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Authors

Luu, Kieu-Yen
Zhao, Min
Mannis, Mark J

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PERSPECTIVE

The Use of Electrotherapeutics in Ophthalmology

KIEU-YEN LUU, MIN ZHAO, AND MARK J. MANNIS

• PURPOSE: **To present a perspective on the use of electrotherapeutics in the history of ophthalmology along with the development of novel contemporary ophthalmic instrumentation.**

• DESIGN: **Perspective study.**

• METHODS: **We reviewed historical journals, articles, and books discussing the use of electricity and electrotherapeutics in ophthalmology.**

• RESULTS: **Electrotherapeutic applications have been researched and used to treat ocular diseases as far back as the 18th century. By the 20th century, research in electrotherapeutics in ophthalmology had caught the eye of Edward Jackson, the first president of the American Academy of Ophthalmology and Otolaryngology and first editor of the present (third) series *American Journal of Ophthalmology*. Edward Jackson published an extensive review on this topic and reported a variety of modalities used to treat ocular diseases.**

• CONCLUSIONS: **While many early therapeutic uses of electricity did not produce effective and replicable results, studies on electrical stimulation of the eye provided the foundation for the development of clinically significant vision enhancing and restoring instrumentation. (Am J Ophthalmol 2019;■:■–■.**

THERE HAS BEEN A FASCINATION WITH THE USE OF electricity in medical practice for centuries. From the use of electric fish for treating headaches and gout to the use of artificial electrical devices for the treatment of muscle spasms and tremors,[1–5] electricity as a form of treatment has continued to play a role in modern medicine. Edward Jackson, founder of the present (third) series of the *American Journal of Ophthalmology* and first president of the American Academy of Ophthalmology and Otolaryngology, chronicled the use of galvanic and faradic currents commonly used to treat ocular diseases in the early 20th century. He argued the efficacy of using electrotherapeutics to treat ophthalmic diseases including, among others, the use of electrolysis and the electromagnet, both of which are still used in contemporary ophthalmology.[6] The earliest uses of electricity in ophthalmology date to the 18th century, with a proliferation of electrical applications in the late 19th and early 20th centuries.[7] Nonetheless, while electrotherapy was at the forefront of medicine in the early 20th century, its use fell out of practice with the development of alternative techniques.

In the last 50 years, there has been a resurgence in the popularity of electrotherapeutic applications, many of which were foreseen by ophthalmologists cited in Jackson's paper in the early 20th century. Electric stimulation of the cornea, lens, choroid, and retina have proved efficacious for the development of devices such as iontophoresis, transcorneal electrical stimulation (TES), the Argus II epiretinal implant (Second Sight Retinal Products, Lausanne, Switzerland), and the Alpha AMS subretinal implant (Retina Implant AG, Reutlingen, Germany).[8–11] This perspective looks at the various electrotherapeutics recognized by Edward Jackson and discusses the electrical devices that are being used or developed in contemporary practice.

EDWARD JACKSON

IN 1902, ELECTROTHERAPY PIQUED THE INTEREST OF Edward Jackson (Figure 1). He initiated the implementation of educational courses during the American Academy of Ophthalmology and Otolaryngology meetings in 1917 and emphasized the need for further education in areas such as ocular pathology, anatomy, and optics, and he promoted continuing education for practicing ophthalmologists.[12] In 1902, Jackson wrote a paper on the uses of electricity in diseases of the eye in which he discussed a variety of ocular diseases, such as optic atrophy, retinal detachment, trachoma, and trichiasis, among many others that were amenable to treatment with electrotherapy.[6] He acknowledged the benefits of electrotherapy in treating

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From the Department of Ophthalmology and Vision Science (K-Y.L., M.Z., M.J.M.) and the Department of Dermatology (M.Z.), University of California, Davis, Sacramento, California, USA.

Inquiries to Mark J. Mannis, Department of Ophthalmology and Vision Science, University of California, Davis, 4860 Y St, Sacramento, CA 95817; e-mail: mjmannis@ucdavis.edu

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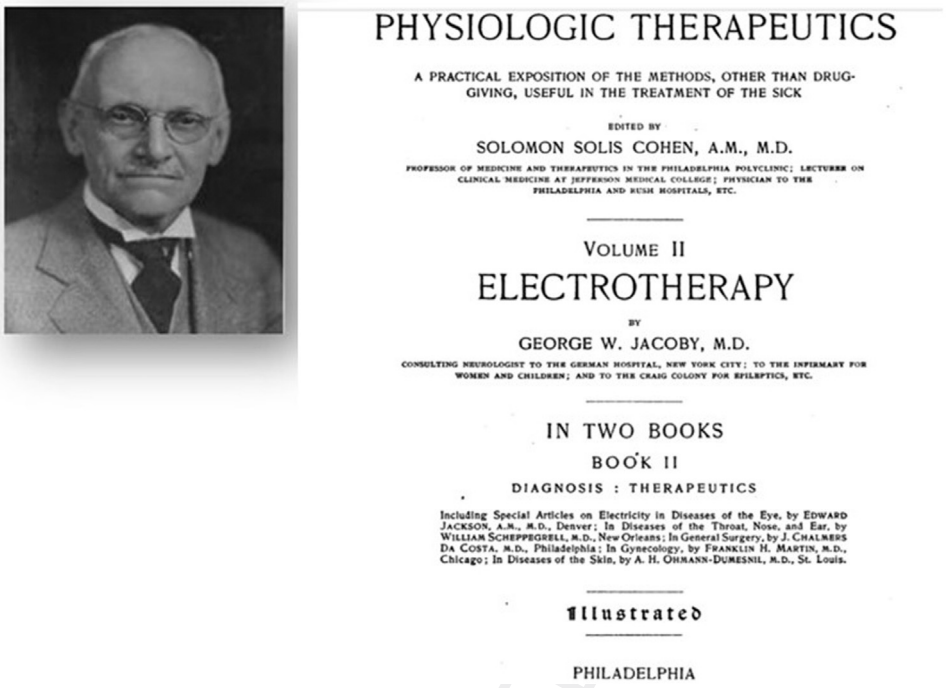

FIGURE 1. (A) Edward Jackson and (B) his article on "Electricity in the Diseases of the Eye."

certain diseases of the eye, despite having some reservations on many other applications.

