Clinical review

Science, medicine, and the future

Artificial means for restoring vision

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Degeneration of the retina occurs in age related macular degeneration and retinitis pigmentosa, resulting in loss of vision. Age related macular degeneration is a major cause of visual impairment among people over 65 in Western countries¹; in the United Kingdom its incidence has increased by 30-40% over the past 40 years.² Retinitis pigmentosa generally occurs in a younger age group (incidence 1 per 4000 live births) and affects 1.5 million people worldwide.³

In both conditions patients are visually impaired due to loss of photoreceptors. At present few treatments can remedy this and lead to recovery of vision.^{4 5} Photodynamic laser therapy has been beneficial in some patients with age related macular degeneration, but this therapy does not address photoreceptor loss. Different gene and drug therapies have been tried,^{4 5} but their ability to replace lost photosensitive tissue is limited. Researchers are therefore investigating the possibility of using prostheses to restore vision.

Advances in microtechnology have facilitated the development of a variety of prostheses that can be connected to the brain or implanted in the eye. Some of these approaches have improved the eyesight of patients with visual impairment. This article gives an overview of the methods that are being assessed to restore vision in patients with severe sight loss.

Methods

We carried out a comprehensive search through Medline and PubMed using the terms "age related maculopathy", "visual prosthesis", "retinitis pigmentosa", "retina", and "eye". We also searched for the latest developments in artificial vision through the website of the Association for Research in Vision and Ophthalmology.

A brief history of visual prostheses

Efforts to develop visual prostheses are not new. Attempts at artificial vision began in the 18th century with direct electrical stimulation of blind eyes.⁶ In the 1920s, the German neurosurgeon Otfried Foerster developed this approach further by investigating direct electrical stimulation of the visual cortex.⁷ Several of his patients experienced limited subjective visual phenomena. By the '60s, investigations began on devices that could be implanted on the surface of

Summary points

Artificial means of restoring vision include cortical implants, optic nerve stimulation, and retinal implants

These approaches are being assessed in clinical trials

Patients with implants have a crude level of visual perception

Problems with implants include availability of a power source, surgical complications, and long term viability

No visual prosthesis has yet restored vision

the visual cortex.⁸ In 1977, electrodes were implanted in the eye to try to evoke a visual response.⁹ Since the '20s several types of visual prostheses have been examined.¹⁰ Most of these earlier devices were limited by a lack of visual resolution (pixels) or by their overall size and the electrical constraints this imposed. Early approaches were also prone to complications after implantation.⁸ With recent advances in microtechnology, however, progress has been made in the development of implants, some of which can be placed in the eye. These implants have greater potential for visual resolution and remain viable for several years.

Three methods to restore vision are currently being developed: stimulation of the visual cortex using cortical implants, stimulation of the optic nerve, and retinal devices implanted either in the retina or on its surface.

Cortical implants

In the 1960s investigators implanted electrodes on the visual cortex (epicortical implants) of human patients through a burr hole.^{7 8 11} The patients reported seeing spots of light or "phosphenes."^{7 12} These early studies were limited by problems such as flickering phosphenes and interactions between phosphenes. The excessive electrode currents also irritated the meninges, causing pain around the implant.¹¹ Later

modifications to the implants enabled them to be embedded in the visual cortex (intracortical implants), and thus smaller electrodes and lower electrical currents could be used. These advances led to localised intracortical stimulation with less pain.^{7 12 13} Visual prostheses have the disadvantages of the surgical complications of any artificial implant, and complex mapping of the visual cortex is required to achieve visual perception.¹¹ Despite these limitations, patients with implants can be trained to navigate around objects, perform simple tasks, and identify large letters.¹⁴

Intracortical implants have two main advantages over other methods for restoring vision. Firstly, the electrodes are protected by the skull. Secondly, the technique bypasses disease proximal to the primary visual cortex, making it potentially useful for treating diseases of the optic nerve and retina.

