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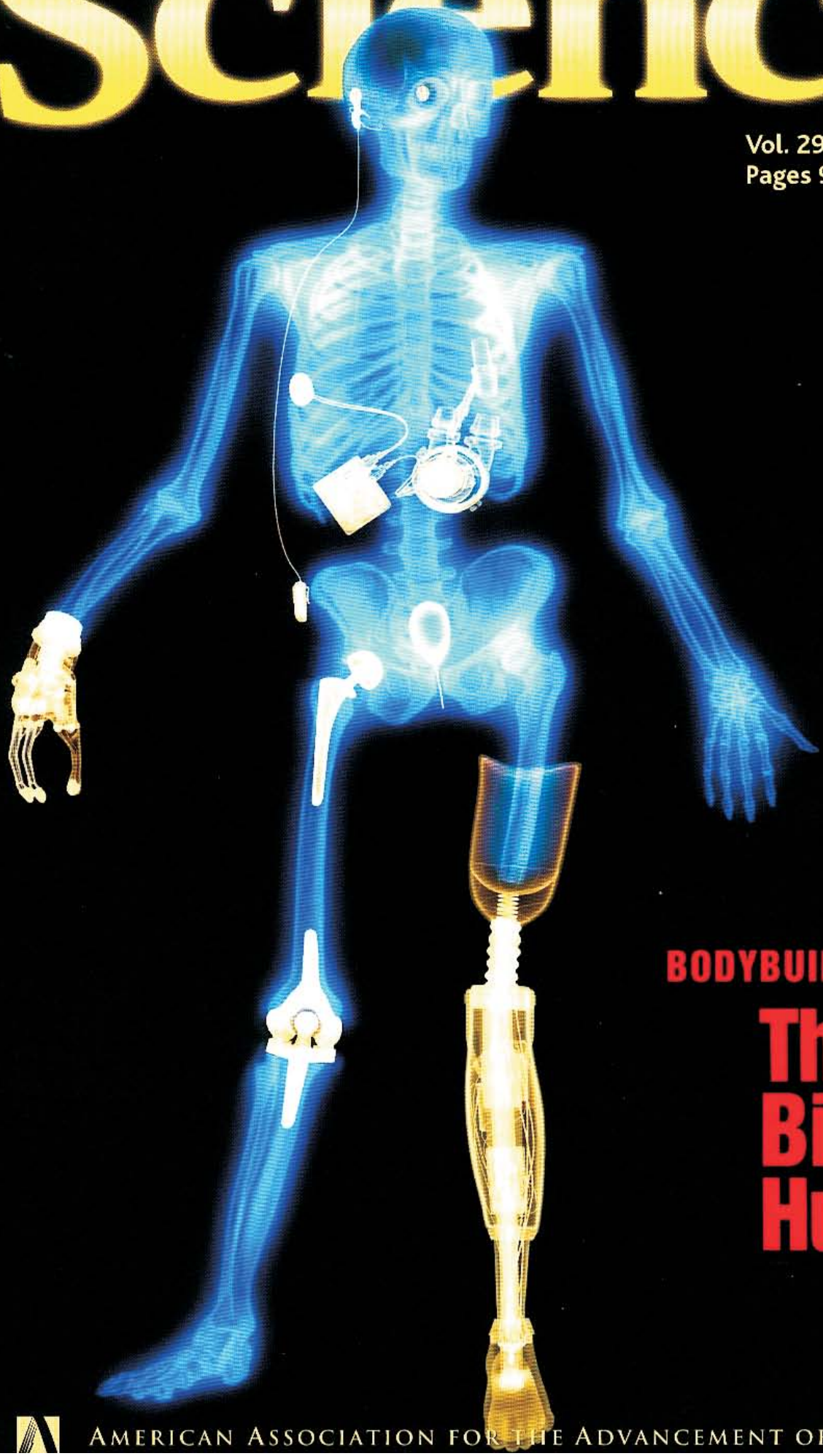

BODYBUILDING:

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VIEWPOINT

Will Retinal Implants Restore Vision?

