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## Subretinal implantation: a step forward to restoring dying photoreceptors

'My hope is that microchip implants will help preserve vision in millions of visually impaired patients.'

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Udjat is the all-seeing eye of Greek mythology, which has become one of the symbols for veterinary ophthalmology. After a violent fight, Horus' eye was ripped out by the evil god Seth. Tuoth, the god of magic, found the Udjat and through this eye restored Horus' vision. This is an early mention of a visual prosthesis and actual attempts were made to replace this vital organ as early as the end of the 19th Century [1].

Since then, the art and science of ophthalmic replacement surgery has developed tremendously. At least six research teams in the world are developing some 23 different types of device. A 'critical mass' of research teams using innovative methods has developed [2]. At the latest Association for Research in Vision and Ophthalmology (ARVO) meeting in 2007, there were more than 100 abstracts in the field.

Seeing is a complex process that depends on light from the outside world falling onto the eye and the eye efficiently transmitting and properly focusing images of objects on the retina, causing initiation of photochemical activity, thereby making it possible for the brain to receive impulses and further process the specific information [3]. The act of vision is not simply a recording of every feature of a scene as a camera would do. That would overwhelm the system completely with massive amounts of information. Instead, the

photoreceptors, the second- and then the third-order neurons and the ganglion cells continuously process huge amounts of information and transmit volleys via the optic nerve to the visual cortex of the brain. This information is categorized into specific 'topics', which are channeled to specific areas of the brain for further processing [4]. Unlike a camera, the brain then compares this input

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with previous images and other types of input, such as that from previous information and input from hearing, smell and touch. Only the information that is relevant for survival rises to the

level of conscious attention. The act of seeing depends therefore not only on the normal function and health of the eye but also on the cognitive processing of the brain [5].

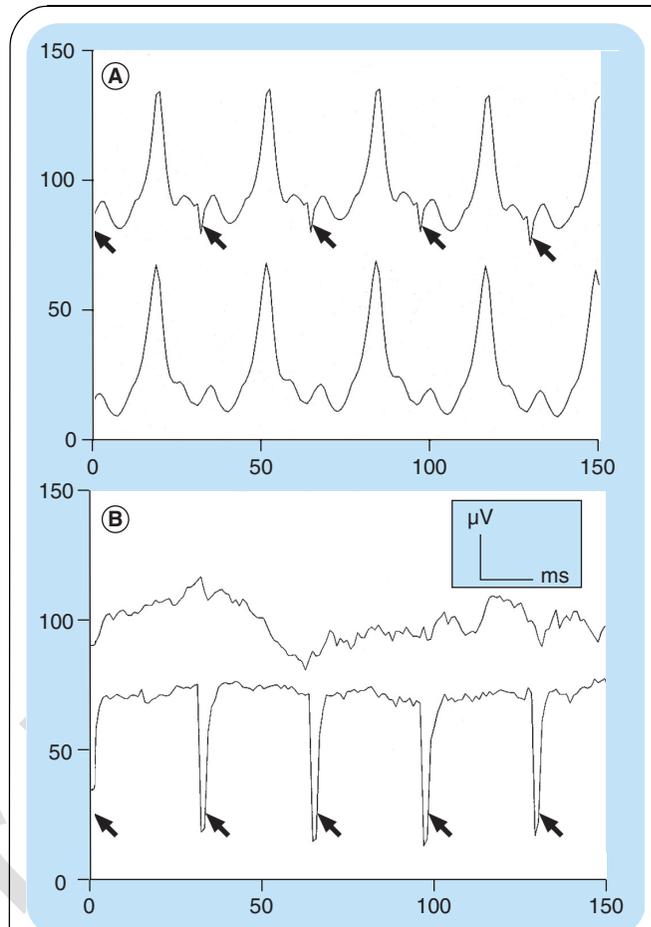
Primarily with the hope of replacing dying first order neurons of the retina (the photoreceptors), epiretinal and subretinal implants have been constructed. The first type usually relies on video input from a spectacle-mounted camera and a microprocessor that sends signals directly to a receiver, which transmits them on to an electrode-studded array tacked directly to the retina. The receiver sends signals to the array, stimulating it to emit pulses, which travel through the optic nerve to the brain. It has been shown that intraocular stimulation of retinal nerve fiber layer evoke phosphenes (light flashes)

and/or perception of patterns in retinitis pigmentosa (RP) patients [6,7]. Patterns of light and dark spots are thus perceived corresponding to the electrodes stimulated. RP patients have undergone surgery to obtain such devices. After some practice they could distinguish between light patterns given off by various objects, such as a plate or cup, by moving their head-mounted cameras to scan the objects. Some could even detect motion when a bar of light was moved in different directions in a darkened room. Upgraded devices are under development with increasing numbers of electrodes to improve the ability of patients to obtain more visual perceptions and possibilities of vision with higher resolution. The downside of the epiretinal implants is, however, that the surgery is somewhat traumatic, with wiring needed to connect the receiver outside of the eye with the implant. Furthermore, the image that is obtained depends entirely on the implant's number of pixels, since impulses are obtained directly from the receiver's transmission to the eye, where ganglion cell axons transmit impulses to the brain. All of this occurs without involvement of the other surviving parts of the inner and outer retina.

