Chapter 5
Medical Technology

Over its 50-year history SRI has made relatively few excursions into the world of new medical technology. But because of its passion for innovation and an ability to deal with fundamentals, it has made a number of significant contributions. Of those efforts, we concentrate here on telepresence surgery, eyetrackers, laser photocoagulation, ultrasonic imaging, and automatic blood pressure measurement. Each of these efforts has created unique capabilities, providing new and better approaches to medical diagnosis and treatment.

Telepresence Surgery

In the mid-1980s, Phil Green, a laboratory director and one of SRI's more prolific inventors, had a new idea that would extend the limited notions of telerobotics. In this case it would enable the capability of the human hand to access formerly inaccessible realms and make interactions there increasingly realistic for the human operator. Specifically, he saw how microscopic and endoscopic surgery, then quite limited in the range of functions they could perform, could be endowed with the natural dexterity of a surgeon's hands. He requested and received internal SRI funding to assemble a new system that would give surgeons the sensory perspective and manipulative ability they would have in a normal surgical setting. The system would have many of the characteristics diagrammed in Figure 5-1.

SRI submitted a proposal to the National Institutes of Health (NIH) in October 1989 for support in building a prototype system for microscopic and endoscopic surgery.[A] Although that proposal was not accepted, Green continued building the limited prototype system with SRI funds. With the excellent control system design of John Hill and assistance from Yonael Gorfu and Lynn Mortensen, the working model they built closely resembled the notional drawing shown in Figure 5-1, except that the model was built for just one hand.

SRI UNVEILS A STARTLING APPROACH TO SURGERY

It is early 1995 and SRI's new surgical system is in place at the University of California Medical Center in San Francisco. SRI's concept has caught the attention of surgeons such as Larry Way. The machine has some startling features, such as removing the surgeon from direct patient access. Its telerobotic design, which anticipates the day when many kinds of surgery will be minimally invasive, makes it particularly exciting. Does the telerobotic design hamper or, given computer-assisted features such as those for microsurgery, enhance the surgeon's skill over conventional open surgery? The claim: Because of the system's intuitive nature, telepresence surgery will afford the surgeon essentially the same dexterity as regular surgery and, with computer augmentation, will eventually greatly increase the surgeon's hand stability.

The system has two major segments: the surgeon's workstation, which contains the grasping half of the telerobotic surgical instrument; and an effector station, where the other half of the instrument interacts with the patient. Anxious to test this new kind of operating system, Way, having set two clamps, grasps the surgeon station end of a scalpel and severs a small live bovine artery. Using normal open-surgery suture techniques, he proceeds to reunite the separated artery, and blood flows again. The surgeon has performed this feat with almost no specific training on the new system and at 10 feet from the operating site! Dr. Way recalls how the machine became "invisible" while he was using it, offering a tremendous advance over earlier laparoscopic techniques.

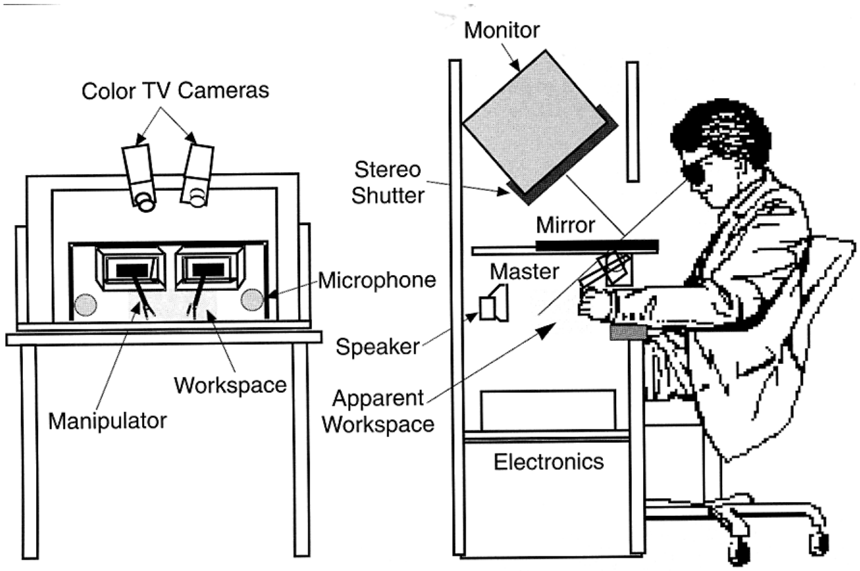


Figure 5-1. Schematic of the first SRI surgical telepresence system.

