Excimer Laser Surgery: Laying the Foundation for Laser Refractive Surgery

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Discovery of Excimer Laser Surgery

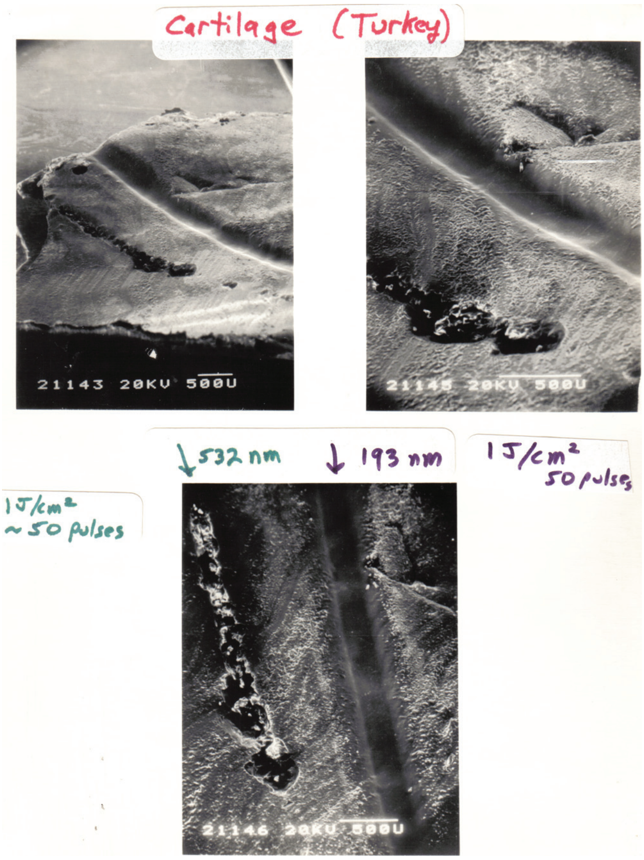
On 27 November 1981, the day after Thanksgiving, Rangaswamy Srinivasan brought Thanksgiving leftovers into the IBM Thomas J. Watson Research Center, where he irradiated turkey cartilage with ~10-ns pulses of light from an argon fluoride (ArF) excimer laser. This irradiation produced a clean-looking "incision," as observed through an optical microscope. Subsequently, Srinivasan and his IBM colleague, Samuel E. Blum, carried out further irradiation of cartilage samples. Srinivasan gave a sample to the author, and, for comparison, it was irradiated with ~10-ns 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. Figure 1 shows three different views and magnifications of scanning electron micrographs (SEMs) 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.

Realizing that Srinivasan, Blum, and the author had discovered something novel and unexpected, they wrote an invention disclosure, describing multiple potential surgical applications. They 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 not produce scar tissue. This insight, a radical departure from all other laser surgery, was unprecedented and underlies the subsequent application of their discovery to laser refractive surgery.

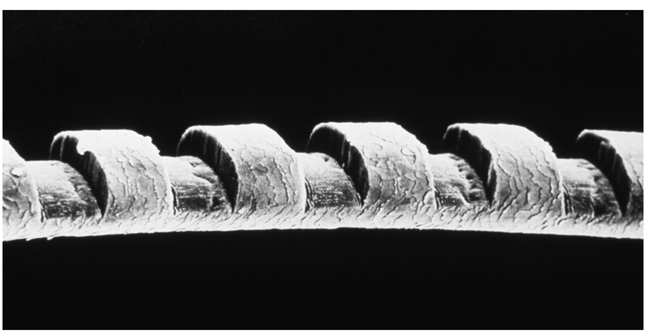
Background to This Discovery

As manager of the Laser Physics and Chemistry department at the Watson Research Center, one of the author's responsibilities was to ensure that there was access to the best and latest laser instrumentation. When the excimer laser became commercially available, the author purchased one for use by the scientists in his department. Since 1960, Srinivasan had been studying the action of ultraviolet radiation on organic materials, e.g., polymers. In 1980, he and his technical assistant, Veronica Mayne-Banton, discovered that the ~10-ns pulses of far ultraviolet radiation from the excimer laser could photo-etch solid organic polymers, if the fluence of the radiation exceeded an ablation threshold [1,2].

Srinivasan and the author then speculated about whether 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. They knew that when skin was incised with a sharp blade, the wound would heal without fibrosis and, hence, no scar tissue. Conceivably, living skin



▲ **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.



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

or other tissue, when incised by irradiation from a pulsed ultraviolet light source, would also heal without fibrosis and scarring.

Physics of Ablation

Ablation occurs when the laser fluence is such that 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 gas then expands away from the irradiated surface, carrying with it 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 that is short compared with 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

