Visual prosthetics 2006: assessment and expectations
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This report provides a brief overview of blinding eye diseases for which prosthetic vision may hold promise as a treatment modality, and of current and near-term technological approaches towards the creation of prosthetic interfaces with the remaining visual system. Principal anatomical, physiological, technological and functional obstacles and possible solutions are outlined, and references are provided to pioneering work by over a dozen groups on four continents.

The desire to restore sight to the blind goes back far into human history. In modern times, depending on the cause of blindness, this desire is being realized, starting with the elimination of optical obstructions blocking image formation on the retina. Cataract surgery and corneal transplants, and more recently, advanced surgical methods to improve the optical quality of the eye’s imaging system as well as preventive care to eradicate infectious diseases affecting the cornea, are sharply reducing the impact of this category of blindness. The subsequent stages of the visual system, retina, optic nerve and visual cortex, do not lend themselves so easily to corrective interventions that bring back vision. As in other parts of the CNS, restoring function through neuron transplantation and reconnection is in most cases not (yet) feasible, even though encouraging initial results have been reported in recent years [1]. In the near term, however, substituting lost function by an electronic or mechanical prosthesis may be the most viable option for functional vision restoration. This article provides an overview of the eye diseases for which these approaches may provide a partial remedy and of the most promising visual prosthesis projects currently underway.

Visual processing fundamentally takes place in stages, beginning in the retina. Not only does the retina transform the pattern of incident light into a pattern of electrochemical signals, it also accomplishes an important degree of preprocessing and reduction of the information before sending signals through the optic nerve to the visual centers in the brain where the information is analyzed in terms of color, movement, shape, texture, depth and many other aspects. This stage-wise process has two important implications: if the retina does not develop well during pre- and postnatal development, neither will the processing areas in the visual cortex [2]; a person functionally blind from birth cannot develop useable vision unless clear images are projected onto the retina within the first months or year of life [3]. Second, replacing function of neural elements at the earliest available stage of visual processing will yield the most ‘natural’ vision, as it utilizes subsequent stages along the visual pathway, and avoids the need for any ‘surrogate’ processing that will inevitably fall short of the intricate accomplishments of the native system. Thus, by way of example, a retinal prosthesis should be used if the optic nerve is intact; by extension of the same logic, such a prosthesis should stimulate the most distal remaining cell population available.

Causes of blindness & the prospects for prosthetic intervention
Blindness diseases & trauma
The most frequent cause of sensory vision loss is degeneration of the outer retina, that is, loss of either the light-capturing photoreceptors – cones for color vision at higher light levels,
rods for vision at very low light levels - or their supporting layer of retinal pigment epithelium (RPE) cells. Depending on the type of primary loss, vision may be affected in different ways. The most common cause of blindness in the aging population, age-related macular degeneration (AMD) affecting over 5 million Americans, is caused by the inability of the RPE cells to fulfill their support function over an ever-increasing lifespan (in addition to nutritional, environmental and genetic factors). AMD causes loss of central vision, limiting these elderly individuals in many aspects of their lives [4]. Several inherited forms of retinal degeneration also affect the RPE cells, but start doing so at a much earlier age. However, most inherited degenerations act on the photoreceptors, through genetic defects of molecules involved in the phototransduction process. Such defects lead to primary damage to one photoreceptor type followed by damage to the underlying RPE cells and the remaining photoreceptors. The most common subgroup of these, known by the joint descriptive term retinitis pigmentosa (RP), affects 1.6 million people worldwide and is the leading cause of blindness between the ages of 10 and 60 years. RP causes a slow and progressive loss of vision starting in the mid-periphery, gradually expanding outward and inward over years or decades, leading to tunnel vision and often functional or total blindness. To date, there are no treatments for retinal degenerations, other than some procedures that may slow down, but not halt, the progression. A final, though not commonly blinding, condition affecting the photoreceptors is retinal detachment, which may be caused by trauma or other excessive mechanical forces on the retina, such as the strain caused by an elongated eyeball in high myopia, or by the pulling force of the vitreous gel on the fragile retinal tissue. Retinal detachments are typically caught early, and can be reattached with laser or traditional surgery, so damage to the photoreceptors is typically localized. They rarely cause damage to the inner retinal cells since their metabolic supply is provided through the optic nerve, and does not suffer from the detachment; in this sense, if photoreceptor damage is extensive, they provide a 'clean' example of outer retinal blindness. All these diseases are strictly localized to a single processing stage, that is, the retina, and therefore are good candidates for a prosthetic approach to vision restoration.