Jackson recognized the potential in the emergence of these novel electrotherapeutic applications in ophthalmology by highlighting several applications that had reproducible success. The article additionally discussed several applications that have been tried with minimal success with the purpose of identifying the need for further experimentation and improvement in the growing field of electrotherapy in ophthalmology. Throughout the 19th and 20th centuries, other physicians, such as Elliot Colburn and Henri Dor, experimented with and published on electrical modalities for the treatment of ocular diseases.

ELECTROTHERAPY IN MEDICINE

• **USES OF THE ELECTRIC FISH:** Scribonius Largus (1st century AD), a Roman physician to emperor Claudius, is often credited as the first to use electrotherapeutics in medicine, when he described the use of a torpedo fish to treat headache and gout.[1] He lists this remedy in a report that Anteros, a freedman of Tiberius, had been successfully treated for this disease and writes, "For any type of gout, a live black torpedo should, when the pain begins, be placed under the feet. The patient must stand on a moist shore washed by the sea, and he should stay like this until this whole foot and leg up to the knee is numb. This takes away present pain and prevents pain from coming on if it has not already arisen."[1] Thirty years after Largus, the famed Greek pharmacologist and physician Dioscorides (40–90 AD) described the use of the torpedo fish to treat a prolapsed anus—a practice that continued until the end of the 17th century.[1] Then, in the mid-16th century, the invention of the Leyden jar sparked similarities between the shock it delivered and the electrical discharge from the electric fish.

• **DEVELOPMENT OF ELECTROTHERAPY:** By the 18th century, there were 3 main forms of electricity being used in medicine: Franklinism, Galvanism, and Faradization. Franklinism, or static electricity, is the use of friction to create an electrical charge, and this charge can be stored into a capacitor, such as the Leyden jar. A Leyden jar stores a high-voltage electric charge between electrical conductors on the inside and outside of a glass jar, and its use in medicine was popularized because of its mobility. It was used to treat various diseases, such as sciatic nerve pain, heart flutters, tremors of the limb, and aphonia.[5,13]

In 1791, "Galvanism" was discovered and introduced by Luigi Galvani, an Italian physician and physicist, who worked on electrical stimuli in animal models (Figure 2). Galvanism refers to the use of chemical decomposition to create an electrical current to stimulate muscle contractions. Galvanism is characterized by

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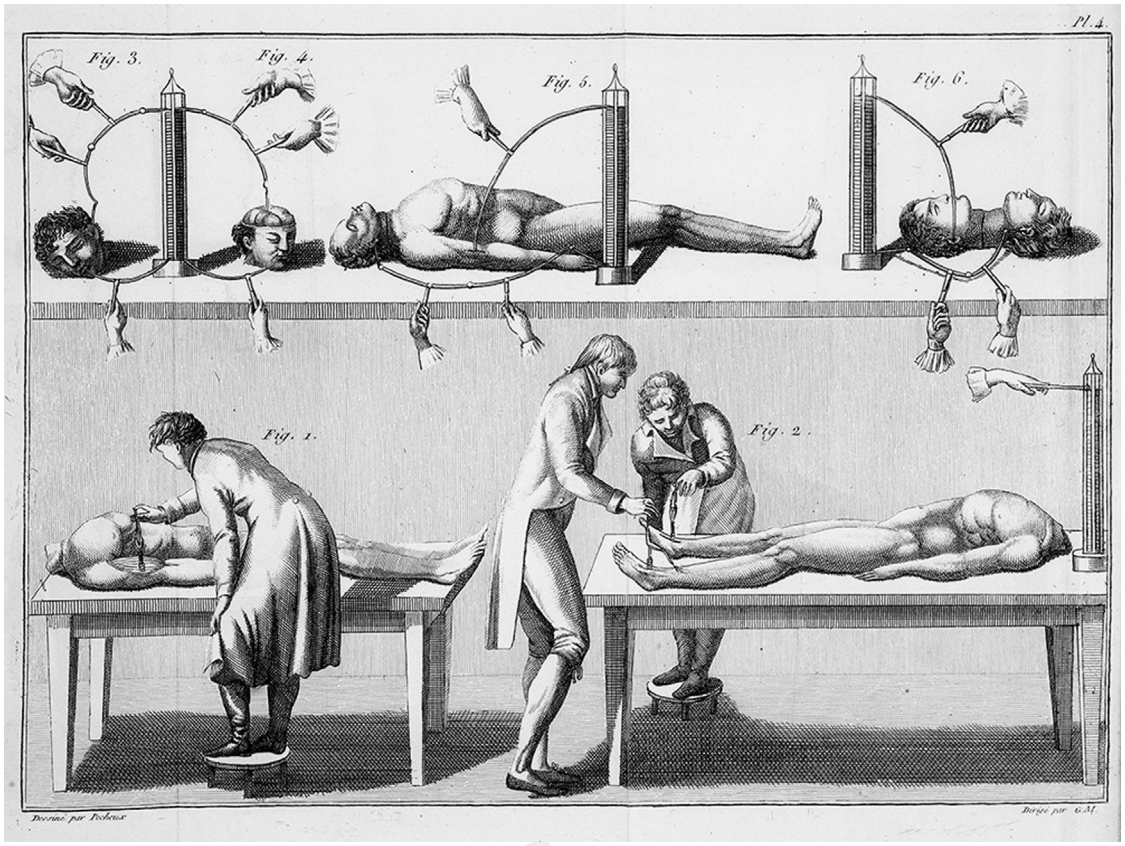

