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PROGRESS REPORT, DOE CENTER OF EXCELLENCE IN LASER MEDICINE

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SUMMARY:
Achievements during the first six months of funding to prepare for a Center of Excellence in biomedical laser development include: (1) limited specific research projects within the Center's three broad interest areas, and (2) program development to establish the Center and its activities. Progress in the three interest areas -- new medical laser systems development, optical diagnostics, and photosensitization, is reported. Feasibility studies and prototype development were emphasized, to enhance establishing a substantial Center through future support. Specific projects are an optimized laser-catheter system for reversal of vasospasm; optical detection of major skin burn depth and cancers using fluorescent drugs, and photosensitization of vascular tissues. In addition, an interdepartmental Laser Center was established at MGH to enhance collaborations and institutional committment to the Center of Excellence. Competitive postdoctoral research fellowships, with provision for matching funds from other departments, have been announced.

SCIENTIFIC PROGRESS:

I. Development of new medical laser systems

A. Pulsed laser vasodilation:
We proposed to investigate and optimize for medical use, the phenomenon of vasodilation caused by microsecond-domain laser pulses to reverse vasospasm. Arterial vasospasm is a major cause of death after hemorrhagic stroke, head injury, trauma, and vascular surgeries -- yet does not respond well to vasodilating drugs. This phenomenon was recently discovered at Wellman Lab, and two patents on the process and a catheter system have been filed. Our intent is to understand the underlying mechanisms and fundamental processes for this effect, and develop a laser-catheter system that can be transferred to US industry.

The basic mechanism for pulsed laser-induced reversal of arterial spasm remains unknown. It is clear from our previous work [1,2] that a suddent, transient fluid cavitation is necessary to achieve the vasodilation, and that some mechanical interaction is involved. But it is unclear whether the primary mechanism involves damage to the contractile elements of smooth muscle cells, alterations in ion transport or membrane potentials, release of vasodilating mediators, or other mechanisms. The mechanism-related studies are proceeding, and thus far have shown:

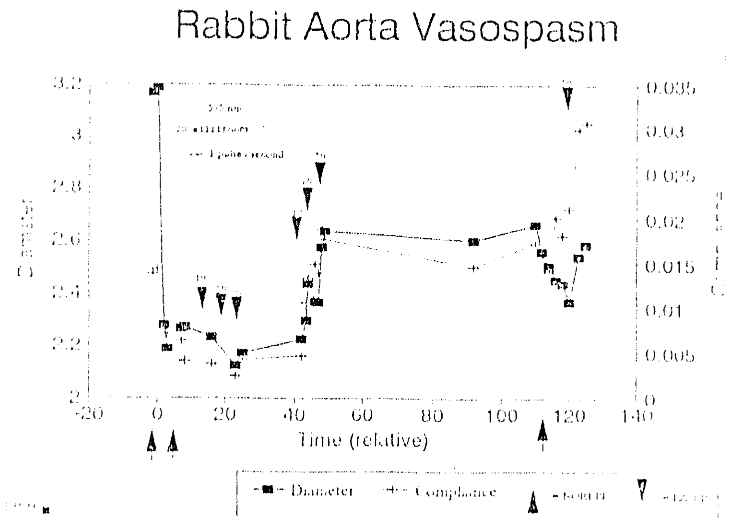
- No apparent injury seen is seen in rabbit arterial vessels walls,
  by transmission electron microscopy,
  after multiple 1 μsec, 480 nm dye laser pulses with sufficient

energy (2-10 mJ) to cause vasodilation. This implies that direct damage to actin-myosin filaments is not the primary mechanism, but sheds no light on the actual mechanism.

- Vasodilation occurs whether the transient cavitation is inside the arterial lumen (delivered via a ball-tipped fused silica fiber in the vessel) or up to several millimeters outside the artery. It is not necessary for laser light to strike the vessel wall.