A second group of diseases leading to blindness at the retinal level are vascular diseases, such as ischemia or occlusion, and diabetic leakage of blood vessel walls. Such diseases do not primarily affect the photoreceptors, since these derive their support from the RPE cells through diffusion, but lead to severe structural damage throughout the inner layers of the retina, affecting visual neurons that process signals from the photoreceptors. In most cases, these diseases are systemic, and possibly life threatening, hence less likely to allow benefit through a prosthetic approach.

A third group of blinding diseases strikes the axons of retinal ganglion cells (RGCs) that form the fibers of the optic nerve transporting visual information to the brain. The most common among these is glaucoma, in which RGC axons are destroyed when the fragile support structure at the transition of the eye and optic nerve is deformed by excess pressure of the fluid in the eye; vision loss often does not become evident until a large proportion of axons have been destroyed. Damage to the optic nerve can also result from disturbances in blood supply to the optic nerve itself and from traumatic causes such as severe facial and head injury. In this group of diseases the pathway to the visual cortex is no longer functional, so a cortical prosthesis may be the only viable approach to vision restoration.

A final group of diseases that may lead to blindness are those affecting the CNS, through demyelination of nerve fibers, elevated intracranial pressure or ischemic or hemorrhagic events affecting portions of the visual pathway. In most cases the effects of such diseases will be widespread, and therefore are not amenable to vision restoration at a more proximal stage such as the visual cortex, but in isolated cases the damage can be limited to the lateral geniculate nucleus or the optic radiation, that is, the pathway from the retina to the primary visual cortex. A prosthesis stimulating the visual cortex may then be a rehabilitative option.

**Developing the interface with the visual system**

The first attempts at vision restoration were directed at the visual cortex, almost 40 years ago. Neurosurgical techniques had progressed to the point where the surface of the brain could be safely exposed for implantation, and stimulating electrodes placed over the cortical surface had been demonstrated to generate reproducible phosphenes. Retinal surgery was not routinely performed until the early 1980s, and even then most ophthalmologists and neuroscientists doubted the survival of a sufficient number of secondary neurons in retinal degenerations to allow reliable activation of the visual system by implants at the retinal surface. Ten years later, intraoperative stimulation in late-stage RP patients demonstrated that phosphenes could be elicited long after photoreceptor degeneration [5]. It was then hypothesized that the remaining neurons in the degenerated retina, that is, bipolar and ganglion cells, would present essentially the same properties as their counterparts in the normal retina [6], but microanatomical studies in the last few years have provided evidence for extensive reorganization of the connections among surviving retinal neurons [7], and for migration of cell bodies outside of their customary layers [8]. This new insight has two important consequences: cells being stimulated by a prosthesis may respond differently from those in healthy retinas. In particular, signals may spread among multiple cell types and functional streams that would not normally be interconnected – for example, rod and cone bipolar cells, on- and off-pathways, chromatic channels – and propagate over substantial distances. Second, the adaptive response of retinal tissue may allow for innovative interfacing between implants and retinal cells. As an example, experiments at Stanford University have shown a tendency of certain retinal neurons to migrate into cavities between stimulating electrodes [9]. Similarly, tissue culture studies from several laboratories (Stanford, Tokyo Institute of Technology [TIT] and Wayne State) have demonstrated that targeted neurotransmitter release by microfluidic assemblies will cause some cell types to form close contacts with these devices [10,11].
Most groups developing tissue interfaces for visual prostheses envisage transmitting image information in the form of pixels, that is, dots whose signal strengths are roughly proportional with the intensity at the corresponding image locations. The only exception to this approach is the Learning Retina Encoder approach being pursued by the German EpiRet consortium. The principle underlying this encoder is based on Rolf Eckmiller’s models of signal processing at the level of the retinal ganglion cells in the normal retina [12]. It will be very interesting to compare the performance of an interface based on this image preprocessing approach to the more straightforward approach pursued by other groups.