FIGURE 2. A drawing of Emil Du-Bois Reymond using a galvanometer to measure skin currents and potentials from a wound. The galvanometer used to detect the signal rests on a separate table by his right arm, the one he appears to be tensing. (Courtesy of Dr. Gabriel Finkelstein).

low intensity but high quantity electrical currents that produce both chemical and thermic sensations, and its uses included the treatment of muscle spasms and coagulation. However, Galvani's theory of animal electricity was met with skepticism and criticism and was discredited by Alexandro Volta, who had reservations about the idea that there was an inherent electricity found in animals. Animal electricity would not be widely accepted until Galvani's contemporaries, including Giovanni Aldini, Benjamin Franklin, and Emil du Bois-Reymond, proved his hypothesis true.[13] In 1843, Emil du Bois-Reymond pricked his finger and used a galvanometer to measure the skin currents and potentials at the wound site, thus establishing that there were biological electrical forces in living tissue (Figure 3).[14,15]

In 1831, Michael Faraday, a pioneering British scientist, discovered "faradization," which is a high intensity induced alternating current that is localized to stimulate muscle and nerve contractions. The induced current is made momentarily by the making or breaking of a galvanic current or a battery and therefore produces no chemical or thermic sensations as opposed to galvanism. Faradization was used in medicine to treat patients with nerve sensory deficits and various nerve palsies.[13]

EARLY USES OF ELECTRICITY IN OPHTHALMOLOGY

• **CATARACT:** The application of electricity in ophthalmology paralleled the emergence of electrotherapy in general medicine. In the early 18th century, Benjamin Franklin reported that patients who were struck by lightning developed rapidly progressing cataracts, which ultimately resulted in blindness.[7] Despite this report, electric and magnetic therapy was practiced in London for the treatment of patients with cataract in 1779.[7] In 1887, Elliot Colburn, professor of ophthalmology and otology in the Chicago Policlinic, published a paper on the use of galvanic currents to treat patients with age-related cortical cataract. He suggested that patients without choroidal and retinal comorbidities and without systemic complications, such as diabetes, nephropathy, and cirrhosis, should expect to have visual improvement after receiving galvanic treatment.[16]

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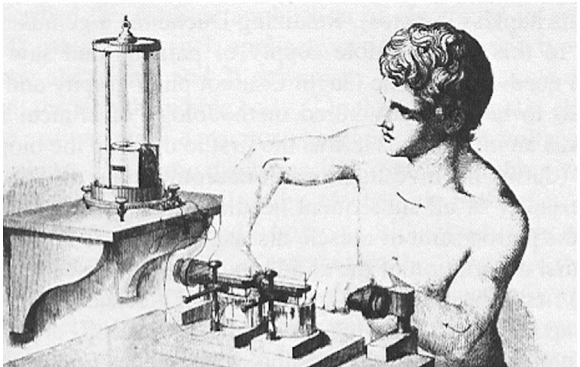

FIGURE 3. A sketch displaying the use of galvanism to induce muscle contractions.

Despite early reports, electric and magnetic therapies were not shown to be widely efficacious for the treatment of cataract. A paper cowritten by Edward Jackson in 1894 discussed the treatment of cataract using electricity and suggests that while there is no evidence to show that electrical current affect the growth of lenticular opacities, the use of "iodids of soda and potash, sedatives, e.g. bromid of potash, and tonics; …diminish the congestion of the choroid coat…[and] relieve the associated asthenopia and permit the patient reasonable use of his eyes."[17]

Edward Jackson mentions a variety of electrotherapeutics in use to treat ocular diseases in his article, including galvanization, galvanocautery, and faradization.

Galvanization. Mild galvanic currents were being used to treat patients with retinitis pigmentosa, inflammation, corneal opacities, and asthenopia. H. Derby and Myles Standish reported 4 cases of retinitis pigmentosa with central and peripheral visual improvement after treatment with mild galvanic currents lasting for 5 minutes every 2 to 8 days for several months. Improvement in corneal opacities after interstitial keratitis and extensive corneal ulceration were also noted, and Beard and Rockwell recommended using mild labile faradization and stable galvanization to treat asthenopia.

For the treatment of optic atrophy for which electricity has been most widely tried, Jackson remarked that the general verdict of ophthalmologists is that, "Electricity has failed to vindicate its pretensions to any real value, although, by its capacity for exciting phosphenes, it fosters of the hopes of a credulous incurable." The idea of activating phosphenes has been used in contemporary ophthalmology for the treatment of diseases such as retinitis pigmentosa from transcorneal electrical stimulation and the development of visual implants.

