Therapeutic and Diagnostic Application of Lasers in Ophthalmology

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Invited Paper

The accessibility of the human eye, its transparency and the absorption properties of its internal tissues have fostered a rapid evolution of applications for lasers in ophthalmology. Lasers are in ubiquitous clinical use for many therapeutic and diagnostic purposes and their application has become the standard of care in the treatment of many eye diseases including diabetic retinopathy, vascular disease, glaucoma, and the treatment of capsular opacification following cataract surgery. The success of laser therapy for eye diseases has been one of the most remarkable success stories in medicine. Millions of patients have had vision preserved or restored through laser treatment. Many new laser applications are under investigation, including refractive surgery, removal of cataracts, vitrea-retinal surgery, and diagnostic studies. Lasers achieve their effects in the eye through photothermal, photodisruptive, or photochemical mechanisms. Herein, we provide an overview of the present status of clinical and research applications for lasers in ophthalmology.

I. Introduction

The most widespread medical application for laser technology in medicine has occurred in ophthalmology. Since the introduction of the ruby laser over three decades ago, ophthalmic laser applications have experienced rapid growth with use of the argon, krypton, argon pumped dye, Nd:YAG, and most recently, near-IR diode lasers. Lasers have achieved remarkable clinical successes in the treatment of retinal diseases, glaucoma, and lens capsule opacification following cataract surgery. The decade of the nineties will likely herald another period of rapid growth of ophthalmic laser technology with the newly devised excimer and diode lasers.

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The reasons for the prevalence of laser applications in ophthalmology are easy to grasp. The eye is one of the most accessible human organs, and its media (cornea, aqueous humor, lens, and vitreous) are transparent to visible light, allowing direct inspection of its internal structures for diagnosis and treatment. Many intraocular tissues contain pigments (such as melanin) that allow absorption of laser energy for photothermal laser-tissue interactions. Transparent intraocular structures (such as the posterior lens capsule and vitreous), have also been amenable to laser treatment with Nd:YAG photodisruptors.

Another factor that has facilitated the growth of ophthalmic laser applications is the ability of ophthalmologists to objectively evaluate the efficacy of new treatment modalities such as laser therapy. Whereas efficacy in other medical specialties is more difficult to assess (evaluating new treatments for patients with cancer or cardiovascular disease requires many patients and years of follow up), ophthalmologists can observe disease processes directly and outcome parameters such as visual acuity, visual field, and intraocular pressure can be measured accurately and objectively. These factors have facilitated the introduction of laser treatment of eye diseases and the rapid determination of their efficacy.

Herein, we review the current status of clinical and experimental applications of laser technology in ophthalmology. Since a basic understanding of ocular anatomy, physiology, and some disease processes is necessary to understand the rationale for laser applications, we provide a brief overview of these subjects for the nonphysician readership. We then discuss therapeutic applications of lasers according to photothermal, photodisruptive, and photochemical mechanisms of laser-tissue interaction. Current diagnostic applications of lasers in ophthalmology are also reviewed.

II. Basic Ocular Anatomy and Physiology

The eye is a slightly ovoid organ measuring about 24 mm in length and 23 mm in diameter (Fig. 1) [1]. It is composed of three distinct tunics or layers. The sclera is the tough outer coat of the eye that comprises the posterior

four fifths of the globe. The sclera is white, because its dense collagen fibrils have varying diameters and cause diffuse scattering of visible light. Anteriorly, the sclera is contiguous with the cornea, the clear watchglass-like covering where the collagen fibrils have more uniform diameters and are arranged in orderly layers, permitting transparency ($T \geq 95\%$ for 400–900 nm; refractive index, $n \approx 1.3765 \pm 0.0005$, Tensile strength, $T \approx 10^6$ Nm^{-2}). The middle layer of the eye is termed the uveal tract and is composed of a rich network of blood vessels that supplies nutrition to the eye. In the posterior segment of the eye, the uvea is termed the choroid. In age related macular degeneration, the boundary between the retina and choroid may break down and allow abnormal blood vessels to grow beneath the retina, causing hemorrhage and loss of vision [2]. Anteriorly, the uveal tract is continuous with the iris, the colored aperture of the eye, that allows light to pass through its central opening (pupil). The diameter of the pupil varies between 1.5 and 8 mm depending upon the amount of light reaching the retina.

The eye is divided into three cavities by intraocular structures. The anterior chamber lies between the cornea and iris. It is filled with a clear water-like fluid, the aqueous humor (viscosity $\approx$ 1.0 cs; $n \approx 1.3335$). Behind the iris and anterior to the lens lies the posterior chamber. The lens of the eye, composed of specialized crystalline proteins, is clear at birth ($n \approx 1.40$–1.42, $T \approx 10^4$ Nm^{-2}) and often becomes progressively cloudy or cataractous with age. The lens is approximately 0.15–0.25 cm^3 in volume, 3.5 mm in thickness, 8 mm in diameter and enveloped in a tough thin (10–14 μm) transparent collagenous capsule (n=1.396, $T \approx 10^7$ Nm^{-2}). The posterior portion of this capsule is left intact following removal of the lens substance during modern cataract surgery to help support the plastic implant. The large cavity posterior to the lens is filled with a transparent jelly-like substance, the vitreous humor ($n \approx$ 1.335, viscosity $\approx$ 10–100 cs). The vitreous body (5.5 cm^3) is often removed surgically for the treatment of diabetic eye diseases and the cavity then fills with aqueous humor with no apparent (thus far) adverse effects upon the eye.

The innermost layer of the eye is the neurosensory retina, an outgrowth of brain tissue that converts visible photon energy into electrochemical impulses that are processed (in both a digital and analog fashion) in the inner retinal layers and relayed to the brain via the optic nerve. The outer portion of the retina contains the photoreceptors and receives its nutrition from the uveal tract, while the inner retina contains its own retinal vascular supply. Normally, the retinal arterioles are sealed tightly, and allow no leakage of blood fluids or proteins into the surrounding retina. In diabetes, and several other vascular diseases, the blood vessels become abnormal and allow fluid to leak into the macula, the posterior region of the retina that is responsible for central vision, causing retinal dysfunction and loss of vision. Fragile new blood vessels may also grow onto the surface of the retina causing both leakage of fluid and hemorrhage into the eye [3].

The eye is internally pressurized with a normal intraocular pressure of about 13 ±3 mm Hg above ambient pressure. Internal pressure is created by the production of a clear fluid, termed aqueous humor, by the ciliary body, a specialized secretion tissue that is contiguous with the retina posteriorly. The aqueous humor flows anteriorly though the pupil to drain through the trabecular meshwork, a specialized filtration structure located in the angle between the cornea and iris. Abnormalities of the pressure regulating system of the eye may result in abnormally high (≥ 22 mm Hg) intraocular pressure, a condition termed glaucoma, that damages the delicate nerve fibers in the optic nerve, causing a loss of vision.

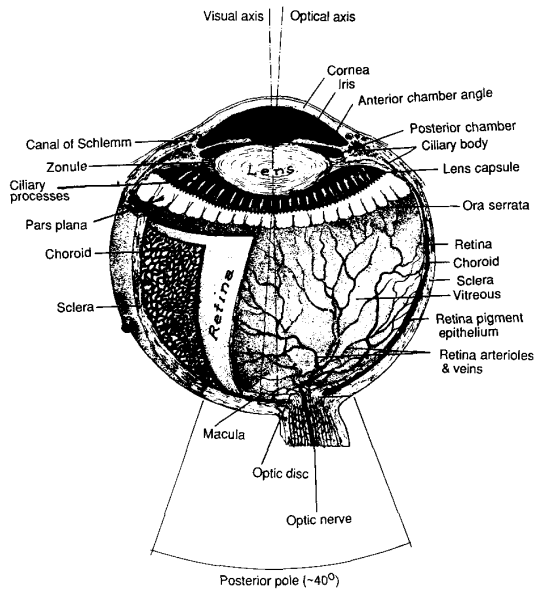
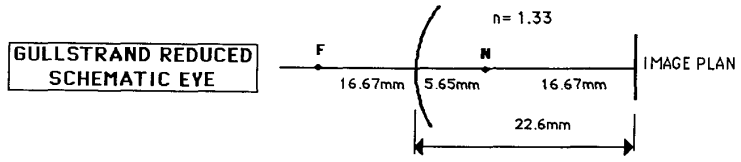


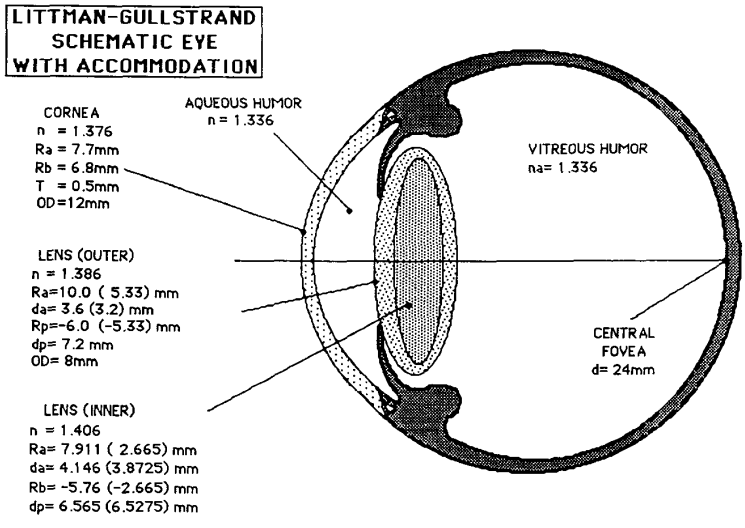
Fig. 1. Anatomical drawing of the eye.

The eye has a focal length of about 16.7 mm in air [4]. Ophthalmologists prefer to use optical units of diopters (1 diopter = $1/F$-meters) when measuring the refractive error of the eye or the power of the eye's optical elements. These are usually determined according to Gulstrand's reduced schematic eye [4], [5] (Fig. 2(a)). For instrument design and computational purposes, opticists use the model described in Fig. 2(b) [6]. Two thirds of the eye's optical power, or about 44 diopters, results from the curvature of the cornea, the remainder is provided by the crystalline lens. The lens can change shape, and increase its focusing power for near vision (accommodation) until about the fifth decade, when reading glasses become a necessity for clear viewing of close objects. Since the cornea is the predominant optical element of the eye, a small change in its curvature causes a large effect on the total optical power of the eye, a principle utilized by corneal refractive surgeons [7], [8].

An emmetropic eye, or one without refractive error, focuses a distant point source of light on the fovea, the region of the macula with the highest density of cones (1-μm diameter with 1.3-μm spacing), the photoreceptors that provide the highest resolution (15–30″ of arc). Nearsighted



(a)



Total system	at rest	accommodation
Refractive power	58.64	70.57
Position of first principal point	1.348	1. 772
Position of second principal point	1.602	2.086
Position of first nodal point	7.078	6.533
Position of second nodal point	7.332	6.847
Position of first focus	-15.707	-12.397
Position of second focus	24.387	21.016
Front focal length	-17.055	-14.169
Rear focal length	22.785	18.930
Position of retinal fovea	24.0	~4.0
Axial refraction	+1.0	-9.6
Position of near point	oo	-102.3

(b)

Fig. 2. (a) Optical model of the human eye. (b) Littman–Gullstrand schematic eye with accommodation.

or myopic eyes have too much optical power for their length, resulting in displacement of the focal point anterior to the retina. Farsighted or hyperopic eyes have insufficient power for their length, with a focal plane that is located "behind" the retina.

III. Transmission and Absorptive Properties of Ocular Tissues

Light entering the eye can be reflected, scattered, transmitted, or absorbed. Reflected or scattered light contains information that can be used for noninvasive diagnostic purposes, discussed in Section VII. In ophthalmic laser surgery, the surgeon must choose a proper laser wavelength that is transmitted through intervening ocular layers to become incident upon the target tissue.

