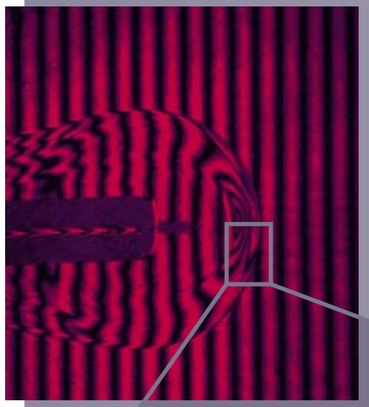


On the Offensive against Brain Attack

Under the leadership of the Laboratory's Center for Healthcare Technologies, a multidisciplinary team is developing a variety of much-needed tools to provide stroke victims with early, aggressive diagnosis and treatment.

In the fall of 1994, a group in Lawrence Livermore National Laboratory's Center for Healthcare Technologies began asking a pointed question whose answer was to profoundly affect the focus of a major part of the Center's research: Given that both heart attack and stroke result from disruption of blood flow, why are cardiovascular conditions treated with aggressive medical intervention while cerebrovascular conditions usually receive passive intervention with emphasis on rehabilitation? Why is stroke not treated as "brain attack"? The answer, they found, was not that there is something fundamentally different about the two potentially deadly maladies. Instead, what they found was that doctors frequently did not have the proper tools to treat stroke as quickly and aggressively as they treat heart attack.

Heart attacks and strokes usually result from decreased blood flow interrupting the supply of oxygen and nutrients to tissue. Most frequently, the flow is decreased because of a blockage, but flow can also be disrupted by malformations or rupture of the vessels. An important difference between a heart attack and a stroke is that the size of the blood vessels involved in a stroke are significantly smaller. Recognizing that Lawrence Livermore has capabilities in microfabrication and other technologies that could be used to reduce the size of medical devices, the Center for Healthcare Technologies established a program to create a new standard of stroke care.

Critical to defining this standard was the "Workshop on New Technology for the Treatment of Stroke," which the Center sponsored in March 1995. The workshop was attended by internationally recognized stroke clinicians and researchers, cardiologists with experience in medical devices used to treat heart attack, and scientists and engineers from Lawrence Livermore and Los Alamos national laboratories. Instead of the typical conference agenda of success stories, clinicians described significant areas of unmet need for diagnosing and treating stroke victims, particularly the want of medical devices that might satisfy those needs.

Out of the workshop grew a vision of the future of stroke care and a framework for the priorities of a multidisciplinary team of Laboratory researchers who, with the help of Laboratory Directed Research and Development funding, are developing much-needed tools to diagnose and treat stroke. The Lawrence Livermore stroke initiative team's vision of the future of stroke care is summarized in Figure 1. It focuses on the greatest unmet clinical needs—restoring blood flow, preventing hemorrhage, improving treatment decisions with sensors, and identifying the at-risk population with new screening technologies. (For a primer on the kinds, causes, and treatment of stroke, see the box on p. 19.)

The Livermore team consists of specialists in biomedical engineering, biology and bioscience, laser medicine and surgery, micro-engineering, microsensors, and computer simulation. It also has key collaborators from academic medical centers and private companies. These partnerships are the basis for rapidly moving the medical device concepts from the research laboratory through development, clinical trials, regulatory approval, and manufacture so that the resulting new tools can have a timely impact on the lives of the thousands of people who have strokes each year.

Since the workshop, the stroke-initiative team's research has developed several proof-of-principle prototypes. The work falls into four categories: microsensors for brain and clot characterization, optical therapies for breaking up clots in the blood vessels of the brain, laser–tissue interaction modeling, and microtools for treating aneurysms (a leading cause of hemorrhagic stroke).

Sensors to Diagnose Clots

The Laboratory's stroke initiative has made substantial progress in developing microsensors that improve understanding of the biochemistry of stroke as well as offer the potential to improve stroke diagnosis, monitoring, and treatment. The sensors have the potential to identify the types of clots that cause stroke, to monitor patients during therapies that dissolve clots or protect brain cells with drugs, and to determine the health of brain or blood vessel tissue at a stroke site prior to treatment.

