# Update In Management Of Heriditary Retinal Degenerations

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The retina is lined with a layer of light -sensitive cells consisting of rods and cones.

The rods function in conditions of low illumination where as cones are responsible for colour vision and all visual tasks that require high resolution such as reading

The rods are located away from the center of the eye and are most concentrated in the retinal periphery.

The highest concentration of cones is found at the centre of the retina, the macula, which is necessary for visual acuity.

These diseases affect the light sensitive cells in different ways and progress at varying rates. Breakdown and degeneration of the cells can be limited to the macula only or can slowly attack the whole retina.

As a general rule, these diseases cause severe visual impairment but rarely result in complete blindness.

Contrarily, heriditary retinal degenerations that attack the whole of the retina tend to be more severe. The most common types of these diseases are RP and ushers syndrome.

## How does an individual with a retinal degeneration see the world ?

- Loss of central vision

- Loss of peripheral vision

- Night Blindness

- Glare Sensitivity.

Early symptoms are night blindness and diminishing of the peripheral vision. Loss of visual field usually begins on the periphery and may result in retention of just the central portion of the visual field. This is called " tunnel vision" In one form of RP the primary symptom is not loss of peripheral vision, but loss of central vision (inverse RP).

## Inheritance Pattern

By tracing the pattern of affected and unaffected family members, it is often possible to determine if the retinal degeneration in a family is dominant or recessive and whether the mutated gene lies on an autosome or on a sex chromosome. An inheritance pattern can be determined only when more than one member of the family has a retinal degeneration. In most cases, RP and other retinal degenerative disease are inherited in either an autosomal dominant, an autosomal recessive or an x linked pattern. Another unusual inheritance pattern, known as digenic has been seen in a small number of families affected by RP.

There are three main types of inheritance pattern for the strongly heriditary retinal degenerations.

- The recessive type often occurs with no known family history of the eye disease and can affect members of either sex. Both parents are carriers. It is estimated that one person in 80 carries a gene for recessive retinal degenerations.

- The dominant type usually appears in successive generations in an affected family. A person with this type has a 50% chance of having an affected child with each birth. Diseases inherited by the dominant type are usually a less severe form.

- The sex-linked type is transmitted by female carriers to their sons. Affected males cannot transmit it to their sons, but all of their daughters will be carriers. The son of a female carrier has a 50% chance of being affected, while her daughter has a 50% chance of being a carrier. Female carriers of some retinal degenerative disorders are detectable.

The inherited outer retinal dystrophies comprise a large number of disorders characterised by a slow and progressive retinal degeneration.

They have been arbitarily divided into macular dystrophies, retinitis pigmentosa (RP), and conerod dystrophies on the basis of their phenotype.

They are the result of mutations in genes that are presumed to express in either the photoreceptor cells or the RPE[1] Retinitis pigmentosa is believed to affect about one in 3500 of the population[2] and the prevalence of remaining dystrophies is probably similar. The mode of inheritance can be autosomal dominant,

autosomal recessive, x-linked recessive[3] or digenic[4,5]. With a few exceptions such as B lipoproteinaemia[6,7] and Refsum disease[8] there is no treatment by which the primary disorder can be modified.

Some symptomatic relief may be derived from cataract extraction[9] and carbonic anhydrase inhibition if there is macular oedema[10]. Vitamin A supplementation may slow the progression although this has been the subject of controversy[11,12] of Research based on the possibility modulation of cell death by growth factors, transfecting the photoreceptor or RPE with functioning genes, transplanting photoreceptor or RPE cells into the subretinal space, or the use of electronic devices to stimulate the retina.

There are three paths of research :
• one involves genetic manipulation of cells in the eye
• other focuses on transplanting retinal cells.
• Third approach is completely artificial in that its goal is to make computer chips that simulate the circuitry of the retina.

The aim is to bring a blind person to a point where he or she can read, move around objects in the house and do basic household chores.