In the visible and near infrared spectrum (400–1400 nm), the absorption characteristics of ocular tissues is determined by a group of chromophores (a molecule or a group of molecules that absorbs a photon of a particular wavelength) within the tissue. Ocular chromophores that absorb light in visible spectrum include melanin, located in the retinal pigment epithelium, iris pigment epithelium, uvea, and trabecular meshwork; hemoglobin, located in red blood cells within blood vessels; and xanthophyll, located in the inner and outer plexiform layers of the retina in the macular region. The light absorption spectra of these pigments is illustrated in Fig. 3. In the mid-infrared spectrum (1.8–10.6 μm), the major molecule absorbing incident photons is water (Fig. 4).

The retina contains at least six pigments: melanin, hemoglobin, macular xanthophyll, rhodopsin, cone photopigments, and lipofuscin. The first three of these are of major

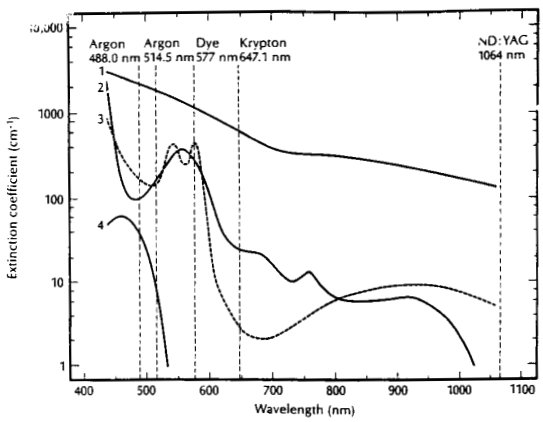


Fig. 3. Transmission spectra of the major ocular chromophores: melanin (1), reduced hemoglobin (2), oxygenated hemoglobin (3), and macular xanthophyll (4). Also shown are the wavelengths of four commonly utilized ophthalmic lasers: argon, krypton, dye and Nd:YAG (Reprinted with permission from *Lasers in Ophthalmology* by F. A. L'Esperance).

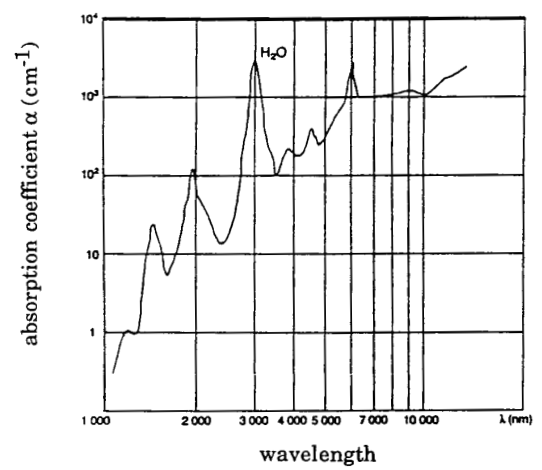


Fig. 4. Absorption spectra of water.

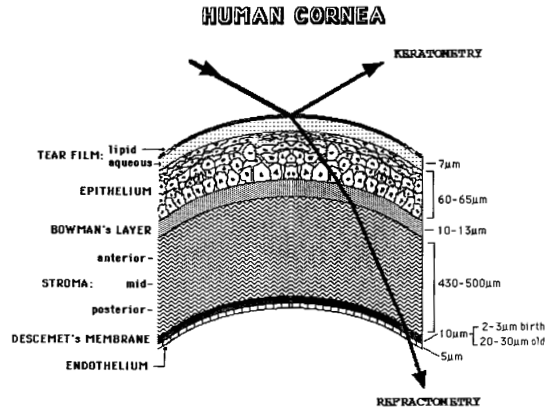


Fig. 5. Detailed structure of the cornea.

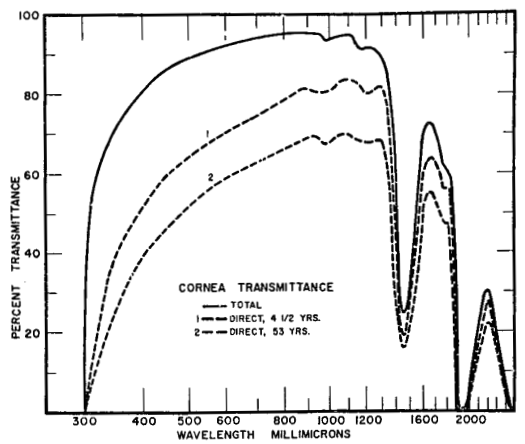


Fig. 6. Corneal transmittance spectrum.

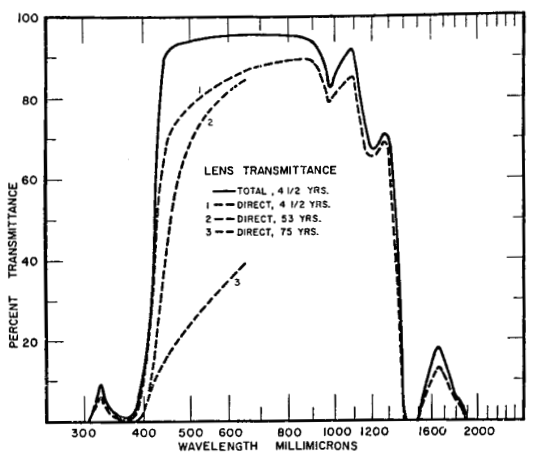


Fig. 7. Lens transmittance spectrum (aging effect).

importance in laser photocoagulation of the retina.

The cornea consists of five principal layers, the epithelium, Bowman's layer, stroma, Descemet's membrane and the endothelium (Fig. 5). The cornea is continuously protected by a tear film that has a high lipid content and a high index of refraction (n = 1.40). Due to its transmission characteristics, the cornea provides an effective window for vision, photocoagulation, photodisruption, imaging, and examination of intraocular structures (Fig. 6).

The transmission and absorption characteristics of the crystalline lens change with age (Fig. 7). The total transmittance at the various anterior surfaces is given in Fig. 8.

IV. Photothermal Laser Applications

A. Mechanisms of Photothermal Laser-Tissue Interaction

Photothermal laser-tissue interactions occur when laser energy is absorbed by the target tissue and converted into heat. The effect upon the tissue depends on both the magnitude and rate of temperature elevation. Low

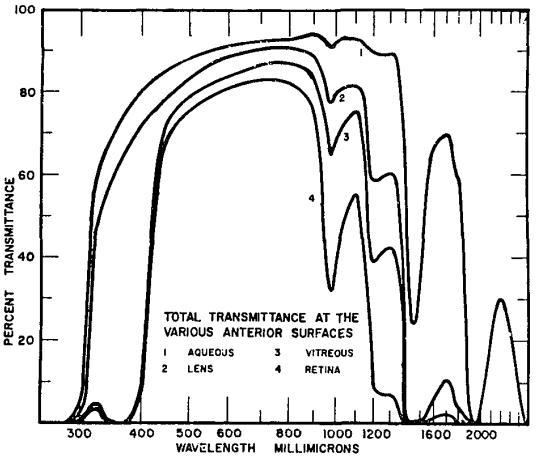


Fig. 8. Total transmittance of the entire eye.

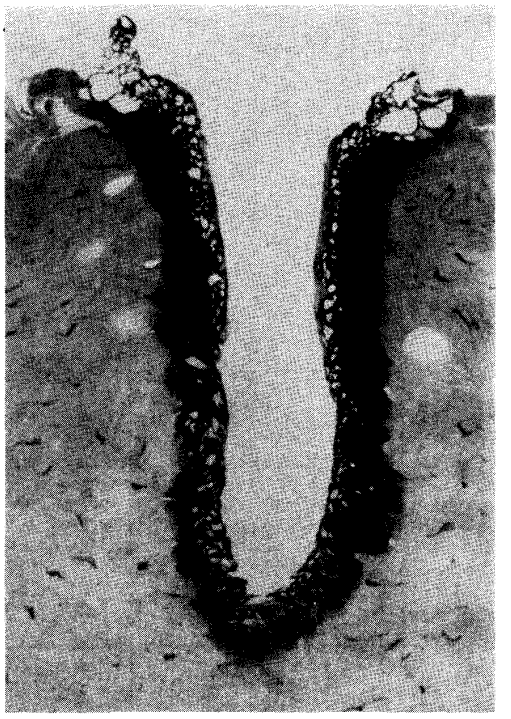
(less than 10°C) temperature elevations that occur over many seconds to minutes (photoheating) generally cause cell damage or death without causing structural alterations to the tissue. Greater temperature elevations (20°–30°C), occurring over shorter time intervals (approximately 1 s), cause thermal coagulation of tissue (photocoagulation), with cellular death and irreversible structural damage to the tissue due to denaturation (loss of the three-dimensional molecular structure) of tissue proteins [9]. Laser energy depositions that rapidly (much less than 1 s) heat the tissue above its boiling point cause thermally-mediated tissue removal by explosive vaporization (photovaporization). The wavelength of laser radiation, the absorption coefficient of the tissue, the power (or energy) density, and the duration of laser radiation determine which of these photothermal effects predominates.

To minimize unwanted thermal damage to surrounding ocular tissue during laser treatment, a wavelength should be selected that is preferentially absorbed by the target tissue and the laser exposure duration should be shorter than the thermal relaxation time of the tissue, given by

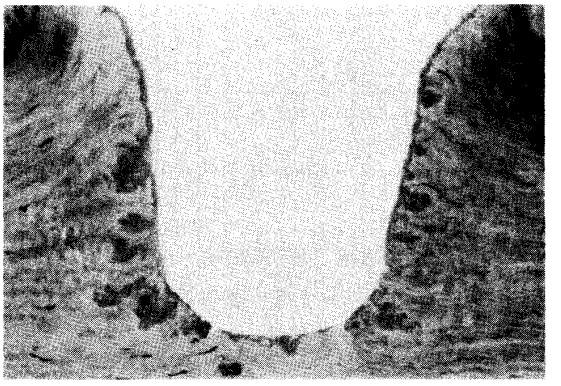
$$T_h = d^2/4k \tag{1}$$

where d represents the absorption depth of the radiation, and k is the thermal diffusivity of the tissue.

For example, mid-infrared (2.94 μm) Er:YAG and Er:YSCG lasers are under investigation for cutting the cornea. Water ($k = 1.5 \times 10^{-3}$ cm^2/s) is the primary absorbing molecule at this wavelength ($d = 1$ μm) and the thermal relaxation time is calculated to be 1.7 μs. Therefore, to achieve efficient photovaporization with minimum damage to the surrounding corneal tissue, the pulse duration of the laser must be significantly less than 1.7 μs. Decreased thermal tissue damage with shorter laser pulse duration has been demonstrated by comparing the tissue damage adjacent to corneal excisions created by a Q-switched (pulse duration 100 ns) to a free running (pulse duration 250 μs) Er:YSCG laser (Figs. 9(a) and (b)).



(a)



(b)

Fig. 9. (a) Er:YSCG normal mode (250-μs pulses). (b) Er:YSCG Q-switched mode (100-ns pulses). Light microscopy of corneal excisions produced by a mid-infrared Er:YSCG laser demonstrate the effect of pulse duration on adjacent thermal damage to tissue. Excisions produced in the normal mode (250 μs) causes significantly more thermal damage than when operated in the Q-switched mode (100 ns).

B. Photothermal Laser Applications

Tables 1a and 1b summarize the present clinical and research applications for photothermal lasers in ophthalmology, respectively.