Galvanocautery. Galvanocautery is the use of galvanic current to heat an instrument (such as a knife or needle). Galvanocautery was preferable for treating suppuration of the cornea and nonhealing chronic corneal ulcers. In addition, embedded powder grains in the cornea, conjunctiva, or lids were preferentially removed with galvanocautery. Jackson also cited a study in which 5 patients with retinal detachments underwent treatment with galvanocautery with improved visual outcomes lasting 1 to 3 years in 4 of 5 patients.

Faradization. Faradization was used to treat patients suffering from asthenopia—idiopathic pain in the eye and orbit. Ocular muscle paralysis was frequently treated with galvanic currents, but if failed, mild faradic currents were tried.

• **ELECTROLYSIS:** Electrolysis, the process of using high electrical currents for cauterization with a fine needle, was used to treat patients with trachoma and bacterial infections of the eye, trichiasis, small-to medium-sized angiomata of the lids or orbit, and lacrimal obstruction. Benjamin Eliasoph from the Pathology Institute of Freiburg University in 1922 published his works on using electrolysis with a fine needle in the anterior chamber to successfully ablate iris cysts.[18]

• **ELECTROMAGNETS:** The electromagnet was first designed by Nicolaus Meyer of Minden (Germany) in 1842, and it was designed to remove intraocular metal foreign body objects from the globe.[19] Many versions of the electromagnet were created, such as the Johnson portal magnet, Hirschberg's electromagnet, and the Haab magnet. The uses of electrolysis and the electromagnet were developed in the early 20th century and are 2 common treatments still used in contemporary ophthalmology.

• **HENRI DOR:** In 1873, Henri Dor was one of the first physicians to perform experiments using electrical stimulation for the treatment of eye diseases, including retinochoroiditis, glaucoma, amblyopia and optic atrophy. His works on electrical stimulation provided inspiration for the development of TES.[9,10]

• **IONTOPHORESIS:** In 1908, Robert Wirtz was the first to use iontophoresis to treat ocular diseases. Iontophoresis is the use of electrical current to drive ionically charged medications into the body. Wirtz developed a "cataphoresis electrode" that increased the surface area of the device on the eye promoting increased penetrance of therapeutic agents to the internal parts of the eye (Figure 4). The device handles were made of celluloid, and the current

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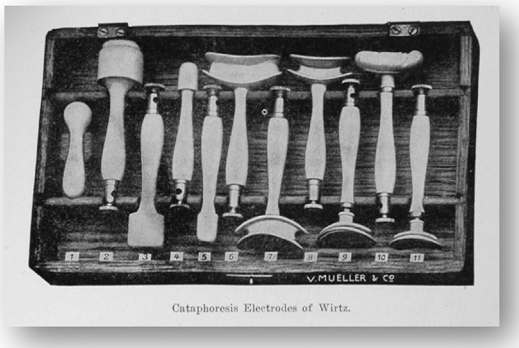

FIGURE 4. Cataphoresis instruments developed by Robert Wirtz for treating corneal diseases using iontophoresis.

entered one end of the device while the opposite end was covered with the dissolved medication. Wirtz was successful in treating a serpiginous corneal ulcer with 0.5% zinc sulphate and interstitial keratitis with 1% sodium iodide solution.[20,21] In 1922, Benjamin Eliasoph and Ludwig Aschoff used a specially designed contact lens with a collared reservoir for medication to control the delivery of medication into the eye using iontophoresis.[18] However, despite the use of iontophoresis in contemporary practice, it has not become a standard procedure.

CONTEMPORARY OPHTHALMOLOGY

DESPITE THE RISE OF ELECTROTHERAPEUTICS IN OPHTHALmology in the late 19th and early 20th centuries, there was a significant decline in its use as a therapeutic modality except for a few successful applications, such as electrocautery and the electromagnet for foreign body removal. It was only in the late 20th and early 21st centuries that new therapeutic modalities emerged. In contemporary ophthalmology, electrotherapy can be divided into 4 categories: standard employment, nonconventional therapy, cutting edge technology, and therapeutics in development.

• **CURRENT STANDARD EMPLOYMENT:** *Electrocautery*. Electrocautery is the use of electrical current to generate heat at a metal tip to the tissue. Electrocautery is used primarily to treat hemostasis after surgery, to induce scarification for the treatment of painful bullous keratopathy, and for punctal occlusion in the management of dry eye.[22–24] Studies have shown that electrocautery is efficacious in treating patients with painful bullous keratopathy and poor visual potential. The electrocautery is used to scarify Bowman's layer to prevent fluid from reaching the surface of the cornea. This substantially reduces the level of discomfort in patients with advanced disease, but does not improve visual outcomes.[23,25] Electrocautery is a safe treatment option for reducing pain and discomfort at the cornea.

Electrolysis. Electrolysis in contemporary ophthalmology uses direct current flow in a unidirectional pattern and produces a strong polarity at each electrode. The use of direct current for electrolysis allows for the dissolution of tissues caused by the hydroxides, and this results in destruction of the hair root. Electrolysis is commonly used as a treatment modality for segmental and minor trichiasis where current is applied at the base of the eyelashes.[24] Removing multiple eyelashes may result in lid scarring and secondary deformities and has a high recurrence rate (60%).[26]

Electromagnet. Electromagnets have been used to treat patients with intraocular foreign bodies. This technique is widely used around the world but is associated with a 23% risk of vitreous hemorrhage and 10% risk of developing endophthalmitis.[19]

