EDITORIAL

Fifty Years of Ophthalmic Laser Therapy

LASER IS A CATCHY SCIENTIFIC ACRONYM THAT we associate intuitively with precision and sophistication, novelty and ingenuity, power and adaptability. Since its invention more than 50 years ago, it has revolutionized and enabled a long list of technologies, from telecommunication to imaging, from lithography of integrated circuits (the brains behind electronic devices) to rapid DNA sequencing, from missile defense to printing. The first medical application of the laser, which occurred less than a year after its invention, was retinal photocoagulation; since then, its effect on ophthalmology is hard to overestimate. Now, lasers are used in all ophthalmic subspecialties; they are critical for many diagnostic and therapeutic devices.

This article reviews the history of ophthalmic therapeutic lasers, from the original concepts to technological breakthroughs that have helped to shape modern ophthalmology. We highlight the story of the initial discovery of the technology and the translation of lasers to ophthalmology, with some personal insights from people who were there. However, we make no attempt to cover all aspects of current laser therapy or the many researchers who have worked in the field.

EARLY HISTORY

The damaging effects of strong light on vision were known in Plato's time, as he describes Socrates' admonition to avoid direct viewing of a solar eclipse.[1] A medieval description of central vision loss from gazing at the sun was provided by Theophilus Bonetus (1620-1689).[2] The concept of ocular therapy using light first was harnessed and publicized by Meyer-Schwickerath, who took patients to the roof of his laboratory in 1949 and focused sunlight on their retinas to treat melanomas. In his groundbreaking book,[2] he notes that the first experiments on retinal damage from sunlight were performed by Czerny in 1867 and others in the late 1800s. In 1927, Maggiore demonstrated light damage in a human eye scheduled for enucleation. In the 1940s, Móran-Salas was doing extensive experiments on rabbits and humans with the aim of therapeutic coagulation. However, he was not satisfied with the effects and did not publish his results until after Meyer-Schwickerath (who had been unaware of this work) had reported his own findings. As with many aspects of science, discovery requires recognition to be successful; Meyer-Schwickerath demonstrated that photic burns could be beneficial therapeutically. But the technique was hardly practical for wide use, and therapy was limited because it required sunny weather. Thus, nonsolar sources were sought. Carbon arcs were used with some success; by the mid-1950s, the xenon arc photocoagulator had been developed and was made commercially available by Zeiss. This instrument was effective for sealing retinal breaks and treating tumors but it was hard to control, and the burns it caused were large and severe.

Development of the laser provided a tool for more precise and effective delivery of photic energy. The theoretical foundation of the laser is based on the concept of stimulated emission of radiation, as predicted by Albert Einstein in 1917.[3] This effect allows for the multiplication of photons having the same wavelength and propagating in the same direction at the same phase. In 1953, the group led by Townes at Bell Laboratories[4] and the Russian team of Basov and Prokhorov[5] nearly simultaneously developed the MASER (microwave amplification by stimulated emission of radiation), in which microwave emission could be greatly amplified and well collimated, and for which they received a Nobel Prize in Physics. Five years later, Schawlow predicted the possibility of a similar effect with visible light and proposed using ruby as a laser medium.[6] In 1960, Maiman and colleagues from Hughes Aircraft Laboratories produced the first functioning LASER (light amplification by stimulated emission of radiation).[7]

Laser typically involves a gain medium inside a highly reflective optical cavity and a means to excite electrons into higher-energy quantum states. Material of the gain medium has special properties that allow it to achieve a "population inversion" when the number of atoms in the excited state exceeds the number of atoms in some lower-energy state, which is necessary for amplification of the radiation by stimulated emission. In its simplest form, a cavity consists of 2 mirrors arranged such that light bounces back and forth, each time passing through the gain medium. One of the 2 mirrors, the output coupler, is partially transparent, allowing the output beam to exit through it (**Figure 1**).

Laser radiation has several features distinct from thermal and other noncoherent sources of light: its photons are emitted at the same phase (coherence), its wavelength range is narrow (monochromatic), and its beam is well collimated (directional). The potential of this new technology was immediately obvious in many fields in which focused and powerful light beams could produce damage or repair; the recognition of its potential application to the eye was almost immediate.