All these approaches rely on the availability of image information from a separate source such as a video camera, but some tissue-engineering approaches seek to create novel phototransduction processes inside remaining or implanted retinal cells that will directly convert incident light into electrochemical signals. Essentially, these researchers are hoping to convert secondary neurons into photoreceptors in a retina where photoreceptor cells are no longer available. An example of this approach is Elias Greenbaum’s work at Oak Ridge National Laboratories of Photosystem II, the chromophore at the heart of photosynthesis in spinach [13]. Unfortunately, bringing such techniques from the test tube to the

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Table 1. Survey responses obtained from 16 active prosthesis groups worldwide.

<table>
<thead>
<tr>
<th>Project/group name</th>
<th>Type</th>
<th>Designs</th>
<th>Prototypes</th>
<th>Animal (date)</th>
<th>Human: n (date)</th>
<th>Support</th>
<th>Partners (country)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston retinal prosthesis</td>
<td>RD</td>
<td>T/I</td>
<td>S</td>
<td>A/C: rabbit, pig</td>
<td>A: ~10, C (TBD)</td>
<td>G/D</td>
<td>3 unis: Harvard, MIT, Cornell [101]</td>
<td></td>
</tr>
<tr>
<td>USC Doheny/2nd Sight</td>
<td>RD</td>
<td>S/C/P/T/I</td>
<td>S/C/P/T/I</td>
<td>A/C: rabbit, RD dog</td>
<td>A: ~20, C: 6 (2002 ff)</td>
<td>G/V/D</td>
<td>5 govt labs, 4 unis, 1 corp. [102,103]</td>
<td></td>
</tr>
<tr>
<td>Wayne State Uni.</td>
<td>RD</td>
<td>S/I</td>
<td>S/I</td>
<td>C: rat, cat</td>
<td>D</td>
<td></td>
<td></td>
<td>[104]</td>
</tr>
<tr>
<td>Stanford Uni.</td>
<td>RD</td>
<td>S/P/T/I</td>
<td>S/P/T/I</td>
<td>A/C: RCS rat</td>
<td>G</td>
<td></td>
<td>3 labs, Uni. of Utah microanatomy [105]</td>
<td></td>
</tr>
<tr>
<td>Uni. of Houston</td>
<td>RD</td>
<td>I</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[106]</td>
</tr>
<tr>
<td>German Epi-Ret group I</td>
<td>RD</td>
<td>S/C/P/T/I</td>
<td>S/P/T/I</td>
<td>A/C: rat, rabbit, cat</td>
<td>A: (12/06)</td>
<td>G/I/D</td>
<td>5 uni labs; 3 corp. (D) [107]</td>
<td></td>
</tr>
<tr>
<td>German Epi-Ret group II</td>
<td>RD</td>
<td>S/C/P/T/I</td>
<td>S/P/T/I</td>
<td>A/C: rat, rabbit, dog</td>
<td>A: ~20, C (12/05)</td>
<td>I/V/D</td>
<td>3 uni clinics (D); 1 corp. (CH,D) [108]</td>
<td></td>
</tr>
<tr>
<td>German Sub-Ret group</td>
<td>RI</td>
<td>S</td>
<td>S</td>
<td>A/C: rat, rabbit, pig</td>
<td>C: 2(2005), 8(2006)</td>
<td>G/I/V/D</td>
<td>5 unis/insts (D); 1 corp. (D) [109]</td>
<td></td>
</tr>
<tr>
<td>Seoul Natl Uni.</td>
<td>RD</td>
<td>P/T/I</td>
<td>I</td>
<td></td>
<td>G</td>
<td></td>
<td></td>
<td>[110]</td>
</tr>
<tr>
<td>Univ. New S. Wales</td>
<td>RD</td>
<td>S/C/P/T/I</td>
<td>I</td>
<td></td>
<td>G</td>
<td></td>
<td></td>
<td>[111]</td>
</tr>
<tr>
<td>Tokyo Inst. of Technology</td>
<td>RD</td>
<td>S/C/P/T/I</td>
<td>I</td>
<td>(10 years)</td>
<td>(TBD)</td>
<td>G/I</td>
<td>3 inst: TIT, RIKEN, IDR [112]</td>
<td></td>
</tr>
<tr>
<td>Univ. of Utah</td>
<td>CP</td>
<td>S/I</td>
<td>S/I</td>
<td>A/C: cat</td>
<td>G/D</td>
<td></td>
<td>4 labs, Uni. M., Hernandez (E) [114]</td>
<td></td>
</tr>
<tr>
<td>Illinois Inst. of Technology</td>
<td>CP</td>
<td>S/C/P/T/I</td>
<td>Prototype</td>
<td>A: monkey</td>
<td>G/D</td>
<td></td>
<td></td>
<td>[115]</td>
</tr>
<tr>
<td>Uni. Miguel Hernandez</td>
<td>CP</td>
<td>S/P/T/I</td>
<td>S/P/T/I</td>
<td>A/C: cat, rabbit, rat</td>
<td>A: &gt;10, C: 6/06</td>
<td>G</td>
<td>6 unis (D, E, F, Pt), 1 corp. (E) [116]</td>
<td></td>
</tr>
</tbody>
</table>

