Excimer Lasers in Medicine

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Introduction

Excimer lasers emit light energy, short optical pulses at ultraviolet wavelengths, that results in a unique laser tissue interaction. This has led to an increasing number of studies into medical applications of these lasers in fields such as ophthalmology, urology, cardiology and neurology.

The typical excimer laser is operated with a combination of a halogen (fluorine or chlorine), and a rare gas (argon, krypton,of xenon). Each combination results in emission of a specific wavelength. These wavelengths are listed in Table 1, together with their dimer combinations. Also in Table 1, excimer lasers are compared to other laser systems that are used in medicine.

Table 2 shows the relevant output characteristics of a typical commercial excimer laser system. For a certain medical application, the output parameters can be optimized, and incorporated in the overall design of a medical excimer laser. Each medical application may have a different set of parameters, such as wavelength, energy, pulse repetition rate, and pulse duration.

One aspect that has hindered the use of excimer lasers in medicine has been an optimum delivery system of the excimer radiation to the tissue. Currently, the fibers that are most efficient are pure silica fibers. These are often cladded by other materials such as plastic or doped silica. For XeF, XeCl, and KrF there is a relatively low damage threshold at the input surface which limits the amount of power that can be directed into the fiber for transmission. For ArF however, the critical damage threshold is subsurface [1]. In an attempt to overcome this threshold , fibers with flared input tips have been designed, which increases the input surface area. Furthermore, it has been recognized that with long pulse (200 ns) XeCl lasers, one is able to transmit more energy through a fiber than one is able to with standard short pulse (20 ns) lasers. Immersion of the input tip of the fiber in a high pressure electronegative gas environment, or in a vacuum, increases the damage threshold [2], as does careful polishing of the input face. At the output end, higher energy densities can be delivered by forming a lens at the output tip. Fig. 1 shows this along with other possible possible contoured shapes of optical fibers. Fig. 2 (a), shows the energy distribution for a flat ended fiber (Fig. 1a), while Fig. 2 (b) shows the energy distribution for a rounded tip fiber (Fig. 1b).

Another area which needs to be explored before the excimer laser is accepted more widely in medicine is the potential mutagenic effects of excimer laser radiation. Studies have shown that KrF excimer laser radiation causes mutations in the cells DNA proportionate to the dose of the excimer light. ArF excimer light, however, does not induce mutations above the level observed in dark controls [3]. It is believed that this could be due to 'cytoplasmic shielding', that is strong absorption of the laser light by cellular components surrounding the nucleus. The mutagenic potential of XeCl and XeF excimer lasers is thought to be lower than that of either the ArF and KrF excimer, and these longer wavelength ultraviolet sources are believed to be relatively safe.

Laser-tissue interactions

Sterile, controlled tissue cutting is desirable in many medical procedures. Some of the lasers investigated for medical applications are listed in Table 1. Each laser offers a particular combination of laser-tissue interactions primarily photothermal, photodynamic and photochemical or some combination of these. The choice of laser is determined by a particular medical application.

Excimer lasers principally ablate through a photochemical, rather than photothermal process associated with cw and long wavelength pulsed lasers [4]. Their short wavelength photons have enough energy to break molecular bonds, such that precise etching and ablation can occur [5]. Thus, excimer lasers do not cause thermal or acoustic damage as in the case with other lasers. Fig. 3 compares segments of human aortic tissue ablated with an excimer laser and a pulsed Nd:YAG laser. Ablation by the excimer laser is clean, and shows no thermal or acoustic damage, while the pulsed Nd:YAG laser causes significant tearing characteristics of acoustic damage. This property of excimer lasers has made it very attractive in a number of medical applications, including the following:

Ophthalmology

One of the first applications of lasers in medicine was in ophthalmology. Lasers were used to photocoagulate excess retinal arteries. Excimer lasers have been investigated for ablative procedures in the outer layers of the eye, and in the lens.

The cornea is responsible for 80% of the refraction of the visible rays entering the eye. Thus, by altering the curvature of the cornea, one is able to correct near or far sightedness. The corneas curvature can be altered in two ways. In radial keratectomy, shallow incisions in the periphery of the cornea are etched , in a radial direction, using a diamond knife or laser. This causes the cornea to relax, and thus decrease in curvature, correcting near sightedness. The excimer laser is preferred over the diamond knife since the position of incision and its depth can be more precisely controlled. In sculpturing of the cornea, an excimer laser is used to methodologically graft concentric circles in the cornea, in such a way as to increase or decrease its curvature. Sculpturing of the cornea can be used to correct near or far sightedness. Illustrative diagrams are shown in Fig. 4.