Iontophoresis. In contemporary ophthalmology, there are 2 types of iontophoresis: transcorneal and transscleral.[21] Despite its widespread use during the early 20th century, iontophoresis was never adopted as a standard procedure in ophthalmology because of a lack of controlled clinical trials and the presence of serious complications, such as epithelial edema, inflammatory infiltration, and burns. However, recent contemporary advancements have allowed for the development and optimization of ocular iontophoresis for fast and safe delivery of high drug concentrations in anterior and posterior segments of the eye. With newer technological advancements, iontophoresis has the potential for becoming standard practice in the field.[27]

• **NONCONVENTIONAL THERAPY:** *Biofeedback*. Biofeedback therapy for the treatment of eye pain has been developed and used by Malcolm Ing, Clinical Professor and Chair of the Ophthalmology Division at the University of Hawaii, John A. Burns School of Medicine. The Self-Controlled Energy Neuro-Adaptive Regulator (SCENAR) was a medical device first developed in Russia in the 1970s, and Ing was successful in treating a patient with shingles with SCENAR for her ocular pain from postherpetic neuralgia. Ing then introduced SCENAR to his patients informally for 2 years with reports that pain relief was dramatic in some patients. In 2002, the U.S. Food and Drug Administration approved SCENAR for use in the United States as a class II biofeedback device.[28] Further studies will be required to develop treatment guidelines, parameters, and to determine long-term effects with the use of SCENAR.

TES. TES is designed as a bipolar contact lens or a microfiber Dawson, Trick, Litzkow electrode that is placed on

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the cornea of patients after local anesthesia.[29] The electric current pulses are generated and delivered through a stimulus isolation unit with another inactive electrode placed on the skin around the eye acting as a reference electrode. TES directly activates inner retinal neurons, such as retinal ganglion cells (RGCs and bipolar cells), which bypasses photoreceptors in the outer retina. It has also been used to evaluate the residual function of the inner retinal layer to preoperatively screen suitable candidates for implantation of retinal prostheses because of its noninvasive approach.[30] TES is thought to enhance the expression levels of endogenous neurotrophic factors and increase the intrinsic neuronal sensitivity to these factors. It downregulates the expression of Bax, tumor necrosis factor, and glutamate release in degenerative retinas, which ultimately prevents apoptosis.

Two studies in 2006 and 2007 suggested that patients with anterior ischemic optic neuropathy and retinal artery occlusion had improved visual outcomes after treatment with TES.[31,32] Various clinical trials theorize that the protective effects of TES include vasodilation, neurotrophic activation, antiapoptosis, antiglutamate, and anti-inflammatory mechanisms.

The retina in retinitis pigmentosa (RP) is characterized by restriction of the retinal blood circulation caused by thinning of the vascular plexus and obliteration of vessels, and 1 study showed that TES induced phosphenes and increased vasodilatory effects that protected RP retinas.[10,29,33] Despite evidence supporting the neuroprotective effects of TES, additional studies determining the optimal parameters and the long-term stability of TES are necessary before establishing TES as a standard treatment modality against retinal and optic neuropathy.[29]

• CUTTING EDGE TECHNOLOGY: VISUAL PROSTHETICS: Studies from Kreig, Shaw, Button, and Putnam in the mid-1900s discussed the possible development of a visual prosthesis. However, the possibility of developing such a device did not become widely accepted until human experiments by Brindley and Lewis were published.[34,35] Today there are several prosthetic devices that have been demonstrated to restore visual function in patients that are partially or completely blind because of retinal degenerative diseases, such as RP and age-related macular degeneration. These devices were developed to target potential sites for implementation of the visual prosthetic, such as the subretinal space, epiretinal surface, optic nerve, lateral geniculate body, and visual cortex.[35] The visual percepts provided by visual prosthetics devices, however, do not resemble normal vision because they are devoid of color, depth, and detail. Nevertheless, the devices allow for functional improvements in object detection and mobility task completion.[36]

Subretinal and epiretinal prosthetics are the most commonly implanted and currently only 3 devices—the Alpha AMS, Argus II, and IRIS II—have been commercially approved.[37] Optic nerve, lateral geniculate body, and visual cortex devices are still under development.[38]

While the potential for vision restoration with the development and advancements of visual prosthetics are promising, additional trials are necessary for the development of a stable, long-term, and useful prosthetic. Most affected individuals suffer from progressive diseases, such as RP and age-related macular degeneration, and the long-term viability of retinal prosthetics remains uncertain in the face of continuous remodeling of the photoreceptor network over time. In addition, the best visual acuity estimates for implant subjects have not approached the threshold for legal blindness as defined in most countries.

• SUBRETINAL PROSTHETICS: Subretinal prosthetics are implants that contain light-sensitive components (photodiode) and an electrode to simulate that of a photoreceptor synapse relaying electrical signals to the inner retina.[39] Connecting the implant to the inner retina helps stimulate bipolar cells with local electric currents, and the positioning in the subretinal space is thought to allow for retinotopically correct perception in the visual field in comparison with epiretinal prosthetics. The implanted chip moves with the eye, which helps stabilize the image. In addition, the subretinal space is immunoprivileged and less prone to rejection.[40]

The retinal implant Alpha, devised by Eberhart Zrenner in Germany, has been in development for >20 years. It is the only light-sensitive subretinal implant that has received commercial approval in Europe. A clinical trial at Oxford testing the Alpha IMS (first-generation) showed that 4 of 6 patients with RP reporting improved function for daily living with no adverse events after surgery.[39] The second-generation Alpha implant, Alpha AMS, is marketed to have improved longevity with 1600 pixels and received commercial approval (CE mark) in March 2016.[39,40] A recent study by Thomas Edwards at the University of Oxford showed that the Alpha AMS improved visual performance of 5 of 6 patients with end-stage RP for ≤24 months.[41]