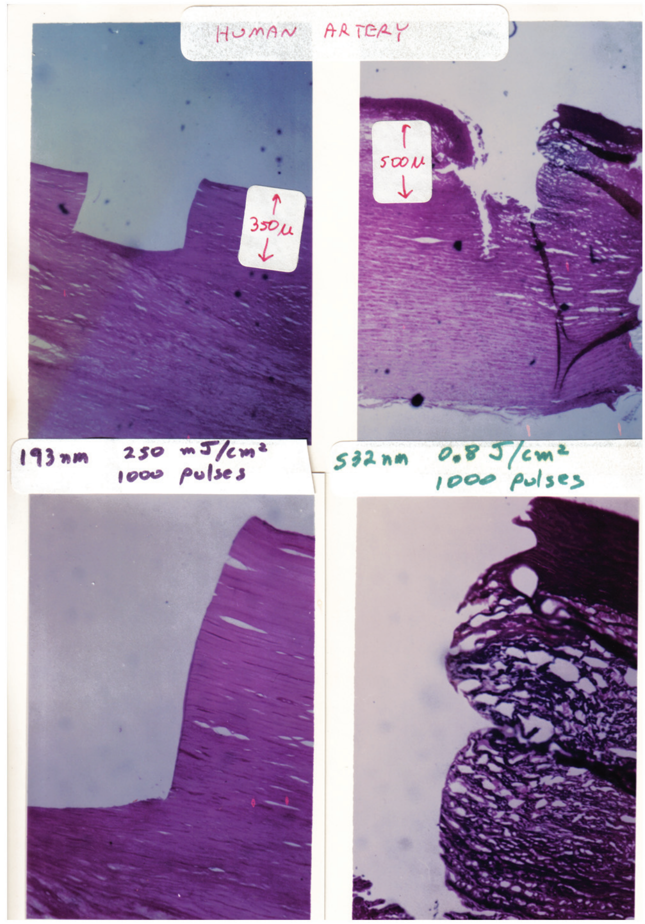
To develop practical innovative applications, Srinivasan, Blum, and the author needed to collaborate with medical/surgical professionals. To interest these professionals, they etched a single human hair by a succession of 193-nm ArF excimer laser pulses, producing an SEM micrograph (Fig. 2), showing 50-μm-wide laser-etched notches.

While IBM was preparing a patent application, Srinivasan, Blum, and the author were constrained from discussing their discovery with people outside IBM. But a newly hired IBM colleague, Ralph Linkser, with an M.D. and a Ph.D. in physics, obtained fresh arterial tissue from a cadaver, and Linsker, Srinivasan, Blum, and the author 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].

This experimental study on freshly excised human tissue confirmed that excimer laser surgery removed tissue by a fundamentally new process. Srinivasan, Blum, and the author's 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 their patent application was filed, Srinivasan, Blum, and the author submitted a paper to *Science* magazine. Their paper was rejected because one of the referees argued that irradiation with far-ultraviolet radiation (far-UV) would be carcinogenic, making the technique more harmful than beneficial. Since Srinivasan had been invited to speak about his work on polymers at the upcoming CLEO 1983 conference co-sponsored by the OSA, Srinivasan, Blum, and the author wanted to get a publication into print as soon as possible. Therefore, they resubmitted their paper to *Laser Focus*, including some remarks about the new experiments on human aorta, and the *Laser Focus* issue containing their paper [4] was published simultaneously with CLEO 1983. Srinivasan's talk on 20 May, entitled "Ablative photodecomposition of organic polymer films by far-UV excimer laser radiation," included the first public disclosure that the excimer laser cleanly ablated biological specimens, as well as organic polymers.



▲ **Fig. 3.** Left side: Photo micrographs of human aorta irradiated by 1000 pulses of ArF excimer laser 193-nm light; lower image is a magnified view of the right-hand side of the laser-irradiated region. Right side: Photo micrographs of human aorta irradiated by 1000 pulses of Q-switched, frequency-doubled Nd:YAG laser 532-nm light; lower image is a magnified view of the right-hand side of the laser-irradiated region. (By permission of John Wiley & Sons, Inc.)

From Excimer Laser Surgery to ArF Excimer Laser-based Refractive Surgery

At that very same CLEO 1983 meeting, Stephen Trokel and Francis L'Esperance, two renowned ophthalmologists, gave invited talks on applications of infrared lasers to ophthalmic surgery. The author attended both of their talks and was amazed at the results they obtained in successfully treating two very different ophthalmic conditions that were not candidates for excimer laser treatment. However, Trokel knew of ophthalmic conditions, such as myopia, that could be corrected by modifying the corneal curvature. A treatment known as radial keratotomy (RK) corrected myopia by using a cold steel scalpel to make radial incisions at the periphery of the cornea. Upon healing, the curvature of the front surface of the cornea was reduced, thereby reducing myopia. While this technique rarely yielded uncorrected visual acuity of 20/20, 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. 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 Srinivasan, Blum, and the author's discovery of excimer laser surgery, Trokel, who was affiliated with Columbia University's Harkness Eye Center in New York City, contacted Srinivasan and brought enucleated calf eyes (derived from slaughter) to the Watson Research Center on 20 July 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 calf 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, thought beyond RK and 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 4,665,913 [6] specifically describes this process, which was later named photorefractive keratectomy (PRK).

Soon ophthalmologists around the world, who knew of the remarkable healing properties of the cornea, were at work exploring different ways to use to excimer lasers 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, 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, it 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. 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 cornea is mechanically weaker than a post-PRK 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 had their visual acuity improved by PRK, but it does not accept candidates who had LASIK.

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 30 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. PRK and LASIK offer them a safe alternative that actually may cost less than the accumulated cost of wearing and maintaining contact lenses. Further, the U.S. military encourages 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, soon there may be 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. On 30 January 1987, *The Wall Street Journal* published an article entitled "Laser shaping of cornea shows promise at correcting eyesight," and on 29 September 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 in 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 11 October 1999, *Time* magazine published a cover story entitled "The laser fix."

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 [7].

As for the size of the "business" of laser refractive surgery, at a typical cost of $2000/procedure, patients have spent more than $90 billion on PRK and LASIK through the end of 2012.

Srinivasan, Blum, and the author opened the door to this revolution in eye care through their seminal discovery and subsequent transfer of the technology to the medical/surgical profession. The OSA presented this group 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." In 2013, Srinivasan, Blum, and the author received the National Medal of Technology and Innovation from President Obama and the Fritz J. and Dolores H. Russ Prize from the National Academy of Engineering.

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