CURRENT STATUS OF REHABILITATION FOR PATIENTS WITH HOMONYMOUS FIELD DEFECTS

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LEARNING OBJECTIVES

1) The attendee will be able to describe the disabilities and handicaps in everyday life caused by hemianopia.
2) The attendee will be able to explain the features of the reading disorder and its rehabilitation options.
3) The attendee will be able to understand what rehabilitation approach to improve orientation is appropriate.

CME QUESTIONS

1) Which spontaneous adaptive strategies are favorable to improve orientation?
   a) turning the head to the blind side
   b) saccades towards the blind side
   c) shifting attention to the blind side
2) The hemianopic reading disorder is caused by
   a) low visual acuity
   b) fixation instability
   c) limited size of the reading visual field
3) Which rehabilitation approach to improve the hemianopic orientation disorder is evidence-based?
   a) compensatory saccadic training
   b) visual stimulation of the blind hemi-field
   c) prisms mounted in the spectacles

KEYWORDS
1. Homonymous Hemianopia
2. Reading
3. Orientation
4. Rehabilitation
5. Training

INTRODUCTION

In patients with brain damage, often the hemianopic field defect is not diagnosed, because other neurological symptoms, such as hemiplegia, are predominant. The mean time between the brain damage and the diagnosis of the hemianopia was found to be 3 +/- 2 months (Zhang et al 2006). Additionally, the patients often do not realize the field defect, even though they experience activity limitations in their everyday life.

The classification of the World Health Organization (WHO 2004) for Functioning, Disability and Health (ICF) includes three main aspects, which have to be considered in visual impairment: 1) impairment – related to the organ, 2) disability or activity limitation – related to the person and 3) handicap or participation restriction – related to the society.

Homonymous field defects cause two main disabilities/activity limitations:
1. reading disorder, if the central visual field is involved
2. orientation disorder (bumping into objects, problems with way finding)

These disabilities cause major handicaps, which are listed in Table 1.

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<tr>
<th>Table 1: Handicaps resulting from hemianopia</th>
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<td>• Reduced participation in society</td>
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<td>• Missing spatial information</td>
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<td>• No driving</td>
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<td>• Decreased activities of daily living</td>
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<td>• Reduced social contact</td>
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<td>• Severe reduction of quality of life!</td>
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Because of these severe disabilities and handicaps, rehabilitation is important and should be provided for these patients.
General Aspects Of Rehabilitation

Three main aspects need to be considered:

1. Knowledge and potential utilization of spontaneous adaptive strategies
2. Optical devices
3. Training

It is crucial for training studies to exclude spontaneous recovery. Additionally, placebo effects have to be ruled out by using a control group. Furthermore, it is necessary to define appropriately, which improvement is clinically relevant and to assess the potential success of a training by suitable methods.

In principle, there are two approaches for training methods: restitution or compensation (see below for details).

THE HEMIANOPIC ORIENTATION DISORDER

Patients with homonymous hemianopia are often not aware of their field defect and are confused by unpleasant “events” such as bumping into objects or persons, as well as problems with way finding. The patients often develop spontaneous adaptive strategies: eye movements towards the blind side (Huber et al 1995, Pambakian et al 2000, Trauzettel-Klosinski and Reinhard 1998, Reinhard et al 2005) that are small during fixation tasks (see Figure 1 A) and larger during exploration tasks, where they allow a better use of the field of gaze (Figure 1 C). Furthermore, patients can develop an attentional shift towards the blind side. It is known that attention improves stimulus discrimination (Pilz et al 2006). Some patients get accustomed to a head turn, which is unfavorable. Interestingly, the eye movements during fixation are asymmetric towards the blind side, thus causing a shift of the visual field border towards the blind side. Huber et al (1995) found in a SLO-perimetry study in all 15 patients with hemianopia fixational shifts: 12 patients with 1-5°, 3 patients with 5-15°. This shift of the visual field border is often misinterpreted as an improvement of the visual field. The exact determination of the position of the blind spot helps to identify whether fixation is central or eccentric or whether eye movements shift the field defect together with the blind spot (Figure 1B).

OPTICAL DEVICES FOR BETTER ORIENTATION

Monocular prisms or mirrors can enlarge the binocular field. A benefit was described in 20% of the patients (Hedges et al., 1988). However, the competition between the seeing halves of the retina leads to confusion and impairment of spatial orientation. A newer method uses monocular peripheral prisms, where the prisms are located only in the peripheral part of the glasses in order to avoid the central diplopia (Peli, 2006). This approach has been described to be quite successful: 47% (20 of 32) of the patients where wearing the prisms after 12 months and reported benefits for obstacle avoidance (Bowers et al., 2008). However, this study was not randomized and controlled, and the success was mainly determined by the subjective report of the patients.

Binocular prisms have been shown to be beneficial in or patients with hemineglect (Rosseti et al 1998).

TRAINING

There are two approaches to improve the hemianopic orientation disorder:

1. Restitution by visual stimulation of the blind hemifield.
2. Compensation by increasing the field of gaze with explorative saccades.

Previous studies performed visual stimulation using targets along the visual field border. Zihl and von Cramon (1979) used targets at threshold and described an improvement of up to 40°. These results were not confirmed by a later study by Balliet et al. (1985).

Some years later, Kasten et al. (1998) used supra-threshold targets along the visual field border and recorded an improvement of 5°. The effect of this “Vision Restitution Training VRT” of 5° improvement along the vertical field border was not confirmed by Reinhard et al. (2005) using SLO perimetry, where fixation was simultaneously
controlled during stimulus presentation. The test point grid had a spatial resolution of 0.5° horizontally and 1° vertically. Also in conventional perimetry using a threshold oriented slightly supraliminal static grid procedure (Tuebingen Automated Perimetry) no relevant change in the fields was found (Schreiber et al. 2006; same patient group as in Reinhard’s study, Reinhard et al. 2005). The problem with conventional perimetry is insufficient fixation control and the provocation of eye movement towards the stimulus. Furthermore, light scatter of a bright stimulus near the field border may interfere. Another problem in the studies by Kasten and Sabel’s group is the method used to assess the visual field.

Kasten and Sabel (1998) reported especially on improvement along the vertical field border, where they reported that absolute field defects changed to relative. However, we need to consider that the so-called high resolution perimetry HRP in their studies did not measure relative field defects, but rather how often a stimulus is seen or not seen. It is typical for frequent shift of gaze that at a certain location a stimulus is sometimes seen and sometimes not seen. However, this is not the same as a relative defect. What they interpreted as relative visual field defect is in reality an eye movement artifact. Therefore, it should be emphasized that the assessment of an improvement needs to be performed by an appropriate method. Additionally, regarding the anatomy and pathology, there is no reason why the visual field should improve just along the vertical field border (Horton, 2005).

Therefore, the main limitations of the assessment of the VRT’s effect are as follows: 1. There is insufficient fixation control, which cannot detect eye movements towards the stimulus. 2. “High resolution perimetry” does not measure relative field defects, but the frequency of seen stimuli. 3. We need to consider the possibility of light scatter by a stimulus that is presented directly along the visual field border, especially with unstable fixation. Additionally, an improvement of 5° would not have a relevant effect on the orientation disorder in everyday life (Trobe et al. 2005). For reading, however, this could have a crucial effect (see below), but the patients in the study of Reinhard et al. (2005) did not improve their reading ability after VRT.

To argue against the possibility of eye movement artifacts, later studies with very small sample size were performed with eye movement recordings during HRP (Kasten and Sabel 2006) and with camera-based microperimetry (Marshall et al. 2010). However, they cannot prove their conclusions based on the data of these studies, because several technical and methodological details are not clarified. Furthermore, they do not show clinical relevance.

Another study used supra-threshold targets at 10° eccentricity (Raninen et al., 2007). The authors reported a normalization of contrast sensitivity in the blind field of two patients, but no visual field improvement. The more peripheral stimulus might be safer regarding provocation of saccades, but it is not clear whether eye movement artifacts can be excluded.

