PROGRESS REPORT
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**DIAGNOSTIC AND THERAPEUTIC APPLICATIONS
OF DIODE LASERS AND SOLID STATE LASERS IN MEDICINE**

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Introduction

The Texas Medical Center in Houston and the nearby UT Medical Branch at Galveston together constitute a major center of medical research activities. Laser applications in medicine are under development with the engineering assistance of the collaborating engineering centers at Rice University, UT-Austin, and Texas A&M Univ. In addition, this collective is collaborating with the Naval Research Laboratory, where new developments in laser design are underway, in order to transfer promising new laser technology rapidly into the medical environment.

Our research plan has not changed and we are proceeding along the schedule of the original plan. That research plan is summarized by the following description of DIAGNOSTICS and THERAPEUTICS, which appeared in the original proposal.

DIAGNOSTICS

4.A.1 Reflectance spectroscopy	
4.A.1.1 Bilirubinometry	UTMDA-LL,RICE,UTMSH-Ped
4.A.1.2 Monitoring iv lines	UTMDA-LL,RICE,UTMSH-Ped
4.A.1.3 Assessing body fluids	UTMDA-LL,RICE,UTMSH-Ped
4.A.2 Fluorescence spectroscopy	
4.A.2.1 Cervical ca, dysplasias	UTA, UTMDA-Gyn, UTMDA-LL
4.A.2.2 Atherosclerotic plaque	UTA, UTMBG-Cardio
4.A.2.3 Colonic ca	UTMDA-GIT, UTMDA-LL, UTA
Brain ca	UTMDA-Neuro, UTMDA-LL
Head/Neck ca	UTMDA-HeadNeck, UTMDA-LL
Lung ca	UTMDA-Thoracic, UTMDA-LL
4.A.3 Raman spectroscopy	
4.3.1 Cervical ca, dysplasias	UTA, UTMDA-Gyn
4.3.2 Atherosclerotic plaque	UTA, UTMBG-Cardio, THI

THERAPIES

4.B.1 Photocoagulation therapy	
4.B.1.1 Prostate coagulation	TAMU, UTMDA-LL, UTMDA-Urol, UTMBG-LL, UTMBG-Urol
4.B.1.2 Cyclophotocoagulation	UTA, NRL, UTMBG-LL, TAMU
4.B.2 Laser welding	UTA, NRL, UTMBG-LL, THI
4.B.3 Laser ablation	
Cardiology:	
4.B.3.1 Angiosurgery	TAMU, UTHI, UTMDA-LL
4.B.3.2 Photoacoustic relaxation	UTMBG-LL, THI, UTMDA-LL
Orthopedics:	
4.B.3.3 Vertebral disk laser surgery	UTMBG-LL, UTMDA-LL
Dental:	
4.B.3.4 Dental tissue ablation	TAMU, UTMDA-Dental Oncology
Ophthalmology:	
4.B.3.5 Scleral ablation	UTMBG-LL, UTMDA-LL
4.B.4 Pigmented lesion treatment by pulsed lasers	
4.B.4.1 Prevention of melanoma	UTMDA-LL, UTMSH-Derm, UTMBG-LL
4.B.4.2 Clearance of deep lesions	UTMBG-LL, UTMBG-Derm, UTMDA-LL

4.B.5 Photodynamic Therapy (PDT)
 4.B.5.1 solid-state laser PDT
 4.B.5.2 laser-diode array PDT

UTMDA-LL, UTMDA-VetMed, UTMBG-LL
 UTMDA-LL, UTMDA-VetMed

where the abbreviations in the above table are as follows:

UTMDA	University of Texas M. D. Anderson Cancer Center
UTA	University of Texas at Austin, Biomedical Engineering
UTMBG	University of Texas Medical Branch at Galveston
TAMU	Texas A&M University, Bioengineering Program
RICE	Rice University, Electrical and Computer Engineering
NRL	Naval Research Laboratory
UTMSH	University of Texas Medical School at Houston
THI	Texas Heart Institute

and the suffixes indicate various departments:

LL	Laser Laboratory
Ped	Pediatrics
Gyn	Gynecology
Cardio	Cardiology
GIT	Gastrointestinal Oncology and Digestive Diseases
Neuro	Neurosurgery
HeadNeck	Head and Neck Surgery
Thoracic	Thoracic Surgery
Urol	Urology
Derm	Dermatology
VetMed	Veterinary Medicine

A change in the above outline for proposed work has been made. Section 4.B.3 ablation originally was called "4.B.3 Cardiology: angiosurgery", but the topic of laser ablation has continued to raise basic questions regarding the ablation process. Therefore, our research has expanded to consider the generic nature of laser ablation in a variety of tissues. The applications have been expanded to include 4.B.3.3 vertebral disks (orthopedics), 4.B.3.4 tissues (dental), and 4.B.3.5 sclera (ophthalmology).

Progress Reports

In the following sections, progress reports are presented from each of the collaborating groups. Within each group's report, the interactions between groups are mentioned.

In several instances, reference is made to human studies. These studies are not a part of this DOE program, which does not cite human studies. In each case, these were conducted under approved human protocols. They represent our efforts to translate technology into the clinic. This DOE program supports the basic development and efforts using animal and phantom tissue models which catalyze this technology transfer.

UT M. D. Anderson Cancer Center

Steven L. Jacques, Ph.D.

This grant provided part-time support (15% x 6 months) for Anne Ladner, research nurse, 10% support for Cyndy Soto, a histotechnologist, and partial support for Schwartz, a laser engineer who contributed to the past year's work. Sharon Tho

pathologist, contributed her efforts without compensation since her salary support comes from the State of Texas.

4.A.1 Reflectance spectroscopy

The goal of this project is to develop spectroscopic applications of diode lasers for the Neonatal Intensive Care Unit (NICU).

We have completed optical studies on more than 100 prematurely newborn infants at the NICU at Herman Hospital, UTMSH-Ped (Dr. Oelberg). The method uses the optical fiber spectrophotometer and analysis algorithm described in Table 1 of the original proposal. A research nurse (Anne Ladner, RN) conducted the measurements over a 6-month period. Analysis of the measurements in progress. The results of this work are to be applied in design of optical measurements that monitor three clinical situations:

1. quantifying hyperbilirubinemia (4.A.1.1)
2. monitoring iv lines (4.A.1.2)
3. assessing body fluids (4.A.1.3)

The aim is to establish design parameters and implement the optical techniques using diode laser sources.