Eberhart Zrenner

A number of research groups are developing electrical implants that can be attached directly to the retina in an attempt to restore vision to patients suffering from retinal degeneration. However, despite promising results in animal experiments, there are still several major obstacles to overcome before retinal prostheses can be used clinically.

Vision is an enormously complex form of information processing that depends on a remarkable neuroprocessor at the back of the eye called the retina. Seeing is initiated when light passing through the pupil of the eye is focused by the lens onto the retina's sensory neuroepithelium (Fig. 1). This results in the projection of a reduced, upside-down image of the object onto the roughly 130 million photoreceptor cells (rods and cones) in the outermost layer of the retina. The cones, providing chromatic (color) images of high spatial resolution, and the rods, required for achromatic vision with less spatial resolution in dim light, transform local luminance and color patterns of the projected image into electrical and chemical signals. These signals then activate a complex circuit of retinal neurons: horizontal cells, bipolar cells, amacrine cells, and ganglion cells. Visual information from the retina's 130 million photoreceptors is compressed into electrical signals carried by 1.2 million highly specialized ganglion neurons, whose axons form the optic nerve. The optic nerve transmits visual information via the lateral geniculate nucleus to the primary visual cortex of the brain.

University Eye Hospital Tübingen, Department of Pathophysiology of Vision and Neuro-Ophthalmology, Schleichstr. 12, D - 72076 Tübingen, Germany. E-mail: ezrenner@uni-tuebingen.de

Blindness can result when any step of the optical pathway—the optics, the retina, the optic nerve, visual cortex, or other cortical areas involved in the processing of vision—sustains damage. In Germany, 17,000 patients become blind every year for whom there is no effective treatment or cure; about 50% of all blindness is caused by damage to the retina (*1*). Blinding diseases, such as retinitis pigmentosa or age-related macular degeneration (the most common form of blindness in the elderly), cause progressive degeneration of the outer retina. Although there are many examples of electrical devices that can support or replace the function of defective tissues—such as cochlear implants for the hearing impaired [see the Viewpoint by Rauschecker and Shannon on page 1025 (*2*)] or pacemakers for individuals with heart disease—restoring vision with electrical devices implanted into the retina is much more difficult. The transformation of visual scenes into the electrical "images" carried by the optic nerve to the brain requires that numerous sensory neurons are stimulated in parallel and in a spatially correct order to enable three-dimensional objects to be accurately encoded.

The Evolution of a Concept

In 1956, Tassiker described in a patent (*3*) how a small, flat, light-sensitive selenium cell placed behind the retina of a blind patient transiently restored the patient's ability to perceive the sensation of light. Later attempts to restore vision by coupling electrodes to the surface of the visual cortex of blind patients (*4*, *5*) did not provide useful images because of limited spatial resolution and the fading of phosphenes (sensations of light). Subsequent human trials with cortical implants have been more promising (*6*–*8*), but diminished neuronal excitations and stable spatial resolution are still unsolved problems, even with 100 narrowly spaced intracor-

