The notion that restoring vision to the blind is possible has long been thought to be fanciful. However, beginning as far back as the 1960s vision scientists began to investigate the possibility of restoring vision to the blind by activating neurons in the visual pathways beyond the eye, namely in the visual cortex. These early experiments showed that it is possible to elicit visual sensations in humans by electrically stimulating neurons in the visual cortex.

Most blindness is caused by defects in the eye. It can be caused first of all by damage to the optical pathways that are required for the focusing of a sharp image on the light-sensitive retinal photoreceptors that line the back of the eye. Today, it is generally possible to cure these optical impediments. Cataract surgery to remove an opaque lens and replace it with an artificial lens is carried out routinely in many parts of the world, and corneal transplants with natural or artificial corneas are generally successful. It should be noted, however, that in those parts of the world where such procedures are not available, blindness remains common because of such defects. It is estimated that there may be as many as 20 million blind people in the world because of cataracts.

The major cause of untreatable blindness throughout much of the world today is retinal degenerative disease, most often because of a loss of photoreceptor cells but also, especially in glaucoma, a loss of third order neurons of the retina, the retinal ganglion cells whose axons form the optic nerve and carry the visual signal from the eye to the higher visual centers such as the cortex. Because most retinal degenerations cause blindness by destroying the photoreceptors, much emphasis in the quest to cure blindness is to restore photoreceptive function in the blind eyes, or to substitute for the loss of photoreceptor function. Most success so far has come from two approaches. First, retinal prostheses have been developed that electrically stimulate the second or third order retinal neurons, namely the retinal bipolar or ganglion cells. Indeed, two types of prostheses have been successfully implanted in blind human patients and have restored light sensitivity and low-acuity vision to the patients. The second approach has been successful for patients with specific gene defects that severely compromise photoreceptor function, and the treatment consists of injecting a viral construct containing the normal gene into the eye, thus replacing the defective gene. Again, substantial improvement in vision, especially light sensitivity, has been demonstrated in these patients. A newer approach, not yet tested in humans but which soon will be, is in essence a combination of the above two approaches, namely imparting light sensitivity to retinal neurons via genetic means called optogenetics. Genes that code for light-sensitive molecules linked to an ion channel or pump are introduced into various retinal cells, most often bipolar or ganglion cells. In animals treated this way, the treated cells are stimulated by light, causing the opening of ion channels or activating ion pumps, both of which permit ions to flow across the cell outer membranes, thus electrically activating them. This technique was recently applied in blind animals with some remaining cone cells, but which had lost light sensitivity because the outer segments of the cells (which contain the light-sensitive molecules—the visual pigments) had degenerated. Once light sensitivity was restored to these cones, downstream retinal pathways could be activated and the animals showed visual behavioral responses.

Another approach to replace damaged or destroyed photoreceptor cells is to transplant healthy photoreceptor cells into the eyes of blind animals. This strategy has had limited success so far—the number of transplanted cells that survive and integrate into the retinal circuitry is quite limited—but some restoration of electrical activity recorded from the eyes occurs and the animals do show some behavioral responses to light. Stem cells, which in theory can differentiate into any cell type, have also been introduced into blind eyes, including some human eyes, again with very limited and largely undocumented success. Investigators are now inducing stem cells maintained in culture to differentiate into photoreceptor cells and then are injecting such cells into eyes whose photoreceptor cells have degenerated; this approach appears promising and may be more successful.