Patients might see some shapes and some forms or just light but they wouldn't have reading vision or driving vision.

Transplantation might be useful to preserve central vision white the artificial retinal implant might be useful to maintain visual field.

### Bardet - Biede (Laurence - moon) Syndrome
Multiple physical problems are usually found in a person with Bardet-Biede syndrome. The most common are RP, extrafingers and/or toes, obesity, mental retardation and kidney disease. Not all of these occur in every person with this disease. Bardet- Biede syndrome is an autosomal recessive disease.

### Bassen- Kornzweig syndrome (Abetalipo-Proteinemia)

RP and progressive neurologic problems are symptoms of this disease. Patients also have oddy shaped RBC's Bassen-Kornzweig syndrome is an autosomal recessive disease.

### Best Disease (Vitelliform Dystrophy)

This disease is characterised by a lesion in the macula, which leads to impaired central vision in one or both the eyes. It is an autosomal dominant disease.

### Choroideremia

Choroideremia has symptoms similar to RP, including night blindness followed by loss of peripheral vision. It is characterised by digeneration of the retina and of the choroid. It has an x- linked inheritance pattern and affects males. Female carriers may experience mild symptoms of the disease.

### Gysate Atrophy

This retinal degenerative disease is characterised by deficiency of enzyme ornithine aminotransferase Myopia, night blindness, reduction in peripheral vision and cataracts are characteristic of this syndrome. Gyrate atrophy is an autosomal recessive disease.

### Leber Congenital Amaurosis

It is characterised by severe visual impairment from birth or very early childhood. It is an autosomal recessive disease. It causes visual problems that are different from those of leber optic neuropathy, a condition that is not caused by primary degeneration of the retina.

### Macular Degeneration

Macular degeneration is divided into two broad categories; early onset and age related. Early onset forms are inherited macular degenerations that include Best disease, Stargardt disease, funduo flavimaculatus and other rare macular dystrophies like Sorsby's macular dystrophy and North Carolina macular dystrophy. ARMD is the leading cause of central vision loss in people over the age of 60. The first symptom is usually a blank spot in the center of the visual field, or a distortion of normal central vision. Although it can be found in more than one member of a family, its inheritance pattern is usually unknown. It is some times seen as an autosomal dominant disease in some families.

### Refsum Syndrome

It is a complex disease, believed to be due to the absence of phytanic acid hydroxylase, an enzyme found normally in circulationg blood. In addition to having RP patients may have hearing loss, neurologic problems and dry/and /or flaky skin. It is an autosomal recessive disease.

### Retinoschisis (Juvenile)

Juvenile retinoschisis is characterised by vision loss that is usually diagnosed in childhood. In this disease, the layers of the retina seperate, and the macula may also be affected, Juvenile retinoschisis has the x-linked inheritance pattern and affects males. A non-inherited form of retinoschisis may occur in some individuals as a part of aging and may not affect vision.

### Stargardt Disease/Fundus Flavimaculatus

This form of macular degeneration usually appears before the age of 20. It is characterised by reduction of central vision with a preservation of peripheral vision. The symptoms and progression of fundus flavimaculatus are very similar to that of Stargardt disease. Many researchers believe that these two conditions may be the same. In most affected families, Stargardt and Fundus Flavimaculatus are autosomal recessive diseases, although autosomal dominant families have been identified.

### Usher Syndrome

The combination of RP and congenital hearing impairment in a person is known as Usher Syndrome. It is divided into three types.

**Type I** is characterised by profound hearing impairment, problems with balance and typical RP. **Type II** is characterised by moderate hearing impairment and typical RP.

**Type III** is characterised by progressive hearing impairment and typical of RP. All types of ushers syndrome are autosomal recessive diseases.