Type = level and approach: RD: Retina distributed; RI: Retina integrated; O: Optic nerve; CS: Cortex surface; CP: Cortex penetrating.

Designs = components under study: S: System; C: Camera; I: Image processing; SPT: Signal/power transmission; T: Tissue interface.

Prototypes = components under development (see designs).

Animal and human = current or planned tests, animal species, number of human tests performed: A: Acute; C: Chronic; in parentheses: date or to be determined.

animal or human retina is likely to take many years. Near-term results can be expected from studies by other researchers at the same laboratory, who are studying novel electrode materials and manufacturing methods suitable for implantation on flexible substrates that will conform to the curvature of the retina [14]. Such electrode arrays address the need for biocompatibility, that is, long-term survival of both the implant and the retina, and for optimal contact between the two structures. The creative approaches by these research groups and improved retinal surgical techniques have led to new ideas regarding the device–retina interface. Thus, beyond the original idea of an array of electrodes stimulating remaining cells from the epiretinal surface— that is, the surface facing the front of the eye, where ganglion cell axons course towards the optic nerve head—researchers are now pursuing transducer arrays in either epiretinal or subretinal positions, use of neurotransmitters and photosensitive molecules, and active retinal remodeling as possible tools. Such novel approaches are not currently being envisaged for stimulation of optic nerve fibers or cortical cells.

A different tool, under consideration for use at all three stages of visual processing, is the use of penetrating electrodes. This would allow closer contacts with the stimulated cells, and hence both lower device power and more localized stimulation, for instance, potentially higher resolution. The 100-electrode array developed by Richard Normann at the University of Utah, USA [15] and the 'hatpin' electrodes developed for the discontinued cortical prosthesis project at National Institute of Neurological Disorders and Stroke (NINDS) [16] and since adopted by the group at the Illinois Institute of Technology (IIT) [17] are practical examples of this approach.

Building a visual prosthesis

The tissue interface alone cannot recreate vision. In general, one can envisage a visual prosthesis as a concatenation of four elements: camera, image processor, transmission channel and tissue interface, as depicted in Figure 1A.

The straightforward approach is to implement these four components separately, adapting existing technology wherever possible. Visual prosthesis designs commonly employ a standard video camera mounted on a head-worn visor or (spectacle) frame. Such cameras, based on either charge-coupled device (CCD) or complementary metal oxide semiconductor (CMOS) technology and making use of the wide brightness operating range provided by the automatic gain control of these devices, have a resolution far exceeding that of the planned tissue interface arrays. The image processing stage adjusts the image resolution by either combining multiple input pixels into a single output pixel (Figure 1B) or, in combination with wide-angle camera optics, by selecting a small region as the output window, allowing the user to span this window through the input image (Figure 1C). The processor also adapts the signal at each output pixel to the requirements of the tissue interface, for example, rapid biphasic electrical impulses for neuron depolarization without net charge transfer [18].