1) Photocoagulation Therapies for Retinal Diseases: The use of lasers as a selective heat source to coagulate retinal tissue is one of the most important and widely adopted ophthalmic laser applications. The 694-nm Ruby laser was

Table 1a Photothermal Laser Applications in Clinical Use

Procedure	Disease	Laser/Wavelength (nm)	Rationale	Comment
Pan-Retinal Photocoagulation	Proliferative Retinopathies	Argon-488/514 Krypton 647 Dye-577	Destruction of peripheral retina decreases stimulus for new blood vessel growth	Widespread Application
Focal Macular Photocoagulation	Diabetic Macular Edema, Vein Occlusions	Argon-488/514 Krypton-647 Dye-577	Focal treatment decreases leakage of fluid in retina	Widespread Application
Photocoagulation of Subretinal neovascular Membranes	Age Related Macular Degeneration	Argon Green-514 Dye-577	Destruction of new vessel membranes prevents complication from subretinal hemmorage and leaking vessels	Widespread Application
Trabeculoplasty	Open Angle Glaucoma	Argon-488/514	Focal photocoagulation of trabecular meshwork improves aqueous outflow, decreasing pressure	Compared favorably to medications in recent study
Peripheral Iridotomy	Narrow Angle Glaucoma	Argon-488/514	Hole in iris allows alternative path for aqueous flow, preventing angle closure	Has replaced need for intraocular surgery
Cyclophotocoagulation	Advanced Glaucoma	Nd:YAG-1064 free running thermal mode	Destruction of ciliary body decreases intraocular pressure	Procedure of

Table 1b Photothermal Laser Applications in Experimental Development

Procedure	Disease	Laser/Wavelength	Rationale	Comment
Filtration Surgery	Glaucoma	TmHoCr:YAG-2.1 μm	Small incision, minimal trauma may increase survival of filtration bleb	
Corneal Trephination	Corneal scarring and disease	HF 2.9 μm Er:YAG-2.9 μm	Nonmechanical cutting may decrease postoperative astigmatism	Full thickness trephination possible in 7 seconds
Photothermal Keratoplasty	Hyperopia	Ho:YAG	Shrinkage of collagen steepens central cornea	Early clinical studies
Laser Tissue Welding	Wound closure	Line-tuned HF 2.55 μm	Fusion of collagen and connective tissue	Unsuccessful in clinical applications to date
Cataract Removal	Cataract	HF and other mid IR 2.5-3.0 μm	Cataract removal while maintaining capsular bag	Will facilitate development of an accommodating lens
Laser Induced Hyperthermia	Ocular Tumors	midinfrared	Selective heating causes tumor necrosis	

the first laser introduced to ophthalmology in the early 1960's [10]. Energy from the Ruby laser was absorbed by the retinal pigment epithelium and caused photocoagulation of the outer retina. Unfortunately, this early laser performed poorly in the clinical setting due to its short pulse duration ($\approx$ 100–300 μs), its deep penetration depth ($\geq$ 400 μm) variable power output and crude beam delivery system.

In 1968, the constant wave Argon laser was introduced by L'Esperance [12]. This laser emitted at both 488 and 514.5 nm and offered improved beam stability. It quickly surpassed the xenon arc lamp and Ruby laser as the preferred method for retinal photocoagulation in the 1970's. The irradiance the Ar^+ laser treatment is approximately 100 W/cm^2 with an application time of 0.1–1 s. Photocoagulation has proved most useful in the treatment of proliferative diabetic retinopathy. In this disorder, the retina becomes ischemic (starved for oxygen and nutrients) and releases chemical messengers that are thought to cause the growth of fragile new blood vessels in an attempt to nourish the oxygen starved tissue. The abnormal new blood vessels, and their associated proliferating fibrous tissue, are a major cause of sight-threatening complications in diabetic eye disease. By destroying a portion of the peripheral retina with the laser, retinal metabolic demands are decreased and

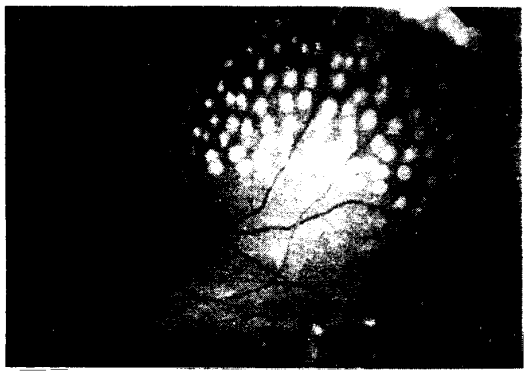


Fig. 10. Pan retinal photocoagulation. Multiple 500-μm diameter laser burns have been applied to the peripheral retina of this diabetic patient using a 488/514-nm argon laser. Several areas of focal treatment in the macula are also present.

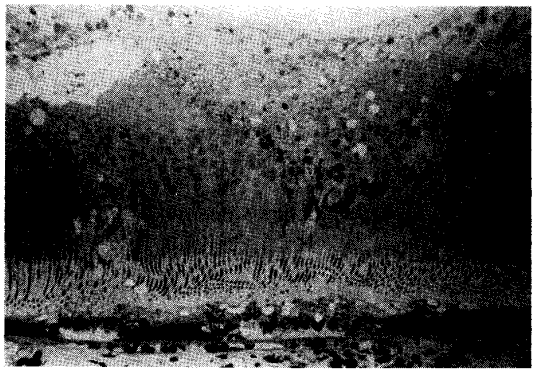


Fig. 11. Histology of macula following photocoagulation with the argon blue (488 nm) wavelength. Note the damage to the inner retinal layers due to absorption of laser energy by xanthophyll pigment. Inner retinal damage can be avoided by treatment with the argon green (514 nm) or krypton (647 nm) wavelengths.

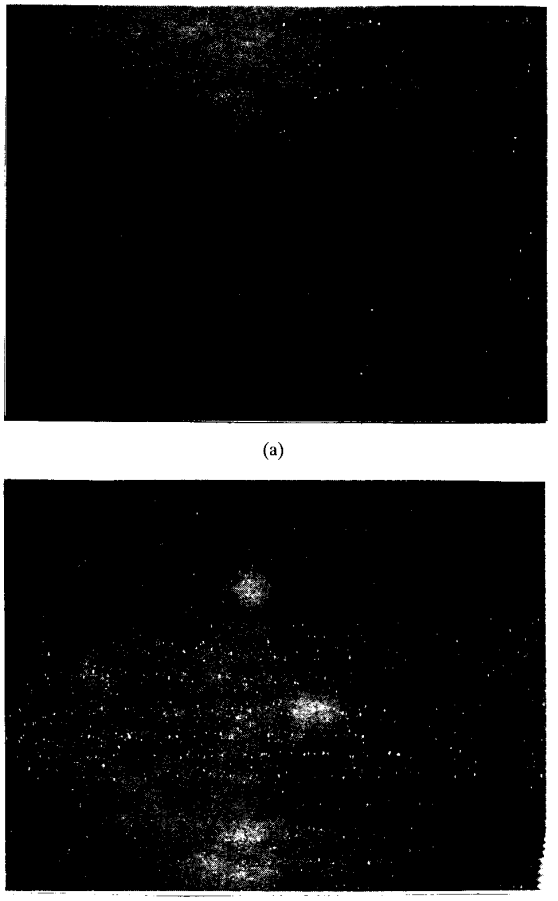
the stimulus for new vessel formation is reduced [3]. This treatment, termed panretinal photocoagulation (Fig. 10) can significantly decrease the risk for vision threatening complications from new blood vessel growth [12]–[14]. The side effects of panretinal photocoagulation—loss of some night vision and constriction of visual field—are far outweighed by the preservation of central vision offered by treatment.

The constant wave Kr^+ laser, introduced in 1972, was also used to effectively photocoagulate the retina with the additional advantage that the 568-nm wavelength can penetrate ocular media clouded by cataract or vitreous hemorrhage better than the 488-nm Argon laser [15]. In addition, because 568 nm is not absorbed by the xanthophyll pigment located in the macula, the krypton laser is best suited to treat microaneurysms located close to the fovea.

The widespread use of the Argon and Krypton laser by ophthalmologists in the treatment of proliferative diabetic retinopathy has been responsible directly for preserving the vision of thousands of diabetic patients.

Laser treatment of the macula was also found to be effective for decreasing the leakage of fluid into the retina (diabetic macular edema) which also can occur in diabetic eye disease [16]. Laser treatment within the macular region requires special consideration for the absorptive properties of the tissue. Within the macula, the inner retinal layers contain xanthophyll pigment that absorbs strongly between 450 and 500 nm. Use of the argon blue wavelength (488 nm) causes heating and destruction of the nerve fiber layer in the inner retina, resulting in loss of vision (Fig. 11). By using the argon green wavelength (514 nm) or a longer wavelength from a krypton or dye laser, absorption by xanthophyll and damage to the inner retina is minimized.

Treatment of subretinal neovascular membranes that occur in age related macular degeneration is another major application for laser photocoagulators. Macular degeneration is the leading cause of acquired blindness in the elderly. Here, the surgeon uses a photocoagulator to destroy the invading vascular membrane, leaving a chorioretinal scar (Fig. 12). The benefit of photocoagulation to preserve vision in this disorder has also been demonstrated by a large clinical study [17]–[21].



(a)

(b)

Fig. 12. (a) Subretinal neovascular membranes (arrows) in the macula in a patient with age related macular degeneration. (b) Same eye after photocoagulation treatment with the argon green laser.

Tunable dye lasers, introduced to ophthalmology in 1981 gave added flexibility to ophthalmologists and allowed them

to select a wavelength for a given photothermal laser application [22]. Ideally, photon penetration depth for a laser wavelength used in vessel closure should be approximately the same length as the vessel's diameter such that effective bulk heating of the blood column occurs without superficial damage and perforation of the vessel wall at the radiation site. Treatment of neovascular membranes is best done with a wavelength maximally absorbed by hemoglobin.

2) Photothermal Laser Treatment for Glaucoma: In addition to treatment of retinal diseases, photothermal lasers have also found widespread clinical application in the treatment of glaucoma. Constant wave argon, krypton, or dye lasers are used to burn a small hole through the iris when narrow angle or angle closure glaucoma is present. Creating a small opening in the peripheral iris allows an alternate pathway for aqueous humor when its normal pathway through the pupil is impeded by the lens (angle closure glaucoma). Melanin is the major absorptive pigment in the iris, and the argon 488-nm wavelength is quite effectively absorbed (Fig. 3). In individuals with lightly colored irides, little pigment is present, decreasing the effectiveness of the laser. In these cases, the use of a Q-switched Nd:YAG photodisruptor, discussed below, offers the clinician an alternative laser that is independent of pigment absorption for its effect [23]. Creating a hole in the iris with the laser is easily performed with the patient seated at the slitlamp (Fig. 13) in the outpatient clinic. This treatment has saved many patients and surgeons a trip to the operating room, and an intraocular surgical procedure with its associated risks, complications, and costs.

Laser trabeculoplasty is performed in eyes with open-angle type glaucoma by applying focal photocoagulation to the trabecular meshwork located in the angle of the eye [24]. For this treatment, the 1–3 W Argon (488 nm and 514 nm) laser is aimed through a mirrored contact lens and focused into a 50- to 100-μm spot. Application times of 0.3–1 s are used. Although the mechanism of action is uncertain, it is thought that laser photocoagulation may stretch open the structures of the trabecular meshwork, facilitating outflow of aqueous humor and decreasing intraocular pressure [25]. Laser trabeculoplasty may play a major role in the management of patients with open angle glaucoma, estimated to be 1.6 million in the U.S. alone [26].