### Our scientific endeavors fall into three major categories.

a) Basic sciences studies on the development and neurobiology of the normal and diseased retina. These studies include cultures of fetal and adult retinas as well as studies on trophic signalling systems, and of specific components of the RPE affecting proliferation and apoptosis of rods and cones in the retina.

b) Experimental approaches to develope effective cinical treatments is retinal degenerative diseases, including full thickness retinal transplantations, stem cell generation and transplantations and experiments with virally introduced antiapoptotic growth factors.

C) Examination of the genotype of patients with defined retinal degenerative diseases.

Recent advances make it likely that significant treatment improvements can be attained.

### Cortical Implant

Hi-tech prosthetic devices that can be surgically implanted in the brain or the retina to partially restore lost vision to people who are blind are being developed.

An experimental visual prosthesis called the "Dobelle Eye" consists of a video camera and distance sensor wired via a computer to platinum electrodes implanted on the surface of the visual cortex of the brain. The visual cortex is the part of the brain that processes visual images because it interfaces directly with the brain, The "Dobelle Eye" is an example of what researchers call a cortical implant. The patient would wear specialised head gear consisting of a miniature camera and sensor connected to a computer and the implant.

**Results :-** In a set of prelimnary experiments a patient who was surgically implanted with a set of 68 electrodes, reported seeing flashes of light or "phosphenes" when the electrodes were stimulated.

The patient also reported perceiving two - inch large letters through a very small island of vision from a distance of five feet, possibly approximating a visual acuity of 20\400.

One of the largest scientific hurdles facing cortical implants is the massive amount of electrical power needed to excite the neurons that process visual information deep within the visual cortex.

In early experiments, researchers found that surface stimulation of the visual cortex with many electrodes might cause seizures and other complications.

Researchers are now developing smaller and more complex cortical implants that can be placed closer to the neurons within the visual cortex. This new generation of cortical implants requires less power to produce meaningful images and thereby transmits safer electrical signals.

A state -of-the-art cortical implant made of silicone rather than platinum was developed. Silicone allows for the design of wafer - thin stimulating electrodes that are smaller than the thickness of a human hair. Hopefully, such a small device can be safely implanted

within the visual cortex.

Long term implantation of electrodes in the brain appears not to evoke immune responses or cause discomfort or pain.

Although further confirmation is needed, the electrodes appear to still function after 20 years. These findings bode well for the long term use of a cortical device.

Lastly, because cortical implants bypass the retina and relay images directly to the brain, it may be possible to restore vision to patients with vision loss from eye trauma and a wide variety of eye diseases including retinal degenerative diseases.

## ARTIFICIAL RETINA

### How does retinal prosthesis work?

The retinal prosthesis works by providing a way for visual data to be sent from a tiny video camera to the retina.

This data is converted into electrical pulses that the retina interprets as images.

The implant has pieces both inside and outside the eye. Patients wear glasses, with a tiny camera embedded in the lens. The camera captures images and sends the data to a micro -processor (concealed in the side of the glasses) which converts the data to an electronic signal. An antenna in the lens transmits the signal to a receiving antenna in the eye. The signal then travels along a tiny wire to the retinal implant and signal causes the implant to stimulate the remaining retinal cells. These cells send the image along the optic nerve to the brain.

Image data is transferred from a wireless link between a video camera outside the eye (possibly embedded into glasses) and an electrode array inside the eye.

- Transmitting antenna -in a video camera outside the eye, possibly with an eyeglass frame or on a belt pack will send signals to the receiving antenna inside the eye.

- Implantable retinal chips- translate signals to viable retinal neurons for simulated sight.

- A sensor will provide feedback about the physiology and mechanics of retinal tissue around the implant.

- Stimulation parameters can be adjusted to protect the viable retinal neurons.

The retina implant is suitable only for patients and diseases in which the optic nerve and the visual cortex are still largely intact which is a prerequisite for implantation.

Since the Retina Implant can only provide limited vision, it is appropriate for patients with little to no visual perception. The device will not be able to compensate for slight visual impairments.