We are also assisting RICE in development of another form of optical reflectance spectroscopy that utilizes diode lasers: Frequency Domain (FD) spectroscopy. This topic is discussed in the RICE report.

4.A.2.3 Fluorescence Spectroscopy

The goal of this project is to develop endoscopic fluorescence spectroscopy as a means of locating and characterizing abnormal tissue sites, which is especially pertinent to screening for early cancer.

In the past year, we have concentrated on a neurosurgery project with UTMDA-Neurosurgery (Dr. Raymon Sawaya, Dr. Chung). The concept is to use fluorescence during surgical excision of brain tumors to indicate whether or not the margins of the tumor have been surgically removed. We used our nitrogen/dye laser system for tunable excitation of fluorescence spectra using a 7-surrounding-1 fiber catheter system. This system allows acquisition of the emission spectra for a series of excitation wavelengths. The resulting data array is called an excitation/emission matrix. We have studied a dozen human brain tumor samples, several model cell lines, and an in vivo rat glioma model. Attention has been paid to the relative quantities of "green" and "blue" fluorescence which largely represent FAD and NADH fluorescence, therefore the blue/green ratio is an indication of high redox potential and active metabolic state.

We have continued our efforts to develop a prototype fluorescence bronchoscope in collaboration with UTMDA-Thoracic (Dr. Garret Walsh). We now have a fully mobile fluorescence spectroscopy cart containing a nitrogen/dye laser, an optical multichannel analyzer (OMA), and computer acquisition, a HeCd laser (440 nm), bronchoscope, and intensified CCD camera. The prototype system strives to meet two goals:

- (1) Initial surveillance

The first step is to illuminate a large area with an excitation beam and use enhanced video images to locate abnormal fluorescence that indicates abnormal tissue sites.

(2) Local spectroscopic characterization

The second step is to obtain fluorescence spectra from specific sites using an optical fiber catheter. Spectroscopic signatures have potential for characterizing tissues sites more specifically than simple changes in the magnitude of fluorescence.

As a result of this effort, we have enlisted the cooperation of Olympus, maker of endoscopic equipment, in development of our system. This is an example of how the DOE grant has catalyzed collaborations which facilitate technology transfer to the clinic.

Our aim is to implement fluorescence spectra using pulsed solid state lasers, for example the second and third harmonics (532 and 355 nm) of the Q-switched Nd:YAG laser. This past year we have been studying the optical properties of soft tissues (liver, prostate, skin) at these wavelengths under the high intensities of Q-switched irradiation.

4.B.1.1 Photocoagulation therapy: benign prostate hyperplasia (BPH)

We are collaborating with UTMBG and TAMU on the development of diode laser coagulation of the prostate.

We have used the 25-W diode laser system (810 nm) of Diomed Ltd., Cambridge, UK, which is portable, self-contained, operates on 110 VAC wall outlet power, and delivers 25 W through a single 400- μ m core diameter fiber.

A finite-difference model has been developed which calculates the temperatures achieved by transurethral delivery of laser energy (cylindrical coordinate system). The model has tested the role of various heat sinks in the process:

- (1) urethral irrigation
- (2) glandular prostate perfusion
- (3) peripheral prostate perfusion

The results indicate that typical tissue perfusion rates will exert a significant effect on the laser heating of prostate.

The results of the finite-difference model indicated that a lower power (15 W) for a longer exposure (3 min) is preferable to the common 60 W for 1 min. By avoiding unnecessary boiling of water at the surface, more of the energy is coupled into the tissue. The modeling guided a series of dog experiments conducted at UTMBG (Dr. Orihuela, M. Motamedi). Their experiments (see UTMBG below) demonstrated that the 15W/3min (2700 J) exposure produced a larger lesion (11 mm dia.) than the 60W/1min (3600 J) exposure (8 mm dia.). The 11-mm dia. lesion involves 88% more volume than the 80-mm dia. lesion, despite the lower total energy required.

When the above results were reported at the Americal Society for Lasers in Medicine and Surgery Conference in New Orleans this Spring, they generated quite a controversy. The practitioners could not believe the results. It is counterintuitive to expect the 2700-J exposure to produce more injury than the 3600-J exposure. But both the theory and the experimental results are clear. This illustrates how the combination of theoretical modeling and quantitative experiments can improve upon the existing protocols obtained by trial and error. Moreover, the

results argue for the use of lower-power diode lasers rather than more expensive high-power Nd:YAG laser systems.

For the prostate therapy, we have produced our own side-directed fiber delivery systems comprised of optical fibers ground to a 40° angle off the normal, enclosed within a small capillary tube. This simple system delivers light within a cone at 80-60° from the forward axis of the fiber, without any heating of the device.

We have purchased a fiber splitter (Canstar Inc., Canada) to split the 25 W into four 5-W fiber outputs. These four output fibers are then ground at 40° as above to provide a side-directed delivery system that can treat several quadrants at once.

4.B.3 Laser ablation

The use of the diode laser in combination with a piezoelectrically driven droplet driver (Microfab Technologies, Inc.) which delivers microdroplets of indocyanine green dye (ICG) has been studied. The experimental study involved human sclera samples and was carried out at UTMBG (Motamedi). Dye droplets were delivered to the tissue and 0.5 s pulses of diode laser radiation (810 nm) were delivered by optical fiber to the ablation site. This two-step process was repeated at about 1 Hz and a hole was drilled in the tissue.

The correlate computer simulation of the ablation process (see figures above, in which upper 100 μm is stained with ICG to start the ablation process) was conducted at UTMDA (Jacques). The finite-difference model was modified to allow several factors:

1. optical penetration
2. thermal diffusion
3. water diffusion
4. surface evaporation
5. rate process of carbonization
6. subsurface explosive vaporization

The ablation process was found to depend primarily on the balance between surface evaporation and water diffusion to the surface. If energy could be deposited in an ICG-stained

layer or in a carbonized layer such that water evaporation exceeded the rate of water diffusion to the surface, then the surface dessicated and carbonization occurred. The new carbonization accelerated the surface heating and soon the temperature rise yielded a superficial subsurface explosive event occurred. (Since heat must diffuse to the surface to evaporate water, a subsurface gradient is required for heat flow to the surface and therefore a subsurface explosive event is almost inevitable, although superficial.) The explosive event exposed a fresh wet tissue surface and the cycle of evaporation, dessication, carbonization, rapid temperature rise, explosion occurred again and again.