In addition to direct deleterious effects of a disease process or gene defect in the photoreceptor cells themselves, such defects can also occur in the associated retinal pigment epithelial cells, and this can cause photoreceptor death. The photoreceptor cells and overlying retinal pigment epithelium are intimately connected, and they depend upon each other to function. The isomerization of vitamin A, to generate the 11-cis retinoid molecule needed to regenerate the visual
pigment molecules after light exposure, occurs mainly in the retinal pigment epithelium, and the phagocytosis and digestion of spent outer segment material as well as recycling lipids occurs in the retinal pigment epithelial cells. Compromise of any of these retinal pigment epithelial cell functions results in photoreceptor cell degeneration in both animals and humans. Thus, gene therapy to correct retinal pigment epithelial cell defects or transplantation of retinal pigment epithelial cells into diseased retinas has been accomplished with promising results. Indeed, the first gene therapy treatment in humans, described above, was for a gene defect in the retinal pigment epithelial cells. Retinal pigment epithelial cells grow readily in culture and are readily transplanted. Unlike photoreceptor cells, they do not need to integrate into the retinal circuitry but interact only with the photoreceptor cells, which they do readily.

It has long been known that nonmammalian species such as amphibians and fish can regenerate retinal cells endogenously but mammals, including humans, cannot. Why can these cold-blooded vertebrates do this but we can't? This is an intriguing question that is now receiving substantial attention. If we could regenerate our retinal cells, presumably we could cure not only blindness caused by photoreceptor degeneration, but blindness caused by degeneration of any retinal cell including the ganglion cells. In fish, for example, new neurons are formed throughout life, and the axons of the newly formed ganglion cells extend into the rest of the brain and make appropriate connections. In mammals, not only do ganglion cells not regenerate, but their axons do not regrow in large numbers after the optic nerve is damaged or cut.

From what cells does the regeneration in the nonmammalian species occur? This may differ among species, but certainly retinal pigment epithelial cells and Müller glial cells appear to be involved. In fish, the formation of new retinal cells throughout life comes from a region in the retinal periphery called the marginal zone, whose cells may derive from the retinal pigment epithelium, whereas when the fish retina is damaged, new retinal neurons derive from Müller cells that dedifferentiate and appear to behave like stem cells. That is, after dedifferentiation these cells first proliferate and then generate progenitors for repairing the retina.

The objective of the present initiative was to evaluate the various approaches presently underway to cure blindness caused by retinal degenerative disease, to identify the most promising and feasible approaches and to indicate the major problems and issues that must be overcome to make an approach useful and effective in restoring vision to the blind. In addition to discussing the approaches outlined above, we also considered other topics that may impact the various approaches being undertaken. For example, the retinal prostheses that have been developed so far provide only low-level vision. Many devices have been developed over the years to help those who are visually impaired and have low-level vision. Can some of these devices be of use to those who have low vision restored as a result of an implanted visual prosthesis? Another example would be for a device to make a retina made light sensitive via optogenetic means more sensitive to light and able to adapt over a range of intensities, something optogenetically induced vision is unlikely to be able to accomplish by itself.

Another area we considered is that of neuroprotection, neuroactive substances that protect neurons and often slow down degeneration in a diseased retina. Can such molecules be used in conjunction with other restorative approaches to enhance their effectiveness? So, for example, we know that after photoreceptors degenerate in a retina, the retina undergoes substantial remodeling, and this could limit success when restoring photoreceptor function, especially if the visual loss is long standing.

A final topic discussed was that of end points—what is the best way to measure the return of visual function in previously blind patients? The gold standard to evaluate vision ordinarily is visual acuity—how many lines on an eye chart can a person read. But there is much more to vision than just acuity, although acuity is certainly critical if we are to restore reading, driving, face recognition, and so forth to blind individuals.

In the chapters that follow, the topics introduced above are described in detail with indications as to what the major questions are that need to be addressed and how to go about answering these questions where possible.

The chapters of this report were written based on the discussions held during the targeted sessions held during the plenary meeting. All members of a session had the opportunity to comment upon and contribute to each chapter, and everyone who participated in the workshops and plenary session had the opportunity to comment upon the final report. We believe this is a consensus document, and we thank all who were involved and contributed so generously with their time. We hope this report is useful and hastens the day when we can restore vision to the blind.

This chapter is part of the Restoring Vision to the Blind report by the Lasker/IRRF Initiative for Innovation in Vision Science. The full report, Restoring Vision to the Blind, including a complete list of contributors, is available in the Supplementary Material.

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