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Excimer Laser Surgery: Laying the Foundation for Laser Refractive Surgery

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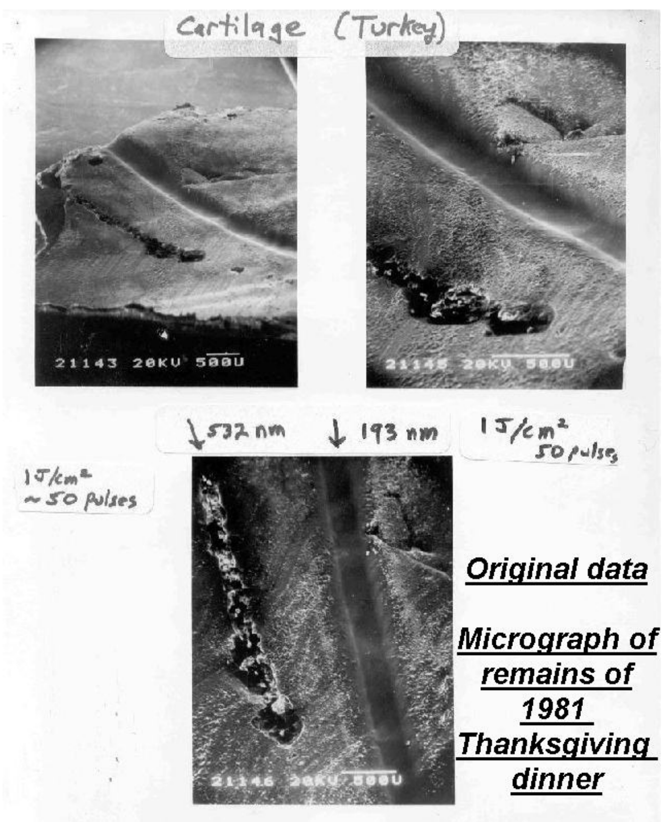
The discovery of excimer laser surgery

On November 27, 1981, the day after Thanksgiving, Dr. Rangaswamy Srinivasan brought leftovers from his Thanksgiving dinner into the IBM Thomas J. Watson Research Center, where he irradiated turkey cartilage with ~10-nsec pulses of light from an argon fluoride (ArF) excimer laser. This irradiation produced a clean-looking "incision" in the cartilage, as observed through an optical microscope. Subsequently, Srinivasan and his IBM colleague, Dr. Samuel E. Blum, team carried out further irradiation of turkey cartilage samples under controlled conditions, measuring the laser fluence and the number of pulses used to produce the incisions. Srinivasan gave a sample to me, and, for comparison, I irradiated it with ~10-nsec pulses of 532-nm light from a Q-switched, frequency-doubled, Nd:YAG laser. This irradiation did not incise the sample; rather it created a burned, charred region of tissue. Fig. 1 shows three different views and magnifications of scanning electron micrographs (SEM) of the sample, revealing the stunningly different morphology of the two irradiated regions, the clean incision with no evidence of thermal damage, etched steadily deeper by a sequence of pulses of 193-nm light, and the damaged region produced by the pulses of 532-nm light.



[**Fig. 1** – Three scanning electron micrographs of laser-irradiated turkey cartilage, recorded from different perspectives and with different magnification. In the bottom micrograph, arrows indicate the regions irradiated with 193-nm light and 532-nm light. For each wavelength, the fluence/pulse and number of pulses of irradiation are given.]

Srinivasan, Blum and I realized that we had discovered something novel and unexpected, and we wrote an invention disclosure, completed on Dec. 31, 1981. Our disclosure described multiple potential surgical applications, on hard tissue (bones and teeth) as well as soft tissue. We anticipated that the absence of collateral damage to the tissue underlying and adjacent to the incision produced *in vitro* would result in minimal collateral damage when the technique was applied *in vivo*. The ensuing healing would be free of fibrosis and the resulting scar tissue. We recognized that we had a laser surgical method that was a radical departure from all other laser surgical techniques that had been developed since the operation of the first laser on May 16, 1960. Rather than photocoagulating the irradiated tissue, the excimer laser was ablating a thin layer of tissue from the surface with each pulse, leaving negligible energy behind, insufficient to thermally damage the tissue underlying and adjacent to the incised volume. This insight was unprecedented and underlies the subsequent application of our discovery to laser refractive surgery.