The alleged effects of the above mentioned restitution studies should be distinguished from the “blindsight” phenomenon, which is an unconscious perception of visual stimuli via the superior colliculus to extrastriate regions without activation of V1 (Pöppel et al., 1973; Vanni et al., 2001; Weiskrantz, 2004). It was shown recently that the thalamic lateral geniculate nucleus has a causal role in V1-independent processing of visual information (Schmid et al. 2010). Whether blindsight training can improve this kind of residual vision to a level that is relevant for everyday life, is an open question (see also Schofield and Leff 2009).

COMPENSATING SACCADIC TRAINING
Several studies reported improvement of efficiency of exploration after compensating saccadic training (Kerkhoff et al., 1992; Zihl, 1995; Nelles et al., 2001; Pambakian et al., 2004; Bolognini et al., 2006). The main exclusion criteria were other visual acuity, and a duration of the disease of at least 6 months (to exclude spontaneous recovery, see Zhang et al., 2006). The main exclusion criteria were other ophthalmological, neurological or cognitive disorders. The patients were randomly assigned: 15 to the explorative saccadic training (EST) and 15 to a flicker-stimulation training (FT) – a potential restitution training.

30 patients with post-chiasmatic lesions were included. The main inclusion criteria were: isolated homonymous hemianopia or quadrant defect, normal or near normal visual acuity, and a duration of the disease of at least 6 months (to exclude spontaneous recovery, see Zhang et al., 2006). The main exclusion criteria were other ophthalmological, neurological or cognitive disorders. The patients were randomly assigned: 15 to the explorative saccadic training (EST) and 15 to a flicker-stimulation training (FT) – a potential restitution training.

The EST consisted of a saccadic search task to improve visual search in the blind hemifield and the use of the total field of gaze. The training was performed on a computer. Positions and latency of all digits found were stored. The FT was designed in such a way that the patients had to fixate a central panel and flickering letters were displayed in 22° eccentricity randomly on both sides. This kind of training was thought to eliminate eye movements, whereas the saccadic training was designed to provoke eye movements.

The patients trained at home, 30 minutes twice a day, five days a week for six weeks (total 30 hours). Data collection was before, directly after and six weeks after training. The main results were: the digit search task at the computer showed a marked decrease of reaction time in EST compared to FT on the blind side. In a natural search task, a table test, where patients had to find 20 objects
(equally distributed in the total field), the patients showed a selective decrease of reaction time on the blind side in EST. The effect to digit search and natural search task still persisted six weeks after the training at follow-up. During natural scene exploration, the number of fixations increased on the blind side and decreased on the seeing side in EST, whereas in FT, there was no difference between the sides. The effect of increasing number of fixations on the blind side even increased after the end of training, which shows that the patients applied their new strategy in everyday life. Quality of life improved in EST in the social domain, i.e. the patients detected other persons in their blind hemifield and could communicate with them. Reading speed did not change in either group, which was expected, because it was not a reading training, and neither did their visual fields.

To summarize the results of the randomized and controlled trial (Roth et al 2009): saccadic training selectively improved saccadic behavior, natural search and natural scene exploration. The patients learned to apply their new saccadic strategy to everyday life. On the other hand, flicker training did not change the visual fields, exploration was unchanged, and fixation became more unstable (unsystematic eye movements). In conclusion, there is still no evidence for visual field restitution by stimulation of the blind hemifield.

Compensating saccadic training is evidence-based and recommendable. Our study showed a clear effect, which could be applied to everyday tasks and which persisted after the end of training.

Interestingly, patients who had a longstanding hemianopia (for many years) also benefited from the training.

Alternative methods: If the use of a computer is not possible, search tasks on a sheet of paper or a game with search tasks (e.g. Domino) can be used (Kerkhoff et al 1992, Zihl et al 1995). Even though there are no randomized and controlled studies of this kind of training, it is in principle the same approach and could be applied in patients, who are too disabled or have additional cognitive or motor problems.

THE HEMIANOPIC READING DISORDER

Reading requires not only sufficient resolution, but also a sufficient size of the reading visual field or visual span during fixation (Aulhorn 1953, legge et al 1997, McConkie and Rayner 1975). A homonymous field defect without macular sparing covers half of the reading visual field and leads to severe reading disability (Figure 2 A). If there is a macular sparing, reading ability can be preserved (Figure 2 C) even though the field defect causes severe orientation disability. On the other hand, a small paracentral homonymous field defect results in severe reading disability, because it covers half of the reading visual field (Figure 2 D), whereas orientation is not involved. These small paracentral homonymous field defects can easily be overlooked in standard perimetry, especially when the test point grid is not dense enough to detect a scotoma of 2° diameter. In these cases, the examiner has to specially look for such small defects by using a dense grid or a manual perimetry.

The side of the field defect in relation to the reading direction plays an important role: In left to right reading, patients with right hemianopia have difficulties to get through the line, make many small saccades and are much more disabled compared with patients with left hemianopia, who have difficulties to find the beginning of the new line (see also TK 2010 JNO).

Spontaneous adaptive strategies during reading:

Some patients without macular sparing can develop a very favorable adaptive strategy: eccentric fixation (Trauzettel-Klosinski 1997). Even though they have normal visual acuity, they are able to shift their fixation by 1 - 1.5° to the side and therefore shift the visual field border towards the blind side. By doing so, they create a small perceptual area along the vertical field border, which is very helpful for enlarging the reading visual field (Figure 2 B). On the other hand, one needs to consider that the eccentric fixation also causes a shift of the field border in conventional perimetry, together with the blind spot, and this behavior is often misinterpreted as an improvement of the visual field, whereas in reality it is an adaptive strategy (Figure 1 B).

Another adaptive strategy is predictive saccades in left hemianopia, where the patients in the early stage make many hypometric saccades to find the beginning of the new line. After some time they can learn to perform one single hypermetric (predictive) saccade, and then start to read the new line (Meienberg 1988).

Reading performance in hemianopia therefore depends on several factors.

1. The side of the field defect (right-sided hemianopic patients are much more disabled).
2. The distance of the field defect to the midline (i.e. the size of the reading visual field).
3. The presence and absence of adaptive strategies such as eccentric fixation and predictive saccades.
CONCLUSIONS
To improve exploration, orientation and mobility, saccadic training methods are recommendable. Training with a saccadic search task is now evidence-based and can be recommended for patients with hemianopia. The training was tested in a randomized and controlled trial (Roth et al 2009) and is available as software (for further information see www.eye.uni-tuebingen.de/low-vision-clinic). Similar search tasks are used in other training methods (Zihl et al 1984, Kerkhoff et al 1992). The training, which was developed in our laboratory, has the advantage that it is designed in a very simple and clear way, so that even patients who have no experience with a computer, can use it easily and independently at home – after an instruction by their ophthalmologist, neurologist or low vision specialist. Other training methods with explorative search tasks use, in principle, the same approach.

For reading, training with scrolled text can be recommended (Spitzyna et al., 2007). Further methods for improving reading need to be developed in the future. Altogether, evidence-based rehabilitation procedures are available and should be provided for the patients to improve their quality of life.

HOW CAN READING BE IMPROVED IN HEMIANOPIA?
- It is always important to support orientation on the page by visual or tactile aids (index finger, ruler or slightly magnifying ruler with a guide line).
- Predictive saccades, especially in left hemianopia.
- Turning the text to a vertical or diagonal orientation is often recommended, however there are no systematic studies in patients and there are only anecdotal reports.
- Computer training with scrolled text has been described to be effective (Zihl et al., 1984; Kerkhoff et al., 1992; Spitzyna et al., 2007).
- Systematic oculomotor training without text (but with the size of reading saccades) has also been reported to be effective (Schütt et al., 2008, 2009).

Despite the reported beneficial effects, more research to develop the optimal training strategies for improving reading performance will be necessary.

CME ANSWERS
1) B, C
2) C
3) A

REFERENCES

HOW SHOULD READING PERFORMANCE BE ASSESSED?
Reading performance should be measured by standardized reading texts, especially paragraphs of texts, which are more favorable than single sentences. The International Reading Speed Texts (IReST), developed in 17 languages, provide a set of ten equivalent texts in each language for repeated measurements and also for the use in international multi-language studies (Hahn et al., 2006, Trauzettel-Klosinski et al, in preparation), (for more information see www.amd-read.net).