Development and use of these sensors, like much of the team's work, are predicated on the availability of microcatheters. These tiny, hollow tubes, which are available from a number of manufacturers, can contain optical fibers to which microsensors and other diagnostic, treatment, and monitoring tools being developed at the Laboratory are attached (Figure 2). Inserted in the femoral artery, the microcatheters are guided by microwires through the circulatory system to the clot

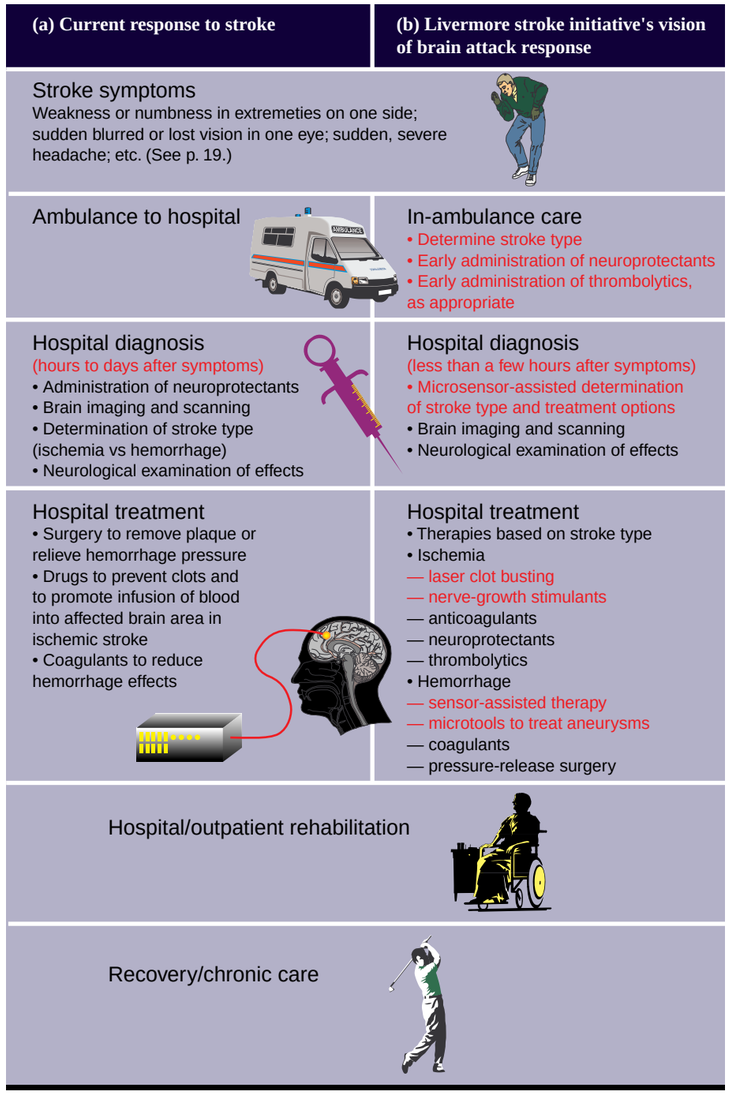


Figure 1. (a) Current response to stroke is more passive than active and lacks urgency largely because of the want of tools to diagnose and treat stroke early. The more time that passes after a stroke, the less the chance of even partial recovery from its effects. (b) The overriding goal of the Laboratory's stroke initiative is to improve those chances through early intervention. The Center for Healthcare Technologies' vision for the future of stroke care concentrates on providing tools for early, aggressive medical intervention to improve a stroke victim's chances for full recovery or more productive rehabilitation.

site in the brain where the tools attached to them can do their work to combat brain attack.

Lawrence Livermore researchers have, for example, demonstrated *in vitro* fiber-optic and electrochemical sensors for measuring pH at stroke sites.[1] These sensors can establish brain tissue viability by direct measurement of pH in brain tissue or through indirect measurement in blood near the stroke site. Livermore scientists have developed miniature intracranial (direct brain tissue) electrochemical and fiber-optic pH sensors, which neurosurgeon collaborators at the State University of New York at Buffalo have used for *in vivo* animal testing.