Background to this discovery

Since 1976, as manager of the Laser Physics and Chemistry department of IBM's T. J. Watson Research Center, one of my responsibilities was to ensure that we had access to the best and latest laser instrumentation. Earlier, I had used a nitrogen laser, emitting short pulses of ultraviolet light at 337-nm, to pump fluorescent dyes that emitted visible and near infrared light, which he used for laser spectroscopic studies. When the excimer laser, a higher-power, pulsed source of ultraviolet radiation became commercially available, I purchased a unit for use by the scientists in my department. Srinivasan had devoted his entire research career since 1960 to study the action of ultraviolet radiation on organic materials, e.g., polymers. In 1980, he and his group discovered that the ~10-nsec pulses of far ultraviolet radiation from the excimer laser could photoetch solid organic polymers, if the fluence of the radiation exceeded an ablation threshold. [1,2]

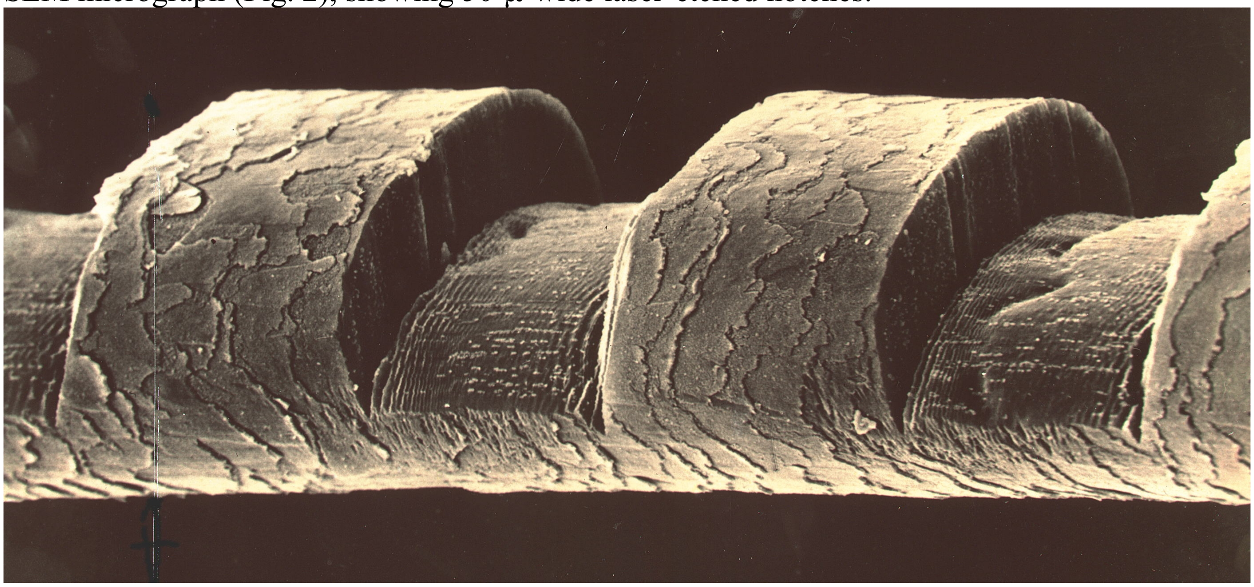
Since organic polymers proved susceptible to etching by the excimer laser irradiation, we reasoned that an animal's structural protein, such as collagen, which contains the peptide bond as the repeating unit along the chain, would also respond to the ultraviolet laser pulses. We knew that when skin was incised with a sharp blade, the wound would heal without fibrosis and the resulting scar tissue. Conceivably, living skin or other tissue, when incised by irradiation from a pulsed ultraviolet light source, would also heal without fibrosis and scarring.

The physics of ablation

In more detail, ablation occurs when the laser fluence (energy/area/pulse) exceeds the ablation threshold, that is when the energy deposited in a volume of tissue is sufficient to break the chemical and physical bonds holding the tissue together, producing a gas that is under high pressure. The resulting gas rapidly expands away from the irradiated surface, carrying away most of the energy that was deposited into the volume that absorbed the energy. If the absorption depth is sufficiently shallow and the pulse duration is sufficiently short, the expanding gas can escape from the surface in a time short compared to thermal diffusion times, leaving a clean incision with minimal collateral damage. These conditions are readily satisfied by a short pulse of short wavelength light having sufficient energy/unit area, given that protein and lipids are very strong absorbers of ultraviolet light.