CURRENT STATUS OF IMAGE-GUIDED RADIATION THERAPY FOR
PATIENTS WITH BASE OF SKULL TUMORS
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LEARNING OBJECTIVES
1. The attendee will be able to learn the differences between ionizing and charged particle (proton beam) radiation.
2. The attendee will be able to learn the strategies used by radiation oncologists to limit collateral damage to normal structures when radiating a tumor.
3. The attendee will be able to learn the advantages and disadvantages of different radiation modalities.

CME QUESTIONS
1. What is the difference between ionizing and charged particle radiation?
2. What is Intensity-Modulated Photon Radiation Therapy (IMRT)?
3. What are the theoretical advantages of charged particle (proton beam) radiation?

KEYWORDS (MAX 5)
1. Skull Base
2. Ionizing Radiation
3. Charged Particle (Proton Beam) Radiation.
4. Intensity-Modulated Photon Radiation Therapy (IMRT)

INTRODUCTION
Management of tumors in the cranial base has been challenging for neuro-ophthalmologists, radiation oncologists, otolaryngologists and neurosurgeons for more than a century. Since tumors are located deep in the skull and can involve important visual and neurovascular structures, surgical treatment was associated with high morbidity and mortality. Visual pathways, both afferent and efferent, originate or traverse the cranial base and are therefore affected by many of these tumors making management difficult. During the 1970s and 1980s, neurosurgeons and head and neck surgeons introduced advances in surgical instrumentation and developed new approaches to the cranial base. Simultaneously, focused stereotactic radiotherapy was introduced to treat localized tumors in a more refined manner. More recently, charged-particle-radiation therapy is being used more commonly to treat many tumors traditionally treated by ionizing radiation.

CLASSIFICATION
Various types of tumors involve the skull base and they include meningiomas, pituitary adenomas, paranasal sinus cancers, chordomas, chondrosarcomas, and schwannomas. There are many ways to classify and manage skull base tumors. Morita et al have suggested that these tumors can be categorized according to their individual histopathologic types and locations. Since there are numerous types of tumors, these authors have limited their classifications to three groups based on biologic aggressiveness, and nine territories based on their location. They argue that biologic aggressiveness directs our decision about which mode of treatment is the best from an oncological standpoint, and the location of tumor and clinical presentation provide information on the risks that are involved in treatment.

BIOLOGIC AGGRESSIVENESS
Skull base tumors can be categorized into three pathologic entities: benign, slow-growing (low-grade), and fast-growing (high-grade) malignancies. Benign tumors grow in an expansive fashion and induce clinical symptoms by exerting pressure on various structures including the optic nerves, chiasm and ocular motor nerves. Therefore, the reduction of the mass effect and, if possible, the complete excision of the tumor with minimal morbidity are the gold standard of treatment. However, there are always associated surgical risks that may depend significantly on the location and extent of the tumor. With the widespread use of magnetic resonance imaging (MRI), asymptomatic or minimally symptomatic tumors such as meningiomas are more frequently being discovered in the skull base. Treatment options of these benign tumors include observation, the excision of the tumor by surgery, or the control of tumor growth by conformal radiotherapy. The long-term benefits and risks of each procedure and the natural history of various tumors should be carefully assessed before choosing a specific treatment option.
**Management Options of Cranial Base Tumors**

For patients presenting with skull base tumors, treatment options include observation with close follow-up, operative excision, radiotherapy, chemotherapy, or a combination of these therapies. Careful neuro-ophthalmic follow-up, including visual fields and imaging studies, is important in detecting changes and in following the progress of the tumor.

**Surgery**

Since cranial base tumors are deep in location and surrounded by critical structures, conventional neurosurgical approaches are disadvantageous because of the need for significant brain retraction, poor control of the lesion and adjacent structures, and often suboptimal exposure. Modern skull base surgery carries certain risks. Because the approaches used in these surgeries require extensive bone removal and often necessitate entrance into or transgression of potentially contaminated spaces (e.g., the paranasal sinuses), the potential exists for complications such as cerebrospinal fluid (CSF) leakage, infection, cosmetic defects, and cranio-vertebral instability. The exposure or manipulation of neurovascular structures also carries risks for stroke or cranial neuropathies. The operative time and extent are increased and pose risks for perioperative medical problems such as pneumonia, hormonal and electrolyte disturbance, coagulopathy, and pulmonary embolus. CSF leakage complicates cranial base surgery in 5% to 30% of cases, whereas major neurological complications have occurred in 4% to 10% of cases. Operatively induced cranial neuropathies occur in 10% to 96% of cases, depending on the region of surgery, the nature of the tumor, and the aggressiveness of resection.

Due to the potential for major morbidity associated with skull base surgery, an experienced treatment team should carefully determine the indication for and the extent of resection, and the benefits, risks, and ultimate goals of the procedure should be thoroughly discussed with the patient.

**Radiotherapy**

The goal of radiotherapy is to deliver a homogeneous radiation dose to a tumor target while minimizing the dose to surrounding normal tissue. In this way, the maximum number of clonogenic tumor cells can be eradicated with minimum risk to normal structures.

**External Beam Radiation Therapy**

Ionizing radiation uses either x-rays, gamma rays, or electron beams produced by a linear accelerator or radiation sources such as radioactive seeds to treat tumors. Ionizing radiation preferentially damages the DNA of tumor cells that ultimately causes cell death. The radiation dose is measured in Gray (Gy) and cellular damage increases with higher absorbed radiation doses. When coming up with a treatment plan, radiation oncologists must balance the desired damage to the tumor and the undesirable damage to adjacent healthy tissue. This is typically accomplished by targeting the beam to the tumor area using paths that spare nearby critical and radiosensitive structures, selecting multiple fields that cross in the tumor area through different paths, and splitting the total dose into smaller dose “fractions” that are delivered over several days or weeks.

**Three-Dimensional Conformal Radiation Therapy (3DCRT)**

Conformal radiotherapy attempts to minimize the volume of normal tissue irradiated, by shaping the dose distribution to conform tightly to the shape of the tumor, reducing the dose to surrounding normal tissues. Adequate immobilization of the target and improved three-dimensional (3D) imaging enable a higher degree of certainty of target localization, which permits the use of narrower margins around the target. Using information from CT, MRI or PET scans, 3DCRT is a technique where the beams of radiation used in treatment are shaped to match the tumor. 3D dose distributions are calculated by a treatment planning computer using dosimetric algorithms. Previously, radiation treatment matched the height and width of the tumor, meaning that healthy tissue had to be exposed to the beams. Conformal radiation therapy uses the targeting information to focus precisely on the tumor.
while minimizing damage to the healthy surrounding tissue. This exact targeting makes it possible to use higher levels of radiation in treatment while minimizing injury to healthy or sensitive structures. Radiotherapy planning studies have confirmed that 3DCRT reduces the volume of normal tissue within the high dose volume compared with conventional radiotherapy. However, it is impossible to spare normal tissue in close proximity to the tumor target because the beams cannot be modulated with this technique.

**INTENSITY-MODULATED PHOTON RADIATION THERAPY (IMRT)**

Historically, the maximum radiation dose that could be given to a tumor site has been restricted by the tolerance and sensitivity of the surrounding nearby healthy tissues. IMRT is a form of conformal therapy that combines several intensity modulated beams. With IMRT, the radiation beam can be broken up into many “beamlets,” and the intensity of each beamlet can be adjusted individually. With this technique, conformal photon radiation is delivered to the target tumor by crossing multiple properly shaped radiation fields with modulated intensities through paths that spare radiosensitive and critical adjoining tissue. The intensity of the radiation in IMRT can be changed during treatment to spare more adjoining normal tissue than is spared during conventional radiation therapy. By shaping the radiation beams to closely approximate the shape of the tumor, an increased dose of radiation can be delivered to the tumor with less damage to normal structures. IMRT therefore offers a significant advance in conformal therapy by improving conformality and reducing radiation dose to radiosensitive normal structures close to the tumor.