In 2004, Chow and associates (Optobionics Inc.) developed an artificial silicon retina (ASR) microchip, a 2-mm–diameter silicon-based chip that contains 5000 microelectrode-tipped microphotodiodes. Chow and associates implanted it into the right eyes of 6 patients with RP. The tresults showed that visual function improved in all patients with no rejection, infection, or inflammation. Additional results showed improved visual function in retinal areas distant from the implant (Figure 5).[42] The ASR implants had good safety and longevity profiles; however, it has been concluded that a device relying on the ambient light without external electrical sources was unable to stimulate a large number of neurons. Optobionics has since closed and there has been no further published results.[37]

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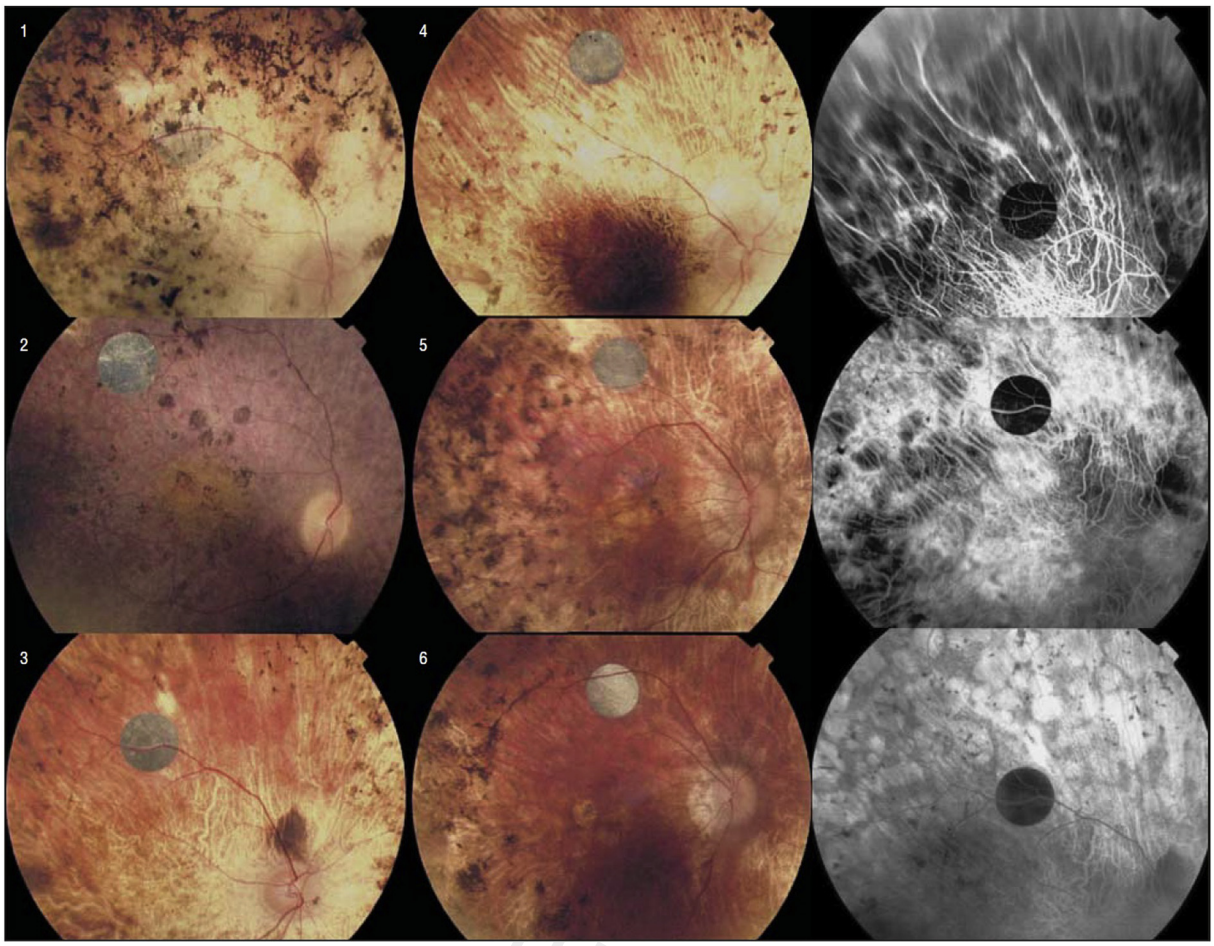

FIGURE 5. The artificial silicon retina subretinal microchip developed by Optobionics Inc. (Courtesy of and with permission for publication by Dr. Alan Chow, Optobionics Inc.)