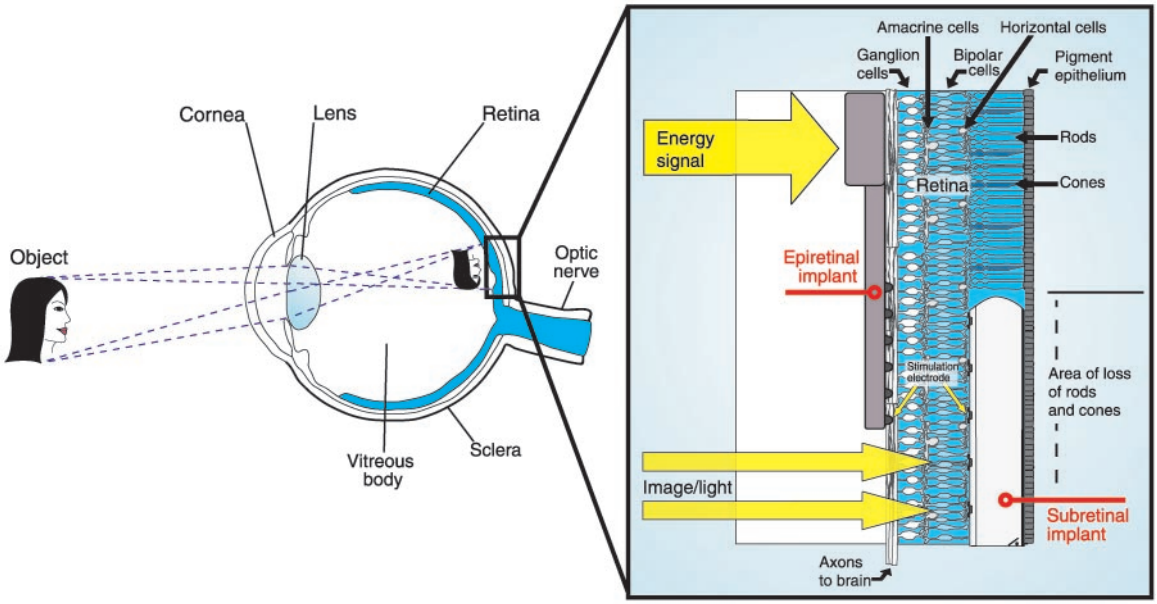

Fig. 1. An object (in this case a face) is projected by the cornea and lens onto the retina in an upside-down manner and is transformed into an electrical image by the photoreceptor cells (rods and cones) of the outer retina. With a subretinal implant, the rods and cones are replaced by a silicon plate carrying thousands of light-sensitive microphotodiodes, each equipped with a stimulation electrode. Light from the image directly modulates the microphotodiodes, and the electrodes inject tiny currents into the remaining neural cells (horizontal cells, bipolar cells, amacrine cells, and ganglion cells) of the retinal inner layer. In contrast, the epiretinal implant has no light-sensitive areas but receives electrical signals from a distant camera and processing unit outside of the body. Electrodes in the epiretinal implant (small black knobs) then directly stimulate the axons of the inner-layer ganglion cells that form the optic nerve [adapted from A. Stett].

tical "needle" electrode arrays (*9*). Taking a different approach, a Belgian group has attempted to attach a cuff comprising a few electrodes around the optic nerve of a blind patient. The patient was able to localize single bright spots of light, but high spatial resolution cannot be expected with such a stimulation arrangement (*10*).

In the early 1990s, many researchers switched their efforts to developing a prosthesis that could be implanted directly into the retina (see the News story by J. Cohen on page 1026). A retinal implant requires the creation of complicated subminiature electrode arrays and electrical circuits consisting of materials that must be stable and relatively inert so that their impact on remaining retinal tissue is minimal. Next, electrical parameters for stimulation of retinal nerve cells must be determined and electronic circuits developed to accommodate the large brightness and contrast variances of the environment. Before retinal implants can be tested in patients, surgical techniques for implanting, removing, and fixing these electronic prostheses in the eye must be developed. In addition, suitable animal models for testing retinal prostheses must be found, ethical questions addressed, and regulatory matters considered. There is also the question of which patients are best suited to receive retinal implants. Retinal implants under development in the United States, Germany, and Japan could potentially enter early clinical trials for functional testing within the next few years.

Two Kinds of Retinal Implant

There are two kinds of retinal implant under development: subretinal and epiretinal (Fig. 1). The subretinal device is implanted between the pigment epithelial layer and the outer layer of the retina, which contains the photoreceptor cells. In the subretinal device, thousands of light-sensitive microphotodiodes equipped with microelectrodes are assembled on a very thin plate and are placed in the subretinal space between the pigmented epithelium and outer layer of the retina. Light falling on the retina generates currents in the photodiodes that then activate the microelectrodes, resulting in stimulation of retinal sensory neurons. In contrast, the epiretinal device is implanted onto the innermost layer of the retina that contains the ganglion cells. The epiretinal implant is essentially a readout chip that receives electrical signals containing image information from a distant camera and processing unit, and is coupled to the ganglion cells and their axons. In response to stimulation by the external image receiver system, the epiretinal implant generates electrical impulses that travel via the ganglion cell axons of the optic nerve to the brain.