The first study regarding the creation of ocular lesions with a ruby laser, in the iris and retina of rabbits, was reported by Zaret et al in 1961.[8] Whereas with the xenon arc, light was applied continuously until damage

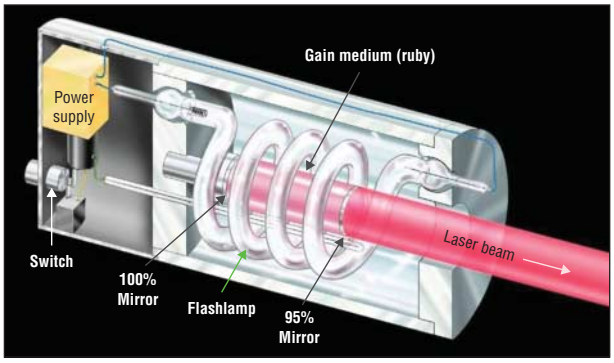

Figure 1. Design of the first ruby laser showing its essential components: gain medium (ruby crystal), 2-mirror optical cavity, flashlamp with a power supply, and output beam. Adapted with permission from LaserFest, American Physical Society.

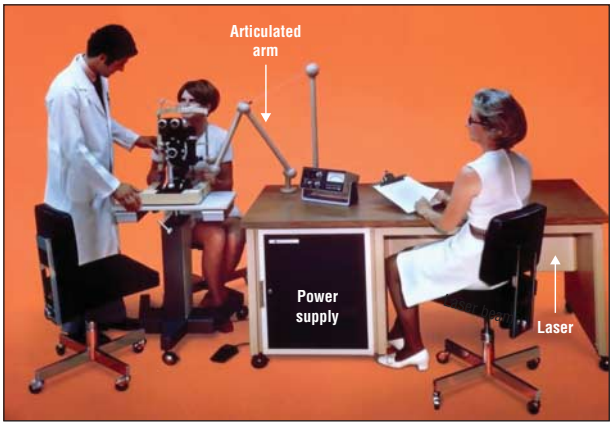

Figure 2. Thomas Brunner from Coherent, Inc, introducing the first commercial slitlamp-coupled argon laser photocoagulator (model 800) at the American Academy of Ophthalmology and Otolaryngology meeting in Las Vegas, NV, on April 24, 1970. It was developed in collaboration with scientists and ophthalmologists at the institutions then known as the Stanford Research Institute and the Palo Alto Medical Clinic.

became visible, laser energy could be delivered in calibrated bursts and adjusted in small increments to achieve a desired level of injury.[9] Lasers intrigued several retina specialists who recognized the potential for clinical applications and the need for improved delivery and better control of the light-tissue interactions: H. Zweng in Palo Alto, California, and Charles Campbell and Francis L'Esperance Jr in New York, New York. Kapany and colleagues described the nature of retinal lesions in rabbits and cats,[10] and Noyori and colleagues studied the thermal effects of laser applications to rabbit retina.[11] Within a year, studies were appearing from these laboratories on retinal applications of the ruby laser.[12-14]

Although the results of ruby laser application were impressive, they were also troubling. The retinal burns were intense and could produce chorioretinal adhesion or destruction of pigmented lesions. The deep red wavelength (694 nm) was poorly absorbed by blood, such that vascular lesions could not be treated effectively. It was hard to produce vascular damage or closure without hemorrhage or intense scarring. The experience of investigators with iris photocoagulation was similar.

Discovery of the argon laser in 1964 by Bridges[15] provided a new tool with emission in the blue (488-nm) and green (514-nm) range of the spectrum, which had the advantage of being strongly absorbed by hemoglobin and melanin. Studies on the retinal application of the argon laser were soon under way in groups headed by Zweng in Palo Alto and L'Esperance in New York,[16] and the latter reported the results of a large clinical series[17] in 1969 with several delivery systems, including biomicroscopy. The results showed the effectiveness of argon lasers for closing blood vessels and vascular lesions. Further progress was achieved by Little and colleagues[18] when the laser was coupled with a slitlamp with a 7-mirror articulated arm, providing an aimed beam and precise control of the spot size, location, power, and exposure duration. This delivery system enabled effective photocoagulation in a wider spectrum of retinal diseases, including small vascular lesions and a variety of maculopathies; in various iterations, it remained the basis for modern clinical photocoagulation for the next 35 years. Coherent, Inc, began to market the argon laser photocoagulator in 1970 (**Figure 2**), and by 1971, a series of clinical articles from Gass, Patz, Pomerantzeff, Schepens, and others[19-21] published by the American Academy of Ophthalmology and Otolaryngology signaled the dissemination and acceptance of the new technology. The era of wide use of retinal photocoagulation in clinical practice had begun.