To study the long term effects of excimer lasers on corneas, monkeys corneas have been ablated to varying depths, within the optical zone, using ArF excimer lasers. Some degree of haze developed within 3 months postoperatively in all corneas except those with ablations of 40 μm. This haze subsequently cleared within 6 months in all the corneas but those with the deepest ablations (160 μm). Histological studies 8 months after ablation showed the essential morphology to be normal in the cornea [7].

Preliminary efforts to investigate the possibility of ablating cataracts lenses using an ArF laser have also been undertaken. Initial results of work done at Rice University warrant further investigation.

Urology

Kidney stones are a common and potentially serious medical problem. They have been treated with shock wave lithotripters, and more recently, pulsed-dye lasers have been used successfully in cases where the pelvic bones shield the kidney stones preventing successful shock wave lithotripsy [8]. Laser treatments of kidney stones involve delivery of laser light to the stone through an interurethral catheter containing an optical fiber, which causes disintegration of the stone.

Excimer lasers may offer some advantages over pulsed-dye laser treatment of kidney stones, and are being investigated for that purpose. Excimer lasers will not heat the surrounding tissues, and may be effective against very hard stones. Also, the ablation residue using excimer lasers will be finer, and so will allow easier passage. Current ablation of kidney stones using excimer lasers is slow however, and advancements in this area will accompany developments in fiber delivery technology.

Angioplasty

Laser angioplasty is a rapidly developing research area. The excimer laser is thought to be an excellent candidate to perform the recanalization of obstructed arteries because of its nearly nonthermal, precise ablative characteristics. The most serious complication with current laser angioplasty systems in testing is uncontrolled damage to the essential vessel wall, which often progresses to perforation of the artery. Therefore, a feedback control mechanism which can appropriately target atheromatous lesions for ablation and monitor the progress of their removal is highly desirable.

In recent years visible laser-induced tissue autofluorescence spectroscopy, as shown in Fig. 5, has been tested as a means of diagnosing atherosclerosis. Since the excimer laser is a likely choice to carry out the plaque removal, it would be highly desirable if this ultraviolet source could be employed to perform diagnostic spectroscopy as well. This would allow for the development of a clinical angioplasty system incorporating a single laser light source, as shown in Fig. 6. For this reason, a study has been performed at Rice looking at XeF excimer laser-induced spectra from atherosclerotic human arteries [6].

Using the experimental apparatus shown in Fig. 7, spectra were acquired from both healthy and diseased sites along the endothelial surface of isolated cadaver artery samples. The tissue sites were characterized as one of three histologic types: healthy arterial wall, fatty or fibrotic tissue (early stage atherosclerosis), and calcified plaque. Since the absolute intensity of a fluorescence measurement is dependant on the collection geometry, a parameter difficult to control in vivo, the resultant spectra were compared purely on the basis of curve shape by normalizing all curves to the same relative intensity scale. Typical fluorescence profiles are shown in Fig. 8A. Normal wall sites were found to consistently produce spectra very similar to that shown, while a variety of spectral shapes were associated with diseased regions (presumably due to the heterogeneous nature of these lesions). Subtraction of the healthy from the diseased traces (Figure 8B) clearly illustrated any deviations. The most significant variations from the normal wall fluorescence response were seen at calcified areas, and these regions could be be clearly distinguished from the healthy tissue by spectroscopic analysis.

Spectra were also acquired after ablative excavation into the arterial wall at both healthy and diseased sites. For the normal artery, the muscular middle wall layer appeared to produce a somewhat different fluorescence response than the overlying endothelium. Spectra taken at calcified sites changed significantly after the excavation had penetrated the hard plaque and reached the underlying tissue, and these curves greatly resembled those taken at depth in healthy wall. Thus this medial arterial layer fluorescence response may be useful as a signal of the appropriate endpoint of the ablation process.