"I did the world's very first bowel anastamosis with [just a] one-armed version of telepresence. No manual. Very intuitive. We got some pig or sheep intestines and Rick [Satava] 'assisted' by holding the two cut ends near each other. I sutured with one armed telepresence dexterity. The significance was not lost on Rick or myself."

As the SRI version of the system was proceeding, Green began conversations with Col. Richard Satava, a surgeon from Ft. Ord (near Monterey, California) whom he had met at a medical conference. Satava suggested that the system would also be a splendid alternative to an increasingly widely used approach to gall bladder removal that employed a minimally invasive technique called laparoscopy. Figure 5-2 shows the basic approach for entering the chest or abdominal cavity; the internal manipulators shown are of SRI design. Laparoscopic surgery had been in development for several decades, mainly in Europe, and was becoming more widely used in the United States. However, the technique was awkward and difficult for surgeons to learn. Long hollow access tubes, called cannula, are inserted into the patient's inflated abdomen, and all internal viewing and instrument activity take place through the tubes. Coping with the fulcrum at the body entrance and axis-aligned movements imposed by the cannula, all guided by a television monitor that presented an often-disorienting perspective, requires many hours of training to attain even modest proficiency. A system could be designed, they reasoned, that would remove the contortions imposed by such a system and offer surgeons the access and perspective available in open surgery. That the SRI system was intuitively usable is evidenced by this account of Col. Irwin Simon, a colleague of Satava's:[B]

As the system progressed, numerous surgeons tried it out, and many wrote of their impressions. A letter from Carl Levinson to Green provides a good example:

> "Truth be known, I expected to walk into your laboratory and have a hood placed over my head, after which I could fulfill my wildest endoscopic flights of fancy. Instead, I was treated to a remarkable exhibition of electronic and technologic know-how which brought to mind three virtually simultaneous thoughts: This is remarkable; How can I use this, or can I? There *certainly* is a place for this! These thoughts still run through my mind." [C]

In 1991, SRI submitted a second proposal to the NIH, this time emphasizing laparoscopic surgery. That proposal, too, wasn't funded, but Green was not deterred. He knew that the program managers at NIH had some discretionary money, and he believed in his system. By this time SRI's internal funding had exceeded $250,000 for his one-arm working system.[1] Green decided to make a video of the SRI system and take it to the head of the NIH

[1] It was interesting to witness the incredulity and chiding of my fellow managers when I petitioned SRI for internal funds for a "telepresence" system. Admittedly, the new name conjured up too many visions of an unachievable future, but it remains a good descriptor of what actually happens. Somewhat before I became aware of Green's notion, I had come up with a communication concept that I had also called telepresence. At one point I assembled some people to look at telepresence in general, and that's when I learned of Green's surgical concept.