**CHARGED PARTICLE RADIATION THERAPY**

Charged-particle-radiation therapy includes external radiotherapy that uses protons, helium, carbon, neon, silicon ions or other charged particles. Currently, only protons and carbon ions are in clinical use today and this charged-particle-beam therapy has been clinically available since 1954 but was not approved as a radiation treatment option by the FDA until 1988. Charged particles represent an advancement over photons because they have a superior depth-dose distribution. Photons (or electron beams) deposit most of their energy near the surface with progressively smaller doses at larger depths and they continue to deposit the dose of radiation in normal tissues beyond the tumor. Charged particles deposit a local dose near the surface and deposit almost all of their energy in the final millimeters of their trajectory in the tumor. There is essentially no exit dose and tissues beyond the tumor receive very little of the dose. This pattern results in a sharp and localized peak dose, known as the Bragg peak. When a fast charged particle moves through matter, it ionizes atoms of the material and deposits a dose along its path. A peak occurs because the interaction cross section increases as the charged particle’s energy decreases. The Bragg peak, named after William Henry Bragg who discovered it in 1903, plots the energy loss of ionizing radiation during its travel through matter (Figure 1). For protons, α-rays, and other ion rays, the peak occurs immediately before the particles come to rest. By adjusting the energy of the charged particles and the intensity of the beam, one can deliver specified doses anywhere in the body with high precision.

Charged particles damage cell DNA in qualitatively different ways than photons or electrons. Therefore the same amount of physical radiation can cause greater cellular damage. The relative biological effectiveness (RBE) is the ratio of the dose required to produce a specific biological effect. Photons are used as the reference radiation and the RBE is 1.1 meaning protons result in approximately 10% more biological damage per unit dose than photons.

Charged particle radiation therapy is expected to deliver biologically equivalent doses more precisely and with less damage to normal structures than conventional photon radiation therapy. It is believed that its ability to maximize the dose and target the tumor with high precision allows for better tumor control. Theoretically, this could be beneficial in children because they are considered more susceptible to radiation side effects including the development of secondary malignancies. It is unclear whether the claimed high precision in dose delivery is beneficial for all tumors in adults and several investigators have suggested that proton-beam radiation therapy may be indicated in approximately 15% of patients undergoing irradiation.

Charged-particle radiation therapy is an alternative mode of radiation therapy that is becoming increasingly available. Seven proton-beam facilities are in operation in the United States as of July 2009 and at least 4 are under construction. The theoretical advantage of this type of radiation therapy over traditional photon treatment has yet to be demonstrated in clinical trials but several are currently ongoing and the results should be available soon.

![Figure 1: Diagram of the energy deposit of electrons, photons and protons. Almost the entire energy of protons is liberated in a very narrow peak known as the Bragg peak.](image-url)
CME ANSWERS

1. Ionizing radiation uses either x-rays, gamma rays or electron beams produced by a linear accelerator whereas charged-particle-radiation can consist of protons, helium, carbon, neon, or silicon ions or other charged particles. Currently, only protons and carbon ions are in clinical use today.

2. Three dimensional (3-D) conformal radiation therapy is a technique where the beams of radiation used in treatment are shaped to match the tumor while minimizing damage to the healthy surrounding tissue. With IMRT, the radiation beam can be broken up into many “beamlets,” and the intensity of each beamlet can be adjusted individually thereby limiting collateral damage to nearby normal structures.

3. Charged particles represent an advancement over photons because they have a superior depth-dose distribution. Photons (or electron beams) deposit most of their energy near the surface with progressively smaller doses at larger depths and they continue to deposit the dose of radiation in normal tissues beyond the tumor. Charged particles deposit a low dose near the surface and deposit almost all of their energy in the final millimeters of their trajectory in the tumor. Tissues beyond the tumor receive very little of the dose.

REFERENCES

STEM CELLS, GENE THERAPY AND THE NEURO-OPHTHALMOLOGIST

“I find nothing more depressing than optimism”
—Paul Fussell

Jeffrey Bennett, MD, PhD
University of Colorado Denver
Aurora, CO

LEARNING OBJECTIVES

1. The attendee will be able to enumerate the challenges facing functional optic nerve restoration.
2. The attendee will be able to elaborate strategies for stem cell therapy for optic nerve disorders.
3. The attendee will be able to list potential gene therapy targets for maintenance of retinal ganglion cell survival and axonal outgrowth following optic neuropathy.

CME QUESTIONS

1. Therapeutic hurdles facing optic nerve restoration include all of the following except:
   a. Functional innervation of target tissue
   b. Modification of the tissue environment in the injured optic nerve
   c. Promoting retinal ganglion cells axon extension
   d. Accentuating astrocyte hypertrophy

2. A second messenger important in multiple steps of optic nerve regeneration is
   a. Calcium
   b. Phosphatidylinositol
   c. Cyclic AMP
   d. Tyrosine phosphorylation

3. Potential sources of adult stem cells include all of the following except:
   a. Dentate gyrus
   b. Retinal pigment epithelium
   c. Fibroblasts
   d. Bone marrow

KEYWORDS

1. Optic Neuropathy
2. Axon
3. Stem Cells
4. Gene Therapy
5. Retinal Ganglion Cells

Neural regeneration and repair has remained the “holy grail” of neuro-ophthalmic therapy. Recent advances in our understanding of neuronal development and survival, axonal guidance, disease pathogenesis, and medical technology are allowing us to view optic nerve restoration as something more than a therapeutic oxymoron.

Optic nerve injuries are a significant cause of visual morbidity. Using ocular coherence tomography (OCT), researchers have demonstrated that ischemic, inflammatory, toxic, and degenerative optic neuropathies result in significant retinal nerve fiber layer (RNFL) loss that correlates with loss of visual function.1-9 In individuals with optic neuritis or multiple sclerosis, significant RNFL loss may occur in the absence of diminished high contrast acuity2, 7 indicating that effective restorative therapy for optic nerve injury is important for acute and chronic optic nerve injuries independent of the final visual outcome. What is the status of current efforts to bring restorative therapy to patients with optic nerve injury? And what are the challenges facing future progress in the field? In this review, we will examine the knowledge, tools, and techniques that are currently available to restore function to the damaged optic nerve and examine the challenges that remain for future research.

OPTIC NERVE RESTORATION: A COMPLEX PROBLEM

Functional restoration or regeneration of optic nerve tissue following injury is a complex problem that requires the consideration of multiple interdependent factors. Any successful strategy necessitates the effective modulation of multiple pathways involved in diverse processes such as injury response, inflammation, cell death, neural development, and axonal pathfinding (Figure).10, 11
First, the injurious mechanism must be alleviated and interventions initiated to optimize retinal ganglion cell (RGC) survival. The timing and nature of these interventions may differ based on both the mode and location of injury to the RGC. Second, damaged tissue needs to be modified to maximize RGC regeneration, stem cell differentiation, and axonal growth. Third, surviving RGCs or transplanted stem cells need to be stimulated to extend axonal processes. And fourth, these processes require correct guidance towards appropriate targets in the lateral geniculate nucleus and superior colliculus. The complex orchestration of events needed for the restoration of optic nerve function following injury is the main reason why recent efforts have met with minimal success. For instance, to date, experimental interventions have been directed at a limited number of key hurdles such as RGC survival or tissue replacement.

RETNAL GANGLION CELL SURVIVAL
Optic neuropathies may result from direct or indirect RGC injury at the level of the cell body or axon. In trauma, RGC axons are injured directly by mechanical stress; while in neuromyelitis optica, RGC axons are injured indirectly due to the loss of trophic astrocytic support. In glaucoma, however, mechanical stress, vascular insufficiency, oxidative injury, and inflammation may combine to damage RGCs at both the level of the cell body and axon. Following injury, cell death may proceed through one of several distinct pathways: programmed cell death (apoptosis), necrosis, or secondary degeneration. Initial therapeutic strategies have focused on inhibiting apoptosis due to the major role of programmed cell death in determining RGC fate following optic nerve injury. Strategies have included direct modulation of apoptotic cell pathway signaling and delivery of trophic factors to injured RGCs. For example, overexpression of Bcl-2, an antiapoptotic protein, or delivery of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), neurotrophin 4/5 (NT-4/5), nerve growth factor (NGF), ciliary neurotrophic factor (CNTF) and glial-derived neurotrophic factor (GDNF) have shown partial success in reducing RGC loss following axotomy in animal models. Unfortunately, technical, strategic and physiologic hurdles need to be overcome before human clinical trials can be developed. Successful gene therapy will require novel strategies to control the distribution and timing of gene expression, as well as new technologies to deliver sufficient transgenes to specific target cells. Successful neurotrophic therapy will require concurrent treatment to enhance the ability of injured RGCs to respond to trophic support. Following injury, RGCs downregulate their neurotrophin (Trk) receptors, and exogenous administration of neurotrophic factors may result in additional receptor tachyphylaxis. These phenomena may be counteracted by recruiting Trk receptors to the cell surface through elevation of intracellular cyclic-AMP (cAMP) or axonal depolarization. A combined approach of neurotrophic factor administration, pharmacologic elevation of cAMP and transcorneal electrical stimulation may be required. To date, the administration of neurotrophic factors to human patients has been limited to small studies focused on retinal degenerative disorders.