MODERN RETINAL APPLICATIONS

It became clear early on that, at least for the treatment of neovascularization in diabetic retinopathy, treating the retinal pigment epithelium (RPE) and retina was safer and more effective than direct coagulation of the new vessels themselves.[22] The initial techniques of focal and panretinal photocoagulation and a later approach for treating macular edema (termed *grid photocoagulation*) were shown to be effective therapies for proliferative diabetic retinopathy and advanced forms of nonproliferative diabetic retinopathy associated with macular edema in large prospective multicenter randomized trials: the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study.[23,24] These trials validated the efficacy and institutionalized the indications and variables for treatment that have remained the criterion standard since that time. Although the initial validation of laser therapy occurred mostly with rather cumbersome water-cooled argon lasers, these have been replaced mostly with much smaller air-cooled Nd:YAG lasers that also can produce green (532-nm) light through use of the second harmonic.

Laser photocoagulation was proposed for the treatment of macular degeneration and other macular diseases in the late 1960s[25] and early 1970s[19,20,26] at a variety of leading American ophthalmology centers. Direct thermal photocoagulation for choroidal neovascularization remained controversial because of collateral damage to the macula and frequent recurrences until the results of a large prospective randomized trial were released nearly a decade later[27]; those results clearly indicated that treated patients fared better in the short term than did the control group, particularly when the lesions did not involve the center of the capillary-free zone. Although the results for eyes with lesions beneath the foveal center were mostly disappointing, laser photocoagulation re-

mained the mainstay for another 20 years until the introduction of photodynamic therapy.

Although controversy still exists regarding whether prophylactic treatment of retinal holes is of long-term benefit in the prevention of retinal detachment,[28] it is widely accepted that treatment of symptomatic horseshoe tears is warranted. Photocoagulation of tears was first proposed in 1960 using the xenon arc.[29] Introduction of the argon laser and the slitlamp delivery system[18,30] made it easier to visualize the retinal periphery and to place smaller and more precise burns around retinal tears.[31] The development of a binocular laser indirect ophthalmoscope[32] further contributed to the popularity of lasers as the preferred method for prophylaxis of retinal detachment in high-risk patients. Although cryotherapy continues to be used more commonly for the creation of a chorioretinal adhesion in patients undergoing retinal reattachment surgical procedures, particularly scleral buckling, the use of laser endoprobe[33] became the method of choice for sealing retinal breaks in patients undergoing primary vitrectomy or vitrectomy and scleral buckling for retinal detachment.

When lasers are used to treat the retina rather than vessels, the light is absorbed by melanin in the RPE and in the pigmented choroid. The energy is converted into heat, which diffuses into the retina and choroid. Laser power in photocoagulation typically is titrated to a visible clinical effect (graying or whitening of the retina), which corresponds to damage to the photoreceptors and, at higher settings, to the inner retina. In panretinal photocoagulation, pulses of 100 to 200 milliseconds have been commonly used, and more than a thousand lesions are typically applied, coagulating as much as 30% of the peripheral retina. Although clinically effective, panretinal photocoagulation frequently leads to unwanted secondary effects, including scotomata, reduced night vision, and disruption of the retinal anatomy through scarring.

One approach toward retinal phototherapy that avoids permanent damage is selective treatment of the RPE (selective retina therapy [SRT]). This concept, pioneered by Reginald Birngruber and his group initially at Wellman Laboratories in Boston in 1986 and then in Luebeck, Germany, involves the application of microsecond laser pulses that confine damage to the RPE layer, sparing photoreceptors and the inner retina.[34,35] The dominant mechanism of cellular damage at such short durations is explosive vaporization of melanosomes accompanied by formation of cavitation bubbles.[36] Subsequent RPE proliferation and migration restores the continuity of the RPE layer. Several small clinical studies have shown the efficacy of SRT in diabetic maculopathy, central serous chorioretinopathy,[37,38] and subfoveal fluid after rhegmatogenous retinal detachment.[39,40] Despite its clinical promise, this technique has not yet been commercialized, to our knowledge.