Optic nerve stimulation

The optic nerve can be directly stimulated to restore vision (fig 1). Stimulation of electrodes placed around the optic nerve of a patient with retinitis pigmentosa resulted in coloured phosphenes throughout the visual field.¹⁵ By changing the duration and amplitude of the electrical stimulus, the patient was able to perceive different levels of phosphene generation as brightness. Similar work has enabled a patient to localise objects and to discriminate between them.¹⁵ Direct stimulation of the optic nerve has several potential advantages over other methods for restoring vision. Firstly, it does not require the surgical penetration of sensitive intraocular or intracranial tissues. Secondly, the photosensitive component, for example, video device, can be placed outside the body, thus allowing the use of an external power source. The main disadvantages of this approach are that a normal functioning optic nerve is required (thus this method has limited use in diseases such as glaucoma) and that there is a risk of infection from the external wires.

Retinal prostheses

Prostheses can be implanted in the retina to act as a substitute for the host's photoreceptors. Retinal prostheses are only viable if the visual pathway distal to the retina is intact and functional. Two types of prostheses are under development according to the

Fig 1 Direct stimulation of optic nerve using external electrical source to stimulate electrodes implanted around nerve (adapted from Veraart et al¹⁵)

Fig 2 Subretinal implant converts light energy from visual sources into electrical impulses for onward transmission (adapted from Zrenner¹⁷)

Fig 3 Localisation of epiretinal and subretinal implants (adapted from Margalit et al¹⁶)

layer of retina receiving the device: epiretinal (on the surface of the retina) and subretinal (under the retina) implants.

Subretinal prostheses

Subretinal prostheses contain microphotodiodes attached to microelectrodes. These implants, such as the artificial silicon retina (5000 microelectrodes),¹⁶ are placed in the subretinal space between the outer retina and retinal pigment epithelium (figs 2 and 3). They are inserted either in the subretinal space through an incision in the sclera (extraocular approach) or by standard vitrectomy followed by retinotomy (intraocular approach).^{8 16 17}

The photodiodes are stimulated by light passing through the retina, and the resulting electric current excites adjacent retinal sensory neurones.¹⁶ The specifications for subretinal implants vary—for example, one device measures 50–100 µm wide, has a diameter of 2 or 3 mm, and carries microphotodiodes constructed on a microelectrode array.¹⁶ These implants do not require an external electrical source as incident light is sufficient for stimulation.^{8 17}

The viability of subretinal devices has been assessed in animal experiments. Several species have shown tolerance to the implants,¹⁸ some for up to 30 months.¹⁶ Histological evidence has shown no important changes to the retina's architecture.¹⁰ Visual perception was improved in six patients with retinitis pigmentosa who received an artificial silicon retina, including subjective improvements in appreciation of brightness, contrast, colour, movement, shape, and visual field.¹⁶ Some patients showed improvement in visual acuity.

Subretinal prostheses have two major advantages over other methods for restoring vision.⁷ Firstly, they utilise forces between the neurosensory retina and retinal pigment epithelium to maintain their position. Secondly, they have the potential to allow for greater spatial resolution as they are positioned closer to retinal nerve cells and can stimulate the nerves at lower electrical currents. The main disadvantages of subretinal implants include impaired nourishment of the inner retina due to the creation of a mechanical barrier between the outer retina and the choroid^{7 8} and trauma to the retina during implantation.⁷ These prostheses also show poor dissipation of heat and therefore could damage the retina.⁸

The mechanism of action of these implants may be by direct stimulation of retinal neurones or by probable neurotrophic effects on photoreceptors.¹⁶ A study of subretinal artificial silicon implants in rats showed a temporary neuroprotective effect on the retina, resulting in increased generation of photoreceptors.¹⁸

Epiretinal prostheses

Epiretinal prostheses comprise an array of electrodes implanted on the surface of the retina between the vitreous and internal limiting membrane. The implants receive electrical signals from a camera positioned outside the body (figs 3 and 4). In one such device—the second sight model—the camera transmits light signals to a microchip within the camera. This microchip deciphers the signal and relays it to a microchip in the epiretinal implant which in turn stimulates the retinal ganglion cells.^{19 20} A vitrectomy is required to implant the intraocular component of this prosthesis.⁷

Early studies in dogs^{22 23} and rabbits^{8 24} showed the feasibility of using epiretinal prostheses. A few clinical trials in humans have reported simple visual perception as phosphenes.²⁰ Perception of light only was reported by three “completely blind” patients with retinitis pigmentosa who received the second sight model: these implants have survived for up to two years.^{7 21 25 26}