The retinal implant is not an adequate aid for people who have been blind from birth, since in these cases the visual cortex is not fully developed. Furthermore it cannot be used in patients with diabetic retinopathy, severe optic atrophy, RD or glaucoma.

### Retinal Implant Project

### DEVICE

The retinal implant project seeks to develope a silicon chip eye implant that can restore vision for patients with heriditary retinal degenerations.

The chip under design will rest on the inside surface of the retina, opposite the damaged rods and cones and in contact with the relay cells to the brain.

The implant will contain two silicone chips, both within the "silicone capsule".

The top chip will receive light entering the eye, initially from a tiny laser affixed to a pair of glasses.

Even damaged retinas can respond to electrical stimulation, so if its would be possible to fabricate a device that could stimulate the remaining retina but in whats' called 'retina topically correct orientation' in other words, that represents the images which fall on implant, perhaps then we could restore some kind of degree of useful vision. And this device eventually became a silicone chip that has embeded on its surface thousands of microscopic solar cells.

The chip called "Artificial Silicon Retina (ASR) is manufactured by Optobionics.

The chip is just 2 millimeters in diameter and 1/1000 of an inch in thickness.

It requires no batteries or wires and is completely self- contained. Since it is powered by the light that enters the eye.

The chip contains 3,500 microscopic solar cells that convert light into electrical impulses. It works by

replacing damaged photoreceptors, the socalled light-sensing cells of the eye.

Healthy cells convert light into electrical signals within the retina.

The chip is useful in conditions such as RP including macular degeneration.

The chip cannot help people with blindness caused by severe glaucoma on diabetes.

## EYE CHIP

### Components of the Chip

- A digital camera

- A computer

- A Computer tissue interface.

The computer processes signals from the camera, defining edges and contrasts. It then sends signals to a microchip on the retina. The chip contains microfluidic orifices that form a two- dimentional array of chemical delivery "pixels" analogous to the output of an inkjet printer.

The microchips holding 4,000-5,000 microscopic solar cells can be implanted into the back of the eye. When light strikes these solar cells, it is converted into electrical signals that travel through the optic nerve to the brain and are interpreted as an image. The piece of silicon can then act as a replacement  for a malfunctioning retina.

Research has shown that patients implanted with microchips showed subjective improvements in vision including improved perception of brightness , contrast, color, movement, shape, resolution, and visual field size.

No patient showed signs of implant rejection, infection, inflammation, erosion, neovascularisation, retinal detachment or migration.

While one of the researchers has positioned the chip near the photoreceptors, some others have placed it near the ganglion cells.

The surgery is performed through three incisions in the sclera smaller than the diameter of a needle. Through the incisions, vitrectomy is done and vitreous is replaced by a saline solution.

A pinpoint opening in the retina is then made to inject fluid in order to lift a portion of the retina from, creating pocket to accomodate the chip. The retina is resealed over the chip and air is injected into the middle of the eye to force the retina back over the device and close the incisions.

Thus the implant is placed in the area called the subretinal space, so in other words the retina is lifted up and the inplant is placed actually underneath much of the retina where the follar receptor cells are These are the light sensing cells. When the retina lays on top of the implant then the remaining cells are in contact with the electodes of these microscopic solar cells.  So now when the light enters through the retina and stimulates these microscopic solor cells, the electrical signal that is produced by these tiny follar cells stimulates the remaining cells that are still there on the surface of the retina.

### Immune Privilege and Retinal Transplantation

Recent advances in cell biology and surgical techniques have made the prospect of retinal transplantation for the cure of blindness a serious possibility.

An important potential barrier to successful orthoptic retinal transplantation is immune recognition and rejection of foreign antigen- bearing neural retinal  and pigment epithelial transplants.

It is necessary to understand:

a)  the nature and expression of transplantation and autoantigens on neural retinal and retinal pigment epithelial tissues.

b)   role of retinal microglia (of graft and of host origin) in alerting the immune system to the presence of an intraocular graft and to serve as targets of an immune attack.

c)  the capacity of neural retina and of retinal pigment epithelium to display their own inherent immune privilege and to resist immune destruction and

d)  the local microenvironmental factors that dictate immune privilege in the subretinal space.