We have also conducted studies of pulsed laser ablation of dental materials using the long-pulsed Er:YAG laser. This laser is capable of effective ablation of enamel and dentin. We studied the pulse energy dependence of ablation efficiency and discovered that increasing the laser pulse energy did not improve efficiency. Therefore, it is repetition rate rather than pulse energy which should be maximized to achieve maximal rates of dental ablation.

4.B.3.2 Cardiology: photoacoustic relaxation

The goal of this project is to use laser-induced acoustic pressure waves to cause relaxation of blood vessels.

Our efforts in the past year have concentrated on the basic photoacoustic phenomena, using both our sputtered lithium-niobate photoacoustic transducer and laser-flash photography to understand pressure wave generation and propagation. We have discovered that even under "matched" boundary conditions such as a saline/tissue interface, the slight but significant mismatch is sufficient to enable tensile negative-stress waves to be reflected by the interface. Such tensile stress waves are sufficient to cause cavitation in liquids and spallation-like events in soft tissues.

We have measured the asymmetry of pressure waves induced in soft tissues by Q-switched laser pulses which indicate the onset of spallation-like phenomena. The area under the pressure wave signature is no longer zero, implying that there has been momentum transfer to the tissue due to tissue mass ejection at the surface. This occurs when only tens of degrees in temperature rise have occurred. This evidence for photoacoustic ablation is still under study.

We have established the behavior of laser-induced acoustic waves in tissues, both theoretically and experimentally. We now plan to initiate experiments on blood vessel relaxation using our dorsal rat skin window chamber model which allows real-time video recording of the vessels during the laser irradiation.

4.B.4.2 Clearance of deep lesions (dermatology)

The pulsed laser treatment of vascular abnormalities has been pursued in collaboration with Stuart Nelson, Beckman Laser Institute and Medical Clinic, Univ. of California-Irvine. The clinical application involves 577-nm pulsed dye laser irradiation to selectively cause thermal injury to abnormal blood vessels. We have pursued an understanding of the thermal energy deposition by the laser and used a pulsed photothermal radiometer (PPTR) to monitor the IR blackbody emission from the front tissue surface as a function of time. By solving the inverse problem, we can convert the $T(t, z = 0)$ surface temperature data into a map of the initial energy deposition, $T(t = 0, z)$. This map yields a picture of the portwine stain lesion. By understanding how deep the treatment will extend, the physician can better design a long-term treatment protocol and counsel the patient.

4.B.5 Photodynamic Therapy (PDT)

We have been studying the use of the metabolic precursor δ -aminolevulinic acid (5-ALA) to produce a natural photosensitizer, protoporphyrin IX (PPIX), in cells. We have undertaken two studies:

(1) The pharmacokinetics of PPIX synthesis

We have studied the de novo synthesis of PPIX, its subsequent metabolism to heme products, and its photobleaching by laser radiation. Experiments with cancer cells in tissue culture were conducted to specify the rate constants of a compartmental model. The model can now predict the drug dosimetry for different protocols involving variations in 5-ALA and light delivery. For example, we have modeled two types of protocols: (1) maximal acute build up of PPIX followed by rapid complete photobleaching, and (2) slow long-term delivery of 5-ALA to yield a low PPIX elevation and the use of long-term light delivery.

(2) Photobleaching studies *in vivo*

Studies in a subcutaneous rat tumor model have investigated the photobleaching encountered *in vivo*. The study required correction for the tissue optics. We found that the subsurface light distribution yielded about 3-fold greater light concentration than was delivered due to backscattering by the turbid tumor. Consequently the exponential photobleaching observed appeared to be 3-fold faster than it should have been based on the delivered irradiance. We consequently deduced the true photobleaching dose constant for our rat tumor model to be 105 ± 23 J/cm² at 630 nm, which yields 67% complete photobleaching.

We have acquired a CW argon/dye laser system and are now comparing the efficiency of PDT using the CW and pulsed doubled Nd:YAG/dye laser source. The issues are the degree of dye saturation and dye photodestruction caused by the high-irradiance Q-switched pulsed laser exposure in comparison to low-irradiance continuous light exposure. Future work will also investigate the optimal duty cycle (on-off light exposure) which allows reperfusion of oxygen into the cancer cells from nearby blood vessels during the off cycle.

Three papers, 16 proceedings papers, and 20 abstracts are related to the work sponsored by this DOE grant.

Papers

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Texas A&M University

S. Rastegar, Ph.D.

The activities for the second phase of this research involved experimental as well as theoretical work. One graduate student at any one time was supported during the second

phase of this project by D.O.E funds. In all, two Ph.D. student's, four M.S. student's, and two undergraduate's research projects at Texas A&M have been/are related to this work. Student names and their sources of support are:

UG	Jennifer Green (G.E. Faculties of Future Scholarship) Ann Marie Chard (NSF-REU research award recipient)
M.S.	Edward Sammons (partial DOE), Beop-Min Kim (partial DOE) Shoban Jagathesan (partial ATP, partial Vet. School) Aamer Azeemi (T.A.)
Ph.D.	Young Lee (ATP, partial DOE), Yonghoon Kwon (ATP)

COLLABORATIONS

Collaborative research were done, as planned, with UT-MDA, UTMB, and UT-Austin, Rice University and the Texas Heart Institute (THI). This involved several trips by the PI and his students to Houston, Galveston, and Austin to perform experimental studies and discuss theoretical developments. One of TAMU Ph.D. student is spending a year at UTMB in Galveston addressing some of the objectives this grant, experimentally and theoretically. UTMB will provide summary of his findings. One Rice University/UT-MDA M.D.-Ph.D. student was co-supervised and did research at Texas A&M; her computations were done via Ethernet on a SPARC workstation at UTMB. Communication between the investigators as well as supervision of remotely located students are being done, effectively, through electronic mail, computer network two-way ('talk') communication, telephone, FAX, and regular visits. Furthermore, our Macintosh computers at TAMU, MDA, and UTMB are linked on Ethernet, through which our research documents (text and graphs) are exchanged, in original form, almost instantaneously.