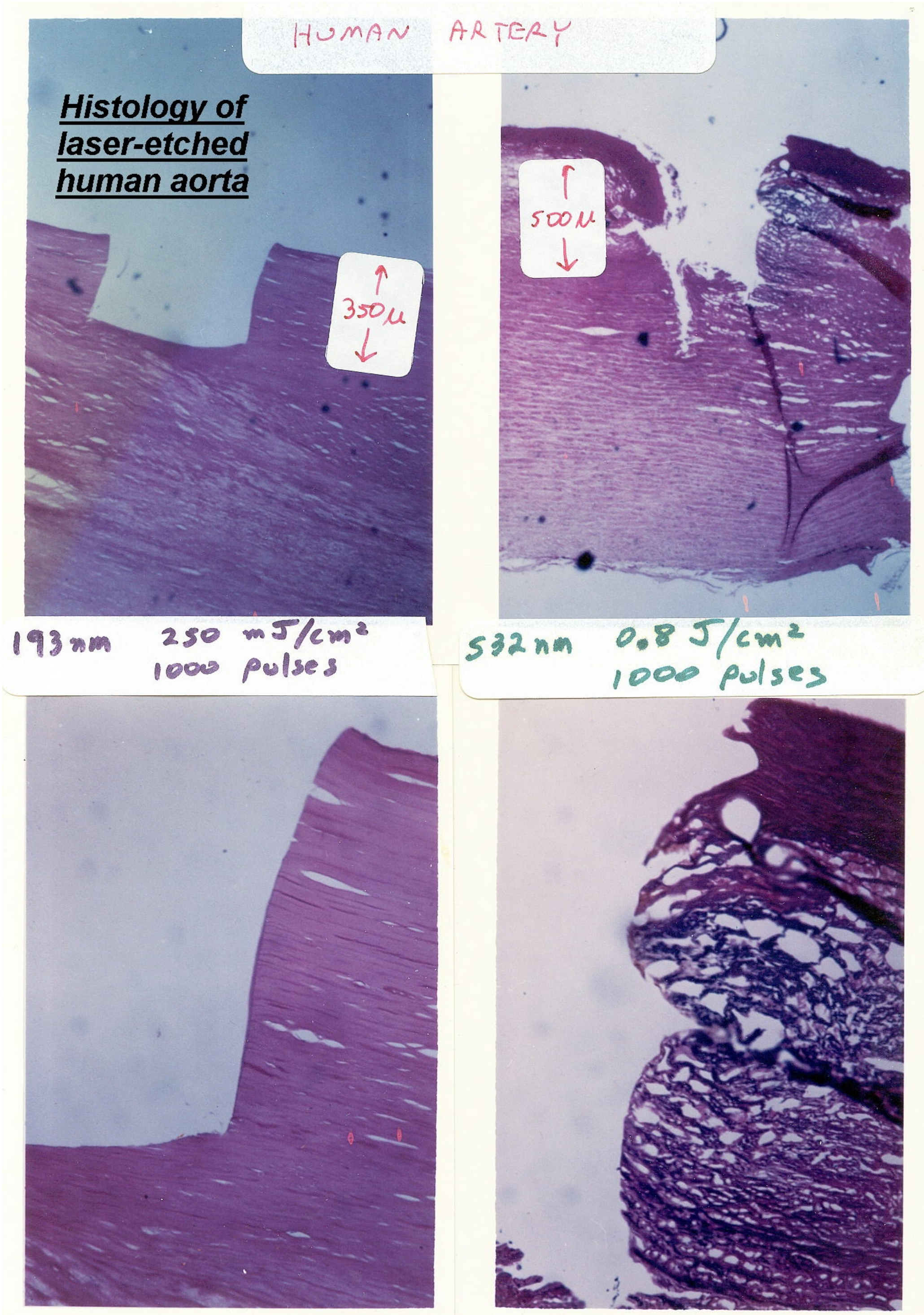
Next steps

To develop practical innovative applications from our discovery, it was clear that we had to collaborate with medical/surgical professionals. In order to interest these professionals, we etched a single human hair by a succession of 193-nm ArF excimer laser pulses, producing a SEM micrograph (Fig. 2), showing 50-μ-wide laser-etched notches.