The ultimate goal is to eliminate immune rejection as a barrier to transplantation so that neural retinal as well as retinal pigment epithelium transplants can be used to cure blindness.

The ultimate goal of transplantation is to replace lost photoreceptors with healthy ones, which would have

the capacity to re-establish the appropriate cellular connections at the outer plexiform layer. Cell survival appears to be related to donor age. Transplanted fetal tissue appears to survive and differentiate, but fails to show normal orientation in the retina[34]. Enzymatic dissociated adult photoreceptor cells can be transplanted by injection into the subretinal space.

Such photoreceptors survive and appear to have synaptic terminals but their outer segments degenerate almost completely[35,36].

Despite the paucity of evidence that this technique may be useful, mechanically dissociated fetal retina of 14-18 weeks' gestation have been grafted in 12 patients with advanced RP. The preoperative visual acuity was perception of light or worse. No rejection or complications were reported. Five patients had reported subjective improvement of vision[38]. However, it is impossible to exclude the placebo effect or the influence of injury. Furthermore, no improvement in vision was found in two patients transplanted with a sheet of adult photoreceptors harvested by vibratome[39].

Another stategy is the transplantation of RPE cells.

In the RCS rat, the RPE failed to Phacocytose photoreceptor outer segment material. The acumulation of outer segment material results in photoreceptor cell death[14]. Transplantation of healthy RPE cells into subretinal space delayed photoreceptor loss and retinal function, as measured by electro-retinogram and pupillary light reflex, is restored following RPE cell grafts in the RCS rats[40-43].

However, this may have limited relevance to most human forms of retinal dystrophy, although it may have a role in slowing the progress of ARMD. The results of human fetal  RPE transplantation in 13 patients with ARMD were recently reported. No visual improvement was observed but the graft was reported to survive in most of the patients.

## Developmental Expression of GABA Receptors in Retinal Transplants

r- Amunobutyric acid (GABA) has transiently been found is certain retinal cells during development, and thus it has been suggested that besides its role as an inhibitory neurotransmitter, it also plays a role during the development of the retina. Further it has been suggested that this developmental role of GABA is mediated through GABAA receptors.

Various neurotransmitters have neen found is retinal transplants, but the receptors which are needed for their action, have not been demonstrated.

It is therefore of interest to see the presece of GABAa receptors during the develpoment of the transplants.

## Stem Cell Hope for Retinal Transplants

Researchers have found that using brain stem cells could eliminate the need for tissue typing before transplantation, offering hope for millions of people who require retinal transplantation.

Brain stem cells are invisible to a transplant recipient's defence mechanism and do not trigger the immune system to reject them.

Using central nervous system stem cells in transplants for diseases of the eye, brain and spinal cord may eliminate the need for tissue typing before transplantation.

This could also rule out the necessity for immunosuppressive drugs after transplantation.

Most tissues when transplanted from one body to another are seen by the recepient as foreign and attacked by the body's immune system.

However, there are parts of the body that are known as "immune priviledged", which do not mount attacks against foreign tissue, because to do so would be self-destructive. Such as sites include the eye, the  brain, the digestive system and reproductive system.

Stem cells already have the advantage of being able to transform or differentiate into various types of cells and can be reproduced  endlessly outside the body.

Experiences were also gained with transplantation of RPE cells especially in animal models, but also in human trials. In contrast to the results of RPE transplantation studies in animals, RPE transplantation in patients were only  of minor sucess. Possible reasons for the lack of sucess were influences of cell isolated, cultivation and preparation for transplantation.

It is well known, that RPE cells loose their functions and typical characteristics after isolation, and techniques to retain functions during cell culture or after cell transplantation have so far not been analysed.