STUDIES

Experimental studies involved the use of diode laser, solid state lasers (Er:YAG and Ho:YAG), Argon pumped Tunable Ti:Sapphire laser, and Argon Laser. A 25 Watt Diomed diode laser was acquired by UTMB and was used by the collaborators either at UTMB or by transporting it to other labs. TAMU used the diode laser in collaboration with UTMB and UT-MDA for a study of interstitial laser coagulation. A Schwartz Ho:YAG/Er:YAG laser is loaned to Texas A&M by the THI, on which several basic studies were performed on ablation of soft and hard tissue; this year's focus was ablation of dental tissue for development of this solid state laser for dental applications.

4.B.3.4 Laser ablation of dental materials.

Theoretical Studies

- Planar Stresses Under Pulsed Er:YAG Irradiation. A Theoretical analysis of these stresses was done using theory of thermal stresses. It was found that radial and circumferential stresses develop during laser irradiation of hard tissue. Radial stresses are all compressive.

Circumferential stresses can be both Compressive and Tensile. Maximum stress may reach failure strength both in tension and compression during a pulse of Er:YAG laser radiation.

Experimental Studies

- Transient Axial Stress Under Pulse Irradiation. A novel technique was developed to monitor transient mechanical (stress) response of dental tissue to pulses of Er:YAG laser. Partial blocking of a collimated He-Ne probe beam was used to monitor axial deformation due to stress at the surface of the enamel irradiated by free running Er:YAG. Deformation rise time was similar to the laser pulse width (250 μ s). Deformation fall time was in the order of a few milliseconds. This method may potentially be used for in-situ estimation of thermomechanical properties under pulse irradiation.

4.B.1 Photocoagulation

Focus of therapeutic studies this year was on coagulation process and the use of feedback for its control. Theoretical studies involved the use of a SUN 3/60 computer at Texas A&M and two SPARC-II Workstation at UTMB (directly and by remote access). UT-MDA and TAMU have recently acquired SPARC-10 Workstations which has added significantly to our collective computational power. Studies were done in computer simulation of light and temperature distribution by Monte Carlo, finite element, finite difference, and analytical methods. These programs were used for analysis of damage in lasers irradiated tissue under various irradiation conditions. Effect of dynamic changes in optical properties were studied in liver and myocardial tissues. Much effort was devoted to develop a feedback model for coagulation control using finite element method. This has great potential in guiding experimental feedback studies which we have begun. The combined findings of the studies and the methodologies developed will have potential use in developing a 'smart' diode laser for coagulation of tissue. The details of the methods and finding are found (or will soon appear) in the publications resulted from this studies. Some of the main finding are highlighted below.

Theoretical Studies

- Multi-rate Kinetics Studies: A multi-rate kinetic model for thermal damage which occurs in certain tissues (e.g. liver as shown by Jacques et al.) was developed by combining Runge-Kutta and finite element methods. Temperature calculations for each 'element' was used in the governing differential equation for multi-rate process and concentration of denatured tissue in each element was calculated. The model was used to compare single rate process of damage with multi-component and multi-stage rate models. In a multi-rate scenario thermal damage would initiate faster than in a single rate scenario. Critical temperatures for 'significant' tissue denaturation would be lower for a multi-rate process. For tissues in which a multi-rate process govern thermal damage coagulation front propagation is more sensitive to temperature-time history than in a single rate process. In particular a significant difference was found in the denaturation time-course when a constant temperature scenario was compared with the temperature-time history of laser irradiation. The engineering usefulness and implication of the results is that, as a margin of safety, a higher requirement should be made for temporal resolution of the feedback system, both in measurement and in control. This would be especially important if the coagulation target volume is near 'critical' tissues that, as a clinical objective, need to be preserved.

- Finite Element Controlled Surface Temperature. Our finite element code was modified to simulate modulation of laser power to achieve a desired temperature history at the tissue surface. The tool was used to investigate various temperature-time history scenarios and its

result on coagulation front movement. A constant (with some oscillations around a mean value) temperature history at the surface was found to be very effective in controlled coagulation of tissue. It was found that a nonuniform pulse sequence is required to achieve a 'constant' surface temperature. 'Critical' temperature for damage accumulation may be a useful guide for choosing a desired controlled temperature. When there is some uncertainty in optical properties, coagulation under controlled temperatures will achieve more reliability in final outcomes and could minimize risk to surrounding tissue. Optical depth of penetration, regardless may be the deciding factor in determining damage progression under controlled surface temperature. The effect of surface convection was also studied and it was found that a lower 'constant' temperature may be required, at high convection rates, in order avoid ablation temperature threshold within the tissue.

- Interstitial Light Distribution. Monte-Carlo code for light distribution was modified to simulate light distribution for interstitial coagulation of tissue. Isolines of (logarithm of) fluence rate were found form an almost circular profile with a center a few 'beam diameters' from the fiber tip. Experiments of interstitial coagulation using diode and Ti:Sapphire lasers were performed at UTMB. UTMB will report on this.

- Ultrasound Imaging of Laser Coagulation. An image processing routine using radial spread lines was developed to analyze Ultrasound images obtained during laser coagulation of beef. A image change was found to be associated with laser irradiation/coagulation of tissue. The strong part of the signal, however, was present only when the laser was on. A partial permanent change remained after the laser was off. Histology dimensions correlated with the dimensions of reversible image. This is explained by correlation of temperature rise with density change which appears as echogenic image in an ultrasound response. Though the final verdict on the ability of the ultrasound technique on predicting coagulation depth is not in yet, the high cost may be prohibitive for any application which would need to integrate the ultrasound into the laser/fiber system.

- Video Imaging of Coagulation Front Egg white model , with controlled absorption and scattering properties, is being used in this study to track the front of coagulation as a function of time. User-friendly image processing routines have been developed to perform this task on a SPARC station. Results will be compared qualitatively as well as quantitatively with theoretical models for a range of optical properties, laser powers, and exposure times.

Experimental Studies

- Optical Property Variation in Egg White Model. Effect of optical properties in coagulation process was studies in an egg-white model. It was found that for a given concentration of absorber, both diameter and depth of coagulum were increased by addition of scatterer. The diameter of the coagulum was more strongly affected by scatterer concentration. More importantly a recipe was developed, in the course of this study, for correlating absorber (Congo red) and scatterer (powdered non-fat milk) concentrations to absorption and scattering coefficient. These concentrations are now used for other studies for quickly achieving a desired degree of absorption/scattering in the samples.