CELL REPLACEMENT THERAPY
In conjunction with RGC preservation, successful regenerative therapy will likely require additional interventions to restore RGC numbers. Cellular replacement therapy using multipotent progenitor cells or stem cells has emerged as the primary method for achieving this goal. Multipotent progenitor cells can differentiate into many cell types, while stem cells are a self-renewing population that are pluripotent. These cells might promote functional recovery by reconstituting depleted RGCs, remyelinating axons, or facilitating axon regeneration. Successful cell replacement therapy requires the survival, integration and differentiation of transplanted cells. The differentiation of transplanted embryonic stem cells is particularly critical since undifferentiated embryonic stem cells are potentially teratogenic. To limit this potential, embryonic stem cells are typically pre-differentiated to a desired lineage before transplantation. Several groups have reported the appropriate differentiation of embryonic stem cells or differentiated progenitor cells following transplantation into injured rodent spinal cords. Transplantation of differentiated embryonic stem cells into the retina and axotomized optic tract has been shown to promote photoreceptor and RGC survival in rodent models; however, no engraftment of the differentiated stem cells was observed.

Adult stem cells may provide an additional source of material for cell transplantation. In contrast to embryonic stem cells, adult stem cells may be recovered from any

Figure. Functional optic nerve restoration: challenges and potential interventions.
individual and used for autologous transplantation. Sources may include retina, adult central nervous system, and skin. Intraocular-administered adult hippocampal stem cells were reported to engrat in the retinal ganglion cell layer following optic nerve axotomy or superior colliculus ablation. In rodent and non-human primate models of inflammatory central nervous system demyelination (experimental autoimmune encephalomyelitis), neural stem cells ameliorated disease and promoted neuronal survival through immunomodulatory effects.

Adult bone marrow contains several different stem cell populations: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). MSCs are multipotential stromal precursor cells that are common precursors of multiple mesenchymal tissues such as fat, bone, cartilage and connective tissues. MSCs have been subsequently reported in many tissues, including the vasculature. In addition, MSCs may have the ability to differentiate into other germ lineages such as neural cells, although the experimental results are not definitive. The potential mechanisms by which HSCs and MSCs act are still unclear, although the elaboration of factors that facilitate neuronal and glial survival, axon elongation, and immunoregulation has been proposed as the primary mechanism. In preclinical trials in multiple sclerosis, MSCs have demonstrated beneficial immunoregulatory properties with limited cell replacement. Nevertheless, MSCs may prove to be a powerful tool to limit RGC loss and promote axonal regeneration after optic neuritis.

MODIFYING THE INJURED OPTIC NERVE

In contrast to the permissive environment of the peripheral nervous system (PNS), the mature central nervous system (CNS) is not conducive to axonal regeneration. Following optic nerve injury, inhibitory glial proteins such as myelin-associated glycoprotein (MAG), Nogo-A, semaphorins, and oligodendrocyte myelin glycoprotein (Ompgp) are released at the site of injury and proliferating astrocytes secrete inhibitory extracellular matrix proteoglycans. In addition, activated glial cells may express axonal guidance proteins in a manner that suppresses regeneration. For instance, semaphorin-3A and netrin may inhibit RGC restoration by acting as repulsive cues to regenerating axons. MAG, Nogo-A and Ompgp inhibit axonal outgrowth through activation of the Nogo receptor (NgR). Experimental inhibition of MAG and Nogo signaling, however, has had variable success depending on the mode of inhibition. Chromophore-assisted laser inactivation of MAG in embryonic chick explants increased axonal regeneration following optic nerve crush injury; however, optic nerve regeneration following crush injury was not facilitated in MAG knockout mice. Similarly, axonal regeneration in animals with genetic deletion of either Nogo-A or NgR was inferior to antibody-mediated neutralization. One explanation may lie in the complexities of the MAG and Nogo-A signaling networks. For instance, MAG may signal through sialoglycans (gangliosides GD1a and GT1b) in addition to NgR. A second explanation is the presence of additional redundant inhibitory signaling pathways. For instance, inhibition of epidermal growth factor receptor and protein kinase C signaling have been shown to benefit axonal outgrowth after optic nerve and spinal cord injury. Since most of these signaling pathways converge on the small GTPase, Rho, therapeutic inhibition of Rho signaling is a focus of active investigation.

The bacterial toxin C3-ADP-ribosyltransferase and cAMP elevation have demonstrated some promise.

Tissue grafts offer an opportunity to bypass the inhibitory environment of the injured optic nerve. In seminal experiments, Aguayo et al demonstrated that a significant number of RGCs could regrow axons through peripheral nerve grafts to reinnervate targets following axotomy. Peripheral nerve tissue provides a permissive substrate for axonal growth due to the salutary nature of the local tissue environment and the trophic support of Schwann cells. Schwann cells may also act to change the injury response of astrocytes and inhibit the formation of glial scar. Potential alternative substrates to peripheral nerve tissue include perinatal optic nerve, genetically-engineered Schwann cells, fetal brain grafts, olfactory ensheathing cells, and Schwann cell impregnated matrices.

REPROGRAMMING THE ADULT RETINAL GANGLION CELL

A major impediment to the successful restoration of optic nerve tissue is the inability of adult RGCs to extend new axons. Embryonic retinal explants or purified embryonic RGCs extend axons more efficiently than their adult counterparts independent of the extrinsic environment. The inability of adult RGCs to extend new axons arises from an intrinsic developmental program. Gene therapy may offer one avenue for reprogramming adult RGCs to behave more like their embryonic counterparts. Recently, Moore et al identified two members of Krüppel-like family of transcription factors, KLF4 and KLF9, that decreased neurite outgrowth when overexpressed in postnatal RGCs. In addition, gene deletion of KLF4 from RGCs increased axonal regeneration following injury. Downregulation of KLF4 or KLF9 in injured in RGCs by siRNA inhibition may offer a novel approach for promoting axonal growth following optic neuropathy.

An alternative approach to enhancing the regenerative capacity of adult RGCs is to upregulate or downregulate the expression of developmental genes. Modulating the level of cAMP in injured RGCs may simultaneously upregulate neurotrophin receptors and reduce responsiveness to MAG/Nogo-A inhibition through upregulation of arginase I expression. Activation of MAP kinase signaling or mammalian target of rapamycin (mTOR) signaling may also promote axonal regeneration and RGC survival.
DIRECTING REGENERATING OPTIC NERVE AXONS TO APPROPRIATE TARGETS

Functional optic nerve restoration requires the reestablishment of appropriate axonal innervation of target neurons in the lateral geniculus and superior colliculus. Regenerating axons must exit the globe at the optic nerve head and be guided through the optic chiasm in a topographic pattern to their ipsilateral and contralateral targets. Molecules important for various steps in this process have been identified: netrin-1 at the optic nerve head,71 semaphorin-5A and Slit in the optic nerve,72,73 and ephrin-B2 at the optic chiasm,74 and ephrin-A ligands in the superior colliculus.75 In adult hamsters, regenerating axons extending through peripheral nerve grafts were noted to migrate to target tissue and form functional synapses. While the percentage of transiting axons were low and the axonal arbors limited, successful reinnervation suggests that appropriate cues are still available to direct axonal guidance should axonal regeneration succeed.

In conclusion, functional optic nerve restoration is no longer the subject of therapeutic fantasy. To succeed, significant yet not insurmountable hurdles must be overcome. Advancements in our understanding of neuro-ophthalmologic disease will contribute significantly to therapies aimed at limiting RGC loss. Technological progress in gene therapy and cell replacement technology will soon lead to human clinical trials with significant hope for functional improvement after optic neuropathy.