Finally, fluorescence profiles were acquired during the actual ablation process (at high excimer laser fluence). When this experiment was performed in air, spectra from calcified plaque sites contained discrete lines superimposed on the broad tissue fluorescence curve. Such lines were not seen during ablation at healthy wall. Based on examination of the wavelengths involved, these lines were attributed to excited state electronic transitions in calcium, magnesium and phosphorous atoms in the ablation plume. These elements are all known components of arterial plaque. Similar lines could not be elicited from samples submerged in saline during the ablation. This technique might be very useful for the in vitro investigation of tissue, where it could complement chemical methods or the electron microprobe.

Nerve Repair

Regeneration of peripheral nerves following traumatic injury is usually limited and can result in severe disability to the patient. Current surgical techniques for reanastomosis (rejoining) of torn or crushed nerves involve cutting the two ragged ends of the nerve by scalpel to form uniform surfaces and then reopposing these surfaces by suturing them together. Individual axons then traverse the gap from the proximal nerve ending to the distal ending and reform the conduction pathways. This surgical approach is less than ideal for two reasons. Cutting the nerve by scalpel itself causes crushing injury to the nerve. Also, the use of sutures induces a "foreign body" allergic reaction which is detrimental to the regrowth.

A proposed laser based nerve repair system is shown in Fig. 9. It has been suggested that an excimer laser could replace the scalpel as a cutting tool since it can produce very uniform cutting without applying mechanical pressure to the nerve. Instead of suturing the fiber endings together, a long pulse or CW laser such as a CO_2 laser could be used in a controlled fashion to actually weld the nerve. Monitoring the progress of this welding process could be accomplished by excimer laser induced tissue autofluorescence analysis in a fashion analogous to that described above for angioplasty. Nerves could be carefully reconnected without causing excess thermal tissue damage by rapidly terminating the welding laser irradiation at the appropriate time based on diagnostic spectroscopy.

Preliminary work on the development of such an integrated laser based system is currently going on at Rice University [9]. Initial work indeed shows that cutting nerves with either an ArF short pulse or XeCl long pulse excimer laser produces a much smaller zone of mechanical damage at the cut end than cutting with a blade. In addition CO_2 laser irradiation of nerves does produce significant changes in excimer induced tissue autofluorescence response, in terms of both absolute fluorescence intensity and spectral shape, so that spectroscopy may be useful in determining the progression of the nerve welding process. It therefore appears promising that excimer lasers will have some utility in nerve reanastomosis procedures.

Summary

The excimer laser has been studied by many investigators for its potential medical applications, and results to date are very promising. Excimer lasers appear to be particularly useful in applications which require high energy photons for ablative procedures. Cardiovascular angioplasty is one such application, and in particular we have been interested in developing diagnostics for cardiovascular tissue with excimer autofluorescence. In ophthalmology the excimer laser is the preferred tool for keratectomy. Furthermore, in urology the excimer laser is under investigation for potential benefits it may offer in kidney stone ablation, and in nerve repair our initial results of the use of an excimer laser as a cutting and diagnostics tool appear promising. Further developments in the use of the excimer laser for these and other medical applications will depend on the further developments in delivery systems for excimer lasers , and on understanding of the mutagenic potential of the different excimer wavelengths.

Acknowledgements

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Tables

Table 1

Laser Type	Wavelength (nm)
Excimer	
ArF	194
KrF	248
XeCl	308
XeF	351
Ion	discrete visible, UV
Dye	320-1000
Nd:YAG	1064
Ho:YAG	2100
Er:YAG	2940
CO_2	10,600
Cu vapor	510, 578
HF/DF	2700-3000
FEL	UV-IR

Table 1. List of lasers investigated for medical applications, and their wavelengths.

Table 2.

Pulse Energy:	0.1 to 1 J
Average Power:	> 10 W
Pulse Repetition rate:	low to 1 KHz
Pulse Duration: 10 to 250 ns (Avalanche discharge)	
Beam divergence:	2 - 6 M Rad
Efficiency:	~ 2 %