One advantage of epiretinal implants over subretinal devices is that the camera can process signals before they reach the implant. This permits optimisation of the signal's quality, which may lead to

Fig 4 Epiretinal prostheses: camera captures image and transmits to processing unit worn on belt, which sends electrical commands by wireless link to unit attached to temporal bone. Unit conducts electrical current through cable that enters eye posterior to limbus and signal relayed by wire to epiretinal implant. Implant stimulates retinal ganglion cells for onward transmission along optic nerve (adapted from Humayun et al²¹)

Ongoing research

Transcleral, intrascleral, or suprachoroidal electrodes to generate electrical evoked potentials by transretinal stimulation^{31 32}

Biocompatible carbon nanotubes as microelectrodes for retinal prostheses³³

Implants with photosensitive dyes to generate impulses³⁴

Neural prostheses that use neurotransmitters instead of direct electrical activity to stimulate retinal neurones^{35 36}

Implantable miniature intraocular telescope in patients with stable age related macular degeneration³⁷

improved visual perception. Epiretinal implants can also use the heat dissipating properties of the vitreous and are therefore less likely than subretinal implants to damage the retina. The superficial location of the implant reduces the risks of trauma during implantation and allows for the implant to be replaced.

The main disadvantages of epiretinal implants are the need for complicated microtechnology and surgical techniques that ensure secure fixation of the implant on the retina. The device also requires a higher electrical current than the subretinal implant.^{7 8} Implants are being developed to generate their own electrical currents on stimulation.

Conclusion

Advances in microtechnology have enabled major improvements in the design of different implants for restoring vision.²⁷ The newer devices allow greater levels of visual perception than before, with the subretinal and epiretinal prostheses showing most promise. As yet, however, no patient has had an acceptable level of vision restored. Clinical results have been limited to small numbers of patients with severe visual impairment, so it is unclear to what degree vision could be restored in patients with less severe disease. Furthermore, no large controlled trials have compared the current approaches. The general and comparative costs of the implants are also not known (E Zrenner, personal communication, 2003).

Ongoing developments are increasing the sophistication of devices for resolving capability,^{28–30} and these advances are likely to further improve visual perception. From a historical perspective, the progress to restore vision using implants has been likened to the clinical success of cochlear implants in treating deafness.⁷ With this in mind, one day it may be possible for visual prostheses to restore vision in patients with retinitis pigmentosa or age related macular degeneration.

Competing interests: None declared.

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Q&A

Corticosteroids and snake bite

Question

Do corticosteroids have any role in the treatment of snake bite?

Swaminathan P Rathinam, *physician, Pondicherry, India*

Answer

Steroid has no role in the management of snake bite, unless the patient develops allergic reaction and anaphylaxis against the antivenin which is given.

Omer Surchi Surchi, *senior lecturer, Iraq*

Answer

The use of steroids in snake bites is still debated; while some say they have no specific role, their administration does provide some help to the patient.

The sequence that occurs in any introduction of foreign material into the human body is inflammation—that is, the release of cytokines. Steroids reduce this inflammatory process.

Although the mainstay of treatment is definitely antivenin, in district settings where the antivenin is not readily available steroids are helpful. If they work in asthma, reducing exacerbation and anaphylaxis, they will also work with snake bites.

In our hospital we see many snake bites. We administer intravenous hydrocortisone to the more serious bites as we find

this hastens recuperation. This may or may not be related to the steroids, but we are interested only in the results at that point.

Gopi Nath Sivasubramaniam, *deputy director, Hospital Kajang, Malaysia*

Answer

No use at all in elapidæ (all Australian poisonous snakes and many Asian and African ones such as cobras and mambas). But remember:

1. Antivenins contain a fairly hefty chunk of horse serum, and if big doses are used (such as for brown snakes in Queensland or with inexperienced users) serum sickness results and may need steroids.
2. Many of those bitten may be regular handlers and have been previously treated and sensitised to horse serum; hence anaphylaxis is a risk.

Peter M Garrett, *staff specialist ICU, Sunshine Coast, Australia*

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