Subretinal Implants

Chow and colleagues (*11*–*17*) in Chicago and our group in Tübingen (*18*–*29*) are developing subretinal implants. A thin plate (~50 to 100 μm thick and 2 to 3 mm in diameter) carries hundreds to thousands of light-sensitive microphotodiodes equipped with microelectrodes of gold or titanium nitride arranged in arrays (*11*, *16*, *18*, *19*, *21*). Light emanating from visible objects is converted by the microphotodiodes into tiny currents at each of hundreds of microelectrodes. These currents are then "injected" into whichever neurons remain of the retinal network, the middle and inner retina thus taking over the information-processing part of vision. Subretinal prostheses have a number of advantages—the microphotodiodes directly replace damaged photoreceptor cells; the retina's remaining intact neural network is still capable of processing electrical signals; positioning and fixing of the microphotodiodes in the subretinal space is relatively easy; no external camera or external image processing is required; and eye movements can still be used to locate objects.

Experiments in several animal models, where recordings are made with electrodes contacting the inner or outer retina, reveal that injecting a charge of about 0.4 nanoCoulombs (nC) per electrode (typically equivalent to a current of ~ 10 μA) is sufficient to excite retinal neurons (*12*, *22*). With a distance of 50 to 150 μm between electrodes implanted in rat outer retina, ganglion cells can receive electrical information in a spatially organized manner (*22*) even in animals that have lost their photoreceptor cells through retinal degeneration (*24*). Coating the surfaces of microphotodiodes with glycoproteins such as laminins may improve their biocompatibility (*25*).

Work in vivo demonstrates that in principle there are two surgical approaches for safe introduction of the subretinal implant: gaining access to the retina through the vitreous humor of the eye (ab interno) (*16*, *26*), and gaining direct access to the subretinal space through a scleral incision (ab externo) (*27*). The retina of cats and pigs remains intact for more than 2 years after implantation of a subretinal device (*14*, *17*, *28*). In rats, the implant remains fixed in a stable subretinal position and continues to work for up to 16 months. Implanted subretinal devices show some damage over time due to accumulation of silicon oxide on their surfaces (*20*) and disintegration of the gold electrodes. Such problems can be addressed by encapsulating the device in an inert polymer. Action potentials in the visual cortex of the brain evoked by subretinal electrodes have been recorded in the pig (Fig. 2) (*29*). Following acute electrical stimulation of the cat retina with subretinal electrodes, a spatial resolution of at least 1° was obtained as measured by multi-electrode (*30*) and optical recording (*31*) from the visual cortex.

In vivo experiments also reveal weaknesses in subretinal implant prototypes. For example, the current generated by a single microphotodiode with its small light-sensitive area is not sufficient to stimulate adjacent neurons with the ambient light available from the environment. Thus, an active subretinal implant supported by an external energy source—such as transpupillary infrared illumination of receivers close to the chip or electromagnetic transfer—is now under development. When illuminated, subretinal microphotodiodes are able to transfer these external currents via their microelectrodes to the retinal neurons in a retinotopically accurate manner. Only with the aid of an external energy source will the light from the normal environment be sufficient to modulate the stimulating current at each individual electrode.

Epiretinal Implants

The epiretinal implant has no light-sensitive elements (Fig. 1). A very tiny field sensor, like a camera, is positioned either outside the eye or within an intraocular plastic lens that replaces the natural lens of the eye and is introduced using techniques developed for cataract sur-