Another approach to nondamaging retinal treatment is transpupillary thermotherapy (TTT), which involves long exposures (typically 60 seconds) of a large spot (1.2-3.0 mm) at low irradiance (approximately 10 W/cm^2) using a near-infrared (810-nm) laser.[41] A few pilot studies[41,42] have shown that TTT decreases or slows the progression of exudation and choroidal neovascularization in age-related macular degeneration. However, the clinical use of TTT for retinal vascular disease has been abandoned owing to lack of efficacy and reports of occasional retinal damage.[43] Today, TTT still is used occasionally for the treatment of thin choroidal melanoma, although its long-term follow-up has shown an increased rate of local recurrence and extrascleral extension.[44,45]

In addition to the long exposures of large spots used in TTT, shorter bursts of near-infrared radiation (810 nm) with small spot sizes (100-200 μm) also have been applied for nondamaging retinal phototherapy. Using bursts of "micropulses," laser energy was applied with no visible lesions and no fluorescein leakage, as observed acutely and in subsequent clinical examinations. Beneficial effects of the treatment on macular edema have been recorded in clinical examinations and by retinal thickness measurements using optical coherence tomography.[46-48]

An idea to treat wet age-related macular degeneration by selectively targeting vascular endothelial cells using specific photosensitizer-carrier complex activated by near-infrared laser initially was adapted from the tumor therapy[49] by the groups led by R. Birngruber, MD, and T. Hasan, MD, at Wellman Laboratories, Massachusetts General Hospital, in 1990 using phthalocyanine, as described by Schmidt et al.[50] Later, this work was continued by Kliman et al[51] at the New England Eye Center and by Miller et al[52] at Massachusetts Eye and Ear Infirmary. Independently, in 1993, Miller and Miller[53] from the Technion–Israel Institute of Technology, Haifa, demonstrated closure of subretinal neovascularization using photodynamic therapy with rose bengal. After successful initial results with phthalocyanine,[50] Quadra Logic Technologies, Inc, became involved and developed the liposomal benzoporphyrin derivative complex that selectively attaches to the endothelium of new blood vessels.[52,54] This molecule later was commercialized as verteporfin (trade name, Visudyne) and became the first standard pharmacologic treatment for age-related macular degeneration.[55-57]

A new method of panretinal photocoagulation recently has been introduced by Blumenkranz et al at Stanford University and at OptiMedica Corporation in which patterns of multiple pulses are applied using a computer-guided scanning laser (PASCAL).[58] Owing to reduced pulse duration (10-30 milliseconds), the heat diffusion into the inner retina and choroid is decreased, resulting in much less pain[59-61] and reduced inner retinal damage[58,62] and scarring.[63] Rapid scanning of the laser beam in this system also allows for microsecond exposures, sufficiently short for selective treatment of RPE.[64,65] Computer-guided laser application allows for diagnostic image-guided therapy and for reliable delivery of subvisible treatments.

Combining laser delivery systems with eye tracking may further advance planning and application of the laser with high precision using a stabilized retinal image.[66] Endoscopic laser delivery via optical fiber is commonly applied to endophotocoagulation. Short-pulsed (nanosecond-microsecond) lasers with shallow penetration depth, such as erbium:YAG[67] and argon fluoride excimer,[68] have been successfully applied to endoscopic vitreoretinal surgery but have not been accepted in clinical practice owing to the complexity and cost of such laser systems.

GLAUCOMA

With the advent of the slitlamp laser delivery system, the option of treating the iris and trabecular meshwork was an obvious application, and argon laser trabeculoplasty was first introduced in the 1970s for iridectomy[69] and trabeculoplasty.[70,71] Its safety and efficacy in patients with newly diagnosed primary open-angle glaucoma was demonstrated in 1995.[72] With argon laser (514 nm) or, more recently, with the equivalent 532-nm Nd:YAG laser, 50 spots of 50 µm in diameter are applied per 180° on trabecular meshwork with pulses of 100 milliseconds.