When medical management fails, glaucoma surgery is indicated to control the intraocular pressure. The objective of glaucoma surgery is to provide an alternate pathway for fluid to egress from the eye and the trend in techniques has been toward smaller incisions and less invasive procedures. Recently, a pulsed TmHoCr:YAG laser (Fig. 14) has been applied subconjunctivally through a quartz fiber-optic probe for a transcleral filtering procedure [27]. In this procedure, a small snip incision is made in the conjunctiva, approximately 0.5 mm posterior to the junction of the cornea and sclera (limbus) and the fiber-optic laser probe is passed through the opening and directed over the pupil until the tip approaches the opposite angle. The beam is shaped and focussed by a cylindrical prism built at the end of the probe which is directed toward the limbus to create a full thickness fistula. The exposure made with energy ranging from 60–150 mJ per pulse, with pulse duration of 300 ms and a repetition rate of 5 Hz. Total energy levels required to produce full thickness channel ranged from 1.35 to 6.6 J. Compared to conventional surgical procedures, this technique avoids the need for large conjunctival flaps and intracorneal manipulations, reduces tissue trauma and hemorrhage, and may limit the outflow of wound-healing agents, which lead to scarring and failure of the fistula [28]. Clinical investigation of this new technique is pending.

Eyes with advanced forms of glaucoma unresponsive to conventional surgical or medical may undergo photocoagulation of the ciliary body (cyclophotocoagulation) with a Nd:YAG laser operating at 1064 nm in the free running (5–20 ms) or thermal mode. Both pulsed ($\geq$ 10 ms) and constant wave Nd:YAG lasers are used to heat and destroy portions of the aqueous humor secreting ciliary body in an attempt to decrease intraocular pressure. Diode lasers have also shown promise used for cyclophotocoagulation [29].

3) Mid-infrared Laser Corneal Surgery: Although the healthy cornea is transparent to visible light and does not interact with argon, krypton, or dye photothermal lasers, wavelengths in the mid-infrared and infrared spectrum (1.9–10.6 μm) are strongly absorbed, largely due to the absorption of water, which comprises $\approx$ 75% of corneal tissue (Fig. 15). Within this spectral region, laser parameters such as wavelength, pulse duration, energy density, etc., can be properly chosen to cut, shrink, and weld tissue by photothermal mechanisms. Although mid-infrared corneal laser surgery is still in its infancy with most techniques still in laboratory or early human studies, there are many promising potential clinical applications.

A. Mid-IR Laser Corneal Cutters or Photocutting

Corneal and refractive surgery demands a high degree of spatial accuracy and reproducibility. Existing surgical techniques make use of metal and diamond scalpels and therefore rely heavily on the surgeon's manual abilities and experience. Even with the help of high power operating microscopes, manual precision is limited to $\approx$ 100–200 μm, contributing to the unpredictability of postoperative refractive errors. Postoperative astigmatism following corneal transplant surgery is a major problem in corneal surgery [30]. The use of a mechanical trephine (the circular blade used by the surgeon to cut corneal tissue for transplantation) produces a torsional moment on the cornea during cutting, leading to an uncertainty in the precise dimensions of the trephined tissue. A tissue size disparity between the donor and host of 100 μm produces about four diopters of astigmatism.

The application of photothermal cutting lasers to corneal transplant surgery provides the potential for a noncontact corneal trephination system. In 1971 Beckman demonstrated that the cornea could be excised with a rapidly pulsed (60–300 Hz) CO_2 laser operating at 10.6 μm, emitting a peak power output of 25 000 W and an average output power of 150 W, but the amount of adjacent thermal damage to the corneal tissue was too excessive for clinical

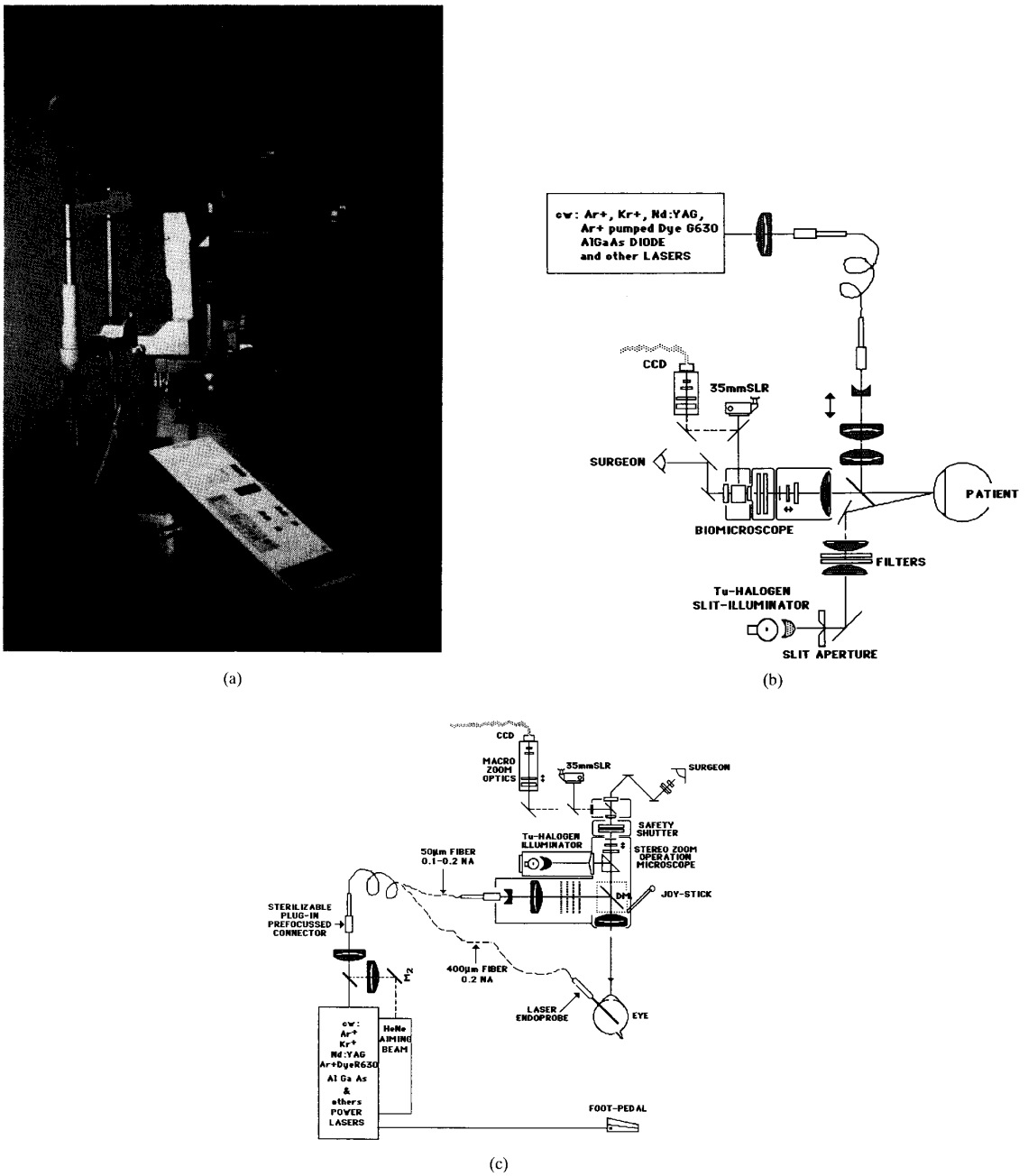
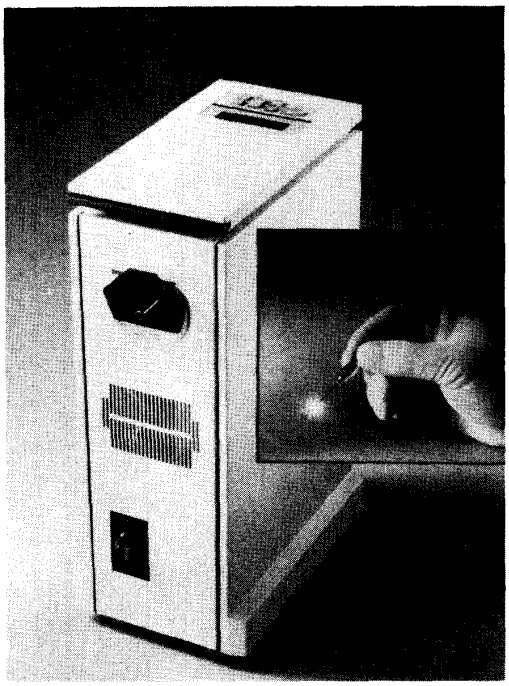
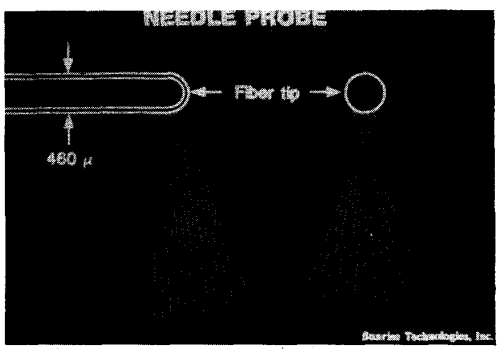


Fig. 13. (a) Typical appearance of a slitlamp laser delivery system. A Keeler diode laser is integrated into the slitlamp optical system. (b) Optical schematic of slitlamp laser delivery system in widespread clinical use. Laser energy is conducted to the slitlamp by a fiber-optic cable and directed toward the eye by means of a coaxial beamsplitter. (c) Operating room delivery systems.

use [31]. More recently, Parel, Jeffers, and coworkers selected the mid-infrared region to investigate laser corneal surgery, and with a pulsed HF laser (2.7–3.0 μm, 50–200 ns, 2.4 J/cm^2), created 70-μm wide uniform corneal excisions with much less thermal damage than that caused by the CO_2 laser [32], [33]. These researchers also demonstrated the feasibility of using the HF laser coupled to a polyprismatic and axicon lens system for 16-point marking and cutting of 8-mm diameter circular corneal buttons in less than 7 s for corneal transplantation (Fig. 16). By shadowphotogrammetry, it was demonstrated that noncontact laser corneal trephination produced more uniform and more precise circular cuts than the manually operated surgical instruments used presently. Therefore, we postulate that the



(a)



(b)

Fig. 14. (a) Sunrise laser system for glaucoma (Sunrise Technologies gLASE™ 210 Holmium Laser System and SUN-LITE™ Handpiece) and (b) their special fiberoptical tip design.

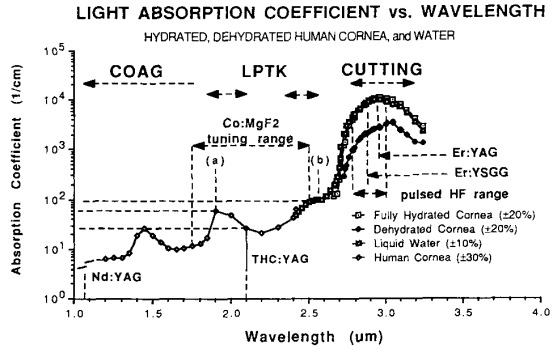


Fig. 15. Light absorption coefficient versus wavelength for the hydrated, dehydrated human cornea, and water. Absorption rises sharply for wavelengths longer than 2.5 μm with a peak absorption coefficient occurring near 2.9 μm. Since the normal cornea is nearly 75% water by weight, the cornea's IR absorption spectra closely parallels that of H_2O.

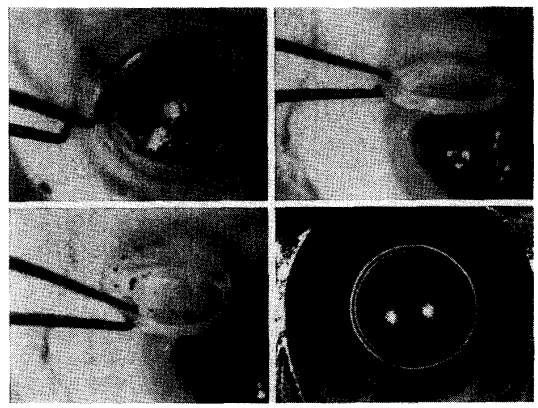


Fig. 16. Circular corneal button excised with pulsed HF laser (2.9 μm, 50–200 ns, 2.4 J/cm^2). Edges of the excised button are smooth and uniform. 360° full thickness trephination is not possible because aqueous fluid egressing from the first penetration site fills the excision and attenuates energy.