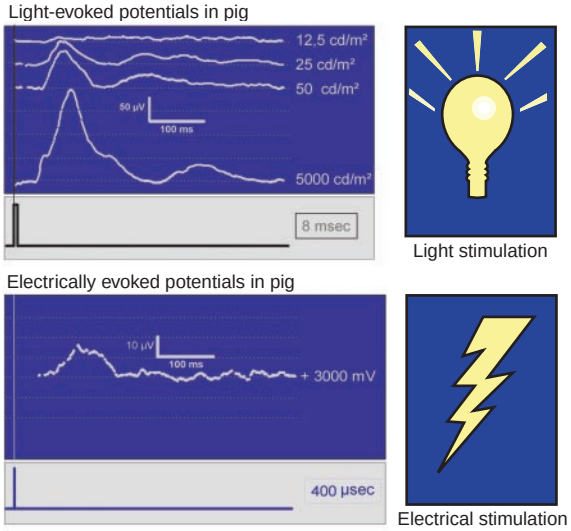

Fig. 2. (**Top**) Cortically evoked potentials recorded with epidural surface electrodes from the visual cortex of the pig. Stimulation with a short light flash (8 ms) evokes a positive electrical deflection with a peak potential about 90 to 100 ms later. The amplitude of the peak is small in low light and large in bright light (measured in cd/m²). (**Bottom**) With electrical stimulation of the outer retina by a wire-bound subretinal multielectrode array (in lieu of light stimulation), an electrical cortical response similar to that evoked by moderate light stimulation is elicited. The charge released with a 3-V electrical pulse of 400-ms duration is about 20 nC and 200 μC/cm², respectively, per electrode [modified from (*29*)].

gery. Foil-bound wires connect the field sensor at the anterior of the eye with an electrode array implanted on top of the inner retina. This array is attached to the inner retinal membrane that separates the neural layer from the vitreous body of the eye's posterior chamber. Epiretinal implants are being investigated by Eckmiller and his colleagues (*32*–*34*), Humayun *et al.* (*35*–*39*), Rizzo and co-workers (*40*–*45*), and more recently by Abrams's group from Detroit and a Japanese consortium lead by Tano *et al.* from Osaka.

Unlike the subretinal implant, the epiretinal implant does not use the remaining network of the retina for information processing. Thus, the epiretinal sensor has to encode visual information as trains of electrical impulses that are then conveyed by the electrode array directly into the axons of ganglion cells, which unite to form the optic nerve. The visual information has to be translated into a spatiotemporal stimulation pattern of electrical impulses that can be understood by the brain's visual cortex. This spatiotemporal stimulation pattern is first conveyed to the electrode array positioned on the inner retinal membrane, which is stabilized either by slight mechanical pressure, or by attachment through cellular contacts or microtacks. As in the subretinal implant, specific surgical techniques have been developed for implanting the epiretinal sensor (*34*, *41*), and the parameters of the current needed for optimal stimulation have been defined (*35*, *41*, *45*). Long-term stability and biocompatibility of the epiretinal implant has been demonstrated in the cat, where the implant provided a cortical resolution of about a 1° visual angle (*30*).

The subretinal and epiretinal approaches both have their advantages and disadvantages. Whereas the subretinal implant uses the remaining neural network of the retina, the epiretinal implant does not and thus must provide additional processing to prepare the visual information. On the other hand, the information-transfer characteristics of the epiretinal implant are more amenable to external control.

Fixing the subretinal implant in the subretinal space is relatively easy because the pigment epithelial cells of the retina "pump out" this space such that the implant is sequestered like "a peanut in a vacuum package." In contrast, fixing the epiretinal implant is very difficult and carries the additional risk of stimulating cellular proliferation. The two-dimensional signal pattern of retinal photoreceptor cells is a mirror image of the outer world so that correct retinotopic stimulation by the subretinal implant, which replaces the photoreceptor cells, can be achieved. The epiretinal implant stimulates both the axons of ganglion cells, which may be far away, and their cell bodies, which are nearby, resulting in a more disordered stimulation pattern that has to be corrected electronically. However, the subretinal implant needs intact optics, whereas the epiretinal implant does not.