Other subretinal implants have been developed by The Boston Retinal Implant Project, Pixium Vision, Yagi and Watanabe (Biohybrid Retinal Implant), Tano, Ikuno, and Ohta (Japan Retinal Implant Group), Li and Ren (C-sight: Chinese Project for Sight), Palanker (Biomedical Physics and Ophthalmic Technology), and Pelizzone (Eye Clinic, University Hospital of Geneva).[35]

• **EPIRETINAL PROSTHETICS:** Epiretinal Prosthetics use a multielectrode array placed on the inner surface of the retina in direct contact with the nerve fiber layer.[8] Epiretinal prosthetics are advantageous because of their easier surgical implantation compared with subretinal implantation. The location of the device is thought to facilitate heat dispersion, but functionally may be disadvantageous to have stimulation directly applied to the RGCs, which may limit the ability to mimic the physiologic retinal topographic organization. Both epiretinal and subretinal implants are produced to stimulate electrically phosphenes, basic visual phenomena received without the perception of light.[40]

The Argus II epiretinal prosthesis was developed by Second Sight and is the first retinal implant to receive commercial approval in 2011 in Europe and U.S. Food and Drug Administration approval in 2013. It was the first device tested in humans to pass safety and efficacy assessments, and it is currently the most widely used prosthesis worldwide.[40] The epiretinal implant is attached to an external glass-mounted video camera. The signals from the external camera are acquired and are transformed into electrical pulses from a visual processing unit. These impulses are sent to the retinal ganglion cells and inner retina to elicit phosphenes through video processing.[8,35,40,43] The Argus II phase II multicenter trial demonstrated the maintenance of visual acuity over 5 years of follow-up with a best-corrected visual acuity of 1.8 logMAR (20/1262 Snellen equivalent) and the 10-year study was completed in 2019. A Functional Q2 Low-Vision Observer Rating Assessment has been refined and developed to assess functional vision and well-being following Argus II implantation.[37]

• **SUPRACHOROIDAL IMPLANT:** In 2014, Bionic Vision developed a suprachoroidal prototype implant that generated phosphene activation in all subjects tested with no serious device-related adverse events. The suprachoroidal

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implant is advantageous in that the insertion of the electrode is minimally invasive in comparison to epiretinal and subretinal implants. The prototype is implanted behind the ear and because of the increased distance between the RGCs and the suprachoroidal implant location, higher electrical currents are needed to be delivered to stimulate phosphenes.[38] A phase I human clinical trial with 3 volunteers with light perception visual acuity because of outer retinal degenerative diseases (2 with rod–cone dystrophy and 1 with syndromic RP) showed significantly better visual acuity using Landolt C optotypes (Lieby P, et al. IOVS 2013; 54:ARVO E-Abstract 1049).

• **OPTIC NERVE IMPLANT:** The AV-DONE device (Direct Optic Nerve Japan) and Microsystems-Based Visual Prosthesis for Optic Nerve (MiViP) in Belgium had been tested and developed as an optic nerve prosthesis. The dense packing of RGC axons in the optic nerve may limit the degree of spatial detail of the induced images that could be achieved and has proved restrictive in the development of such prosthetic devices.

• **LATERAL GENICULATE BODY AND VISUAL CORTEX IMPLANTS:** Whereas retinal implants would not be a viable treatment for glaucoma, lateral geniculate body and visual cortex implantation have been suggested as a treatment option.[35] The visual cortex provides a larger surface area relative to the retina, and the larger surface area allows for implantation of multiple stimulation electrodes that can provide higher-resolution artificial vision. The cortical implants, however, would require a more challenging surgical procedure, with exposure of the dura mater, and possibly the need to stimulate deep into the calcarine fissure where the foveal projections are buried.[38]

A surface cortical electrode array, Orion, developed by Second Sight, has been developed. The first implementation of the Orion prosthetic was performed in January 2018 at the University of California, Los Angeles. The cortical implant aims to restore vision to patients who are completely blind from glaucoma, diabetic retinopathy, cancer, or trauma.[11] Clinical trials for the device began in Germany in 2018. Efficacy, safety, and side effect profiles must be determined before commercial approval.

• **CUTTING EDGE TECHNOLOGY–BRAINPORT:** Visual prosthetic devices are limited to those with functional optic nerves and retinal ganglion cells. For those who do not have visual potential, sensory substitution devices are designed to bypass primary visual pathways and provide visual information through nonvisual, afferent pathways.[36,44]

The BrainPort is an electrotactile sensory substitution device that consists of a wide-angle sensor mounted in the center of a pair of sunglasses that sends live video to a handheld processor. The processer will sample the video and transform the images as an electrotactile sensation to a tethered, removable resin lollipop called the intraoral device. The sensation stimulates a square array of 400 electrodes embedded in the intraoral device for the tongue to perceive as visual information. The BrainPort has now received both commercial and U.S. Food and Drug Administration approval.[36,45]

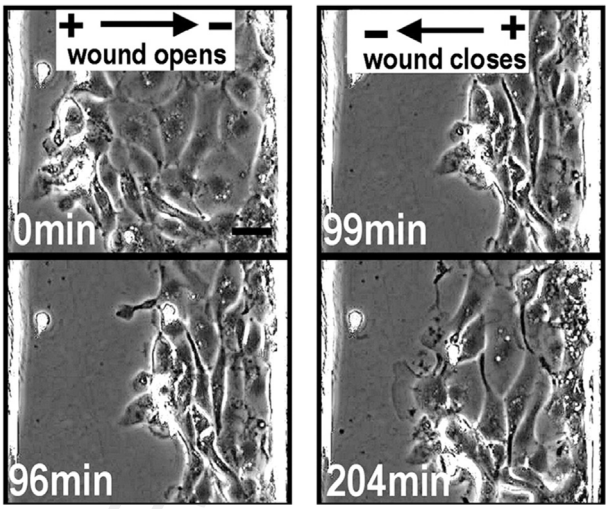

FIGURE 6. The healing of a corneal wound by an induced electrical current. Electrical fields can both open (left) and close (right) a wound. An electric field of physiological strength is applied with the polarity pointing away from the wound center at 0 minutes and at 96 minutes, the cells move away from the wound, thus opening the wound. The field polarity is then reversed at 99 minutes and the cells now migrate into the wound resulting in wound closure at 204 minutes.