The second type is the subretinal implant, which does not utilize external power sources. Instead, the subretinal implant is solely powered by incidental light, which excites the retina's intermediate cell layers and allows these cells to perform their normal processing of visual signals. These implants have the advantage of stimulating the retina in its normal topography, theoretically provoking more natural perceptions. One such subretinal implant is a passive microphotodiode array (MPA). An example is the Artificial Silicon Retina (ASR), produced by Optobionics, Inc. (CA, USA). It is a self-powered device, 2 mm in diameter and 25  $\mu$  thick, which contains approximately 5000 negative intrinsic layer-positive microphotodiode pixels electrically separated from each other by 5  $\mu$  [8]. Pixel current is 8–12 nA with approximately 800 foot-candles of illumination.



**Figure 1.** Subretinal location of an implanted (Artificial Silicon Retina) microchip 4 days after surgery in a cat. Surgeries were successful with the active implants placed subretinally. Retinal function was evaluated objectively using electrophysiology and optical coherence tomography studies.



**Figure 2.** Electroretinographic evaluations of a normal cat implanted in the right eye (upper recording in [A]) and a blind dystrophic Persian cat implanted in the left eye (lower recording in [B]). The 30 Hz photopic electroretinographic recordings are shown for both cats under similar experimental conditions as to light intensity of the stimuli and background adaptation. Note the nonrecordable ('flat') electroretinographic response of the right eye of the dystrophic cat (B), indicative of a nonfunctional retina, in comparison with the high-amplitude flicker responses from the normal cat (A).

Introduction of the MPA design created some controversy in the literature regarding the ability of the microchip to generate sufficient current to produce a biologically relevant signal [9,10]. Recent exciting findings, however, utilizing wild-type and blind RCS rats, showed MPA implant-driven responses recorded in the superior colliculus of the brain, in a small region that corresponded to the retinal sector containing the retinal implant in 100% of the wild-type rats and in 64% of the RCS rats [11]. Furthermore, the data showed that there was a general effect of surgery on overall visual responsiveness in the superior colliculus and a specific effect of the presence of an active implant on the characteristics of the visual response.

It has been shown previously that electrical stimulation has neuroprotective properties for motor neurons [12,13], and has been linked to growth factor production, such as brain-derived growth factor (BDGF). Furthermore, electrical stimulation has been shown to preserve retinal ganglion cells in cat [14] and rat models [15]. Clear neuroprotective effects were shown recently

in blind RCS rats after subretinal implantation [16]. In addition to the positive local benefit of electrical stimulation in the retina, effects of mechanical injury due to placement and the presence of a subretinal prosthetic need to be considered. It has been shown that minor trauma to the retina causes an upregulation of growth factors, such as basic fibroblast growth factor-2, BDNF and ciliary neurotrophic growth factor [17], and thereby preservation of photoreceptors [18].

Implantation of the MPA device into ten human RP patients has shown unexpected improvement in visual function [8,19] for all of them. Objective testing showed improved visual acuity, improved color vision and increased visual fields in areas distant from the implant. Follow-up was performed up to 3.5 years after surgery in some of the RP patients.

Owing to these promising results in relation to human RP, further development and research was initiated using the MPA device in groups of cats with naturally occurring heritable retinal diseases comparable to the early- and late-onset blinding disease processes of humans. The study was aimed primarily at examining the direct activation of visual circuits with implant-induced subretinal electrical stimulation by examining visual function and retinal morphology after implantation. Implant surgeries were performed unilaterally in normal cats and then in a group of Persian cats that were congenitally blind due to rod-cone dysplasia (FIGURE 1) [20]. The plan is to proceed with similar surgeries of Abyssinian cats with late-onset hereditary rod-cone degeneration [21].

Results so far show great promise for the future. The implantation procedure was relatively easy to perform and should be a feasible task for trained vitreoretinal surgeons. No adverse reactions due to the implants were noted during the first 6 months of follow-up. It was clear from studying the visual behavior of one of the blind Persian cats that using a strong light beam at the implanted eye several months after surgery elicited a dazzle reflex in the surgically treated eye, which was not observed in the fellow, unoperated eye. Bilateral electroretinograms clearly showed the electrical artifact of the implant in both the normal control and the affected cats (FIGURE 2), demonstrating electrical activity in the retina induced by the implant.

These are truly exciting times, not only for the researcher in the field but also especially for the 25 million people worldwide affected with severe visual impairment or blindness. I believe that using the subretinal implant, which is relatively easy to insert and has shown benefit promoting cell survival and simultaneously stimulating the second- and third-order neurons directly, is the way forward. My hope is that microchip implants will help to preserve vision in millions of visually impaired patients, be it cats, dogs or people.

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