The transmission circuit provides for transfer of the signals if the camera and processor are located at a distance from the target tissue. Typically, the camera and processor will be located outside the body and a wireless channel will be used to allow communication without risk of infection. Both the multiplexed interface signals and the power to drive the implanted control circuitry are contained in the transmission; some systems may have separate power and signal transmission channels and/or provisions for reverse transmission of operating parameters, for example, electrode impedance levels [19].

The alternative to a component-based system is one whose stages are physically layered together. This is particularly attractive for a retinal prosthesis, where the eye's own optics can provide the imaging function that would otherwise require a camera lens. In its simplest form, such a device can be created in the form of an array of small photodiodes [20,21], but the currents generated with such devices are too weak and not adequately conditioned to achieve depolarization of retinal neurons. For this reason such an integrated system will require a signal amplification and conditioning stage. This poses significant technical obstacles, however. For implantation it needs to be sufficiently compact and hermetically sealed. It requires
an external (preferably wireless) power source to drive the acquisition, processing and stimulation stages. The total power needs to be minimized, and heat dissipated away from the underlying tissue, to avoid tissue damage during long-term operation.

**Current endeavors**

Table 1 lists the principal groups currently developing visual prostheses and provides details about their areas of concentration and planned developments, and references to the most relevant websites.

**Retinal prostheses**

In the area of retinal prosthetics the longest track record belongs to the Los Angeles-based Second Sight/USC project first started by Eugene de Juan, Jr and Mark Humayun at Duke University, and developed at Johns Hopkins prior to their relocation to the Doheny Retina Institute at the University of Southern California [22]. Their current A16 implant uses a 4 × 4 electrode array built by Second Sight Medical Devices, Inc. on the basis of 16-channel cochlear implant electronics [23]. The electrode array is placed over the retinal surface with a surgical tack. The electrode leads pass through the wall of the eye but are not exposed, and connect subcutaneously to a wireless receiver behind the ear. Signals to the electrodes are specified individually by control software and may be computer generated or derived from a camera image. Six RP patients with (at best) light perception vision have received the A16 implant between 2002 and 2004, and can reliably detect phosphenes at (at best) light perception vision have received the A16 implant [28]. Electrodes may be placed under the retina [28]; electrodes may be placed under the retina to avoid the risk of being dislodged over time [29]. The German EpiRet implant consortium has performed intra-operative tests both in RP and AMD patients [30], with funding for two 5-year periods from the German Ministry of Education and Research, and its associated company Retina-Implant are building layered systems in which the camera is formed by an array of phototransistors acting as gates for an amplifier array, which in turn drives an electrode array through a signal conditioning layer [21,44]. The entire system is powered by infrared or radiofrequency (RF) energy transmitted into the eye from an external source, and is self-contained within the eye [31,32,45]. While there has been some skepticism regarding the feasibility of a safe and functional retinal prosthesis based on this approach, the researchers have indicated that the heat generated by the device can be safely conducted away by the choroidal blood vessels under the retina, and that approval for patient testing may be close at hand.

**Optic nerve prostheses**

The next prosthetic approach, pursued by the OptiVip consortium, is to stimulate optic nerve fibers. This cannot be done selectively, due to the tight packing of these fibers, and would not normally be necessary since the fibers only function if retinal ganglion cells are intact, in which case the cell bodies could be stimulated by epi-retinal electrodes. The optic nerve may be the only available substrate, however, if the retina cannot safely support a prosthesis, for example, in long-standing retinal detachments. Claude Veraart implanted two RP patients with cuff implants in 1998 and 2004 [46–48]. Such cuffs do not allow selective stimulation of individual fibers, so the implant contains four
to eight contacts stimulating many nerve fibers simultaneously. Publications suggest that light-dark differences, movement direction and stimulus strength can be learned.

A different approach to optic nerve fiber stimulation is followed by a group at Osaka University. Their implant is designed to stimulate fibers in the optic nerve head inside the eye [49], with two important advantages over the optic nerve cuff electrode: the exposure of nerve fibers across the rim of the optic nerve head allows selective stimulation of small groups of fibers; the intraocular surgical implantation technique is less invasive than insertion around the optic nerve in the orbital cavity.