The measurement of blood pH is one of a number of chemical "markers" that have been identified to assess the health of blood-vessel tissue at the site of a stroke, thereby providing guidance in stroke therapy. When tissue dies, lactic acid builds up and blood pH decreases. So if blood pH is below normal (7.4) at or near the stroke site, then brain cell death has occurred, and the use of neuroprotectant drugs to minimize brain damage is unwarranted. If, on the other hand, pH is close to normal, cell death has not occurred, and neuroprotectant drugs become a therapeutic option.

In the Laboratory's fiber-optic pH sensor, a pH-sensitive dye, seminaphthorhodamine-1 carboxylate (SNARF-1C), is mixed with transparent silica sol-gel and dip-coated onto an optical fiber tip. In laboratory tests, the tip is placed in blood, and the dye is excited by a tungsten–halogen light source or a low energy density laser. The emission spectra of the dye is pH sensitive. These tests showed that the sensor had good sensitivity in the pH range of 6.8 to 8.0, indicating possible use for *in vivo* sensing of blood pH in the neighborhood of a stroke site.

Livermore scientists are also developing a D-dimer biosensor to monitor stroke patients during therapies to dissolve blood clots in the vessels of the brain. D dimer is a substance with antigenic properties (i.e., capable of stimulating an immune response) and is produced as a result of a complex biochemical process when clot-dissolving drugs are injected via a microcatheter into blood clots.

Livermore's D-dimer biosensor can act as a diagnostic tool by indicating whether the blockage is caused by plaque or by a clot. Clot-dissolving drugs will not dissolve plaque; therefore, if an elevated concentration of D dimer is not detected at the site of blockage, then the blockage may be caused by something other than a clot, and alternative therapy is needed. In addition, because treatment using clot-dissolving drugs is highly variable, the D-dimer biosensor could help eliminate the guesswork related to the dosage and infusion rates. It could help physicians develop a diagnosis and treatment plan faster and reduce the risk of hemorrhage resulting from treatment to dissolve clots.

Medical Photonics

Members of the stroke-initiative team are developing a catheter-based system that uses laser energy to break up clots. The system will deliver low-energy laser pulses through a fiber-optic microcatheter (Figure 3). The laser energy will be directed at a cerebral clot, and by conversion of optical light to acoustic stress waves, it will break up the clot and restore blood flow in cerebral arteries. The concept is simple. The challenge is to determine the proper pulse strength needed to break up the clot without harming viable vessel tissue.

Research has focused on the optical and mechanical material strength and failure properties of the clots and tissue found in the cerebral blood vessels.[2] Using a tunable optic parametric oscillator (OPO) laser system at Livermore's Medical Photonics Laboratory (Figure 4), the medical-lasers team has conducted *in vitro* experiments to send laser pulses

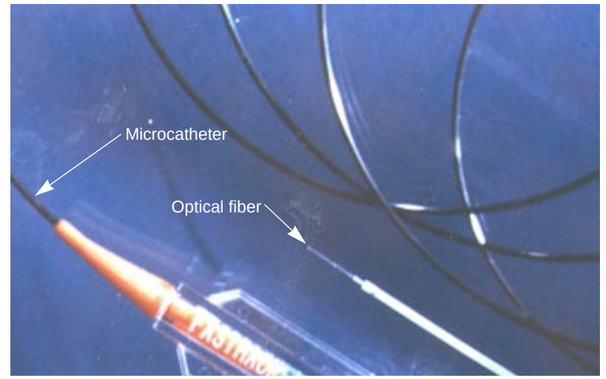


Figure 2. Optical fibers about the diameter of human hair can be enclosed in a hollow microcatheter and steered by microwires through the circulatory system to stroke sites in the brain. Microsensors and microtools are attached to these fibers to provide rapid, improved stroke diagnosis and treatment.