Selective laser trabeculoplasty (SLT), was introduced in 1995[73,74] by Latina and colleagues at Wellman Laboratories at approximately the same time that SRT was developed. Similar to SRT, the short pulses of light absorbed in pigmented cells cause explosive vaporization of melanosomes, leading to their destruction, while sparing the nearby nonpigmented tissue. Selective laser trabeculoplasty has been shown to be effective in the treatment of open-angle glaucoma.[73,75,76] Selective laser trabeculoplasty systems include a Q-switched, 532-nm laser that delivers 3-nanosecond pulses in a 400-µm spot. In contrast to argon laser trabeculoplasty, which results in more extensive scarring of the meshwork,[71] SLT leaves the trabecular meshwork intact, with minimal damage to the nonpigmented endothelial cells lining the meshwork beams.[73] With a 400-µm beam, 100 spots per 360° provide practically complete coverage of the trabecular meshwork. Selective laser trabeculoplasty is easier to perform owing to its larger spot size and it is better tolerated by patients owing to its reduced pulse energy. Similar to argon laser trabeculoplasty, the intraocular pressure–lowering effect of SLT lasts for several years but tends to diminish over time. The PASCAL laser recently has been applied to patterned laser trabeculoplasty using computer-guided patterns providing dense coverage of trabecular meshwork with 5-millisecond subvisible exposures.[77]

CATARACT SURGERY

The cataract surgical procedure is one of the most common in the United States, with approximately 2.5 million performed annually.[78] Lasers long have played an important role in the treatment of secondary forms of cataract, such as posterior lens capsule opacification, which is the most common late complication, occurring in approximately one-third of cases[79]; opacified posterior lens capsule had been incised surgically for more than a century. The potential complications of bleeding and infection associated with such an open procedure became avoidable when the slitlamp-coupled nanosecond laser was first introduced to ophthalmology by Krasnov in 1974.[80] This technique represented the first ophthalmic application of a nonlinear laser-tissue interaction, known as *multiphoton ionization* or *dielectric breakdown*, in which a short-pulsed laser focused in a tight spot can produce extremely high light intensities ($>10^{10}$ W/cm^2). At these irradiances, photons can ionize even transparent materials via several different mechanisms,[81] producing plasma in a focal spot.[82] Plasma energy converting to heat results in rapid vaporization of focal volume, producing shock waves and cavitation bubbles. Rapidly expanding and collapsing bubbles can dissect tissue. After initial applications of this mechanism to iris and trabecular meshwork by Fankhauser[83] in 1977, French ophthalmologist (and physicist by training) Daniele Aron-Rosa applied this process to posterior capsulotomy in 1979.[84] Newer picosecond and femtosecond lasers have a lower threshold energy of dielectric breakdown, with an accordingly reduced cavitation bubble size and associated tissue damage; therefore, they allow for more precise surgical procedures.

Ultrashort-pulsed lasers have been applied to softening of the aging crystalline lens in an attempt to restore accommodation. Initial attempts at generating intralenticular incisions to soften the lens tissue and to reestablish its flexibility were performed by Myers and Krueger[85] and Krueger et al[86] using a nanosecond laser. Threshold energy and the associated generation of residual gas bubbles later were reduced with the application of femtosecond pulses.[87] An in vivo animal investigation[88] has shown that this process does not induce cataract, but, to our knowledge, there has been no confirmation of improvement in accommodation in human patients undergoing laser lentotomy.

Recently, a new laser-based technique has been developed for anterior capsulotomy and lens segmentation.[89,90] A scanning femtosecond laser can produce fine cutting patterns in tissue, with their placement defined by integrated optical coherence tomography imaging. Laser incisions in the anterior capsule are much more precise in size and shape than is manual capsulorrhexis, and segmentation and softening of the lens simplify the subsequent ultrasonic phacoemulsification.[90] Femtosecond lasers also have been applied to the construction of multiplanar self-sealing cataract incisions to improve the safety of the procedure and for exact placement of limbal relaxing incisions to reduce residual astigmatism.[90]