Table 2: Typical Excimer laser outputs

Figures

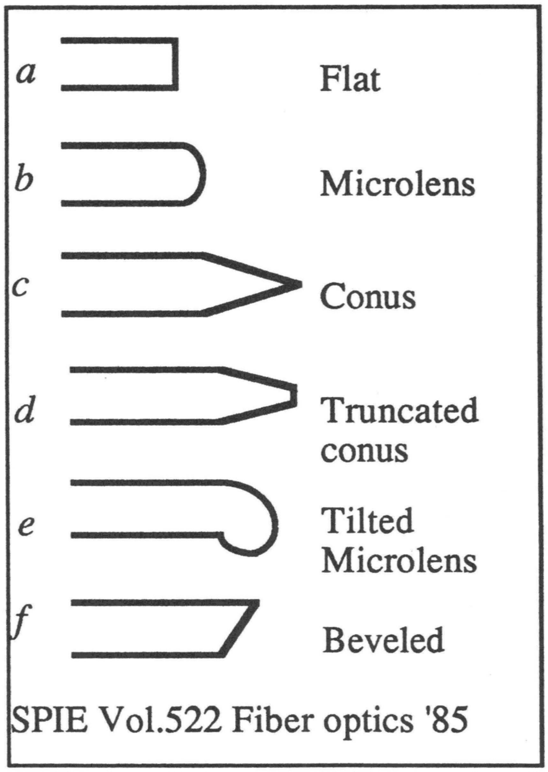

Figure 1. Various output tip geometries of silica fibers that may be used for medical applications.

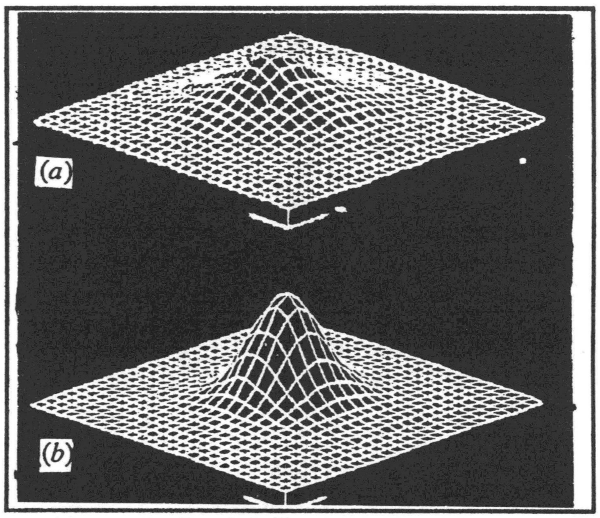

Figure 2. Spatial distribution of laser energy obtained with the optical beam profiling system of (a) a flat tipped output fiber such as fiber a of figure 1, and (b) of a rounded tip output fiber such as fiber b of figure 1. This shows a higher energy density that may be achieved at the center of the output by rounding the fiber tip.

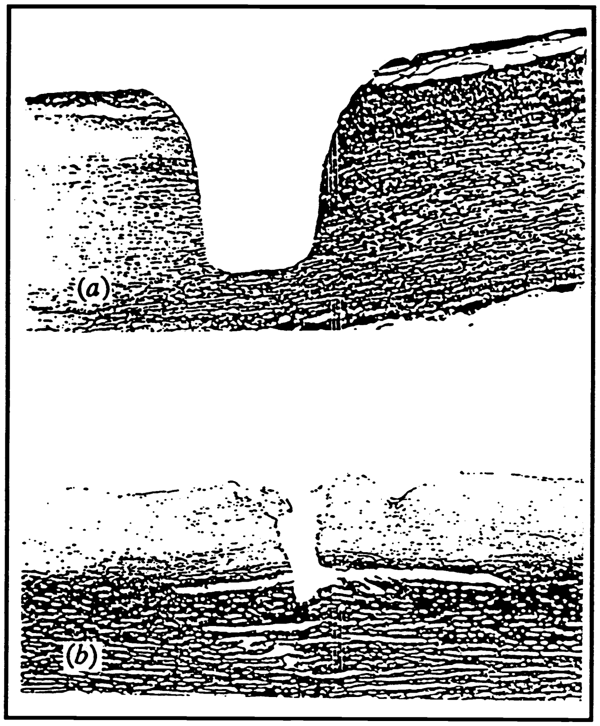

Figure 3. Segments of human aorta ablated with (*a*) an excimer laser, and (*b*) a pulsed Nd:YAG laser (7 ns pulses). The excimer laser ablation is seen to be clean and has no thermal or acoustic damage, while the Nd:YAG laser ablation is seen to show only tearing, characteristic of acoustical damage.