CME ANSWERS
1) d
2) c
3) b

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LASER-ASSISTED TRANSPLANTATION OF STEM CELLS INTO THE ADULT EYE

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KEY WORDS
1. Stem Cell
2. AION
3. Laser Photocoagulation
4. Retinal Ganglion Cells

INTRODUCTION
Regenerative approach to treat anterior ischemic optic neuropathy is of sound rationale and significant clinical demand because the central nervous system has limited repair and regenerative capacity and there are no effective neuron- or nerve-protective methods to treat this devastating condition. However, stem cell transplantation into the adult eye to reconstitute neurons and neural circuitry is difficult and often of low yield. In our study, we tested the potential benefit of retinal laser photocoagulation, a clinically proven form of controlled injury used to treat patients with diabetic retinopathy, on intravitreal stem cell transplantation into the adult eye.

METHODS
We performed unilateral retinal laser photocoagulation in 130 adult wildtype 129 mice followed by bilateral intravitreal injection of enhanced green fluorescent protein (GFP)-expressing neural progenitor cells derived from murine embryonic stem cells (ES-NPCs). Different laser parameters were tested to assess optimal conditions for transplantation. We analyzed the retina of lasered vs. unlased eyes following transplantation at 2-weeks, 1-month, and 2-months with immunohistochemistry and morphometric analysis.

RESULTS
Retinal lasering led to a dramatic increase in the number of GFP-positive ES-NPCs at all time points. Lasering of twelve 100-micron spots at 300 mW was sufficient and most efficacious compared to 3 spots or lower power. Two months following transplantation, many GFP-positive ES-NPCs survived and integrated predominantly into the inner retina, expressing neuronal marker beta-tubulin or glial marker glial fibrillary acidic protein. Many ES-NPCs formed dense clusters which extended beta-tubulin-positive processes that coalesce to form bundles that projected into the posterior pole.

CONCLUSION
Our data provided strong evidence that retinal laser photocoagulation facilitated the intravitreal transplantation of a large number of ES-NPCs into the adult mammalian inner retina. This form of controlled injury provided a permissive environment for stem cell differentiation into the neuronal pathway and formation of nerve-like structure within the inner retina.

FINANCIAL DISCLOSURE
Burroughs Wellcome Foundation
THE FIELD OF VISUAL PROSTHETIC DEVICES: CONCEPTUAL FOUNDATION, STATUS AND CONTROVERSY

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LEARNING OBJECTIVES
1. The attendee will be able to understand the conceptual foundation of the field of visual prosthetic devices.
2. The attendee will develop an appreciation for the level of vision that visual prosthetic devices currently provide to patients.
3. The attendee will develop an appreciation for the type of information that might be relevant for patients who inquire about whether they should consider having a visual prosthetic implant.

CME QUESTIONS
1. What types of blinding conditions are amenable to treatment with a visual prosthetic device?
2. Which type of visual prosthetic device (eg. retinal, optic nerve, cortical) is the most favourable for use in patients who are severely blind from retinitis pigmentosa?
3. What are the factors that would seem to limit the visual potential of retinal prosthetic devices?

KEYWORDS
1. Blindness
2. Visual Prosthesis
3. Retinal Prosthesis
4. Visual Rehabilitation
5. Retinal Reorganization

INTRODUCTION
The field of visual prosthetic devices has produced a remarkable array of sophisticated technologies over the last 20 years that offer hope for improving the quality-of-life for patients who are severely blind from retinitis pigmentosa. Five companies have already performed chronic implants in humans, and all five report fairly positive results. In the best case, a legally-blind patient (implanted and tested in Germany) was able to “read” only one week after receiving a sub-retinal implant. This and other very positive results are encouraging but also surprising, given the seemingly reasonable assumptions that the level of technology is not sufficiently mature and that retinal pathologies (following loss of the photoreceptors) would confound attempts to communicate effectively with the retina using artificial stimuli. This conundrum will be discussed, and a blueprint of information that might be provided to patients who inquire about the field of visual prosthetic devices will be presented.

Blindness is a major health problem and a common form of disability. In industrialized countries, the most common forms of blindness are the result of neural diseases, either of the retina or the optic nerve. Most retinal forms of blindness are caused by loss of photoreceptors, and these outer retinal diseases affect at least 800,000 United States citizens each year, roughly 10% of whom are legally blind. Most blindness caused by optic nerve disease is the result of glaucoma, which affects approximately 1% of the general population. There is no treatment to restore lost vision for any form of neural blindness.

CONCEPTUAL FOUNDATION FOR VISUAL PROSTHETIC DEVICES
A prosthesis is an artificial device that is designed to replace the function of a damaged or lost part of the body. In the context of a visual prosthetic device, a prosthesis could be utilized to stimulate the visual pathway distal to the location of the neural damage that caused the blindness. Visual prosthetics are being pursued to be implanted on the sub-retinal or epi-retinal surface (for outer retinal diseases); around the optic nerve (for outer or inner retinal disease); at the lateral geniculate body (for optic nerve or more proximal disease); and at the visual cortex (for blinding diseases proximal to the primary visual cortex). At present, there is no evidence to support the advantages of one type of approach over the other. The concept for a visual prosthetic device is exactly homologous to the use of cochlear prostheses, which have been remarkably successful in restoring hearing to patients. Over 150,000 cochlear prosthetic devices have been implanted worldwide.

The hope that a visual prosthesis can create sufficient vision to improve the quality-of-life for severely blind patients is based upon the generally predictable topographic order within and across each neuronal level within the afferent
visual pathway. Given this anatomical orderliness, it seems reasonable to assume that direct electrical stimulation of visual neurons might generate phosphenes at locations within the visual field similar to those that would have been obtained by photic stimulation. Similarly, electrical stimulation of the optic nerve could produce an orderly arrangement of phosphenes because of the generally faithful topographical organization of optic nerve axons to points within the visual field.

VARIOUS APPROACHES BEING EXPLORED FOR VISUAL PROSTHETIC DEVICES

The first type of visual prosthetic devices to be developed were cortical implants, the first effort for which began in the 1970s.1,2 The only active programs at this time are based at the Illinois Institute of Technology and in Spain (under the direction of Philip Troyk and Eduardo Fernandez, respectively). The first real opportunity to create devices that could be made small enough to fit into the eye occurred slightly more than 20 years ago with availability of customizable microfabrication methods. Two retinal prosthetic groups emerged at roughly the same time, our group at the Harvard Medical School and the Massachusetts Institute of Technology, and the other at Duke and North Carolina State Universities (the latter eventually became the nucleus of the Second Sight Company). The visual prosthetic field then enjoyed enormous growth and now includes 22 visual prosthetic research groups in seven countries.

Comparison of different types of visual prosthetic devices

Each of the locations being studied as a site for a visual prosthesis has certain advantages and disadvantages. For instance, with respect to a visual cortical prosthesis, the need for extensive neurosurgery to implant a device would seem to be an impediment, but modern techniques used for “functional electrical stimulation” of sites in the deep brain (as is done for Parkinson disease, for instance) make it possible to implant devices into the brain through relatively small incisions in awake patients. Implantation at the level of the optic nerve is best approached by placing a cuff-style electrode array around the intra-orbital segment of the optic nerve, but approaching the optic nerve within the orbit is complicated by the fact that at this location the optic nerve here is invested by all three meningeal sheaths; thus, the electrodes would lie outside of the dura mater which would increase stimulation thresholds and make it more difficult to create highly localized areas of stimulation. The dura mater and arachnoid are not present along the intracranial segment of the optic nerve, but implanting electrodes intracranially would require much more extensive surgery. The pursuit of a lateral geniculate body (LGB) prosthesis has the advantage that the LGB neurons are spatially and physiologically segregated, but it would be very challenging to implant a large number (i.e. hundreds) of electrodes this deep into the brain.