[**Fig. 2** – Scanning electron micrograph of a human hair etched by irradiation with an ArF excimer laser; the notches are 50 μ wide.]

While the IBM Intellectual Property Law was preparing an invention disclosure, we were not allowed to discuss our discovery with people outside IBM. But we had a newly hired IBM colleague, Ralph Linsker, with an M.D. and a Ph. D. in physics. Linsker obtained fresh arterial tissue from a cadaver, and we irradiated a segment of aorta with both 193-nm light from the ArF excimer laser and 532-nm light from the Q-switched, frequency-doubled Nd:YAG laser. Once again, the morphology of the tissue adjacent to the irradiated/incised regions, examined by standard tissue pathology techniques (Fig. 3), was stunningly different, with irradiation by the 193-nm light showing no evidence of thermal damage to the underlying and adjacent tissue. [3]



[**Fig. 3** – Left side: Photo micrographs of human aorta irradiated *in vitro* by 1000 pulses of ArF excimer laser 193-nm light; lower image is a magnified view of an area of the upper image, namely the right-hand-side of the laser-irradiated region

Right side: Photo micrographs of human aorta irradiated *in vitro* by 1000 pulses of Q-switched, frequency-doubled Nd:YAG laser 532-nm light; lower image is a magnified view of the upper image, namely the right-hand-side of the laser-irradiated region]

This experimental study on freshly excised human tissue confirmed that excimer laser surgery removed tissue by a fundamentally new process. Our vision--that excimer laser surgery would allow tissue to be incised so cleanly that subsequent healing would not produce scar tissue--was more than plausible, it was likely, subject to experimental verification on live animals.

First public disclosure

After IBM filed our patent application on December 9, 1982, we were authorized to publically disclose our discovery. We wrote a paper and submitted it to Science magazine, but it was rejected, because one of the referees argued that the irradiation of living humans and animals with far ultraviolet radiation would be carcinogenic, making our laser surgical technique more harmful than beneficial. Since Srinivasan now had an invitation to give a presentation about his work on polymers at the upcoming CLEO 1983 conference in Baltimore, MD, co-sponsored by the Optical Society of America, we wanted to get a publication into print as soon as possible, so we resubmitted our paper to the trade journal, Laser Focus, including some remarks about the new experiments on human aorta. Serendipitously, the Laser Focus issue containing our paper [4] was published simultaneously with CLEO 1983, where Srinivasan gave an invited talk on May 20 entitled “Ablative photodecomposition of organic polymer films by far-UV excimer laser radiation.” In this talk he gave the first oral public disclosure that the excimer laser cleanly ablated biological specimens as well as organic polymers.

From excimer laser surgery to ArF excimer laser-based refractive surgery

At this very same CLEO 1983 meeting, on May 18 Stephen Trokel and Francis L’Esperance, two renowned ophthalmologists, gave invited talks on applications of infrared lasers to ophthalmic surgery. I attended both of their talks and was amazed at the results they obtained in successfully treating two very different ophthalmic conditions. I was well aware that the ruby laser was first used to eradicate a retinal lesion in late 1961, and retinal surgery with lasers had become widespread in the ensuing two decades, in particular to repair retinal tears and to treat diabetic retinopathy. But these treatments required a laser at a wavelength for which the ocular media anterior to the retina was transparent. Excimer laser light would be absorbed in a thin layer upon entering the cornea, so the excimer laser would be useless for treating retinal maladies.

But Trokel knew of ophthalmic conditions, such as the refractive imperfection known as myopia, that could be corrected by modifying the corneal curvature. A treatment known as radial keratotomy (RK), developed in the Soviet Union and being practiced in the United States, corrected myopia by using a cold steel scalpel to make radial incisions at the periphery of the cornea. When these incisions healed, the curvature of the front of the cornea was reduced, with the consequence that the patient’s myopia was also reduced. The technique could rarely give the patient uncorrected visual acuity of 20/20, but the patient’s myopia was definitely reduced. One serious drawback of RK was that the depth of the radial incisions left the cornea mechanically less robust, and the healed eye was more susceptible to “fracture” under impact, such as might occur during an automobile collision. Trokel speculated that the excimer laser might be a better scalpel for creating the RK incisions.