- Temperature Feedback and Shutter Control. A surface temperature control set up was developed that is composed of two computers and A/D boards, one to monitor temperature and the other to control the laser power and/or shutter speed. Presently, the system has about ten millisecond resolution for control of laser shutter so as to maintain a desired temperature range

at a given point on the surface. This would be appropriate for applications involving several tens of seconds to minutes of irradiation. Microthermocouples are used for temperature measurement. Self-absorption of laser light by the thermocouple is accounted for by monitoring the temperature during intermittently imposed 1 second off time durations (aside from those dictated for maintaining constant temperature) during irradiation. A naked beam of an Argon laser is presently used for building the first complete system. A range of off-on times and surface locations have been studied and more are undergoing while the current data is being analyzed. The system is being tested both on the egg white model and on beef.

• Reflectance of Coagulated Live (Ti:Sapphire laser). Ti:Sapphire laser is a useful tool for studying the role wavelength in the near IR, a relevant range for diode laser applications. Reflection of Ti:Sa laser light collected by a lens at different angles from the surface of coagulated and uncoagulated beef liver samples was studied between 785-890 nm in 5 nm increments. A large difference in the reflectance was observed in the values between 785-800 nm range as compared to the values for the rest of the interval (800-900). Reflectance was found to increase monotonically with coagulation depth up to nearly 1.5 mm depth of coagulum at which point the signal would reach steady state. This indicates that total reflectance as a feedback tool would not have an appreciable dynamic range. Other investigations are under way at MD Anderson which use more detailed studies of reflectance, looking at reflectance as a function of radial distance and time which hold better promise.

Two papers, 2 proceedings papers, and 8 abstracts are related to the work sponsored by this DOE grant.

Papers

• Kadipasaoglu K., Rastegar S., Sartori M., Watson L.E., Clubb F.J., Jr., Conger J.L., Hare W.D., Edelen B., Moore M.S., and Frazier O.H., "In vitro Ablation of Human Aorta under Saline and Blood with the Holmium:YAG Laser" *Lasers in the Life Sciences*, 4(3), 1992.

Papers submitted:

• K. Kadipasaoglu, S. Rastegar, F. J. Clubb, Jr., L. Moreau, J. L. Conger, C. R. Reichart, W. D. Hare, R. Matsuwaka, N. Furusho, O. H. Frazier, "Acute and Chronic Response of Normal Canine Endothelium to Ho:YAG Laser Irradiation," Submitted to *Lasers in Surgery and Medicine*, 1992.

Proceedings

• Rastegar S., Jacques S. L., Motamedi M., and Kim B-K., "Analysis of Equivalency of High-Power Diode Laser (810nm) and Nd:YAG Laser (1064nm) for Coagulation of Tissue," *SPIE Proceedings*, Vol. 1646, pp. 150-158, 1992.

• Rastegar S., Kim B-K., and Jacques S. L., "Role of Temperature Dependence of Optical Properties in Laser Irradiation of Biological Tissue," *SPIE Proceedings*, Vol. 1646, pp. 228-235, 1992. [Invited]

Abstracts

• Glenn T. N., Rastegar S., and Jacques S. L. "Simulation and Analysis of the Use of Temperature Feedback for Control of Laser Coagulation of Tissue," Annual meeting of the American Society of Lasers in Medicine, New Orleans, April 18-20, 1993.

- Rastegar S., Chard A. M. , Jacques S.L. , Motamedi M. , and Thomsen S., "Kinetics of multi-component and multi-Rate thermal damage in laser irradiation of Tissue," Annual meeting of the American Society of Lasers in Medicine, New Orleans, April 18-20, 1993.
- Rastegar S., "Thermomechanical Response of Dental Tissue to Pulse Laser Irradiation," Invited poster presentation at a Workshop on Dynamic Response of Materials to Pulsed Heating at Los Alamos National Laboratory, Los Alamos, New Mexico, Feb. 22-26, 1993. [Invited]
- Azeemi A. and Rastegar S., "Video Imaging for The Coagulation Front in Laser Irradiated Albumin," Eleventh Biomedical Engineering Research Conference in Houston, February 11-12, 1993.
- Anvari A., Torres J. H., Motamedi M., and Rastegar S., "Effect of Surface Cooling During Intraluminal Laser Irradiation of Tissue," Eleventh Biomedical Engineering Research Conference in Houston, February 11-12, 1993.
- Glenn T. N., Rastegar S., Jacques S. L., and Tittel F., " Finite Element Analysis of Damage Front Propagation with Controlled Surface Temperature in Laser Irradiated Tissue," Eleventh Biomedical Engineering Research Conference in Houston, February 11-12, 1993.
- Lee Y. and Rastegar S., " Photocoagulation Response of Controlled Egg-White Samples," Eleventh Biomedical Engineering Research Conference in Houston, February 11-12, 1993.
- Jagathesan S. S., Rastegar S., Kehtarnavaz N., Torres J.H., and Motamedi M., "Tracking of the Advancement of The Coagulation Front of a Laser Irradiated Tissue Using Ultrasound Imaging," Eleventh Biomedical Engineering Research Conference in Houston, February 11-12, 1993.

Rice University	Frank Tittel, Ph.D.
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This work involved the efforts of Andrew Hielscher, a Ph.D. candidate in Electrical and Computer Engineering, Rice University, who was supported by this grant.

4.A.1 Reflectance spectroscopy

The past year has seen considerable progress in development of a frequency-domain (FD) spectroscopy system using a frequency-modulated diode laser source.

Theoretical studies

It became clear through our theoretical efforts in the past year that the frequency-domain diffusion theory widely used to interpret FD signals was inadequate. Therefore, we developed time-resolved Monte Carlo simulations of photon propagation (see figure below) which allowed for various boundary conditions or multilayered tissues. Then the Fourier Transform of the time-resolved signals were taken to yield the real and imaginary components of detected signal in the frequency domain. Finally, these real and imaginary components were used to compute the phase and modulation of the detected signal, which are experimentally measured values.

In other words, we could simulate FD signals under complex conditions (mismatched boundaries, multilayered tissues). We also could simulate FD signals under simple conditions for comparison with the predictions of diffusion theory.