A prospective, within-subjects repeated measures study evaluated the performance of real-world functional tasks using the BrainPort in persons blinded by trauma. Results demonstrated significant improvements in task performance after 1 year of independent use. All participants were able to identify objects, 41% were able to identify words, 71% could avoid obstacles, and 71% could walk through a doorway without collision. These results show that the BrainPort can support the integration of profoundly blind individuals into independent community life.[44]

• **CONTEMPORARY INVESTIGATION: ENDOGENOUS ELECTRIC FIELDS IN THE EYE DURING WOUND HEALING:** Naturally occurring electric fields are found at the cornea, lens, and retina.[15] In fact, the eye is one of the organs with the most abundant naturally occurring electrical activities in the human body, from the surface of cornea all the way to the visual cortex.

The cornea maintains an electric potential difference (PD) between the epithelial, stromal, and endothelial layers of the cornea.[46] The transport of ions in the 3 compartments (tear film, cornea, and aqueous humor) generate the PDs and electrical fields (EFs). When injuries break the epithelial barrier, laterally orientated electric fields are

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established pointing toward the wound center (positive potential to negative potential).[47] The PD is maintained in areas with intact epithelium and the difference between wounded and intact areas is termed "wound EF." The endogenous wound EFs provide a powerful signal to induce directional migration (galvanotaxis or electrotaxis) for wound healing.[15,48]

Using corneal wounds as a model, it was found that applied electrical fields of physiological strength would override other directional cues produced by the wound and therefore manipulate directional cell migration in wound healing (Figure 6). Genetic and pharmacological studies demonstrated that phosphatidylinositol-3-OH kinase-γ and tumor suppressor phosphatase and tensin homolog were the 2 proteins responsible for electrically induced directional epithelial migration in corneal wound healing. Manipulating the transepithelial ion transport using pharmaceutical intervention indeed regulates wound healing of rat cornea. Solutions of silver nitrate increase the efflux of chloride ions and influx of sodium ions in the corneal epithelium, which amplified the transcorneal potential difference and endogenous wound electric field, resulting in faster corneal wound healing. Furosemide was noted to have the opposite effect, which decreased the transcorneal epithelial difference (Figure 7).[48] This discovery suggests the potential of bioelectric stimulation without the use of electrodes.[15,50]

The crystalline lens has a remarkable electric "circulation" with currents flowing out from the equator and entering the anterior and posterior poles.[51] Restoring circulation of the currents appears to be involved in lens regeneration.[52] The retina exhibits active electrical activity, which can be recorded at the front of the eye and serves as an indicator of retinal function and pathology.[15] This activity is the basis for contemporary electrophysiologic testing in clinical practice. The manipulation of EFs at the cornea, lens, and RPE may be the potential for therapeutic target for relevant ocular diseases.

In conclusion, electrotherapy in the field of medicine has been practiced for centuries. The world's fascination with electricity is justified considering the vital role of electrical impulses in biological life. Edward Jackson explored the efficacy of electricity as a therapeutic modality in ophthalmology—albeit in the context of many bogus applications in the early 20th century.

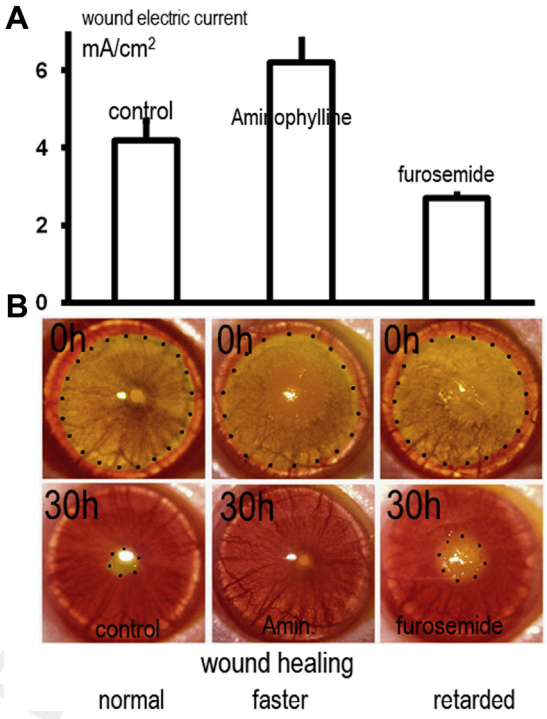

FIGURE 7. The use of pharmaceutical manipulation and the effects on corneal wound healing. (A) Pharmacologic manipulation of corneal epithelial transportation of Na^+ and Cl^- significantly enhances (aminophylline) or decreases (furosemide) endogenous wound electric currents. (B) The healing of circular lesions in the cornea is shown over time. Circular keratectomy was performed on corneas at 0 hours. Lesions were labeled yellow with fluorescein and are shown here outlined with dots. Aminophylline was used to increase the wound current, which subsequently showed significantly increased wound healing; furosemide that was used to decrease the wound current significantly decreased wound healing. Modified from Reid and associates.[49] Q8

The development of visual prosthetics and electrotactile devices provides novel advancements for improving visual function in degenerative ocular diseases. In addition, pharmaceutical manipulation of electrical fields suggests great potential for improved healing of ocular diseases. This renewed interest in understanding electrobiology gives promise for new applications in many areas of ophthalmology.

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