Upon learning of our discover of excimer laser surgery, Trokel, who was affiliated with Columbia University’s Harkness Eye Center in New York City, contacted Srinivasan and subsequently brought enucleated calf eyes (derived from slaughter) to our IBM Research Center on July 20, 1983. Srinivasan's technical assistant, Bodil Braren, participated in an experiment using the ArF excimer laser to precisely etch the corneal epithelial layer and stroma of these veal eyes. The published report of this study is routinely referred to by the ophthalmic community as the seminal paper in laser refractive surgery. [5]

To conduct studies on live animals, the experiments were moved to Columbia's laboratories. Such experiments were necessary to convince the medical community that living cornea etched by the ArF excimer laser does not form scar tissue at the newly created surface and the etched volume is not filled in by new growth. The first experiment on a live rabbit in November, 1983, showed excellent results in that, after a week of observation, the cornea was not only free from any scar tissue, but the depression had not filled in. Further histological examination of the etched surface at high magnification showed an interface free from detectable damage.

L'Esperance, also affiliated with Columbia's Harkness Eye Center, thought beyond RK and, in November, 1983, filed a patent application describing the use of excimer laser ablation to modify the curvature of the cornea by selectively removing tissue from the front surface, not the periphery, of the cornea. His U.S. Patent No 4,665,913 [6] specifically describes this process, which was later named photorefractive keratectomy (PRK).

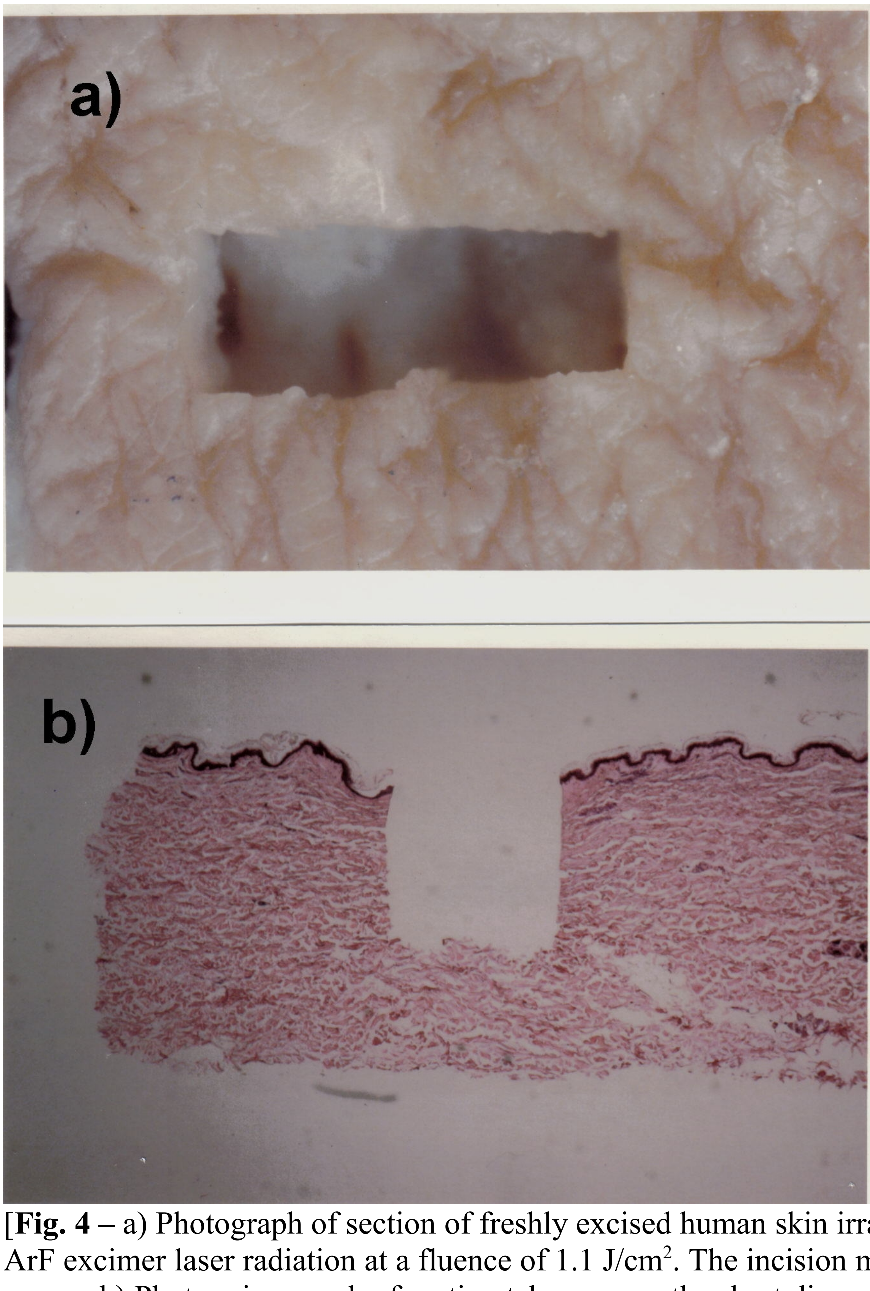
Soon ophthalmologist around the world, who knew of the remarkable healing properties of the cornea, were at work exploring different ways to use to excimer laser to reshape the cornea. From live animal experiments, they moved to enucleated human eyes, then to blind eyes of volunteers, where they could study the healing. Finally, in 1988, a sighted human was treated with PRK, and after the cornea had healed by epithelialization, this patient's myopia was corrected.