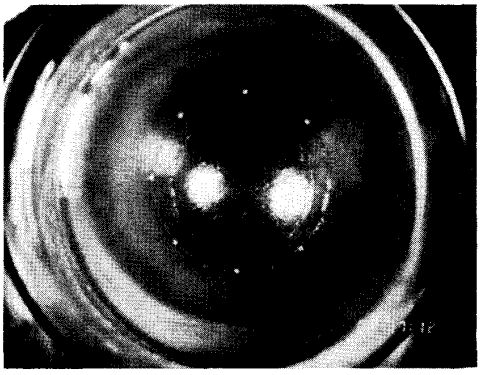
laser might significantly decrease the amount of undesirable postoperative astigmatism [34] and have begun comparative studies in animal models. For clinical application, solid-state lasers generating mid-infrared wavelengths are desirable because of their simplicity, reliability and safety in the operating room. A Q-switched Er:YAG solid-state laser system (2.94 μm, 100 ns, 1.5 J/cm^2) coupled to an axicon-lens combination was successfully used in preliminary corneal trephination studies [35], and research to develop this technology is continuing.

B. Laser Photothermal Keratoplasty (LPTK) or Photoshrinking

Since collagen, the major structural component of the cornea, shrinks when heated to 55°C–58°C [9], the shape of the cornea and consequently, the refractive power of the eye, may be changed by creating focal burns in the stroma. Due to excessive mechanical and thermal damage to the cornea, previous attempts to thermally alter the shape of the cornea by heated metal probes (≥ 100°C–600°C) have been unsuccessful (Fig. 17(a)). Seiler and others [36]–[38] recently demonstrated that the refractive power of the cornea can be adjusted by shrinkage of corneal collagen fibers with lasers emitting around 2 μm [39]. A small series of hyperopic patients treated with the holmium laser coupled to a fiber-optic probe delivery system has shown reasonable predictability and fair stability of the refractive outcome.

By heating the corneal stroma with a noncontact mid-infrared TmHoCr:YAG laser system operating at 2.1 μm in the free-running mode (≈ 300 μs, 1 Hz), fresh cadaver eyes and the eyes of rabbits, cats, and nonhuman primates have been studied topographically and histologically (Fig. 17(b)). The energy density applied to the target varied from

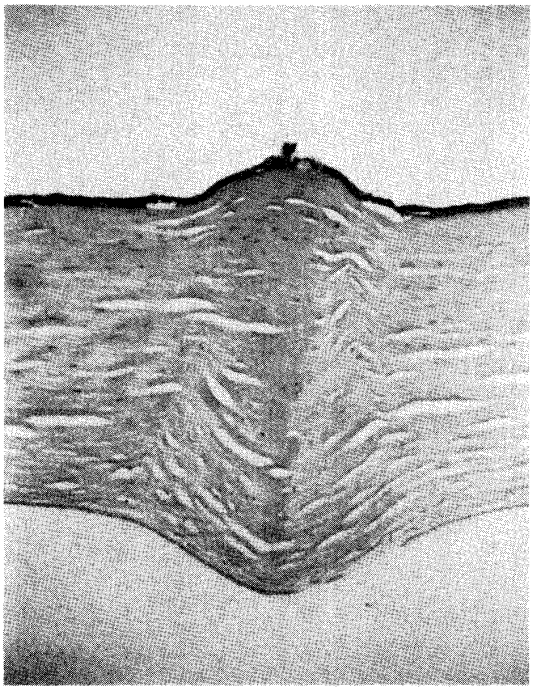
(a)



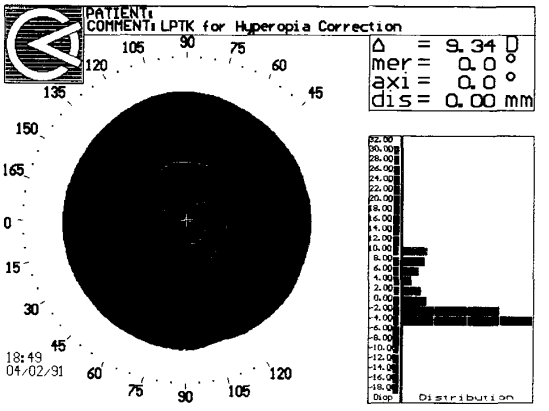
(b)

Fig. 17. (a) Corneal burns induced by a heated copper filament. Note ring of coagulation damage extending 0.5 mm from center of in injury. Topographic changes are evident by stress lines in the cornea seen by retroillumination in the pupil. (b) Appearance of cornea immediately following focal stromal heating with a noncontact 300 μs, 2.1 μm TmHoCr:YAG laser. Large dioptric changes are possible with gross coagulation injury.

5 to 20 J/cm^2 and the total number of pulses from 5 to 50. Changes of 10 diopters were obtained with five 10-J/cm^2 pulses placed in a semiannular pattern designed to correct astigmatism (Fig. 18). With noncontact treatment, the treatment zone was found to be limited to an inverted cone having an epithelium base of $\approx$ 300 μm in diameter and a stromal depth of $\approx$ 250 μm, the endothelium was spared and the damage to the adjacent stromal and epithelium tissue was limited to 50 μm of the treatment zone.



(a)



(b)

Fig. 18. (a) Histology of laser photothermal keratoplasty burn in rabbit cornea. The injury is conical in shape and spares the endothelium. (b) Color-coded map of topographic changes (in diopters) induced in human cadaver eye treated by LPTK with a TmHoCr:YAG laser operating q at 2.1 μm (300 μs, 1 Hz).

C. Laser Tissue Welding or Photowelding

Laser tissue welding involves the use of laser energy to directly fuse tissue or activate biological agents to bond tissue. Laser tissue welding may allow sutureless wound closure and reduction of surgical time, and find application in corneal transplantation, epikeratoplasty, cataract, glaucoma, and vitreoretinal surgery. Laser welding has been applied successfully in other surgical fields including vascular surgery, dermatology, urology, otolaryngology, and neurology [40]–[42]. The pathophysiologic mechanisms of laser tissue welding are not yet fully understood; however, it is postulated that tissue fusion is due to the denaturation and homogenization of collagen with interdigitation of individual fibrils that occur when tissue is heated by absorption of laser radiation [43].

Welding synthetic collagen lenticules to the cornea with and without the use of solders has been attempted using a milliwatt CO_2 laser [40]. Direct welding, either lenticule to lenticule, lenticule to cornea, and cornea to cornea was not successful without the use of bio-solders. Since

the mechanism for laser tissue welding is probably heat dependent, the short penetration (10 μm) of CO_2 laser radiation tends to overheat and char tissue, producing weak welds. More recently, unique matches between laser and tissue characteristics have been identified that may lead to improvements in tissue welding. Instant welding of corneal and scleral tissue has recently been obtained in the Helios Laboratories of Longmont, CO, using line-tuned HF laser radiation (2.55–3μm) with proprietary coupling optics (unpublished data).

4) Cataract Surgery with Endolaser System: The future goal of cataract surgery is "Phaco-Ersatz," cataract surgery designed to restore accommodation [44], [45]. This procedure involves the removal of the cataractous lens through a small opening while preserving the lens capsule and its zonular attachments. The empty lens capsule is then filled with a bio-compatible and optically suitable synthetic gel creating a physiologically compatible artificial intraocular lens *in situ* (Fig. 19). This procedure will demand a more precise and less damaging method for cataract removal, currently performed by ultrasonic probes (phacoemulsifiers). Endolaser systems for removing the cataractous lens are the most promising candidates.

By directing laser energy into a flexible fiber, cataract removal could be performed endoscopically while minimizing iatrogenic trauma to healthy tissue. Bath demonstrated successfully the use of the 308-nm XeCl excimer laser for cataract removal [46], [47]. Despite several advantages, such as a rapid tissue removal rate (25 μm/pulse at 6.5 J/cm^2), limited thermal damage to adjacent tissue ($\leq$ 50 μm) and the availability of inexpensive silica fibers with good transmission properties, the fluorescence induced by 308-nm laser pulses may cause significant retinal damage [48]. Potential carcinogenesis and cataractogenesis of UV light (308 nm) to the operator and the patient also raises serious concern about the use of this wavelength.

Mid-infrared (2.5–3.5 μm) lasers offer an alternative possibility for laser cataract removal. In this spectral region, the optical penetration depth can be controlled to less than 1 μm by choosing an IR wavelength that corresponds with the absorption peak of lens tissue (2.9–3.0 μm). The laser energy will then be confined to a very small volume, preventing photons from reaching other intraocular structures such as the retina or the corneal endothelium. The short penetration depth of mid-IR laser radiation also minimizes thermal damage to adjacent tissue, providing the pulse duration is shorter than the thermal relaxation time of the lens tissue. In addition, laser excitation in the mid-IR region precludes electronic absorption, eliminating undesirable fluorescence.

Transmitting mid-infrared (2.8–3.1 μm) short laser pulses ($\leq$ 500 ns) through an optical fiber is a challenging technical problem [49] and may require the use of exotic materials such as zirconium fluoride (ZnF_4) and specially designed probes (Figs. 20 and 21). Efforts to refine this approach and to integrate a micro irrigation-aspiration system that will be practical for clinical use are underway by a number of investigators.

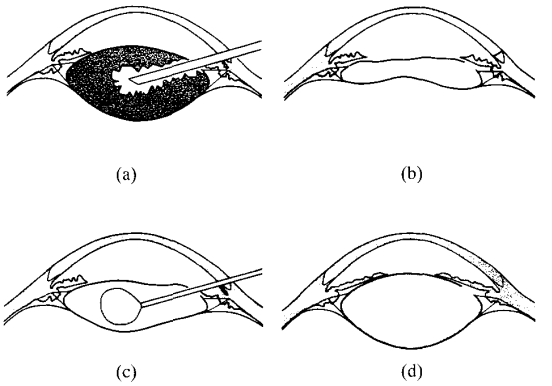


Fig. 19. Phaco-Ersatz. The cataractous lens is removed through a small incision with an integrated endolaser-irrigation-aspiration system The capsular bag is retained, allowing injection of a suitable polymer that has optical and mechanical properties similar to those of the natural lens. Such a procedure may allow restoration of accommodation, the ability of the lens to increase its optical power and focus upon near objects.

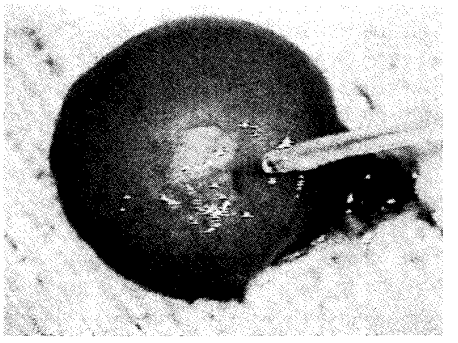


Fig. 20. Photovaporization of a dense human lens nucleus in vitro with a pulsed HF (350 nm, 2.9 μm, 10 Hz) laser conducted through a shielded ZrF fiber. Practical clinical use will require coupling the laser fiber to an irrigation-aspiration system to remove lens by-products and prevent excessive heat build up.

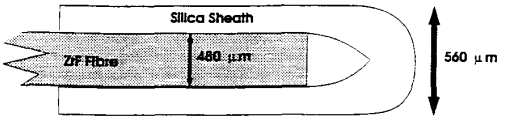


Fig. 21. Silica cladded ZrF fiber used for conducting 2.9-μm Hf laser energy for experimental cataract removal.