REFRACTIVE SURGERY

The first ideas for reshaping the cornea to correct refractive errors were published by Lendeer Jans Lans from Holland in 1896[91]; he proposed using penetrating corneal cuts to correct astigmatism. In 1930, Japanese ophthalmologist Tsutomu Sato demonstrated that the radial cuts in the cornea he performed in military pilots could correct vision by as many as 6 diopters.[92,93] However, this procedure was not accepted in medical practice owing to its associated high rate of corneal degeneration. Starting in 1974, Svyatoslav N. Fedorov (also spelled Fyodorov) in Moscow, Russia, popularized this procedure for correcting myopia.[94] The first attempts at corneal carving, a technique termed *keratomileusis* (from the Greek κέρας [kéras: horn] and σμίλευσις [smileusis: carving]), occurred in 1963 at the Barraquer Clinic in Bogotá, Colombia.[95] However, the initial surgical maneuvers were inherently imprecise; modern refractive surgery dates to the discovery of excimer laser photoablation in 1980 .

R. Srinivasan, a photochemist in J.J. Wynne's group at the laser physics and chemistry group of the IBM Thomas J. Watson Research Center, was studying the application

of a newly developed 193-nm argon fluoride excimer laser to material processing. He discovered that this laser could ablate organic polymers with high accuracy and without noticeable collateral damage. In October 1981, Srinivasan, Wynne, and S.E. Blum placed turkey cartilage under a 193-nm laser beam and observed the beautiful crater that formed, which was much cleaner than that created by any other laser they tested. These results were submitted for publication to *Science* but were rejected with the argument that this radiation may cause cancer. Discouraged but undeterred, they published these results in a trade journal, *Laser Focus*, in 1983.[96] Srinivasan and Wynne researched the application of 193-nm laser to dermatology, and Srinivasan presented the results at the Conference on Lasers and Electro-Optics in May 1983.[97] S. Trokel and F. L'Esperance Jr, of Columbia University, became interested in excimer photoablation for corneal surface reshaping because of its previously unattainable level of exactitude of 0.2 μm. The proposed approaches included using the 193-nm laser as a replacement for the scalpel in radial keratotomy and for direct ablation of the corneal surface. In 1983, Trokel visited the Thomas J. Watson Research Center, where he, Srinivasan, and B. Braren irradiated the cornea of enucleated eyes, producing incredibly clean incisions with no evidence of collateral damage.[98] Later, the problems of slow and uncomfortable recovery of the epithelial layer were eliminated by an improvement to a refractive procedure called *laser-assisted in situ keratomileusis*, in which a flap was cut in the cornea and pulled back to expose the corneal bed for laser ablation. The term *LASIK* was coined in 1991 by Pallikaris et al.[99]

Another revolutionary step in refractive surgery was the development of the femtosecond laser for corneal flap cutting, pioneered by Kurtz et al[100] in 1998 (principal investigator: T. Juhasz) and later commercialized by IntraLase Corporation and others. Unlike mechanical microkeratome, laser cutting allowed the formation of vertical walls around the planar flap, which enabled better positioning of the corneal flap back into its original location after ablation. This improved the consistency of refractive outcomes and led to wide acceptance of the femtosecond laser in refractive surgery.[101,102] Ultrafast lasers also enabled refractive surgical procedures based on intrastromal cutting without excimer laser ablation: extraction of lenticules[103] and production of pockets for intrastromal rings.[104] The same laser systems have been applied to transplantation of the whole cornea or corneal endothelium,[105] known as endothelial keratoplasty.

EPILOGUE

Lasers also have revolutionized ophthalmic imaging and diagnostics. Because this article is focused solely on therapeutic laser applications, we just briefly list the laser-based imaging techniques, including optical coherence tomography, scanning laser ophthalmoscopy, microperimetry, Doppler velocimetry, wavefront analysis, adaptive optics, optoacoustic imaging, confocal microscopy, and multiphoton microscopy.

During the past 50 years, laser technology has revolutionized practically all subspecialties in ophthalmology. Laser therapy has significantly reduced vision loss from the 3 major causes of blindness: diabetic retinopathy, glaucoma, and age-related macular degeneration. It has enabled the treatment of secondary cataracts and refractive error, greatly advanced optical diagnostics, and enabled image-guided ocular surgery. It may play an increasingly prominent role in primary cataract surgery. Undoubtedly, the future advancements of laser technology will continue to benefit ophthalmic diagnostics and therapy. Viva laser!

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