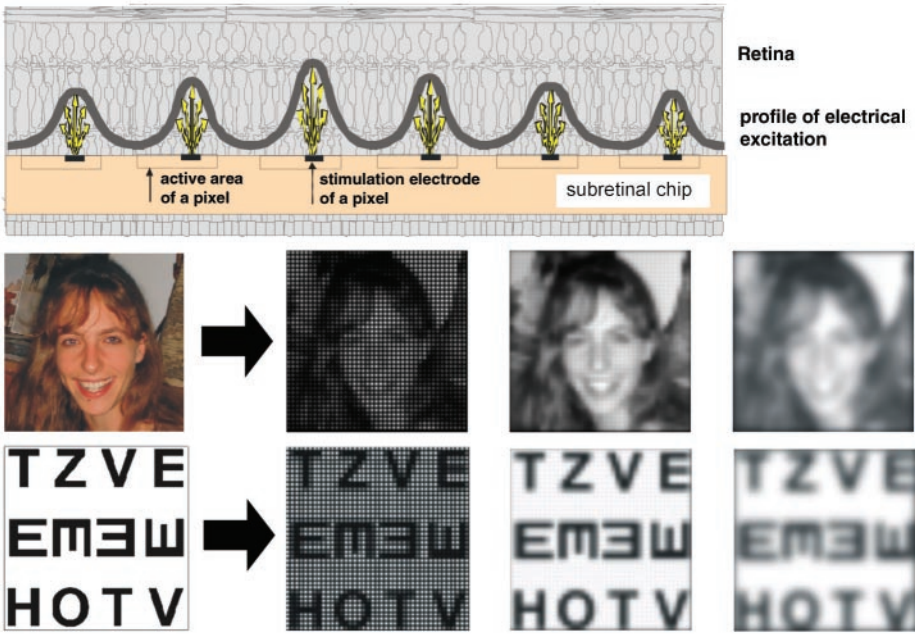

Fig. 3. (**Top**) Example of a profile of electrical excitation produced by light-sensitive areas of a subretinal implant, activated by electrodes spaced 70 μm apart. (**Bottom**) If a regular three-dimensional image (the face or optotype) is transformed into a two-dimensional excitation profile, the image would be represented by a two-dimensional array of 40 by 40 small excitation spots (pixels), sized according to the width of the local electrical wave (see second column). When the light intensity is increased, each of the excitation spots enlarges and a more homogeneous picture emerges (see third column). A further increase in luminosity causes a merging of excitation spots, resulting in a blurred picture (see fourth column) (*20*, *23*).

What Spatial Resolution Can Be Achieved?

The best spatial resolution provided by an electrical excitation pattern at the retinal level can be calculated from in vitro and in vivo experiments (Fig. 3) (*20*, *23*). If a portrait (Fig. 3, middle row) or an optotype image (Fig. 3, bottom row) is pixelated in a 40 by 40 grid, the pattern shown in column 2 of Fig. 3 corresponds to the number and distance of electrodes on a microphotodiode array (3 mm by 3 mm) of a subretinal implant, where electrodes 70 μm apart evoked discernible patterns in vivo; the stimulation current is assumed to be near threshold so that many little excitation dots with grosser distributions are achieved. If the current is increased (for example, by increasing the illumination), each point becomes larger and the current waves (top row) as well as the points merge, resulting in the images shown in column 3. Very strong stimulation produces patterns with even more confluent points, resulting in the images in column 4. This is, of course, only valid if one assumes that each electrode in the array can be connected appropriately with a retinal neuron, a question that remains to be addressed. Certainly the very high spatial resolution of natural photoreceptor cells cannot be achieved because this resolution is based on highly specialized pre- and postsynaptic structures that ensure high gain and high-fidelity transmission to second-order cortical neurons.

Will Retinal Implants Work in Patients?

Humayun *et al.* (*35*, *38*), as well as Rizzo and Wyatt (*42*, *45*), have stimulated the retina of blind patients with epiretinal electrodes that were transiently inserted into the eye through a scleral opening. Both groups reported a sensation of light patterns by the patients, but perception of geometric patterns was reported in only a few instances. Limited perception was achieved only at high charge densities at the site of the epiretinal implant (*45*). During the available intraoperative stimulation time (up to 4.5 hours), the perceptual responses elicited by epiretinal electrodes did not often meet expectations in relation to the pattern of stimulation (*45*). These results are still far from true object recognition. However, they do demonstrate the feasibility of generating perception of light patterns in blind people.