Cortical prostheses
Like the retinal prosthesis, the cortical prosthesis maps the visual field onto a 2D tissue surface, but there is a distinct difference due to the convoluted retinotopic organization of the visual cortex. While a square electrode array over the retina elicits a square grid of phosphenes, such an array of electrodes over the foveal projection in the primary visual cortex would elicit a curved radial pattern of phosphenes in the half-field opposite to the cortical hemisphere being stimulated [50]. New techniques such as transcranial magnetic stimulation may assist in determining eligibility of individual blind implant candidates, and establish crude cortical maps prior to prosthesis implantation [51]. Due to statistical and self-organizing properties of the cortical projection during fetal and infant development, and overlapping receptive fields in the primary visual cortex, this phosphen pattern is likely to be quite irregular [16]; moreover, in practice it will prove difficult to avoid the inadvertent implantation of electrodes over the extrastriate visual cortex, even with advanced cortical mapping techniques [52]. Figure 2A shows the layout of a square 6 x 6 penetrating electrode array, and Figures 2B and 2C show an idealized and a more realistic version of the phosphen patterns such an array may elicit when placed over the foveal projection in the primary visual cortex, exactly adjacent to the V1/V2 border.

![Figure 2. Phosphene maps created by a square grid of penetrating electrodes over the foveal projection in the primary visual cortex. (A) Represents a 6 x 6 electrode array over the occipital pole of the left hemisphere, adjacent to the V1/V2 border and straddling the projection of the horizontal meridian. (B) Presents an idealized view of the phosphenes elicited by this array, while (C) takes into account the irregularities in the cortical projection. Note that all phosphenes are located in the right visual hemifield, adjacent to the point of fixation (F); phosphene size and spacing, as well as irregularities, increase with eccentricity, in agreement with the cortical projection map. Color coding has been added for clarification only, in order to facilitate matching electrodes with phosphenes.]

Two groups in the USA and two elsewhere are designing a cortical visual prosthesis. The Utah Visual Prosthesis group, in addition to developing the penetrating electrode array, has performed prosthetic vision simulations and performed stimulation experiments in nonhuman primates. A group at the IIT is building on expertise gained in a previous implantation at NINDS [16] to create a complete system in 64 electrode modules [53], and has tested this system in nonhuman primates [17,21]. Implantation of four such modules in a blind human volunteer awaits completion of hardware and software testing in animal models, and approval by regulatory authorities (US FDA and Institutional Review Board). The European Cortivis consortium based at the Miguel Hernandez University in Spain [54] and a Canadian group based at the University of Montreal [55] are each developing components for systems very similar to the one being developed at IIT.

Only one cortical prosthesis group has performed multiple implants and allowed patients to use a camera for visual tasks. These implants use electrodes located at the cortical surface, avoiding the potential complications of tissue encapsulation that may over time alter the properties of penetrating electrodes [56]. Following implantation, a mapping procedure is used to determine the location of each electrode’s phosphen in the visual field. The real-time image processing software of this system extracts contour features, and projects those onto electrodes whose phosphen locations are closest to the true location; while this does not convey real form vision it does allow the wearer crude localization of outlines in the scene [57]. A consortium led by William Dobelle performed these implants in a clinic in Lisbon. Twelve patients had received such an implant by the time of his death in the autumn of 2004.

Related concerns
Using an implant to maintain system function
The Optobionics Artificial Silicon Retina (ASR™) by Alan and Vincent Chow is not a true visual prosthesis since it does not elicit phosphenes. It is a 2 mm diameter multiphotodiode array with 5000 photovoltaic ‘pixels’. In a preliminary clinical study it was placed under the retina at 20° eccentricity in ten RP patients with crude remaining form vision. The recipients reported improved color and contrast perception, and in some cases an expansion of the visual field and/or improved visual acuity was documented [58]. The current hypothesis is that this beneficial effect is mediated by a neuroprotective or neuromodulating agent released by the microcurrents generated by the ASR [59], although some have speculated that any improvements in vision may have been due to nerve growth factors released by the implant surgery rather than to the implant itself [60]. Only longer-term studies or
Phosphene appearance

As illustrated in Figure 2, phosphenes elicited by stimulation of the visual pathway do not necessarily appear in a regular grid, nor do they all have the same size and shape. In fact, the idealized view of phosphenes elicited by retinal or cortical stimulation as small round dots is inaccurate [24,26,57], and hence, the visual system after long-term deprivation can be expected to be small, but they can be widely scattered for cortical prosthetic phosphenes. The methods applied to study device properties is accelerated aging at high temperature and in corrosive environments. Not surprisingly, this has become an area of very active research in materials science and neuroprosthetics over the last 5 years [61].