Our results have indicated where diffusion theory fails, and also how to properly use diffusion theory to side-step the artifactual errors. These lessons have been incorporated into a simple calculational protocol for interpreting phase and modulation signals in terms of tissue absorption and reduced scattering properties. This protocol will be of service to the many investigators world-wide who are now actively investigating the use of FD spectroscopy.

Experimental studies

Our efforts to build an FD spectroscopy system have been slowed because we have concentrated on specifying the analysis algorithms required for accurate interpretation of measurements, so that we might appreciate the design constraints required of equipment to be purchased. We resisted the urge to buy available equipment immediately and concentrated on being sure what we bought is adequate for the task.

Mr. Hielscher has visited the FD laboratories of Enrico Gratton, Univ. of Illinois, Urbana-Champaign, Britton Chance, Univ. of Pennsylvania, and Joseph Lacowicz, Univ. Maryland Medical School. He is preparing experiments to be conducted at the Lacowicz laboratory which will test the design specifications required for medical applications.

In particular, we continue to focus on the issue of making measurements of neonatal brain oxygenation and blood perfusion which is a critical problem in the Neonatal Intensive Care Unit (NICU).

Two proceedings papers and one abstract are related to the work sponsored by this DOE grant.

Proceedings papers

Jacques S.L., A.H. Hielscher, L. Wang: How source/collector placement and subsurface absorbing layer affect time-resolved and phase/modulation-resolved photon migration. paper 1888-34, in *SPIE Proceedings, Photon Migration and Imaging in Random Media and Tissues*, 1888, 1993.

A.H. Hielscher, S.L. Jacques, F.K. Tittel: Noninvasive near-IR monitoring of blood oxygenation by phase-resolved transmission spectroscopy. paper 1888-31, in *SPIE Proceedings, Photon Migration and Imaging in Random Media and Tissues*, 1888, 1993.

Abstracts

A.H. Hielscher, S.L. Jacques, F.K. Tittel: Time- and phase-resolved spectroscopy of multilayered tissues. American Society for Lasers in Medicine and Surgery, New Orleans, April 18-20, 1993. in *Lasers Surg. Med.*, Suppl 5, abstract 17, 1993.

Naval Research Laboratory

Leon Esterowitz, Ph.D.

The work was accomplished with the efforts of Bob Stoneman, supported by this grant.

Development of compact tunable 2- μm solid state lasers continues in the Solid State Laser group at Naval Research Laboratory (NRL). We continue to follow a two-track program, providing Ti:sapphire-laser-pumped 2.0- μm thulium and 2.1- μm holmium lasers for laser-tissue interaction studies to the Biomedical Engineering Program at the University of Texas at Austin (UTA), while developing in our laboratory at NRL diode-pumped tunable thulium solid-state lasers. The Ti:sapphire-laser-pumped 2- μm lasers provide a short-term means to study laser-tissue interaction, while the diode-pumped lasers are a longer-term development project which will result in compact, lightweight, and portable devices.

During the current work period we have provided to UTA a Ti:sapphire-laser-pumped holmium:YAG laser. This laser provides 400 mW of power at 2.1 μm when pumped with 1.5 W of power from the Ti:sapphire pump laser. It is expected to produce approximately twice this power level when the Ti:sapphire laser is adjusted to produce its optimum output power of 3 W. The holmium has been used at UTA to compare the effects on tissue of the 2.1- μm holmium laser with the 2.0- μm thulium laser. The thulium:YAG laser was supplied by NRL to UTA last year. The thulium laser provides 700 mW at 2.0 μm when pumped with 3 W from the Ti:sapphire laser, and is also currently in use at UTA.

The holmium:YAG laser was provided with an improved system for mounting and cooling the laser crystal. The modified crystal mount allows for the necessary optical alignment of the crystal while maintaining good mechanical stability. This design results in greatly improved stability of the output power of the 2- μm laser, and can be used with both the new holmium:YAG laser and the previously supplied thulium:YAG laser.

Also during the past year we have developed a higher power Ti:sapphire-pumped tunable thulium:YAG laser. This laser produces more than 1 W when pumped with 2 W from the Ti:sapphire laser. The output wavelength is tunable over the range 1.90 to 2.15 μm . This laser also makes use of the more advanced cooling system and has excellent output power stability owing to the improved mechanical stability. This laser will be provided to UTA in June, 1993.

We are also continuing development of diode-pumped versions of all of the above lasers. This development effort will result in vastly more compact and portable 2- μm laser devices than are currently available. To date we have achieved more than 500-mW output from a diode-pumped thulium:YAG laser. This laser utilizes a 3-W continuous (cw) laser diode as the

pump source. We are currently developing a 2- μ m thulium:YAG laser system which utilizes a 7-W quasi-cw laser diode pump source. This system should allow us to achieve a 2- μ m output power exceeding 1 W. This development has required an entirely new system for focusing the laser diode pump light, which has a geometry completely different from that of the cw diode lasers. This 2- μ m laser system should be available in approximately six months.

UT Medical Branch at Galveston

Massoud Motamedi, Ph.D.

4.B.1.1 Laser Treatment for Benign Prostate Hyperplasia

Benign Prostatic Hyperplasia (BPH) is a significant health problem for primarily elderly men, many of whom have major pre-existing medical problems. Based on autopsy studies, about 60% of men have evidence of prostatic hyperplasia at age 61-70, and about 50% of men of the same age will present with clinical signs and symptoms of BPH. Annually approximately 500,000 surgical procedures are performed to treat BPH. In order to reduce the morbidity of the surgical treatment and to offer acceptable therapy to high risk patients, the potential role of non-surgical treatment of BPH has been recently considered. Recent applications of laser for this treatment suggest that this procedure causes less patient trauma, fewer complications, a shorter hospital stay, and can be performed much faster than current techniques.

In the past year, we investigated the effects of two different laser dosimetry regimes on prostatic tissue and, particularly, compare the sizes of the coagulation zones they produce on the same individual prostates. The choices of the two dosimetry regimes for the comparative study were based on our previous work. One regimen corresponds to a new approach of slow heating of the prostate with low laser power, and the other corresponds to fast heating with high power as currently done.