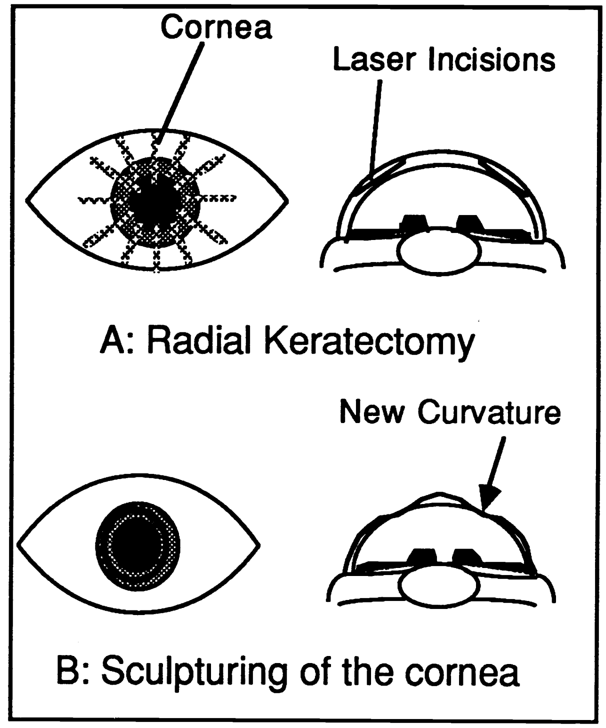

Figure 4. Illustrations to show the two photorefractive correction procedures. In radial keratectomy (*a*), shallow radial incisions are made from the center allowing the cornea to relax, and thus decrease in curvature. In sculpturing of the cornea (*b*), concentric circles are grafted in the cornea to increase or decrease the curvature of the cornea. In this figure the concentric circles are used to increase the curvature of the cornea.

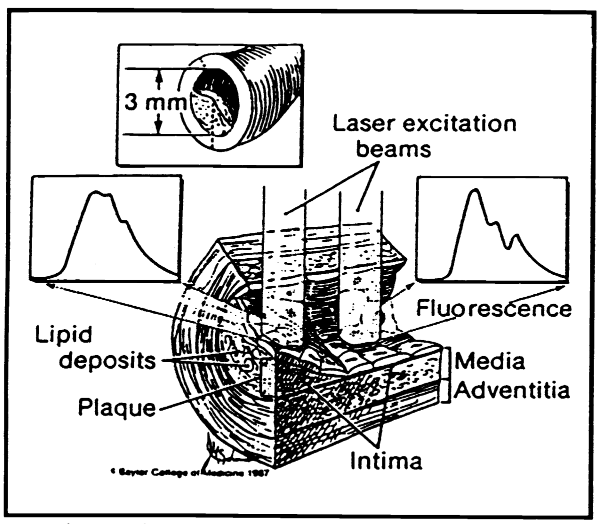

Figure 5. An illustration of a segment of artery showing hypothetical differences in laser induced fluorescence from healthy and atherosclerotic tissue.

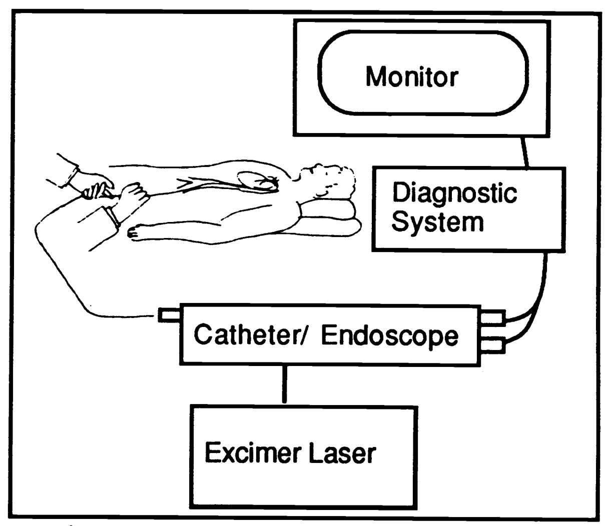

Figure 6. An illustration of a proposed laser angioplasty system used to recanalize obstructed coronary arteries. Ablation is controlled by monitoring in real time the induced fluorescence from the artery wall. The fluorescence of healthy tissue would differ from that of atherosclerotic tissue, and this can be used to determine the type of tissue the catheter points to.