It is also reassuring to learn (*28*, *36*, *39*) that ganglion cells and other cells of the inner retina are still present in patients with retinitis pigmentosa, even after many years of blindness. Consequently, even in these patients, there may be enough neural cells available for efficient stimulation by subretinal or epiretinal implants.

Chow and colleagues (*46*) have reported implantation of a passive subretinal device (without an external energy supply) into the eyes of patients using the method of Peyman *et*

al. (*16*). Their study was designed to examine biocompatibility of the device but not its function. The results in six patients (three received the chip in 2000, and another three in 2001) have not been released as yet.

The Future

It is indeed feasible to elicit action potentials in the visual cortex using electrical impulses generated by subretinal or epiretinal devices, but a number of obstacles remain to be overcome. We need to know whether the encoding of orientation and movement perception as well as feature localization is maintained at the level of the visual cortex. How can the long-term stability of these implants, whose surfaces do deteriorate after long-term implantation, be achieved? Will retinal neurons tolerate long-term electrical stimulation without themselves being altered morphologically or functionally? What type of image can be perceived by blind patients through an epiretinal implant or the light-sensitive microphotodiodes of a subretinal implant?

The patient group best suited to test such questions by implantation of retinal prostheses may be patients with hereditary retinal degenerative diseases who are stricken with blindness yet still have intact middle and inner retinal layers. In addition, a second group of patients with certain forms of macular degeneration, including the age-related type, could benefit from retinal prostheses even at advanced stages of disease. We need to instigate long-term clinical trials to ensure that the peripheral vision still present in patients with macular degeneration is not endangered by surgical procedures and the effects of the retinal implants themselves.

In 1993, there were only two papers on retinal implants among the thousands presented at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO). Encouragingly, 1999 saw the number of presentations rise to 33, and the numbers continue to increase. Successful testing of each major step in retinal implant development—production of implant prototypes, surgical procedures, long-term stability and biocompatibility of implant material, electrical testing in vitro as well as in animal models, recording electrical activity in animal brains—is providing essential data about the resolution required for blind patients to regain mobility in a world that very much depends on visual information. A number of international groups (*44*) are tackling the remaining problems associated with epiretinal and subretinal implants, and we await the outcome of clinical trials to determine the value of refined nanotechnology for treating blinding eye diseases.

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VIEWPOINT

Sending Sound to the Brain

J. P. Rauschecker[1] and R. V. Shannon[2]

The cochlear implant, a microelectrode array that directly stimulates the auditory nerve, has greatly benefited many individuals with profound deafness. Deaf patients without an intact auditory nerve may be helped by the next generation of auditory prostheses: surface or penetrating auditory brainstem implants that bypass the auditory nerve and directly stimulate auditory processing centers in the brainstem.

Partial or total hearing loss has many different causes. Defects in either the outer ear or middle ear (composed of the tympanic membrane, ear drum, and auditory ossicles) result in a conductive hearing loss that can usually be remedied by insertion of a hearing aid, which amplifies sound vibrations. Profound deafness, on the other hand, is caused by loss of the sensory hair cells in the fluid-filled, snail-shaped inner ear, or cochlea, that transduce sound waves into electrical impulses, which are then transmitted to the brain (Fig. 1). Profoundly deaf individuals who still have an intact auditory nerve have profited from the dramatic advances made over the past 30 years in the field of cochlear implants (CIs) (*1*, *2*). The CI is a microelectrode array implanted in the cochlea that directly stimulates the auditory nerve. With more than 40,000 patients worldwide, the success of these devices is nothing short of miraculous: Most adults are able to converse on the phone, and most children are able to be edu-

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[1]Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, DC 20007, USA. [2]Department of Auditory Implants and Perception, House Ear Institute, Los Angeles, CA 90057, USA.