Nd:YAG laser irradiation of prostate was performed transurethrally in 16 mongrel canines. The laser used was the Optilase 1000 from Trimedyne, Inc. The laser beam was delivered to the tissue via a UrolaseTM optical fiber (Bard Inc.) which reflects the light in a 90° angle. Irrigation with normal saline solution was maintained throughout the irradiation procedure which was performed under direct visualization. Each prostate was irradiated on 4 separate sites, 2 on each lobe, approximately located at the 2, 4, 8 and 10 o'clock positions. In 6 dogs, three different heating rates were investigated with incident powers of 15, 30 and 50 W (measured at the fiber tip) for time periods of 3 minutes, 1.5 minutes and 54 seconds, respectively, providing the same total energy of 2700 Joules. In other 10 dogs, low power (15 W) was applied to the left prostatic lobe for 3 minutes (2700 J total energy), and high power (50-60 W) was applied to the right prostatic lobe for 1 minute (3000-3600 J total energy).

The results of this investigation have shown that, for the same applied energy, larger volumes of prostatic tissue can be coagulated by irradiating the prostate with low Nd:YAG laser power over a longer period of time. In dogs treated with low laser power, we measured an average depth of coagulation zone was 12 mm. Whereas, the lesions induced using high power laser, the average depth of tissue necrosis was limited to 8 mm. Assuming spherical geometry for each lesion, we demonstrated a significant improvement in the lesion size using low laser power and long exposure time. This approach reduces the risk of complications and maintains the integrity of the laser delivery system.

4.A Spectroscopy

4.3.2 Fluorescence Spectroscopy

In collaborative with UTMD, Dr. Dick Sterenberg from , Laser Center in Amsterdam, The Netherlands developed a spectroscopic system to monitor laser-induced fluorescence and detect skin cancer. The detection system consists of a CCD camera, OMA, and nitrogen laser. In a clinical studies of 27 patients, the spectroscopic features of both non-melanoma and melanoma skin lesions have been studied and correlated to pathologic findings. Preliminary analysis suggest that skin autofluorescence alone may not provide accurate information on pathologic conditions of the lesion. However, application of exogenous dyes such as ALA may improve the correlation between the spectroscopic signature of tissue and the lesion pathology..
Education and Training:

4.A.3 Raman Spectroscopy

To measure glucose level in patients with diabetes non-invasively, we applied Laser Raman Spectroscopy to monitor glucose and lactate from human and rabbit aqueous humor specimens We used Argon and Ti:Sa lasers (514 nm, 805 nm) and a Spex 500M Raman System. Raman peaks indicative of the systematic vibrations of methylene and methyl groups associated with glucose and lactate, respectively, were clearly observed in all specimens. A second stretching mode characteristic of lactate between the carbon atom and the carbocyclic acid group was also observed providing a distinguishing feature between the glucose and lactate Raman peaks. We are in the process of constructing a fiber-optic based near-IR Raman system to perform these studies in vivo in rabbits. Based on the results of the in vivo studies, the next phase of the study could be to initiate clinical trials of this technique.

TRAINING

a. Training of Physician and Residence

Dr. Tom Cammack who is the chief residence at the Division of Urology at UTMB this year, has spent the last nine months working on the project related to development of smart laser catheter for treatment of benign prostate hyperplasia (BPH). Dr. Cammack was trained in use of laser for prostate coagulation and application of Ultrasound Imaging for monitoring tissue response real time by performing in vitro as well as in vivo studies. He recently received two awards for his work on the optimization of laser dosimetry for treatment of BPH.

Dr. Susan Dozier who is fourth year residence in the department of Dermatology at UTMB has been working on the use of pulsed laser for removal of tattoo and other pigmentations in skin. She has been trained to use Q-switched Alexandrite and Nd:YAG lasers in an animal model.

b. Training of Graduate Students

As part of our training effort, Bahman Anvari, a Ph.D. candidate at the Bioengineering Program of TAMU has been working in the Laser Laboratory at UTMB on developing a computer model to predict tissue response during photocoagulation of prostate. The model will enable us guide the animal studies and account for variables such as prostate geometry and the effects of blood perfusion on the laser induced thermal field during laser therapy. This work should further allow us to investigate the feasibility for development of a smart laser catheter for treatment of benign prostate hyperplasia. Some of the preliminary results of this research have already been presented and additional work has been submitted. He recently received a

graduate student award to present his work at the annual meeting of American Society for Lasers in Medicine and Surgery.

Abstracts, Proceedings and Papers:

A total of 18 abstracts, 4 proceedings and 4 papers have been presented, accepted or submitted which are related to the work sponsored by this DOE grant.

UT Austin

AJ Welch, Ph.D.

4.A.2 Fluorescence Spectroscopy

A preliminary clinical study involving 30 patients was conducted by Rebecca Richards-Kortum and two UTA graduate students at M. D. Anderson Cancer Center in Houston (UTMDA), in collaboration with Dr. Michelle Follen-Mitchell, Dept. of Gynecology. A prototype fluorescence catheter system was assembled, involving a nitrogen laser (337 nm) for excitation, an optical multichannel analyzer for detection of fluorescence, and a DOS 486 computer system for data acquisition.

The results indicated that fluorescence could distinguish cervical dysplasia from cervical inflammation, which is a useful clinical discrimination. The physicians were impressed with the rapid noninvasive technique which hopefully can replace biopsies in many situations as a means of assessing tissue status. Biopsies and subsequent healing can affect the tissue site making subsequent diagnosis at a later date more difficult.

4.B.1.2 Thermokeratolasty

A unique continuous wave (CW) holmium laser ($\lambda = 2.09 \mu\text{m}$, Rare Earth Medical) has been evaluated as a new heating modality for thermokeratoplasty. Thermokeratoplasty is a refractive surgical procedure for the correction of hyperopia which uses selective heating to reshape the cornea. The holmium laser is highly effective in this procedure due to the high absorption coefficient ($\mu_a = 27.55 \text{ cm}^{-1}$) of the cornea at $2.09 \mu\text{m}$. The depth of corneal photocoagulation has been evaluated with histological studies of enucleated porcine eyes that were irradiated with the CW Ho:YAG laser. Laser power and exposure time ranged from 300 mW to 800 mW and 100 ms to 800 ms respectively. The laser was delivered to the eyes via a $600 \mu\text{m}$ low-OH optical fiber. Coagulation depth was determined by birefringence microscopy of the corneal sections. Our studies also compared the effects of contact and non-contact irradiation and found significant advantages with the contact mode. The optical laser parameters determined from the histology studies were used for *in vivo* rabbit studies to quantify the refractive correction possible. One coagulation was placed on each of sixteen equiangular rays taken from a central, clear, optical zone in the cornea with a diameter of 7 mm. Refractive changes in the central cornea were quantified with a keratoscope. Initial procedures resulted in refractive changes up to five diopters (D). The keratoscope results showed a significant regression at three weeks post-operatively.