- When blood was replaced by a physiologic dye solution (Evans blue in Ringers solution), pulsed laser vasodilation still occurs. Thus, the mechanism does not require the presence of blood, which essentially eliminates release or binding of serum factors as a mechanism.

- We have set up a collaboration with Dr. Wm. Abbott's vascular biology lab to study changes in vessel wall compliance produced by the laser vasodilation process. As proposed, rabbit aorta was used; thus far we have only established that this animal model and the computer-aided video motion analysis system used to assess compliance works. A typical preliminary result is shown below, with vascular compliance and vessel diameter plotted before (time zero), after norepinephrine-induced vasospasm, and after pulsed laser reversal of vasospasm.



In addition to investigating primary mechanism, we further optimized our catheter design for use in cerebral arteries, to the point that preclinical testing in dogs can now be performed. A Tracker-18 cerebral arterial catheter was modified by insertion of a 200 μm core diameter fused silica fiber optic, coupled to a Candela 1 μsec pulsed dye laser operating at either 480 or 580 nm, at 1 - 5 Hz. The fiber tip was fused to form a spherical end about 400 μm diameter, to allow its insertion into the plastic catheter without damage. We studied the effect of placement of the fiber tip at various distances from the opening of the catheter into the artery. After insertion into rabbit carotid or femoral arteries placed into spasm by a cuff of extravascular hemolysate, the laser pulse energy needed to cause vasodilation was measured by gradually increasing the pulse energy. The pulse energy was then further increased until perforation of the vessels occurred, or the maximum deliverable energy of about 30 mJ was achieved. Recessing the fiber optic tip 2-4 mm into the catheter produced reliable vasodilation, with no perforations even at the highest energies available. In contrast, extending the fiber tip into the vessel allowed only a two-fold difference between vasodilation and perforation pulse energy thresholds. These studies were performed by an M.I.T. M.D.-graduate student, Ralph Delatorre, as a master's thesis in mechanical engineering.

Further studies: We need to
- produce a scaled-down prototype catheter/fiber combination, for use in dog basilar (brain) arteries in spasm. This may be the final prototype for animal use, before a phase-I human clinical trial application to the F.D.A.
- test the vasodilation system in 12 dogs, to be sacrificed at intervals after the procedure. This study was proposed, has been properly approved, and will be performed during the next six months.
- perform further electron microscopy.
- determine whether vessel wall compliance is affected acutely and chronically (helps predict aneurism formation).
- determine the duration for release of vasospasm after a single laser treatment.
- determine whether endothelium is necessary for vasodilation to occur.
- take stroboscopic pictures of the process in the 10 μsec - 10 msec after arrival of laser pulses.

B. Other laser systems development:

MRI + laser systems:
- The proposed collaborative studies involving Dr. Jolesz for magnetic resonance imaging (MRI) guidance of laser surgical procedures have been postponed. Dr. Jolesz has suffered a major illness. However, we have initiated discussions with other MRI scientists in the spirit of preparing for this aspect of the proposed Center of Excellence.

Severe skin burn detection and treatment:
- We have further advanced the optical detection and "smart" laser treatment of severe skin burns, by hiring a systems engineer (Ed Hanel), with expertise in high-power guided laser systems. A prototype burn detection and debridement system, employing a donated high-power CO_2 laser, should be ready for testing in the summer or fall of 1992. One of the research fellowships funded by this grant will be used to bring in a burn specialist research fellow (to be named) beginning in July of

1992.

Lasers in cardiology:

- We have taken the initiative of establishing regular research seminars with the MGH cardiology department, which will lead to further laser system development projects in the future that may become part of the planned Center of Excellence.

II. Optical diagnostics

The proposed studies for multispectral imaging of fluorescence and reflectance in tissue will begin when the Lyott filter system needed for computer-addressing the imaging system wavelength, is available. The company producing this new and proprietary device can now supply it, as planned. We expect delivery in two to four weeks, at which time the proposed studies can begin.