Development of an alternative technique using an excimer laser for modifying the curvature, known as laser in situ keratomileusis (LASIK), commenced in 1987. In LASIK, a separate tool is used to create a hinged flap at the front of the cornea, preserving the epithelial layer and exposing underlying stroma, which is then irradiated and reshaped by the ArF excimer laser. After such irradiation, the flap is repositioned over the irradiated area, adheres rather quickly, and the patient is soon permitted to blink, while the surgeon makes sure that the flap stays in place. No sutures are required. The flap acts like the cornea's own "bandaid," minimizing the discomfort of blinking, and negating the epithelialization of the front the cornea that occurs after PRK. LASIK offers the patient much less discomfort than PRK and much more rapid attainment of ultimate visual acuity following surgery. For these reasons, patients prefer LASIK to PRK, and far more LASIK procedures are performed than PRK procedures.

However, patients whose corneas are much thinner than average are not good candidates for LASIK, because a post-LASIK healed cornea is mechanically weaker than a post-PRK healed cornea, making the cornea more susceptible to impact or high acceleration injury. In fact, the U.S. Navy accepts candidates into training programs for the Naval Air Force who have had their visual acuity improved by PRK , but it does not accept candidates who have had LASIK.

Other excimer laser surgery studies

I, personally, never did any experimental work on eyes. My studies were of skin, which continues to be my primary interest. In 1983-84, my IBM colleagues and I collaborated with dermatologists from NY University Medical Center, using the excimer laser to irradiate freshly excised human skin and the skin of live guinea pigs, studying the subsequent healing of the incisions produced in these animals. [7,8] Fig. 4 shows images of ArF excimer laser-irradiated human skin, *in vitro*.



[**Fig. 4** – a) Photograph of section of freshly excised human skin irradiated by 1000 pulses of ArF excimer laser radiation at a fluence of 1.1 J/cm^2. The incision measures ~3 mm x 1 mm.

b) Photo micrograph of section taken across the short dimension of the incision, stained with hematoxylin-eosin, showing no evidence of thermal damage to the sides or bottom of the incised volume. The incision is ~1 mm deep.]