5) Laser Induced Hyperthermia for Ocular Tumors: Ocular tumors include uveal melanoma in adults and retinoblastoma in children. Conventional treatments for these tumors include enucleation, ionizing radiation, external beam or brachytherapy, photocoagulation, and cryotherapy. Tumor selective hyperthermia (41°C–45°C), and nonselective hyperthermia, (>45°C), are techniques that show potential synergistic effects with other forms of tumor treatment such as ionizing radiation, chemotherapy, and photodynamic [50].

Present methods of producing hyperthermia in ocular tumors include the use of microwaves, radio frequency

waves, and ultrasound energy sources. The localization of the heating by electromagnetic radiation, either transcorneal or transcleral, is very difficult to control and can lead to significant side effects, such as cataract formation.

Near infrared light (700–1200 nm) can also induce significant tissue heating. Additionally, such wavelengths effectively penetrate tissue. Infrared laser wavelengths are predominantly scattered in most light to medium pigmented tissue, and absorbed by heavily pigmented tissues. Additionally, the cornea, lens, and vitreous are relatively transparent to infrared wavelengths. These two factors make infrared laser wavelengths a potential source for producing localized heating in ocular tumors [51].

C. Beam Delivery Systems for Photocoagulation

In ophthalmology, four types of optical delivery systems are currently used. Two are used in the outpatient setting: 1) A joy-stick controlled delivery system mounted on the slit-lamp-biomicroscope for treatment of the patient in the sitting position (Fig. 13(a) and (b)) and 2) a surgeon head-worn indirect ophthalmoscope delivery system used with the patient in a 45°–70° reclined position. Two other modalities are used in the operating room with the patient in the supine position: 3) a joy-stick controlled system mounted on the binocular operating microscope to treat readily visible and accessible tissues and, 4) a hand held fiber-optic probe system used for endocular and endoorbital surgical treatment (Fig. 13(c)).

All types of delivery systems are connected usually to medium power (5 to 8 W) constant wave argon krypton, dye, pumped dye, constant wave Nd:YAG, and (1 to 3 W) AlGaAs diode lasers via a 500-μm diameter monofilament silica fiber having a numerical aperture of 0.1 to 0.2. Articulated arm delivery systems are no longer used in ophthalmic photocoagulator designs. The optics for the first three types of delivery systems are designed to produce a small focal spot on the target (range 50–1000 μm). The endophotocoagulator probe uses a 300- to 400-μm core diameter fiber that produces a 500 μm–2 mm spot depending upon the distance of the probe tip to the tissue. Recently, Rol introduced a series of novel endoprobes equipped with micro-optics to further reduce the spot diameter and focalize the laser beam on target [52]. This system's output power is in the range of 100 mW–2 W and the energy delivered to target is 100–10 J. With most commercially available delivery systems, the laser power output (0%–100%) and pulse duration (0.1 to 1 s, in 0.1 s increments) are preset on the control panel by the surgeon who activates the laser using a foot-pedal switch. For safety, several interlocks are provided by the manufacturer in accordance with laser safety regulations.

To prevent contamination and permit mobility of surgical equipment, single-phase (110 or 220 VAC) and air cool laser operation are preferred in the clinic and almost mandatory in the aseptic operating room. As with many medical instruments, miniaturization of the laser and delivery systems are prerequisites for ophthalmological use.

The use of subminiaturized endoscopes designed for intraocular photocoagulation of the ciliary body and anterior retina under visual control have been introduced recently [52]. Thus far, this technique has been restricted to *in vitro* and animal studies.

For other ophthalmic surgical procedures, subminiature fiber-optic endoscopes provide the surgeon with a good view and illumination and lead to more precise surgical procedures than the more conventional "open-sky" surgical techniques. At the present time, endolaser surgical procedures require different types of fibers for tissue ablation, coagulation, shrinkage, welding, and sensitization of tissue and illuminating and imaging of the surgical field. In the future, these different functions may be integrated into a single fiberoptical delivery system, facilitating surgeon control.

Diode lasers, recently introduced in 1987, are the newest photocoagulators [53]. These lasers have the advantage of greatly decreased size, cost, and reduced maintenance. Presently, AlGaAs diode lasers emitting at 805 nm with output power 1–3 W have been used for the treatment of retinal vascular disease. Clinical advantages to the diode laser include minimal absorption and scattering in cataract or mild vitreous hemorrhage compared to the argon green wavelength and low absorption in intraretinal hemorrhage. Excellent laser penetration through macular edema and serous retinal thickening have also been demonstrated. Present technical disadvantages to the diode laser include limited power output and a more divergent beam cone angle than the argon and krypton lasers. Since semiconductor laser technology has rapidly advanced in recent years, the future outlook for semiconductor lasers is very promising. Diode lasers and diode-pumped solid-state lasers with multiwatt power output at wavelengths that are desirable for various clinical applications will be available to replace the more expensive and bulky argon, krypton, and dye lasers for ophthalmic applications. Q-switched and mode-locked diode lasers with sufficient energy density in the nanosecond to picosecond range may also replace the Nd:YAG laser as a photodisruptor for iridectomy, trabeculoplasty, and cyclophotocoagulation.

V. Photodisruptive Laser Applications

A. Photodisruptive Laser-Tissue Interaction

A disadvantage to laser applications utilizing photothermal mechanisms is that the laser wavelength and absorption properties of the tissue must be carefully matched. Tissues transparent to the incident wavelength will be unaffected.

In the late 1970's, short pulsed 1064-nm Nd:YAG lasers ($\approx$ 30 ps for mode-locked and $\approx$ 10 ns for Q-switched) were introduced to create optical breakdown and photodisruption of ocular tissues. The Nd:YAG photodisruptors are now in common clinical use. The laser beam is brought through a high numerical aperture beam expander-focusing lens system (20°–40° cone angle) to a sharp focus ($\approx$ 10- to 50-μm diameter) to achieve extremely high irradiances ($10^8 - 10^{11}$ W/cm^2) such that ionization of molecules

Table 2 Photodisruptor Laser Applications

Procedure	Disease	Laser/Wavelength	Rationale	Comment
Posterior Capsulatomy	Capsular opacification after cataract surgery	Nd:YAG-1064	Photodisruption allows small opening to be created without IOL damage	Widespread use. Replaced need for intraocular procedure
Lysis of Vitreous Strands	After trauma, surgery	Nd:YAG-1064	Adhesions can be severed without entering eye.	
Peripheral Iridotomy	Glaucoma	Nd:YAG-1064	Hole in iris allows alternative path for aqueous flow, preventing angle closure.	Alternative to photothermal laser in patients with lightly pigmented iris.
Intrastromal Corneal Ablation	Refractive errors	Nd:YAG-1064 2nd harmonic-562	Removing tissue from stroma changes corneal refractive power	Experimental
Endolaser Vitreous Surgery	Diabetes, trauma	Nd:YAG-1064 Er:YAG-2.9 μm	non-contact cutting	Experimental

occurs at the target. The irradiated material disintegrates into plasma, a collection of ions and electrons plasma which reaches peak temperatures of $\geq 10^4$ °C. Shock waves emanating from the site of plasma formation cause mechanical disruption of structures adjacent to the site of optical breakdown. Since optical breakdown is a threshold phenomenon that depends upon the strength of the electrical field, photodisruption is not dependent upon absorption of the wavelength by the target tissue, photodisruptors may be used in tissues that are transparent to the incident laser wavelength. It is only necessary for the photodisrupting laser delivery system to achieve the required high irradiance within a small volume of tissue for optical breakdown to occur.

B. Photodisruptor Applications

Photodisruptor laser applications are useful for cutting, incising, or vaporizing intraocular tissues. Table 2 summarizes the clinical and research applications for photodisruptors in ophthalmology.

1) Posterior Capsulotomy: By far the most common photodisruptor application is the creation of a posterior capsulotomy with a Nd:YAG laser, performed several months to years following extracapsular cataract surgery when the posterior capsule, left intact by the surgeon to support a plastic intraocular lens (IOL), opacifies due to proliferation of retained lens epithelial cells [54]. The patient, who experienced improvement of vision following surgery, suffers slowly declining vision as the capsule opacifies. The surgeon uses the Nd:YAG photodisruptor to create a central opening in the capsule, restoring vision. The surgeon must be careful to focus on or slightly behind the posterior capsule, or undesirable pitting or cracking of the polymethyl methacrylate intraocular lens can occur.

The use of the Nd:YAG laser in ophthalmology was simultaneously introduced by glaucoma specialist Franz Fankhauser in Switzerland (Q-switched) and cataract specialist Danielle Aaron-Rosa in France (mode-locked) in 1980. Two years later the first international congress dedicated to the theory and clinical use of these lasers was held in Munich, Germany and the technique gained rapid acceptance thereafter.

2) Vitreo-Retinal Surgery: The Nd:YAG photodisruptor has also been used for cutting vitreous strands in the vitreous cavity and anterior chamber, creating peripheral iridectomies, severing trapped IOL haptic loops, and cutting sutures. These lasers allow outpatient surgical treatment and have reduced postoperative complications, such as inflammation and infections associated with intraocular surgical procedures.

In 1980, Parel and Fankhauser designed a 1-mm diameter Q-switched Nd:YAG laser miniature endoprobe delivery system for severing vitreous and proliferative retinal membranes (Fig. 22). In these early experiments, Fankhauser's group and ours failed to transmit short 10-ns pulses through the silica fibers that were available at the time. After designing a novel laser-to-fiber focussing mechanism and repetitive attempts, Rol and Fankhauser were successful in transmitting 10 ns (Q-switched), and 250 μs to 20 ms (free-running) Nd:YAG pulses, of sufficient energy for photodisruption and photocoagulation of intraocular tissues using high purity silica fibers. More recently, Margolis and coworkers successfully photoablated intraocular proliferative membranes using a free-running Er:YAG coupled to a bare ZrF_4 fiber optic [55]. However hygroscopic, mechanical, and optical problems, including laser beam spatial stability, remain formidable and further research is required in fiber and laser technology before a clinically usable endolaser photodisruptor instrument is available.

3) Intrastromal Corneal Photodisruption: Recently, picosecond and nanosecond photodisruptors have been designed for use in corneal surgery. Focused in the middle portion of the central cornea, the high frequency (103–104 Hz) pulsed laser beam is scanned parallel to the corneal plane. Photodisruption transforms the thin lamellae of the corneal stroma into gas which, after absorption, may change

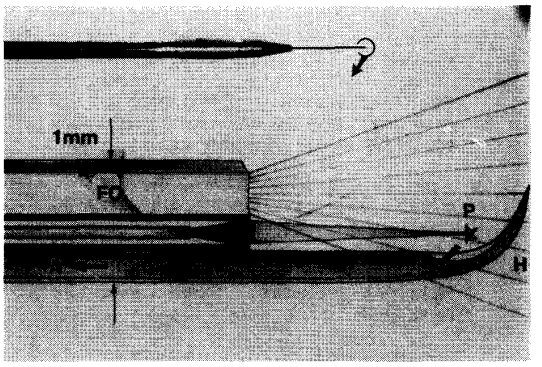


Fig. 22. Endolaser probe. An aspheric microlens focuses the laser beam above the vitreous fluid aspiration port. Endoscopic illumination is provided by a conventional coaxial 12-μm fiber bundle. The hook is designed to lift and separate the membranes to be cut from the delicate retinal tissue and provides a shield that prevents laser radiation and plasma-induced secondary radiation from reaching healthy tissues. An electromechanical beam switcher (Nd:YAG to Argon) located in the remote console allowed intraoperative photocoagulation of intraocular bleeding vessels.

the outer corneal curvature, resulting in a change in the eye's refractive power. The theoretical advantage to this approach is that the epithelium and Bowman's layer are left intact and therefore the unpredictable refractive effect of corneal wound healing may be minimized. In addition, this technique is thought to minimize thermal damage to the collagen lamellae adjacent to the photodisrupted zone. Two systems are presently under development; a frequency doubled (562 nm) mode locked (30 ps) Nd:YAG (562 nm, 30 ps) laser and a Q-switched 1064 nm (5 ns) Nd:YAG. Both use very high numerical aperture aberration-free optical systems to minimize the volume of photodisrupted tissue. Although this approach is intriguing in theory, thus far no data has been published indicating intrastromal photodisruption can alter the refractive status of the eye effectively or predictably. Basic laboratory and clinical research with this technique is continuing.