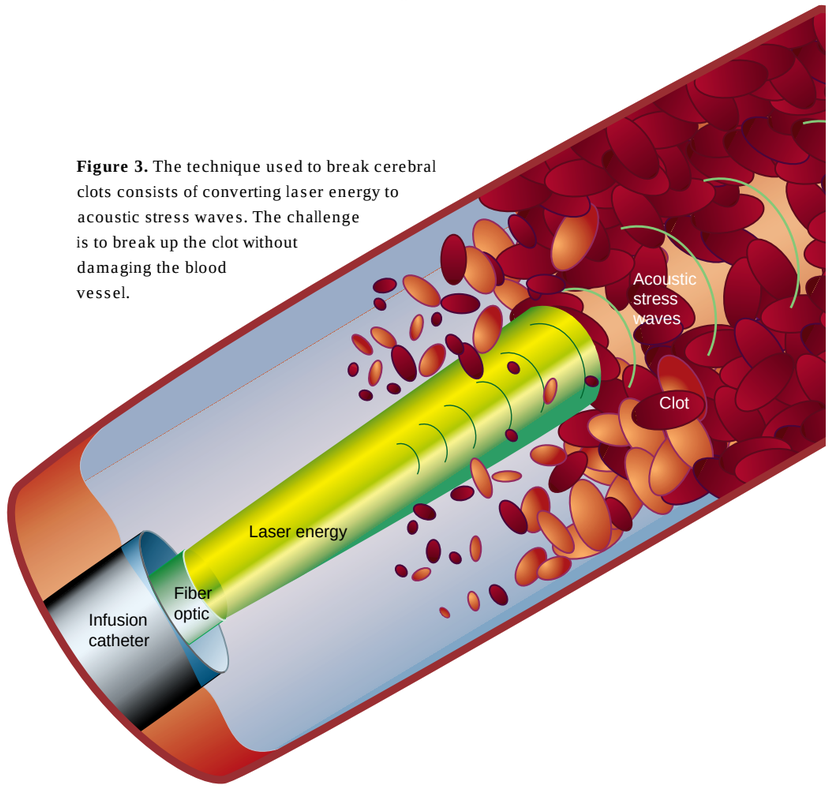


Figure 3. The technique used to break cerebral clots consists of converting laser energy to acoustic stress waves. The challenge is to break up the clot without damaging the blood vessel.

into a blood phantom (water colored with red food coloring). They have identified two distinct regimes of dynamic response, one due to strong laser light absorption, the other to moderate absorption.

In both cases, the confined stresses imparted to the liquid are substantial and determine most of the important dynamics. In the strong absorption case, energy is deposited in a thin zone near the fiber tip (Figure 5a). A thermally generated vapor bubble develops around the tip, and the initial stress wave, which can generate high peak pressure within 400 nanoseconds (billionths of a second), quickly propagates away from the tip. In the moderate case, energy is deposited in an extended zone beyond the fiber tip (Figure 5b). The initial stress evolves from the heated region within 500 micrometers (millionths of a meter) of the end of the tip, and the largest stress gradients, which develop within 20 nanoseconds, are directed radially and are situated in the immediate vicinity of the tip.

Eventually (within 100 nanoseconds), a cloud of tiny bubbles develops in response to the stress caused by laser heating. In both cases, this expansion and collapse of bubbles exert pressure and shear forces on a clot, which lead ultimately to its breakup.

The Laboratory recently entered into a Cooperative Research and Development Agreement (CRADA) with EndoVasix Inc. of Belmont, California, which will eventually market the laser "clot-busting"

Figure 4. Livermore scientists use a tunable optic parametric oscillator (OPO) laser to create a series of laser back-lighted images (see Figure 5 below) of the pressure distribution of laser energy within a blood-like fluid.