While the survival of the device inside the body is very important, the survival of the tissue substrate is crucial: if long-term stimulation or mechanical effects on the tissue are even minimally toxic, the device may continue to work, but its prosthetic function will fail. Optimal choices for high-capacitance electrode materials and nontoxic yet durable packaging materials will be of the utmost importance. Understandably, this is also an area of very active research [62].
different prosthesis groups, experimental results will be scarce, and may be hard to interpret by researchers and clinicians who cannot themselves experience prosthetic vision.

For all these reasons there is an important role for simulations of what prosthetic vision may look like. Initially, such simulations were created to study the minimum requirements of pixelized vision for the performance of everyday tasks, and to determine to what extent the visual system might adapt to severely degraded vision. Starting with a series of experiments in Richard Normann's laboratory at the University of Utah over 10 years ago [67–69], and more recently in the laboratories of Jörg Sommerhalder in Geneva [70–72], Nigel Lovell in Sydney [73] and the author at Johns Hopkins [74–76,118] researchers have shown pixelized images to normally sighted and low vision observers and determined these subjects' performance in a number of representative tasks, such as moving around in real or virtual environments, locating and recognizing familiar objects, discriminating faces and reading meaningful text. All reports of such experiments agree that subjects can learn to perform visual tasks even under severely degraded conditions, if given enough practice. A major limitation of the studies reported to date was that the stimuli did not adequately represent the high degree of difficulty of real prosthetic vision, but this can be addressed as better quantitative measures of retinal reorganization and phosphen appearance become available. Notwithstanding their limitations, prosthetic vision simulations can help in determining requirements for vision tasks; exploring and understanding future prosthesis wearers' reports and finding solutions for their problems; conveying the 'prosthetic experience' to clinicians and the public; and designing rehabilitation programs for future prosthesis recipients.

**Sensory substitution**

Until functional visual prostheses exist, and have been demonstrated to provide useful and long-term visual information to their wearers, it remains important that research into other substitutes for vision be continued. Braille and cane travel are two well-known examples of such sensory substitution, but these only cover a limited set of daily activities. There are several other approaches to present visual image information through other sensory modalities such as auditory [77,78] (BAT [119], VOICE [120]), electrotactile [79,80] (Bach-y-Rita [121]) or vibrotactile [81] (VideoTact [122]). These novel techniques have all been shown to be highly effective to blind users, yet they have not gained widespread acceptance. In their current form they have low resolution, occupy another sensory modality and can be unpleasant (older vibrotactile devices). Most importantly, however, like other forms of sensory substitution they require a prolonged training period, and this is thought to be the main reason for their limited acceptance, especially among those with late-onset blindness.

**Expert commentary: the future of rehabilitation for the blind**

The overwhelming majority of legally blind patients in the developed world have intact visual pathways, either with intact optic nerves (AMD and RP) or with an intact cortex (glaucoma). These patients should be eligible for a visual prosthesis once their remaining natural vision has faded beyond the level such devices can recreate. In comparison with a tactile or auditory substitute, the severely restricted vision level that can be expected from near-term visual prostheses may still be preferable, because it will be more intuitive and easier to learn, especially for patients who have already spent years adjusting to severely impaired vision.

Conversely, visual prostheses will not provide useful vision to the congenitally blind, with the possible exception of very young children. They are also of little use to those whose higher visual pathways have been profoundly damaged by disease or trauma. For these reasons it is important that research be vigorously pursued in the areas of both visual and nonvisual prosthetic substitutes for natural vision, to maximize the likelihood for blind individuals to regain sensory self-sufficiency.