The ease of surgically approaching the eye, and the planar and distributed architecture of the neurons in the retina are some of the reasons that have driven the development of retinal prosthetic devices. All but four visual prosthetic research programs have chosen to build retinal (vs. other types of visual) prosthetic devices. Intraocular visual prosthetics are being designed for use in the epi-retinal, sub-retinal and supra-choroidal spaces, though only one group is investigating the latter. Slightly more groups are pursuing the epi- versus the sub-retinal approach. Implantation within the eye is complicated by the fact that the retina is exceptionally delicate (much more so that cerebral tissue), the eye is prone to persistent inflammation, and the three dimensional curvature of the retina presents a challenging substrate for implantation of the two dimensional devices that are being developed. Failure to implant the stimulating electrode array close to (within 10 microns) and conformal to the retina over a wide enough area (≥ 3mm) could raise the stimulation thresholds to an unacceptable level and possibly compromise the quality of induced percepts or the width of the visual field that is generated. Some of these considerations are also relevant for implants that are positioned elsewhere along the afferent visual pathway.

COLLECTIVE ACHIEVEMENTS OF HUMAN PSYCHOPHYSICAL TESTING WITH VISUAL PROSTHETIC DEVICES

The following is a brief summary of the results of human testing for each type of visual prosthetic device. At present, retinal prosthetic devices are the only type of device that is being implanted in humans.

Visual Cortical Prostheses

In 1967, Brindley implanted an electronically-primitive device into the visual cortex of a patient who was completely blind from glaucoma.1,3 These experiments and those that followed by Dobelle showed that multiple phosphenes could be perceived simultaneously following stimulation of multiple electrodes, and that there was a perceptual alignment of the phosphenes that roughly correlated with the spatial organization of the visual cortex.2,3 These experiments were conducted by delivering stimulation to the surface of the cortex, which required using relatively high charge levels because of the substantial distance between the electrode and neurons. Surface stimulation produced only coarse two-point discrimination of phosphenes. The limitation of these findings motivated the development of electrodes that could be implanted into the visual cortex. Subsequent engineering work, much of which has been performed at the University of Utah and the Illinois Institute of Technology, has greatly advanced this field, but presently no human trials are being conducted with these devices.
Retinal Prostheses
Five companies (two from the United States; three from Germany) have performed chronic implants of retinal prosthetic devices in humans. The first company to perform implants (Optobionics, Inc.) declared bankruptcy after it was understood that the device was not creating any visual benefit based upon electrical stimulation from the sub-retinal device. Rather, a “trophic effect” was offered as the basis for the visual improvement that was reported by their patients. The collective results of the other four groups has provided important “proof-of-concept” evidence in support of the potential value of a retinal prosthesis, including demonstration: 1) of acceptable stimulation thresholds; 2) that severely blind patients can reliably see phosphenes; 3) that modulation of electrical stimulation alters percepts; 4) that object orientation and movement can be detected; and 5) that vision of 20/1000 is possible, although this usually required head movement to scan letters and considerable time, sometimes many tens of seconds, to assimilate the optotypes. The most notable claim, which comes from Tubingen, is of a patient who could read one week after implantation, which would seem to defy both intuition and substantial scientific evidence. Collectively, these results are encouraging but fall short of the goal of providing a sufficiently better level of vision that is easily perceived to justify the risk of surgery and the cost of the device compared to whatever strategy a patient might already be using, like a white cane or computer-assistive technologies.

Optic Nerve Prosthesis
Veraart and Delbeke implanted a cuff with four electrodes around the optic nerve of two patients with retinitis pigmentosa. Using a camera-based system to capture visual images, their patients were able to judge the shape, size, basic structure, brightness, location and brightness of objects. With regard to pattern recognition experiments of basic forms, these researchers reported an 87% success rate, but with a relatively long time delay of 53 seconds for patients to discern and report on the perception of objects. With training, the subjects learned to scan more effectively and to more quickly discriminate objects on a table (e.g. cup, eating utensil). The patients could use this information to reach out and grasp the objects. Stronger electrical pulses made the phosphenes appear brighter and more central. One patient reported being able to perceive a letter “C”.

CONUNDRUM
Retinal prosthetic devices reportedly have enabled severely blind patients to navigate better, recognize letters, and even to read. Despite the quite different technologies used, each of the four groups that have performed more advanced psychophysical testing (i.e. beyond simple determination of stimulation thresholds) has reported success. Every one of these successful outcomes has occurred in a patient with end-stage retinitis pigmentosa.

These outcomes would seem to exceed the level of success that might have been predicted with this population of end-stage patients and with the level of technology that has been available. The following factors each present would seem to argue against some of these successful outcomes:

1. The presumption that a larger number of electrodes, each of which can be controlled independently, would be needed to create spatially detailed vision; (the largest number of individually-controlled channels currently available is 64);

2. Patients with end-stage retinitis pigmentosa would not have sufficient survival of retinal neurons to enable spatially-detailed vision;

3. The compelling evidence from Robert Marc that has shown widespread and profound “retnal reorganization” of the inner retina following loss of photoreceptors;

4. The mismatch between the very positive and relatively early outcomes with retinal prosthetic devices and seemingly reasonable factors that would argue against such successes creates a conundrum. How can such successes have occurred so quickly with devices that seem to have inadequate technology for the task? How can such successes have occurred if the neural substrate is so depleted and disorganized?

A framework for considering these puzzling factors will be presented.

WHAT PERSPECTIVE TO SHARE WITH INTERESTED PATIENTS?
The discussion between physician and patient on the topic of visual prosthetic devices is challenging because of the complexity of the field and because of the vulnerability of many severely blind patients who long for a cure. At the least, it would be entirely proper to relate that visual prostheses: a) are a legitimate approach for vision rehabilitation in selected instances of acquired, neural blindness; b) the field has produced a remarkable array of very sophisticated devices; c) that the implant devices from each group seem to have been well-tolerated by the eye; d) that the majority of severely blind patients reported at least crude percepts of vision (even without any real training); and e) that in the best cases, unexpectedly good vision, including the ability to read, has been reported. Personally, I present these successes together with the perspective that there is considerable scientific information that would seem to suggest that such good vision would not have been possible, not without further advances both in technology and a better understanding of to deliver electrical stimulation to the nerve tissue. I explain to my patients that it is difficult to resolve these conflicting types of evidence, but that the positive outcomes have been reported by each group that is studying the use of these devices, which provides some reassurance. I also indicate
that the field is still relatively early in development, and that it is likely that a much more clear understanding of what can be achieved will be realized in the next 5-10 years. Even higher quality vision may be realized as the devices are upgraded. I also discuss other potential types of research that might restore vision to the blind, including stem cell therapy. I also emphasize the importance of vision rehabilitation to maximize a patient’s potential for vision for whatever level of vision they might have.

CME ANSWERS

1. A visual prosthesis could potentially offer a strategy to restore vision to patients with acquired forms of neural blindness that affected the afferent visual pathway anywhere from the photoreceptors to the optic radiations. Theoretically, a visual prosthesis could be used at higher visual cortical levels, but presently the field is exploring strategies that depend upon having a (nominally) intact primary visual cortex.

2. No particular embodiment of visual prosthesis has shown consistently more promise or problems than other devices. At present, only retinal prosthetic devices are being implanted in humans, and both the epi- and sub-retinal implants have shown significantly positive results. The sub-retinal device from Retina Implant AG (based in Tubingen) has been reported to allow a blind patient to read without the need for head scanning and with a shorter time to acquire the image compared to the most positive reports of an epi-retinal device, though there is no ability to scientifically compare these different approaches.

3. The potential for retinal prosthetic devices to restore vision would seem to be limited by at least two factors: 1) pathologies that develop in retinas following loss of photoreceptors (i.e. “retinal reorganization”); and 2) by the state of engineering development that has yet to produce devices with a large enough number (hundreds, perhaps) of individually-controllable stimulation sites using electrodes that can be positioned close to (within 10 microns, or so) neurons without inducing mechanical or electrical damage to the neurons.

REFERENCES

LEARNING OBJECTIVES

1. The attendee will be able to describe the current status of the Utah Artificial Vision Project.

2. The attendee will be able to list anatomic constraints and advantages of cortical implantation for vision restoration.