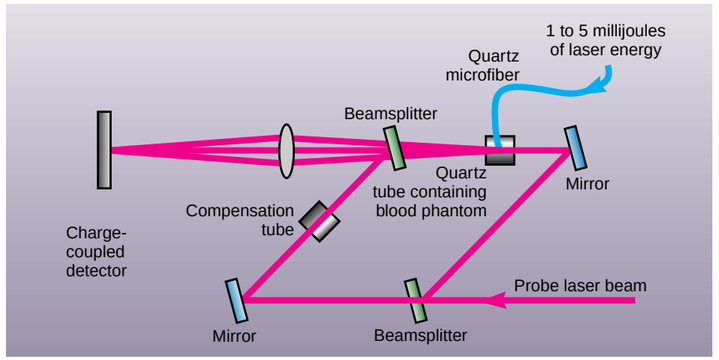
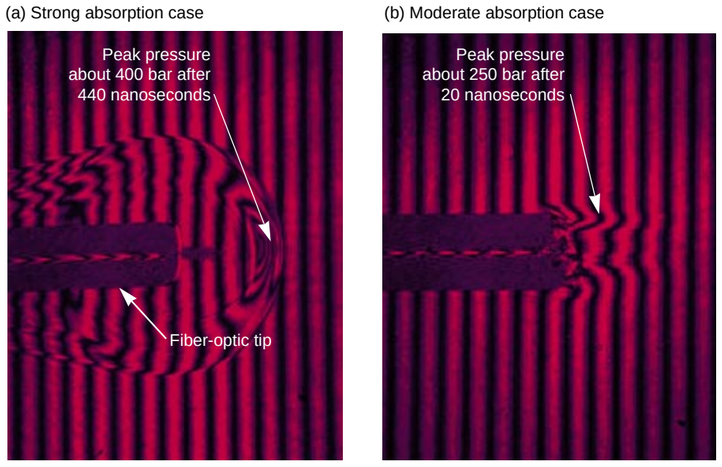


Figure 5. In laboratory experiments to develop a laser system to break up clots, Livermore researchers have identified two regimes of dynamic response. (a) In the strong absorption case, heat from the laser energy generates a vapor bubble about the fiber tip. (b) In the moderate case, initial stress evolves from the heated region very near the fiber tip. Within 100 nanoseconds, a cloud of tiny bubbles develops in response to the stress caused by laser heating. The expansion and collapse of these bubbles exert pressure and shear forces on the clot, ultimately leading to its breakup.



Brain Attack Facts*

Stroke (or "brain attack") results from vascular disease affecting the arteries supplying blood to the brain and occurs when one of these vessels bursts or is clogged. Part of the brain is deprived of the oxygen and nutrients it needs to function, the nerve cells die within minutes, and the part of the body controlled by these cells cannot function. Sometimes the devastating effects of stroke are permanent because the dead brain cells are not replaced.

Stroke is the leading cause of permanent disability in the U.S. and the third leading cause of death. Each year, 550,000 Americans have strokes. One-third of them die. Many of the survivors, who currently total over 3 million, have decreased vocational function (71%); of these 16% remain institutionalized, and 31% need assisted care. The personal cost is incalculable; the annual cost for treatment, post-stroke care, rehabilitation, and lost income to victims (but not their family caregivers) is $30 billion.

Types of Stroke

There are two main types of strokes, ischemic and hemorrhagic. Clots—cerebral thrombuses or cerebral embolisms—cause ischemic strokes. Cerebral hemorrhage or subarachnoid hemorrhage causes hemorrhagic strokes. Ischemic strokes are the most common, hemorrhagic strokes the most deadly.

Cerebral thrombosis occurs when a blood clot (a thrombus) forms in an artery in or leading to the brain, blocking the blood flow. It is the most common cause of ischemic stroke. Cerebral embolism occurs when a wandering clot (an embolus) or some other particle occurs in a blood vessel away from the brain, usually the heart. The clot is carried by the bloodstream until it lodges in an artery leading to or in the brain.

A cerebral hemorrhage occurs when an artery in the brain bursts, flooding the surrounding tissue with blood. Bleeding from an artery in the brain can be caused by a head injury or a burst aneurysm, a blood-filled pouch that balloons out from a weak spot in the artery wall. A subarachnoid hemorrhage occurs when a blood vessel on the surface of the brain ruptures and bleeds into the space between the brain and the skull (but not into the brain itself).

Hemorrhagic strokes cause loss of brain function both from loss of blood supply and from pressure of accumulated blood on surrounding brain tissue. The amount of bleeding determines the severity. If hemorrhagic stroke victims survive (which they do in 50% of the cases), their prognosis is better than that of ischemic stroke victims. With ischemic stroke, part of the brain dies and does not regenerate. With hemorrhagic stroke, pressure from the blood compresses part of the brain, but the pressure diminishes gradually and the brain may return to its former state.