C. Photodisruptor Delivery Systems

Since it is technically difficult to transmit Q-switched laser pulses and impossible to transmit mode-locked laser pulses with sufficient energy for tissue photodisruption through optical fibers, the optical delivery of the photodisruptor laser beam is accomplished via sets of high quality mirrors and high precision articulated arms. The laser optics are normally integrated physically in a conventional slit-lamp biomicroscope or operating microscope in a fashion similar to that shown for the photocoagulating instruments (see Fig. 12). Since focusing of the photodisrupting laser beam on target is very critical, a set of two or more confocal He–Ne laser beams are focused on the target tissue while observing under magnification (20–40 $\times$). To facilitate focusing, the He–Ne laser beams are made to rotate or synchronously alternate so as to produce a single stable spot when focus on target is reached. To minimize the optical aberrations produced by the cornea and off-axis treatment, special contact lenses are normally used. These lenses further increase the numerical aperture of the optical delivery system and therefore minimize the spot diameter and improve overall efficacy. With such lenses, capsulotomy can be performed with as little as 0.5 mJ using a 10-ns Q-switched Nd:YAG laser. The systems designed for corneal intrastromal ablation also incorporate an eye tracking device in order to achieve the high spatial resolution necessary for this procedure. These systems may also be used for conventional photodisruptor applications such as capsultomies and iridotomies.

VI. Photochemical Laser Applications: Photoablation and Photodynamic Therapy (Table 3)

A. Photoablation Mechanism

A new form of laser-tissue interaction was discovered in 1983 by Trokel and Srinivasan working at IBM [56]. Srinivasan was studying the far-UV (193 nm) argon fluoride excimer laser for photoetching applications when Trokel, an ophthalmologist, noted that corneal tissue could be removed discreetly and precisely without any histological evidence of thermal damage to the adjacent corneal tissue. Trokel recognized the potential of the excimer laser to offer a new approach to corneal surgery: corneal sculpting.

Photoablation occurs because the cornea has an extremely high absorption coefficient at 193 nm, and the photons at 193 nm are highly energetic, possessing more energy than the carbon–carbon bonds interlinking the protein molecules of the cornea. Consequently, 193-nm photons rupture the intermolecular bonds and a discrete volume of corneal tissue is removed with each pulse of the laser (Fig. 23) [57], [58]. The depth of the ablation is dependent upon the radiant exposure and typically varies from 0.1 to 0.5 μm per pulse at a fluence of 50 to 250 mJ/cm^2 (Fig. 24) [59].

The laser-corneal tissue interactions of other far-UV excimer wavelengths including 157, 248, 308, and 351 nm have been investigated and the 193-nm wavelength generated by the argon fluoride excimer has been found to achieve the best quality corneal excisions for clinical use (Fig. 25). The 157 nm produced by the fluorine dimer produced similar quality excisions [60], but its use is not practical clinically because of high atmospheric absorption at this wavelength.

Initially it was suggested to use the excimer laser as a "laser scalpel" for corneal surgery in operations such as radial keratotomy [61]. However, the excimer laser was found to be a poor replacement for a cutting scalpel, because the laser removes rather than cuts a defined volume of tissue. Even with high quality aberration-free optics, excisions smaller than 60 μm were difficult to produce due to multimode operation and poor beam homogeneity. Clinical attempts to use the excimer laser with a set of linear slit-masks for radial keratotomy resulted in even wider (250–300 μm) excisions (Fig. 26). Because of the wide excisions and poor corneal stromal wound healing that

Table 3 Photochemical Laser Applications: Photoablation and Photodynamic Therapy

Procedure	Disease	Laser/Wavelength	Rationale	Comment
Photorefractive Keratectomy (PRK)	Refractive Errors	ArF Excimer-193	Precise sculpting of cornea possible	Large clinical study underway in U.S.
Phototherapeutic Keratectomy (PTK)	Corneal Scars and Disease	ArF Excimer-193	Precise removal of opaque and diseased superficial corneal tissue	Clinical study underway
Ab Externo Laser Filtration Surgery	Glaucoma	ArF Excimer-193	External filtration pathway created by laser	
Photodynamic Therapy	Ocular Tumors	Dye-630	Laser activated photosensitizers cause tumor destruction	Investigational

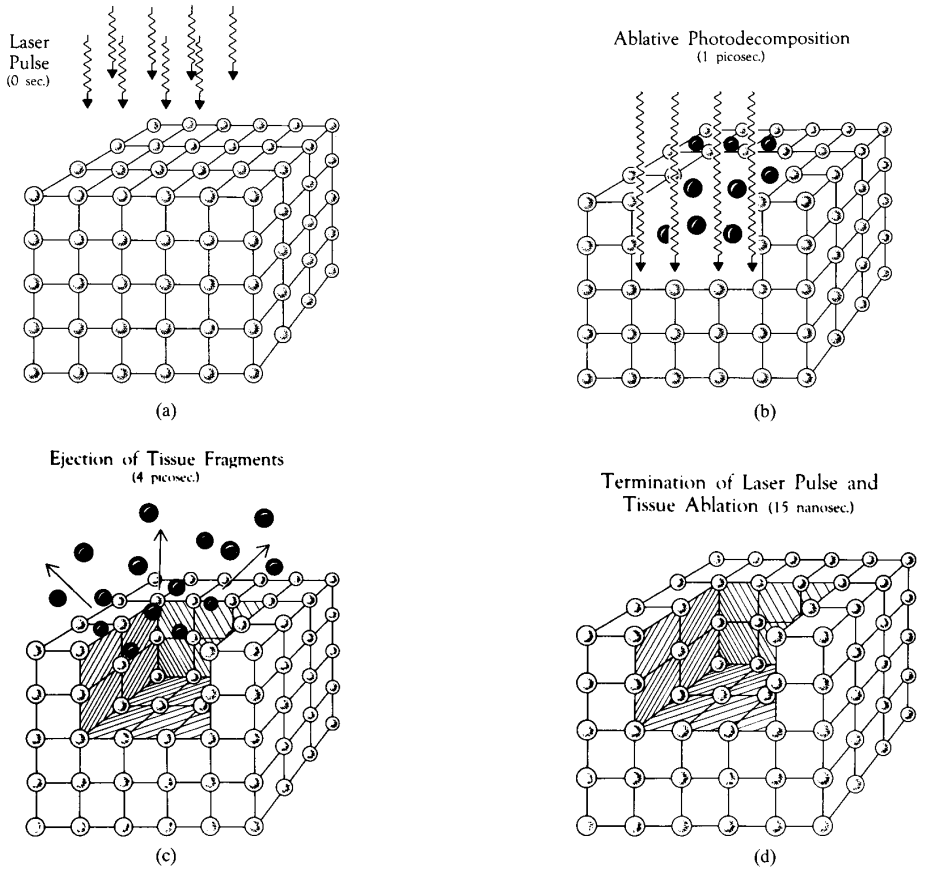


Fig. 23. 193-nm argon fluoride laser pulses result in a unique photochemical interaction with the cornea termed photoablation. The (a) laser pulse is highly absorbed in the first several microns of corneal tissue, primarily by protein chromophores (b). Since the 193-nm photons have energy in excess of the carbon-carbon intermolecular bonds of corneal tissue, the bonds are photoelectrically decoupled, resulting in (c) the ejection of many small fragments from the surface. (d) The photoablation process is completed after 15 ns, leaving clean, precise edges with only 0.3 μm of adjacent tissue alteration.

followed after deep laser excisions, the use of the excimer laser for this type of surgery has generally been abandoned.

The most exciting application of the excimer laser was found to be its ability to sculpt or reshape the outer de-epithelialized surface of the cornea to correct refractive errors. This relatively new surgical procedure was named photorefractive keratectomy (PRK) by its developers (Fig. 27) [62]. PRK underwent considerable scrutiny because

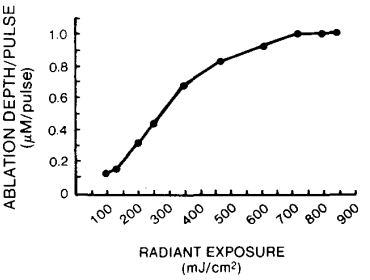


Fig. 24. Ablation depth of the human cornea per pulse versus radiant exposure with the 193-nm excimer laser. Tissue ablation rate will vary with the hydration of the cornea.

Fig. 25. High quality graded corneal excisions produced with the 193-nm excimer laser using the Hanna-IBM moving slit delivery system. Single epithelial cells (Ep) have been cleaved with the laser. Note the recontouring of Bowman's layer (BM) possible with the laser (S=Corneal stroma).

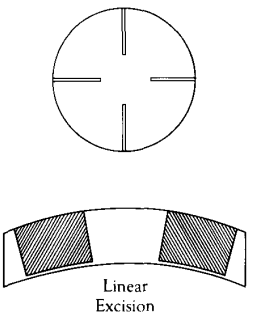


Fig. 26. Deep linear corneal excisions produced with a 193-nm excimer laser and mask system. The excisions filled with an epithelial plug and were found to heal poorly resulting in abandonment of this approach.

treatment of the central cornea—the most important image forming element of the eye—was involved. Early animal studies were encouraging [63], [64], and as the laser

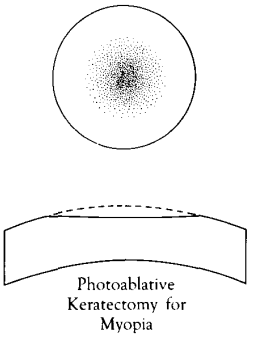


Fig. 27. PRK for myopia with the 193-nm excimer laser. The stromal surface of the cornea is recontoured with the laser following removal of the epithelium by the surgeon. Following reepithelialization, the anterior corneal curvature is flatter, reducing myopia. Preliminary evidence indicates that this technique is safe and effective for reducing myopia up to six diopters.

and delivery system technology matured, confidence was gained that sighted human eyes could undergo excimer laser corneal sculpting without vision threatening complications. The first sighted eye was performed in 1989 [65], and since that time several thousand procedures have been performed in Europe and several hundred in the U.S. as part of a carefully controlled FDA study conducted by three manufacturers: Summit Technology (Watertown, MA), Taunton Technologies, and VisX (Sunnyvale, CA), (the latter two companies have recently merged). Present data indicate that PRK appears to be a safe and effective method for reducing myopia up to six diopters with few side effects or complications [66]–[69]. Treatment of myopia greater than six diopters has been less successful due to regression of the refractive effect from corneal wound healing [70]. To date, attempts to steepen the cornea to treat hyperopia with the excimer laser have been unsuccessful because the wound healing processes of the corneal stroma and epithelium cause the curvature to return to its preoperative shape, negating the refractive effects of the procedure.

If approved for general use, the laser may offer an alternative to glasses and contact lenses for millions of myopic individuals, and may represent the most widespread application for a laser in ophthalmology [71]. Longer term studies to assess the overall predictability, stability, and safety of the procedure are underway.