3. The attendee will be able to describe the psychophysical issues of cortical implants.

CME QUESTIONS

1. How many electrodes are in the Utah Electrode Array?

2. What is the apparent cause of long term cortical electrode implant recording and stimulation degradation?

3. What is the apparent cause of long term cortical electrode implant recording and stimulation degradation?

KEYWORDS

1. Artificial Vision

2. Utah Electrode Array

3. Occipital Cortex

4. Cortical Implants

5. Phosphenes

INTRODUCTION

The Utah Artificial Vision Project (UAVP) is a multidisciplinary effort to explore and implement the use of direct occipital lobe stimulation to provide useful visual information to blind humans. The project has involved participants from many departments of the University of Utah. These include bioengineering, neuro-radiology, neurosurgery, and ophthalmology. Richard Normann PhD is the director of the project, and Bradley Greger PhD is the director of primate studies. Some human subjects have also been participants in these efforts, both in the laboratory and in the surgical suite.

In 1968, Brindley (1) showed that electrical stimulation of the visual cortex resulted in perception of a point of light known as a phosphenes. In 2000, Dobelle (2) (who was a graduate student at the University of Utah in the 1970s) announced implantation of surface cortical stimulating systems in humans, initially performed in the US and later in Portugal. The stimulating electrodes were hooked up to a digital video camera, computer and associated electronics. The patients received cortical stimulation through the device. One patient, Jens Naumann, was widely reported in dramatic news stories and videos (3). The stimulating electrodes were on the surface of the cortex, requiring moderately intense stimulation to elicit a phosphenes – 1-10 milliamps. Unfortunately, the system induced seizures and later lost its efficacy and had to be removed. With Dr. Dobelle’s death in 2004, little information is now known about the subjects, their percepts, or the long-term outcomes. In the same year (2000), a single subject at the NIH had intracortical stimulating electrodes implanted for a short time (4). He died after a subarachnoid hemorrhage from an unrelated intracranial aneurism. NIH briefly considered continuing the project with outside assistance but eventually decided not to proceed.

The Utah Artificial Vision Project (UAVP) is a multidisciplinary effort to explore and implement the use of direct occipital lobe stimulation to provide useful visual information to blind humans. The project has involved participants from many departments of the University of Utah. These include bioengineering, neuro-radiology, neurosurgery, and ophthalmology. Richard Normann PhD is the director of the project, and Bradley Greger PhD is the director of primate studies. Some human subjects have also been participants in these efforts, both in the laboratory and in the surgical suite.

The strategy of the UAVP is to translate real-time video into patterned stimuli and directly stimulate the visual cortex with penetrating electrodes (5,6). This strategy takes advantage of the occipital cortex foveal magnification and its retinotopic organization. The device developed has been named the Utah Electrode Array (UEA). The Utah Electrode Array is built from silicon and is a cluster of 100 microelectrodes. The stimulating tip has a sputtered iridium oxide film. This array is designed to be implanted into the surface of the occipital cortex, to provide direct stimulation to the underlying cortical neurons in patterns directed by the real time video apparatus. Each electrode communicates with 2 to 3 neurons. The electrodes are powered and controlled remotely. Dr. Normann estimates 6 UEAs could restore useful visual sense to those with profound blindness. The advantage of the strategy of
occipital stimulation, as opposed to retinal or optic nerve stimulation, is that it can be used even in patients with severe injury to the anterior visual system. Therefore, it could be used in patients after enucleation or with severe retinal or optic nerve damage. Normann’s group believe that the UEA will be more successful than the Dobelle system because of substantially lower stimulation requirements (1-10 microamps instead of milliamps) due to penetration of the electrodes.

Other laboratories around the country and around the world are studying the concept of artificial vision. One, also using the occipital cortex, is the laboratory of Dr. Philip Troyk at the Illinois Institute of Technology. This group includes many members of the short lived NIH human experiment. The device studied at IIT has penetrating electrodes similar to the UEA, but it is smaller and has fewer electrodes. His most recent direction of research appears to be a wireless electrode array (7). Other labs are working on stimulating the retina, optic nerve and lateral geniculate nucleus.

PSYCHOPHYSICS
A great deal of time has been devoted to the question of what input to the visual cortex is necessary to provide useful vision. Psychophysical experiments on graduate students in the 1990s used volunteers who attempted to navigate a maze and read using Artificial Vision goggles simulating pixelized vision. Most researchers have agreed that 600 to 700 pixels of information are needed to navigate and even to read. In addition, the goggles do not take into account the phenomenon of cortically stimulated phosphenes, which move with movement of the eyes (8,9,10).

ANATOMIC CONSTRAINTS
The surgical approach to this endeavour must be borne in mind. As we are all aware, based on years of study by great anatomists, including our own Horton and Hoyt, the occipital cortices occupy the mesial surface of the posterior lobes of the brain. This region, encompassing the primary visual cortex, is challenging to access surgically. Therefore, most attention has been paid to the portion of V1 on the more surgically friendly outer surface. Fortuitously, numerous studies have confirmed the macroscopic pattern of cortical representation of the retina, with the macular regions located at the occipital tips. Those same studies have confirmed tremendous variability in the amount of total V1 exposure. Dobelle and colleagues (11) conducted a study of the location of the line of Gennari in 1974, with 52 cadaver hemispheres fixed in formaldehyde, and found a four fold variation from 359 to 1208 mm², with 1/3 on the mesial surface, and 3% exposed on the occipital pole. These authors found the average exposure on the occipital pole was 68 mm² with a range 0-260 mm² (Stensaas et al 1974). More recently, studies using high-resolution 3T MRI in-vivo have shown that we can identify the line of Gennari to map V1 (12,13,14) with reasonable accuracy in vivo in just over half of individuals.

The anatomic benefit of the occipital pole is the magnification of the retinotopic map, from a small, densely packed area of the retina, to the largest area of the occipital cortex. Thus, theoretically, Dr. Normann believes that UEA stimulation of the neurons of the occipital pole could provide high-resolution vision with a relatively low-resolution electrode array, our most sought-after goal in vision restoration.

One of our former residents, Paul Yang, is working on the issue of cortical changes that might be induced after prolonged blindness. He is addressing the question of identifying and assessing the occipital cortex in patients with recent versus long-term blindness.

LONG TERM IMPLANTS AND ELECTRODE SURVIVAL
In the early 2000’s Dr. Normann collaborated with our neurosurgical department (15,16) to perform histological studies of cortical tissue subjected briefly to the implantation of the UEA. Patients scheduled to undergo corticectomy for intractable epilepsy agreed to have the device implanted into tissue that was then removed and examined. The implantation procedure was adjusted to minimize cortical deformity and microhemorrhages. The devices were able to record single neurons from these human subjects.

The devices have been implanted in cats and in a single non-human primate. The electrodes function to record as well as to stimulate. In the cats, single neuron recordings have been made from up to 75 of the microelectrodes of the UEA for as long as 8 months. On histological examination of tissue, there is fibrosis surrounding the electrode sites, which does not correlate with signal degradation. There is also some inflammation, which correlates better with degradation of signal (Normann, personal communication).

Primates with approximately 1 year of training can indicate whether or not they perceive a photic stimulus on a monitor. They gaze at a central fixation target. A second visual stimulus of a random location, brightness, and size appears. After a tone is sounded, the monkey lifts one hand if it saw something and lifts the other hand if it saw nothing. When the occipital cortex is stimulated with an implanted UEA, the monkeys indicate that they perceive phosphenes. However, there are concerns that only the minority of the microelectrodes evoke a response. This may be because the monkeys are too discriminating in what they deem worthy of “calling” a percept. They may not respond to stimuli that evoke a percept that is too large, an untested colour or shape, etc. It may also be that the implant is too distant from the majority of neurons, having migrated away from the cortical surface (Normann, personal communication).
CONCLUSION
As we speak, permission is being sought from the FDA to implant these devices in human volunteers for 30 days. There are many questions to be answered before and after human implantation occurs. As in animals, long-term electrode stability and phosphene thresholds will have to be determined. Critically, can complex spatial percepts be created from phosphenes? How will neighbouring electrodes be perceived when stimulated individually or separately? What adaptation can occur over time, both in “making sense” of new percepts, and to the motion of the percepts induced by eye movement? New electrode arrays that stimulate different layers of the cortex are also being studies.

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CME ANSWERS
1. 100
2. Phosphene
3. Reactive Inflammation

REFERENCES
3. Kotler S. Vision Quest. A half century of artificial-sight research has succeeded, and now this blind man can see. Wired, 2002[ Archive online 10.09].