Another optical diagnostic effort funded in part by this grant, is the design evaluation of alternative methods for detection of major skin burn depth by a fluorescent tracer drug, indocyanine green. This general method was recently established by our laboratory [3], but has not been optimized or incorporated into a usable system. An optical systems engineer who is supported from this grant, and an MD-Ph.D. graduate student funded by other support, have recently begun this process. We have not yet reached the stage of system evaluation. However, a flashlamp-driven dual-wavelength CCD imaging system, providing excitation energy at 400 nm and 780 nm sufficient for burn depth analysis, has been designed and is under construction.

III. Photosensitization of vascular tissue

The broad area of photosensitization within the planned Center of Excellence is represented by this single topic. A study has been completed and was just published [4] with partial support and acknowledgement, of this grant. A copy of this paper is attached. The study showed that neovascularization, rather than simple permeability, was a major determinant in retention of photosensitizers used to treat cancer. At least one of the DOE-supported research fellowships this year will be related to photosensitization research.

PROGRAM PROGRESS:

Consultants:
Major steps to define, organize, and promote a Center of Excellence in Laser Medicine have been taken. Dr. Brian Wilson, who directs a radiation physics and photodynamic therapy center in Hamilton, Ont., was asked to consult as proposed, on elements necessary to the Center. Drs. Ronald Newbower, Robert Webb, Reginald Birngruber, and Franz Hillenkamp, all scientists with major administrative responsibilities for biomedical engineering and/or physics programs, provided further and ongoing assistance. Admiral J.D. Watkins from the DOE also paid a brief visit to assess our program.

The MGH Laser Center:
A degree of separation of the clinical/medical aspects, from the more basic research and development goals of the COE, will provide better focus and synergism between these two areas. Therefore, a Laser Center spanning all MGH departments, and the MGH Office for Technology, was established, with strong support from the MGH administration. The MGH Laser Center includes an executive committee composed of department chiefs, and a medical director and a research director who are full time faculty at Wellman Labs. This structure is highly syergistic with the proposed Center of Excellence, by drawing upon the excellent academic medical environment of MGH, minimizing interdepartmental barriers to progress, supporting projects as they go past the research and development phase into clinical use, and closing the feedback loop between new developments and their early implementation in medicine. Whereas the COE will extend well beyond the MGH Laser Center in its engineering, scientific, and industrial efforts, the MGH Laser Center can fully develop the clinical potential of new developments arising from the COE program. Organizational materials about the MGH Laser Center are attached.

DOE-supported postdoctoral research fellowships:
The availability of the DOE-supported laser fellowships has been announced, and is attached. The MGH Laser Center is being used as a vehicle to supplement the number of fellows supported, by matching funds for three of the four competitive fellowships. All of the fellows will do research at Wellman lab, with collaborative studies matching the COE's goals, including the specifically proposed research.

Cost effectiveness and longevity of a COE:
It is clear that a COE, once established, must address the issue of sustained research support through its own activities. Success is tied not only to scientific success and more diversified support, but to the ability to transfer and license new developments to industry. At the heart of this is the development of laser and optical diagnostic approaches that actually reduce net medical expense. Among the many possible new avenues within this emerging field and its associated technology, our COE will focus developing new capabilities which are (1) cost-effective, (2) replace or minimize invasive surgery, and/or (3) reduce chronic morbidity. Two of the pilot projects now being supported are good examples. If we can reverse vasospasm, the number of young victims of aneurismal stroke requiring extremely expensive, life-long care can be minimized. Similarly, the lifelong care of major burn victims is extremely difficult; using an optimized "smart" laser to spare as much normal skin as possible, eliminate the need for transfusions, and reduce contraction scarring, fully justifies the cost of the technology involved.

Need for integrated engineering sciences:
It became increasingly clear that the COE must establish, support, and maintain an excellent engineering capability. Wellman Lab already has much more engineering expertise than most biomedical laboratories because of our research in photobiology, optics, and spectroscopy. However, dedicated space and stronger ties to MIT, other excellent

engineering universities, faculty at national laboratories, and industry is still needed and being sought.

References

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