On June 22, 1984, I gave a presentation entitled "Ultraviolet-laser ablation of skin and other tissue" at the CLEO 1984 conference, co-sponsored by the OSA, where I outlined the discovery of excimer laser surgery, described our results on skin, and discussed a myriad of applications to different areas of soft tissue and hard tissue (e.g., bone, tooth) surgery. Together with Randall J. Lane, a college student at Cornell who was my summer intern, I wrote a review article of potential applications, ranging from incising skin, muscle, nerve, and brain tissue, to incising cartilage, bone, and dental enamel.[9] In this article, we speculated on using the excimer laser to bore pilot holes in nerve tissue, into which electrodes could be placed, to enable interfacing nerves with microelectronics to control prosthetic limbs. We also speculated on using the excimer laser to remove tissue from the muscles surrounding the globe of the eye, as a surgical treatment for strabismus.

More recently, I collaborated with dermatologist Dr. Jerome Felsenstein to study the potential of the excimer laser as a tool for skin resurfacing, yielding two patents on laser dermablation, U.S. Nos. 6,165,170 and 6,447,503 . We are currently collaborating to develop the ArF excimer laser as a "smart scalpel," a tool that will debride necrotic lesions from skin without producing collateral damage to the underlying and adjacent viable tissue. Burn eschar and other necrotic lesions of the skin are relatively dry compared to the underlying viable tissue. A 193-nm ArF excimer laser, emitting electromagnetic radiation at 6.4 eV at fluence exceeding the ablation threshold, will debride such necrotic areas. However, debridement will cease when moist (with chloride ions) viable tissue is exposed, because such radiation is strongly absorbed by aqueous chloride ions through the non-thermal process of electron photodetachment, thereby, avoiding collateral damage to this tissue. Such tissue will be sterile and ready for further treatment, such as a wound dressing and/or a skin graft. [10]

Pervasiveness of laser refractive surgery

Since the U.S. Food and Drug Administration (FDA) granted approval to manufacturers of laser refractive surgery systems in 1995, more than 24 million patients have undergone the procedure to improve their eyesight. While patients choose to undergo this procedure for the obvious cosmetic reasons, many patients are unable to comfortably wear contact lenses, and PRK and LASIK offer them a safe alternative, which actually may cost less than the accumulated cost of wearing and maintaining contact lenses. Further, the U.S. military is encouraging its ground troops to have laser refractive surgery to eliminate the problems inherent in wearing glasses or contact lenses in combat situations (e.g., the desert sands of the Middle East). Laser refractive surgery can restore visual acuity to better than 20/20, as is required for certain aviators. With further refinements in so-called "custom wavefront-guided" laser refractive surgery - in which measurement are taken of higher-order aberrations in the refracting part of the eye and the laser beam that reshapes the cornea corrects for these higher-order aberrations - we may soon see a time when patients undergoing laser refractive surgery may expect to achieve visual acuity of 20/10.

Public awareness and interest in laser eye surgery was intense even before FDA approval was granted in 1995. On Jan 30, 1987 The *Wall Street Journal* published an article entitled "Laser Shaping of Cornea shows promise at correcting Eyesight," and on Sept. 29, 1988, *The New York Times* published its first article on PRK, entitled "Laser may one day avert the need for eyeglasses." Subsequent articles in the press dealt with the progress on the research on PRK, the formation of three U.S. companies to market this procedure, and approval by the FDA in 1995. At this point, the surgical procedure was discussed at length in all the popular media, including *The Washington Post, The San Francisco Chronicle, Newsweek* and *The New York Magazine.* On Oct. 11, 1999, TIME magazine published a cover story entitled "The Laser Fix". (Fig. 5)

[**Fig. 5** - Cover of Oct. 11, 1999 issue of Time Magazine]

In August 1998, *The National Academy of Sciences* issued a pamphlet entitled "Preserving the Miracle of Sight: Lasers and Eye Surgery," the stated purpose of which was to show 'The Path from Research to Human Benefit.' One section describes the first experiments that were done at

IBM Research and, subsequently, at Columbia University, leading to the development of PRK. [11]

As for the size of the "business" of laser refractive surgery, at a typical cost of $2000/procedure, patients have spent more than $80B on PRK and LASIK through the end of 2011.

R. W. Wood Prize

Srinivasan, Blum, and I opened the door to this revolution in eye care through our seminal discovery and subsequent transfer of the technology to the medical/surgical profession. The OSA presented us with the R. W. Wood Prize in 2004 "for the discovery of pulsed ultraviolet laser surgery, wherein laser light cuts and etches biological tissue by photoablation with minimal collateral damage, leading to healing without significant scarring."

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