About 10% of all strokes are preceded by "little strokes" called transient ischemic attacks (TIAs). They are more useful for predicting *if*, rather than *when*, a stroke will happen. They occur when a blood clot temporarily clogs an artery and part of the brain does not get the blood it needs. The symptoms, which are the same as stroke symptoms, occur rapidly and last a relatively short time, usually between 1 and 5 minutes. TIAs can last up to, but not more than, 24 hours. Unlike stroke, when a TIA is over, people return to normal, because the nerve cells were not deprived of oxygen long enough to die.

Diagnosis and Treatment

Diagnosing that a stroke has occurred and its type and severity takes time—time that stroke victims may not have. Diagnostic tools are tests that image the brain, such as computerized axial tomographic (CAT) scans, magnetic resonance imaging (MRI) scanning, and radionuclide angiography or nuclear brain scan. Tests that show the electrical activity of the brain are also used. The two basic tests of this type, an electro-encephalogram (EEG) and the evoked response test, measure how the brain handles different sensory stimuli such as flashes of light, bursts of sound, or electrical stimulation of nerves in an arm or leg.

Tests that show blood flow to and in the brain are also used for diagnosis. One of these is the Doppler ultrasound test, which can detect blockages in the carotid artery. Another is carotid phono-angiography, wherein a stethoscope or sensitive microphone is put on the neck over the carotid artery to detect abnormal sounds (bruits) that may indicate a partially blocked artery. Yet another is digital subtraction angiography, in which dye is injected into a vein in the arm and an x-ray machine quickly takes a series of pictures of the head and neck. From these x rays, doctors can determine the location of any blockages, how severe they are, and what can be done about them.

Surgery to remove plaque from artery walls, drugs that prevent clots from forming or getting bigger, acute hospital care, and rehabilitation are all accepted ways to treat stroke. Sometimes treating a stroke means treating the heart, because various forms of heart disease can contribute to the risk of stroke, particularly those caused by clots that form in a damaged heart and travel to the brain. But compared to the diagnosis and treatment tools that have been developed for heart attack, those for brain attack seem extremely limited and have not advanced greatly in recent years.

* *Heart and Stroke Facts* (The American Heart Association, Dallas, Texas, 1994), pp. 21–27. This booklet is available from the American Heart Association's National Center, 7272 Greenville Avenue, Dallas, Texas 75231-4596 (telephone: 1-800-242-8721).

technology. EndoVasix is investing in the development of a prototype system for clinical demonstrations beginning with animal stroke models. Some of the preliminary animal tests have already taken place.

Laser–Tissue Interaction

Central to the design of clot-busting tools is the refinement and use of computer codes for modeling laser–tissue interaction. Based on the laser–matter interaction codes developed for inertial confinement fusion at Livermore, the Laboratory's LATIS (laser–tissue) code provides a basis for predicting how short-pulse, low-energy medical lasers affect tissue.[3] It thus promote the rational design of clot-busting devices by modeling laser–tissue interaction during the process. By taking into account a raft of variables—size and composition of the clot, strength of blood-vessel tissue, and buildup and transport of heat during laser clot busting—this code can numerically simulate the hydrodynamics of the laser-created energy needed to break up clots and predict the amount of energy needed to do so without damaging other tissue.

The modeling team has made significant progress in simulating the laser clot-busting process with a focus on short-pulse (1- to 10-nanosecond) interactions of laser light with water and blood clots.[4] These advances in LATIS are being used to improve the laser clot-busting technology discussed earlier. They will be refined and expanded to better determine the parameters of the hydrodynamics at the heart of a safe, effective laser clot-busting system.