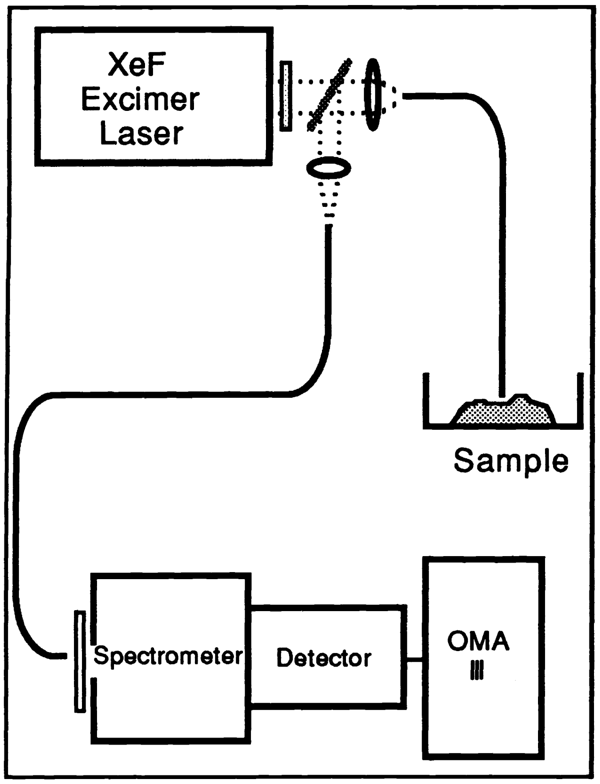

Figure 7. The experimental setup to excite arterial tissue by an excimer laser, and measure the induced fluorescence. The same fiber is used for excitation and collection of optical light at the arterial surface.

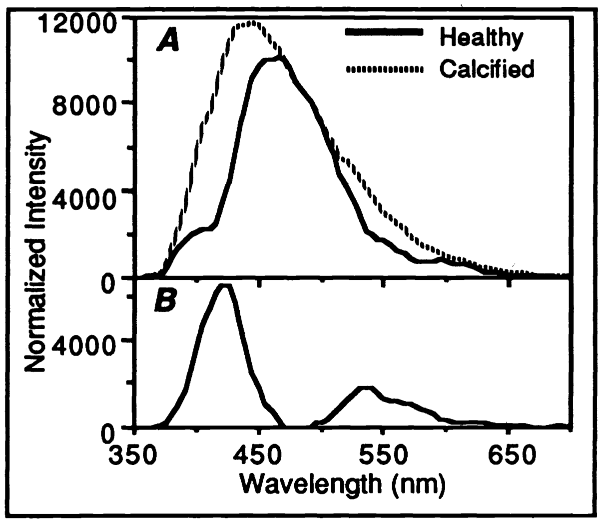

Figure 8. Results of excimer laser induced fluorescence from the endothelial surface of healthy and calcified arteries. The solid line shows the normalized fluorescence spectra from healthy tissue, while the dotted line shows that from the calcified tissue. Subtraction of the healthy spectral curve from the calcified spectral curve highlights the difference between them.

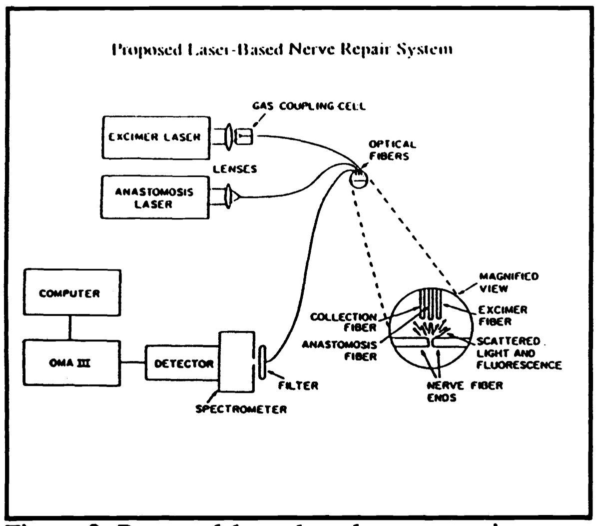

Figure 9. Proposed laser based nerve repair system. The excimer laser is used to cut the nerve ends. The nerve ends are welded together using a low power CW laser, and the welding is monitored by excimer induced autofluorescence analysis. The CW laser can be automatically shut off when a critical change in the shape of the fluorescence spectrum is determined.