Although the excimer laser is entering clinical use, this gas laser has several disadvantages. The apparatus is large and bulky, complicating its use in the clinical environment. Fluorine gas is toxic (ED_{50} = 0.3 ppm) and requires special safety considerations. Therefore, a solid-state laser source in the far UV is desirable. Ren and coworkers have demonstrated generation of 213 nm from a frequency quintupled Nd:YAG laser using nonlinear frequency multiplying crystals (Fig. 28) [72]. They demonstrated high quality photoablation of corneal tissue, similar to 193-nm excimer excisions with the 213-nm wavelength. Whether or not the frequency multiplied solid-state lasers can become clinically practical remains to be seen.

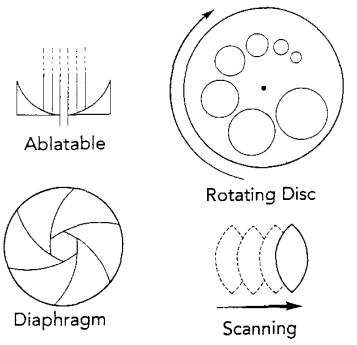


Fig. 28. Different methods of shaping the excimer laser beam include an ablatable polymer mask, computer controlled diaphragms, rotating discs, and movable elliptical masks.

C. Delivery Systems for Photoablative Lasers

Several beam delivery systems have been developed to homogenize, shape, transmit, and focus the ArF excimer laser for corneal ablation. Methods of beam homogenization include moving lens arrays and cylindrical optics. Beam shaping strategies include the use of one or several apertures whose dimension, shape, and position relative to the corneal apex is normally controlled by a computer. Rotating wheels that contain apertures of several shapes and size [73], expanding or constricting iris-diaphragms that expand or constrict [74]–[76], mathematically defined slits, and mathematically defined perforated masks that move have been used to regulate the energy delivered to the cornea in optical delivery systems. A different approach utilizes a preshaped photoablatable synthetic mask positioned immediately above the corneal surface. A uniform irradiation beam pattern is required with this technique. All of these concepts are based on surface ablation using commercially available excimer laser systems with quasi-rectangular beam patterns (usually 25 mm × 7 mm) and low repetition rates of 10–20 Hz (Fig. 28). The low repetition rates require that these systems treat relatively large areas of the cornea with each pulse in order to complete the treatment within a reasonable clinical time frame (30–60 s). Therefore, with the exception of the synthetic photoablatable mask, the present delivery systems available are limited to creating simple spherical or spherocylindrical optical corrections.

A laser diode pumped, rapidly pulsed (KHz range) UV solid-state laser (Frequency-quintupled Nd:YAG laser emitting at 213 nm) might offer an alternative laser source for corneal sculpting. State-of-the-art scanning technology could be used to "paint" the cornea in any desired pattern, which may facilitate aspheric and spatially irregular corneal sculpting [77]. However, multiple technical challenges that face this technology including low crystal damage thresholds, small spot sizes, and unstable power outputs must first be overcome.

D. Photodynamic Laser Applications

Photodynamic therapy (PDT) utilizes a selective laser wavelength to activate a photosensitizing agent that in turn causes damage or destruction to malignant or abnormal tissue. A photosensitizer is a molecule or compound that produces singlet oxygen or free radicals when irradiated by a particular wavelength. Phototoxicity results from the biochemical interaction of tissues with the singlet oxygen and radicals and is a function of the photosensitizer's quantum efficiency and absorption spectra, its concentration in tissue and the wavelength and fluence of the irradiation.

Only recently has photochemical reaction with cellular and vascular structures been introduced as a means of therapy [78]. Dougherty was first to recognize the potential of di-hematoporphyrins ether (DHE) in the treatment of malignancies. Following intravenous injection, these photosensitizing agents remain longer in rapidly proliferating cancerous tissues, and allow a localized phototoxic effect to be induced by use of adequate photoirradiation. Dougherty developed this procedure which he named DHE photodynamic therapy (DHE-PDT) over 20 years ago. The treatment method consisted of injecting 25 μg/ml of DHE (Photofrin II) per Ka body weight followed by a 100–250 J/cm^2 irradiation at 630 nm with a dye laser 48 hours after injection. Irradiation was performed near a DHE absorption peak at 630 nm because this wavelength has a deeper tissue penetration than DHE's other absorption peaks. For photoactivation of DHE, a constant wave argon pumped R630 dye laser with 1–2 W output is normally used. Postoperative complications to photodynamic therapy include long lasting (up to three weeks) hyperphotosensitization in certain patients. Several centers are investigating the use of other photosensitizers, including phtallocyanides that can be photoinitiated at longer wavelengths.

Apart from the treatment of basal cell carcinomas of the face and eyelids, ophthalmic applications of photodynamic therapy have been limited to attempts to treat ocular melanomas and conjunctival carcinoma [79]. Since, HDP-PDT has failed to demonstrate efficacy to date, several authors are investigating the use of other photosensitizers, including rose-bengal [80] and phtallocyanide [53]. In addition, other authors are investigating photodynamic therapy for the treatment of proliferating vascular disorders of the cornea [81] and retina [82], the treatment of infections [83] and the treatment of proliferative lens epithelium following cataract surgery [84]–[88]. As the later type of treatment is superficial in nature, the constant wave argon 514.5-nm wavelength has also been used successfully. However, since the peak absorption of rose bengal is highest at 562 nm, a solid-state laser operating near this wavelength would facilitate ophthalmic applications.

The laser delivery systems used for PDT are similar optically to those shown in Fig. 12(a) and (b); A timing mechanism connected to the laser foot-switch control is used to calculate the total radiant dose given to the patient. The clinicians have been plagued by technical problems associated with the argon pumped dye laser. Present systems have not incorporated means to adjust and control the output wavelength in the laser console and in many instances

irradiation is performed with an on off-peak wavelength. Furthermore, the laser output power tends to fluctuate during treatment. These problems lead to subthreshold dose, and inadequate treatment. In addition, dye laser breakdown is too common in the clinical setting. Since DHE is injected 48 hours prior treatment, instrumentation breakdown might cause serious medical complications, since the clinician must wait five days to several weeks for drug clearance in hypersensitive patients before repeating treatment. A solid-state laser providing an output of 1 W at the wavelengths used for photodynamic therapy would be of tremendous clinical value and facilitate the investigation of this new therapeutic modality.

VII. Diagnostic Laser Applications

The high radiance, monochromaticity, and spatial and temporal coherence make the laser a unique light probe for noninvasive diagnostic applications in ophthalmology. The information contained in laser light reflected or scattered by intraocular structures can be detected and analyzed for diagnostic purposes. In general, light scattering is a phenomenon inversely proportional to the wavelength of light to the fourth power, thus blue light is scattered more than red light.

A. Visual Acuity Measurement

In this application, the spatial coherence of lasers is used to form interference fringes on the retina. These are dark lines with variable spacing and orientation whose formation is largely insensitive to the optical clarity of the intervening media. The retina's functional health may be evaluated even when it is obscured by a cataract or other cloudy media existing in the eye. The spacing of the fringes is varied by adjusting the angle of two interference beams and the patient indicates whether or not they are visible, facilitating prediction of the patient's acuity after cataract surgery. Fringe contrast may also be varied by adjusting the relative intensity of two laser beams, yielding the retinal modulation transfer function (MTF)—termed the contrast sensitivity function when plotted reciprocally. The light source used for interferometry is generally a He–Ne laser, and the retinal irradiance is in the range of 1 $\mu W/cm^2$. This technology has widespread clinical use today and is very helpful to the ophthalmologist in deciding whether or not cataract surgery will be of benefit to the patient.

B. Laser Doppler Velocimeter (LDV)

In LDV, laser light scattered by moving blood cells is shifted in frequency and is used to measure the rate of blood flow in the veins and arteries of the retina. In this application, the temporal coherence of lasers is used. The light scattered at a particular angle by the flowing particles as well as the light scattered from the vessel wall is collected by a photodetector. The light scattered from the vessel wall is unshifted in frequency and thus acts as the reference beam. Interference between the reference beam and the scattered light can be used to generate a difference in frequency which is directly related to the maximum red blood cell velocity at the measurement site. In this application, it is important to keep a well defined spot on the site to be measured and to know reliably the angle between the incident and scattered light.

LDV is a research tool that is providing important information to scientist studying retinal blood flow.

C. Scanning Laser Ophthalmoscope

The scanning laser ophthalmoscope (SLO) was developed by Webb for viewing the retina and its supporting structures including blood vessels, nerve bundles, and underlying layers [89]–[91]. In scanning laser ophthalmoscopy, a laser beam, about 1 mm in diameter at the eye's pupil, is focused to a 10-μm spot on the retina. The beam is scanned over the retina, without changing its location at the pupil (it "pivots" within the entrance pupil). At any instant only a 10-μm spot on the retina is illuminated, and that instant may last only 100 ns. Light in the illuminating spot may be absorbed or scattered. If absorbed, the detector at that instant records no response, and the display shows black. If the light is scattered, however, some of it will reach the detector, the detector records a voltage and the display shows a spot with the corresponding gray level intensity.

The SLO uses a highly collimated laser beam for illumination, thus requiring a smaller entrance aperture and less sensitive collection optics than conventional optical systems imaging. The image detected by the SLO are temporally coded rather than spatially coded, as with an indirect ophthalmoscope.

The scanning laser ophthalmoscope has opened a new dimension in psychophysics, since it allows direct observation of the retinal location on which the stimulus is presented. Future applications of the SLO include use as a therapeutic device (photocoagulator) and a retinal eye tracker.

D. Spectroscopic Diagnosis of Ocular Diseases

Spectroscopic techniques such as fluorescence spectroscopy, and Raman spectroscopy are under investigation as noninvasive means to detect various abnormal states of ocular tissues and ocular diseases. Much of the research effort has been concentrated on detection of early cataract formation and certain vitreous disorders.

The transparency of the lens changes normally with age, and sometimes degenerates entirely with the formation of a cataract. Laser Raman spectroscopy has been employed as a noninvasive probe to study the metabolic and structural features of the lens [92]–[94]. With newly developed near-infrared (NIR) Fourier transform (FT) Raman spectroscopy, fluorescence interferences from heavily pigmented ocular lenses can be eliminated and spectroscopic information can be remotely acquired via fiber-optic probe and analyzed in real time [95]. An automated laser-scanning-microbeam system has been developed for the fluorescence/Raman imaging of the human lens. Aging related fluorophor con-

version (from blue fluorophor to the green fluorophor) and intensity change in spatial distribution have been identified [96], [97]. This spectroscopic information has added to our understanding of the biochemical changes associated with cataract formation.

VIII. Summary

During the past two decades, laser technology has revolutionized many aspects of ophthalmic surgery. Millions of patients have benefitted from the restoration or preservation of vision from laser treatment. The use of lasers to successfully treat retinal diseases, glaucoma, and capsular opacification following cataract surgery is now the standard of care. The end result of the interactions between basic scientists, clinicians, and industry that have produced this revolution has markedly improved in the ability of ophthalmologists to help their patients.

Nevertheless, potential for abuse and exploitation of laser technology exists and should be resisted. The use of expensive lasers should be limited to procedures they can do uniquely or do more effectively than simpler, inexpensive technology. Use of lasers for dubious indications for a medical marketing advantage not only unnecessarily escalates the cost of health care, but further elevates the public's unrealistically high expectation of what laser technology can actually delivery.

Still, the future of laser technology in ophthalmology looks very bright. The excimer laser may offer improvements in the safety and efficacy of refractive surgery, and could offer millions of myopic individuals a viable alternative to the dependence on glasses and contact lenses for clear vision. Like parallel advances in computer technology, ophthalmologists can expect existing lasers to become smaller, more capable, and less expensive as solid-state laser technology matures.

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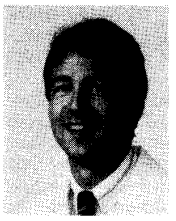

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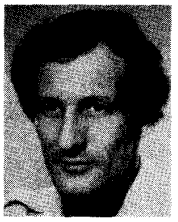

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