It remains questionable, if cells can be transplanted immediatley after isolation or after a preceeding culture phase, or if transplantation of cell sheets may be superior to transplanting cell suspensions. Moreover, inmunological reactions, which may contribute to graft failure, are still not fully understood. To overcome or avoid problems of graft failure, other stategies have been developed including the transplantation of autologous iris pigment epitheial cells.

In addition new reserach concepts eg transplantation of adult bone marrow stem cells which can be isolated from the patient himself to prevent immunological reactions are being developed.

**Genetherapy in Heriditary Retinal Degeneration**

In most recessive and some dominant diseases cell dysfunction is due to lack of functionial genes and the objective of therapy is replacement of defective gene with genes that express normally.

Gene therapy holds promise of revolutionising the treatment of genetic diseases. Firstly, the genetic basis of heriditary rentinal degenerations is well characterised and the biochemical defects are known in several diseases (eg. Refsum disease, gyrate atrophy, kearns-sayre syndrome). Secondly, efficient gene delivery techniques that can be relatively well controlled are available and allow even local ocular application.

Lastly, reliable animal models of heriditary retinal disease are available that permit preclinical testing.

One of the mosrt significant hurdles preventing clinical application of gene therapy is the lack of safe gene transfer systems.

Of all the gene delivery vectors available today, viral vectors, including replication dafective adenorises, adenoassociate a viruses herpers simplex, and lentiviruses, dominate the field. Replication defective adenoviral vehicles are probably the most versatile vectors to deliver plasma DNA to retinal cells.

Following intravitreal injection of an adenoviral vector carring a reporter gene, a significant rescue of photoreceptors was observed when injections were payformed in T cell depleted rd mice.

Although previous studies already reported that ocular injury, such as intravitreal injection itself, can inhibit photoreceptor cell degeneration, it is not considered as a significant factor.

Three different gene therapy stategies have been followed in attempts to slow the degeneration -

*   introduction of a functional copy of the ß PDE gene to photoreceptor cells in order to test the efficacy of gene replacement therapy

*   introduction of additional copies of the bcl -2 gene to photoreceptor cells in order to block apoptosis directly and -

*   introduction of genes encoding secreted neuro trophic factors to cells in the anterior segment of the eye inorder to support degenerating photoreceptors by indirectly blocking apoptosis.

The latter two stategies while not capable of improving vision may help maintain it by preserving rods and therefore indirectly preserving cones which do not have the rod specific enzyme defect but are nevertheless eventually lost.

Adenoviral vectors (AV) have been widely used for gene transfer to the eye and there have been a number of reports of delayed retinal degenerration following subretinal delivery of AV and AV encapsulated vectors.

There are two general approaches by which genes can be introduced into the eye, ex vivo or in vivo.

In the ex vivo techniques, the genes are introduced in vitro into retinal cells, retinal pigment epithelial cells, or fibroblasts. The transfected cells are then injected into the eye.

In vivo, or direct gene transfer, gene are introduced into adeno-associated virus (AAV), and retinovirus.

Gene therapy can also be used to deliver neurotrophic factor.

As long term gene expression is the goal,sucess depends on

a)  efficient uptake into the target cells

b)  avoidance of endocytosis and lysosomal degradation

c)  import into the nucleus

d)  stable retention in the nucleus, either as a circular episome or by integration into the host genome

e)  target cell specific expression of the therapeutic gene, driven by the natural promototer and enhancer elements

f) appropriate translation and subcellcular localisation of gene product.

There are several possible sites for introducing genes into the retina.

Intravitreal injections, a relatively safe and easy method of approach but potential complications such as vitreous haemorrhage, RD and endophthalmitis cannot be ignored.

Others include subretinal injection, which produces local and often transient detatchment of retina.

Other possible stategies include horoidal or scleral gene implants or episcleral injections, with or without contophresis to drive the vetor into the retina, propulsion of DNA coated gold particles into the retina with a pressurised gene gun, intravenous or intracarotid injection of the transducing agent.

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