reversal of the stimulation polarity, it is considered to be an electrical artifact). The magnitude of the cortical responses declined as the stimulating charge density was reduced from 1×10^{-7} to 2.8×10^{-9} C/cm^2. These results demonstrated the general concept of converting light into electrical energy, stimulating the retina, and recording EER at the level of the visual cortex.

A similar study was performed with rabbits and micropigs.[50] In this experiment, no light source was used but instead the subretinal implanted electrodes were pulsed with 3V 400 μsec electrical stimuli. EER was recorded in both species in response to electrical stimulation.

IV. Optic Nerve Prostheses

Investigators have also stimulated the optic nerve.[133,134,153] The optic nerve is a compact compartment of ganglion cell axons running from the retina and synapse on the lateral geniculate body. This condensed cable can be reached surgically, and theoretically has a good location for implanting a surface or penetrating stimulation electrode array. However, the high density of the axons (1.2 million within a 2 mm-diameter cylindrical structure) could make it difficult to achieve focal stimulation and detailed perceptions. In addition, any surgical approach to the optic nerve requires dissection of the dura and can have harmful side effects, including CNS infection, disturbance of blood flow to the optic nerve, and so forth. Similar to the retinal prosthesis approach, optic nerve stimulation requires intact RGC and is limited to outer retinal pathologies.

Recently, one of the groups chronically implanted a self-sizing spiral cuff electrode[21] with four electrical contacts around the optic nerve of a 59 year-old blind RP patient (Fig. 6). Electrical stimuli applied to the optic nerve produced localized, often colored, phosphenes that were broadly distributed throughout the visual field and were still reliably reinduced 118 days after surgery. Changing the pulse duration, pulse amplitude, or pulse repetition rate could vary phosphene brightness.[153] After training, the patient could recognize different shapes, line orientations, and even letters[151]

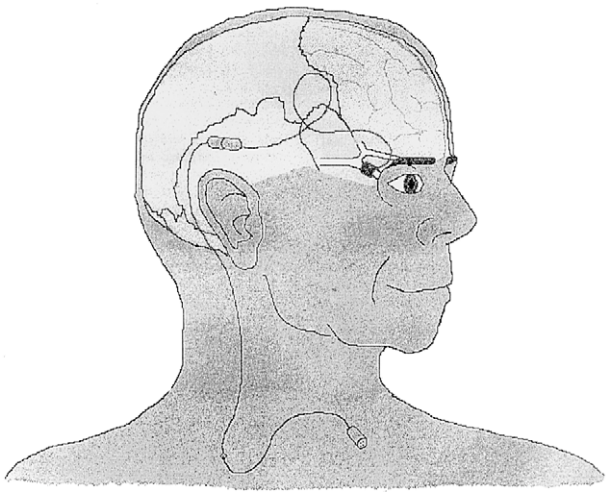

Fig. 6. A sketch of a right optic nerve device after implantation. The cuff electrode was implanted intracranially. The cable passes through the skull and courses below the skin and along the outer surface of the skull. It then passes down the neck to exit the skin below the clavicle. (Reprinted with permission of *Brain Research.*[153])

During this unique intracranial implantation of optic nerve stimulating electrodes in a human, no acute or chronic side effects were noted.[153] No acute damage was noted after electrical stimulation of the sciatic nerve of cats with similar cuff electrodes.[152]

Yet another approach called a "Hybrid Retinal Implant" proposes to develop a visual prosthesis, which would include both electronic and cellular components. The electronics will perform image recognition and the neurons on the device will extend their axons to synapse with the lateral geniculate body, thus create the device–CNS interface, and restore vision.[165,166] The advantage of this approach is to be able to replace an eye with total or inner retinal degeneration. Disadvantages include difficulties in precisely directing axons to the lateral geniculate body, developing the interface between the electronics and neurons, and developing the matrix to enable survival of the cellular components while being housed in microelectronics. The Hybrid Retinal Implant is in the early stages of development and its successful implementation will depend on advances in retinal cell culture as well as microelectronics.

V. Sensory Substitution Devices

As an alternative to direct stimulation of the visual system neurons, several other approaches have attempted to convert visual information into vibrotactile or auditory signals (i.e., sensory substitution devices[12,115]). The distinct advantage of these approaches is that the device is wearable and not implantable. However, these devices have never reached widespread acceptance because they do not

restore the sensation of vision, have low resolution, occupy another sensory modality, can evoke pain, and can have a prolonged learning period.

VI. Summary

The three levels of hierarchy in the sensory systems (i.e., receptor organ, sensory pathways, and perception) suggest a similar architecture for artificial and prosthetic sensory systems. Accordingly, artificial systems should include a transducer corresponding to the receptor organ, an encoder corresponding to the sensory processing system, and finally an interpreter corresponding to perceptual functions. In other words, the visual environment will be captured and processed by a photosensing device such as a digital camera or photovoltaic units. This pixelized information is then transformed to electrical energy by microphotodiode array or conducted to a stimulating component that in turn activates an electrode array with a similar pixelized pattern.

Adjusting pulse parameters and minimizing interactions between pulses on adjacent electrodes can improve the neural response. The electrical stimulator device output should be characterized by the flexibility of several parameters such as amplitude, pulse width, repetition rate, pulse shape, and so on.

Attempts at implanting electronic devices at various parts along the visual pathways were discussed. Both major achievements and obstacles remaining were summarized. Given that intact neurons along the visual pathways can be found in almost all blind patients, only our lack of experience and capabilities in physiology, biocompatibility and device–tissue interfacing is preventing us from stimulating them in a safe and effective manner. We believe that as our knowledge increases about how to stimulate neurons with microelectronics and as microelectronics and material sciences continue to evolve, we should one day be able to restore vision to the blind. Given the advances that have been made in this field we can only hope that the day such devices are widely used is in the near future and not decades away.

Method of Literature Search

A literature search of the PubMed data was performed (1966–present). The following key words were used: *artificial vision, blindness, cortical prosthesis, electrical stimulation electronic implants, macular degeneration, optic nerve, optic nerve prosthesis, retina, retinal prosthesis, retinitis pigmentosa, visual cortex and visual prosthesis.* In addtion, some abstracts from relevant recent conferences and annual meetings were reviewed. The search was not limited to English language, but only English abstracts were used. We included references that we considered to have made a major contribution to research and development in this field. Minor references were included if they supported a certain point made by other references or contributed new ideas, methods, or very recent advances.

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Outline