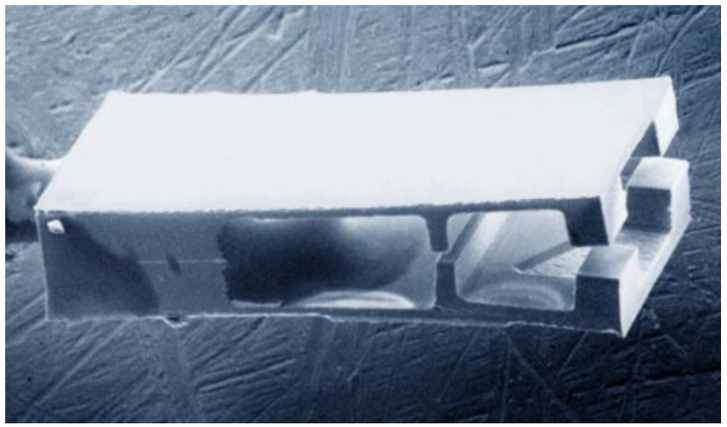


Figure 6. Microtools such as this silicon microgripper with "shape memory" will be used to treat the cerebral aneurysms that lead to hemorrhagic stroke. The microgripper is less than 1 cubic millimeter, that is, about the size of the head of a straight pin. (Approximate size:□)

The medical applications have also had positive "spin-back" to the core programs at the Laboratory. For instance, because the medical applications required simulation of how laser beams interact with highly scattering materials, a bug in one of the Monte Carlo x-ray transport subroutines used in national security applications was discovered and corrected.

Microtools

Miniaturization expertise from Lawrence Livermore's Microtechnology Center, Precision Engineering Group, and Plastic Shop has produced a variety of silicon, metal, and plastic microsensors and actuators for the stroke initiative. One of these with the potential to prevent strokes caused by hemorrhage rather than clots or other blockages is the "shape memory" microgripper (Figure 6). These tiny devices (less than a cubic millimeter) have a variety of applications, but the initial one is for treating aneurysms. Very fine metal thread is placed into the microgripper, which is connected to a guidewire cable and maneuvered to the site of the aneurysm. Closed, it slips into the aneurysm through the narrow neck connecting the aneurysm with the vessel wall. Once inside, the microgripper's heater is activated by power sent through the guidewire tether, and the gripper opens, releasing the metal thread into the aneurysm. The gripper then cools, "remembers" its closed shape, and can be withdrawn through the neck, leaving behind the metal thread. The thread embolizes (acts as a clot in) the aneurysm, reducing blood flow and pressure in the aneurysm. Without the pressure, the aneurysm eventually fills with scar tissue and is significantly less likely to rupture and cause a hemorrhagic stroke.

New Vision of Stroke Cure

The work of the stroke initiative at Lawrence Livermore hopes to remedy the paucity of tools for diagnosing and treating strokes. Its vision of stroke care includes medical devices for screening people without symptoms for stroke risk. It places special emphasis on the development of tools to provide earlier rather than later diagnosis of stroke type and assessment of brain cell damage so that appropriate treatment can be initiated rapidly. It has guided Livermore researchers in the development of technology to break up stroke-causing clots with laser energy as well as microsensors and microtools to assist in the diagnosis and treatment of various kinds of brain attack. And it looks forward to providing the means for more instances of full recovery, fewer stroke-related disabilities, and less need for chronic care.

—Dean Wheatcraft

Key Words: brain attack, laser "clot-busting," laser–tissue interaction modeling, LATIS code, medical photonics, microsensors, neuroprotectant drugs, shape-memory microgripper, stroke.

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About the Team

The stroke-initiative team at the Laboratory is a multidisciplinary group of scientists and engineers from several directorates—Biology and Biotechnology, Engineering, Laser Programs, Physics and Space Technology, Defense and Nuclear Technologies, and Chemistry and Materials Science. The team's members have combined their expertise in biomedical engineering, biology and bioscience, laser medicine and surgery, micro-engineering, microsensors, and computer simulation to create a variety of tools to respond quickly and urgently to brain attack and thereby improve the chances of a stroke victim's survival and recovery. They are collaborating with academic medical centers and private companies to move these proof-of-principle prototypes as quickly as possible from the research stage to development, clinical trials, regulatory approval, and manufacture so that they can benefit as soon as possible the lives of people who have strokes. Pictured left to right are: ABRAHAM LEE, ROBERT GLASS, WILLIAM BENETT, LUIZ DA SILVA, PATRICK FITCH, RICHARD LONDON, SHEILA GRANT, and STEVEN VISURI. (Not shown are PETER CELLIERS, PETER KRULEVITCH, and DENNIS MATTHEWS.)