In a second series of experiments the Ti-Sapphire pumped CW Holmium:YAG laser ($2.09 \mu\text{m}$) was used to place lesions on *in vitro* porcine eyes. The development of the lesion during irradiation was tracked by measuring the reflectance to white light. Two detector systems were used: a ccd array and a single photodiode. Also a thermal camera was used to measure surface temperature (60 fields/second) of the cornea. The reflectance signal from the photodetector was highly correlated with the temperature rise at the end of the laser pulse.

4.B.1.2. Cyclophotocoagulation

The results of these experiments suggest that there are profound similarities in the mechanism of photocoagulative necrosis of tissue during transscleral Argon and diode cyclophotocoagulation. It appears that both wavelengths are highly absorbed and attenuated at the ciliary muscle and vasculature.

A number of recent studies have attempted to characterize the mechanism of IOP lowering due to transscleral Nd:YAG cyclophotocoagulation, through histologic study of the treated tissue. These studies report selective tissue damage in the form of "focal coagulation necrosis and hemorrhage in the ciliary and iridial processes, accompanied by focal vacuolization, degeneration, and disruption of pigmented and non-pigmented epithelium" when using the Nd:YAG laser. This discrepancy between the Nd:YAG versus diode and visible wavelength

lasers, in the extent and selectivity of photocoagulative necrosis in the treated tissues, may be explained by the substantial difference in the scattering properties of the tissue for these wavelengths. Figures 1 and 2 show the optical properties of the conjunctiva, sclera, and the ciliary body, based on a delta-Eddington diffusion approximation to the radiative transport theory. The graph in Figure 1 shows that the reduced scattering coefficient in the ciliary body (which includes the ciliary muscle, as well as the epithelial layers) is approximately 3.5 times higher for the Argon, and 2.1 times higher for diode wavelengths, as compared to the scattering coefficients for Nd:YAG. Moreover, according to the graph in Figure 2, the Argon laser is absorbed approximately 4.5 times, and the diode laser wavelength (810 nm) is absorbed 2.5 times more than the Nd:YAG laser wavelength within the ciliary body structure. These optical properties can clearly account for the difference in the coagulation necrosis of the treated issue using Nd:YAG versus diode or Argon cyclophotocoagulation.

4.B.2. Feedback Controlled Tissue Welding

In Dr. A.J. Welch's Biomedical Laser Laboratories at The University of Texas at Austin, graduate students have been investigating possible feedback control mechanisms for laser radiation assisted tissue welding for the past five years. Temperature of reflectance from forming coagulum have been investigated as markers of thermal damage. A feedback-controlled surgical laser system for the control and regulation of photothermal damage is currently under development.

An automated system for constant temperature vessel welding was developed and quasi-constant temperature vessel welding was performed using *in vitro* human saphenous veins. Three to five millimeter long longitudinal incisions were anastomosed with radiation from a shutter controlled argon ion laser. A lead selenide detector was employed to measure tissue surface temperature, and the temperature signal from the detector controlled the laser radiation by closing a shutter whenever a preselected control temperature was exceeded. The bursting strength of the welded veins was determined for 30 samples. The average bursting pressure of controlled temperature welds at temperatures from 100 to 120°C were 80% higher than welds at temperatures from 70 to 90°C.

Solid state lasers were supplied by the Naval Research Laboratory. A low power CW Holmium:YAG laser (2.09 μm) was installed in April 1993. This unit is pumped by a Titanium-Sapphire laser which is in return pumped by the Argon ion laser mentioned above. The Holmium laser's maximum output power is about 400 mW. Moreover, a continuously tuned (1.9 μm - 2.1 μm) CW Holmium-Thulium laser will arrive in June 1993. The peak output power is expected to be about 500 mW. Both lasers will be used for investigating feedback controlled tissue welding around the 2.0 μm water absorption peak.

Figure 1. Average reduced scattering coefficient ($\mu_s' = \mu_s(1 - g)$, where μ_s is the scattering coefficient, and g is the anisotropy of the medium) vs. wavelength for seven different samples of porcine conjunctiva, sclera, and ciliary body

Figure 2. Average absorption coefficient (cm^{-1}) versus wavelength (nm) for seven different samples of porcine conjunctiva, sclera, and ciliary body

Along with temperature feedback, a ccd spectrograph system will be used to characterize the transient spectral reflectance changes of tissue during photocoagulation. Studies have shown that the reflectance change in certain near infrared wavelengths is quite prominent during laser irradiation. This reflectance change will be used to monitor and control collagen-rich tissue denaturation and tissue welding.

4.B.5. Photodynamic therapy

We are also investigating the use of reflectance spectrophotometry as a monitor of the *in vivo* photodynamic process. The efficacy of the photodynamic therapy of many animal tumor models has been linked to the destruction of tumor microvasculature. Due to the strong characteristic absorption peaks of hemoglobin, the reflectance spectrum of most tissues may be used to monitor changes in the tissue blood volume and oxygenation state. In addition, photobleaching of the drug may be related to changes in the reflectance spectrum at the location of the photosensitizer's absorption maximum. We are using the rat window chamber model to evaluate the use of reflectance spectrophotometry as a monitoring method. In a preliminary study, the change in transmission of 577 nm light, the spectral location of an oxyhemoglobin absorption maximum, through the rat skin chamber were correlated to visually observable changes in tissue microvasculature due to the photodynamic treatment. Studies being conducted now use an optical multichannel analyzer to record the reflectance spectrum of the irradiated area during PDT, and a CCD camera imaged on the irradiated area to record visible changes in the tissue.

PAPERS, ABSTRACTS

Eight papers were published, 9 accepted, 12 submitted, 9 proceedings papers published, and 7 abstracts presented on work related to the projects sponsored by this DOE grant.

SUMMARY OF PUBLICATIONS AND PRESENTATIONS

	UTMDA	UTA	TAMU	UTMBG	RICE
Journal papers	3	17	2	3	
Journal papers submitted		12		1	
Proceedings papers	16	9	2	4	2
Abstracts	20	7	8	18	1

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