Major unknown factors in the pursuit of visual prostheses remain. Pre-eminent among these is the long-term safety, for instance, whether neural tissue will be able to sustain electrical or chemical stimulation and the mechanical effects of a foreign body on the tissue substrate. One aspect of this will be the adaptive response of the visual system at the molecular, cellular, perceptual and cognitive levels; the degree to which such adaptive behavior occurs will determine whether an interface based on image preprocessing as advocated by the German EpiRet group is required, and indeed superior to the more straightforward approach pursued by other groups. Conversely, the survival of prosthetic implants in the biological milieu is a factor of concern. However, with improved biomedical engineering techniques this is unlikely to pose a long-term obstacle on the path to functional visual prosthesis development.

**Five-year view**

The next 5 years promise to be among the most exciting ones in the history of visual prosthesis development. The momentum that has been building over the last 10 years has propelled this field into rapid development, carried by research in over 100 laboratories worldwide, and supported by a wide array of public, private and charitable sponsors. In the next 1–2 years the number of clinical trials of retinal implants in blind patients will jump from one to four, and before the end of the decade at least two cortical prosthesis groups are likely to initiate clinical safety and efficacy studies.

It is important to realize that the coming 5 years will only mark the dawn of visual prosthetics. It is virtually certain that early implant recipients will experience unforeseen difficulties in understanding the activity of these implants, and in learning to use them to their advantage. This is in addition to the inevitable shortcomings that accompany any new technology, especially one exposed to continuous operation inside the human body. It is unlikely, therefore, that the next 5 years will bring visual prostheses into many clinics, but almost certainly they will take their first steps out of the laboratory and into clinical research.
Key issues

- Retinal, optic nerve and cortical prostheses are in full prototype development, and early clinical trials of all three types of devices will expand in number and geographic spread over the next few years.
- Current interfacing techniques are crude, primarily consisting of electrodes at the tissue surface; penetrating electrodes and novel interfacing techniques based on tissue engineering promise to improve the density and efficacy of interface rasters.
- Thorough understanding of the neuronal substrate following years of blindness, and of the prospects for its response to renewed stimulation, is of crucial importance, but has only just begun.
- Integrating phosphenes into patterns representing the visual world is a condition for the advent of prosthetic vision, but demonstration that such integration occurs awaits verification through large-scale implants. However, anecdotal results from cortical implants are encouraging.
- Learning new visual experiences following implantation of visual prostheses is likely to be a long and arduous process; a variety of mapping and simulation techniques will be needed to guide the development of this new field of low vision rehabilitation.

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Oppotunities for prosthetic vision


Websites
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102 Doheny Eye Institute www.usc.edu/hsc/doheny/
103 Second Sight www.2-sight.com
104 Kresge Eye Institute www.med.wayne.edu/kresgee/ikon/
105 Palanker Group: Biomedical Physics and Ophthalmic Technologies www.stanford.edu/~palanker/lab/retinaipro.html
106 ‘Bionic’ Eye www.svec.uh.edu/BIONIC.html
107 Universitas – Augenklinik Aachen www.eyenet-aachen.de/05–07–1-implants.html#pi_ret
109 Retina Implant www.retina-implant.de/
110 Nano Bioelectronics and Systems Research Center http://nanobio.snu.ac.kr/eng/index.html
112 Tokyo Institute of Technology: Shimizu and Yagi Laboratory www.io.mt.titech.ac.jp/eindex.html
113 Accueil UCL: Gren www.md.ucl.ac.be/gren/intro.html
114 Sight Restoration For Individuals With Profound Blindness www.bioen.utah.edu/cni/projects/blindness.htm
115 The Laboratory of Neuroprosthetic Research http://neural.iit.edu/index.htm
116 Cortical Neuropresentation for the Blind http://cortivis.umh.es/
117 Polystim neurotechnologies Laboratory www.polystim.polyml.ca/
118 Gislin Dagnelie http://lions.med.jhu.edu/lvr/gd.htm
119 The BAT ‘K’ Sonar-Cane www.batforblind.co.nz/
120 Vision Technology for the Totally Blind www.seeingwithsound.com/voice.htm
121 Tongue Display Technology http://kaz.med.wisc.edu/Publicity/Synopsis.html
122 Advanced displays for the blind www.abtim.de/home__e_/home__e_.html

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