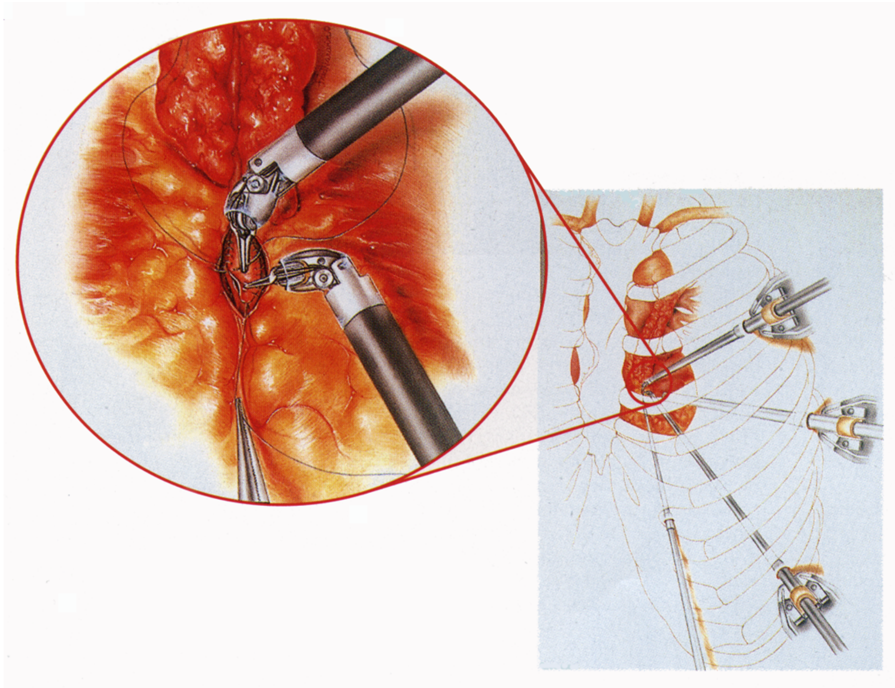


Figure 5-2. An illustration of how the new instruments are inserted into the body and used. (From William Leventon, Tech. Editor, *Product Design and Development*, November 1998, © by Cahners Business Information)

office to which he had submitted the second proposal. The video showed activities intended to verify both the feasibility and precision of the SRI system but, somewhat surprisingly, nothing directly to do with surgery. Green and Mortensen recorded several activities. First, Mortensen used the system to paint the small flower shown in Figure 5-3. Second, while she held an ordinary grape, Green used the system to slice it into almost transparent layers. The tape may have included some of the bead stacking that is still used in demonstrating the system's three-dimensional capabilities. The tape made the case well enough that the NIH program office decided to fund the proposal.

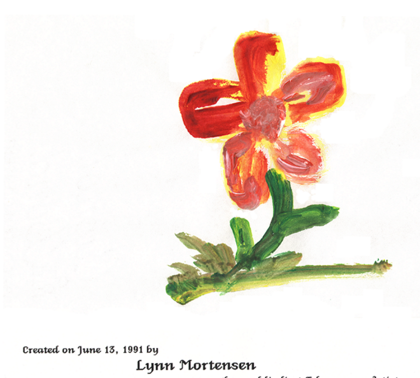


Figure 5-3. A sketch made with the first SRI telepresence system (done in color).

In October 1991, SRI received a 3-year grant to design and build a more complete and capable demonstration system. The new system had essentially the same configuration shown in Figure 5-1. That same concept, consisting of workstation, viewing arrangement, and manipulation configuration first proposed in 1989, is still used in the commercial form of the system. The SRI project team that refined the next working versions was the same throughout, except for the addition of Joel Jensen. Figure 5-4, a picture from a special medical issue of *Time Magazine* in fall 1996, shows the new version.

As mentioned, several surgeons who helped foresee the surgical uses of the system were from Ft. Ord, Satava in particular. He became intrigued with the idea behind telepresence surgery, as well as with other surgical training concepts more akin to virtual reality. He visited SRI often to test the system and offer advice. In mid-1992, after showing the Surgeon General of the Army a videotape of the SRI system, he asked the Army for and received an assignment to the DARPA where he participated in its new program in medical technology. Part of this program would help fund the third-generation SRI telepresence system. The context for the DARPA work became battlefield casualties and exploring the relevance of remote surgery for the important "golden hour" for casualties; that is, the time immediately after sustaining a wound when emergency treatment is most efficacious. Several systems were built and demonstrations given, one just outside the Pentagon for the Secretary of Defense and his aides. The well-designed SRI system provided users with both stereovision and delicate tactile response. SRI delivered one system to the Department of Defense's (DoD's) joint medical training facility near Washington, D.C. SRI engineers Ajit Shah and Gary Guthart and surgeon Jon Bowersox joined the team for this phase.

During SRI's development of surgical telepresence, more than 30 practicing surgeons were invited to try out the new surgical system. In addition, the equipment was taken to the University of California Medical School in San Francisco where surgeons gave feedback about the system after using it in trial operations on swine. Their experiences were important in the evolution of the system and, although procedures took slightly longer using it, the trials confirmed the concept and the intuitive and useful properties of the system. This exposure and the papers written for medical journals by the SRI staff and by surgeons Satava and Bowersox helped publicize surgical telepresence as a serious and important contribution to surgery.

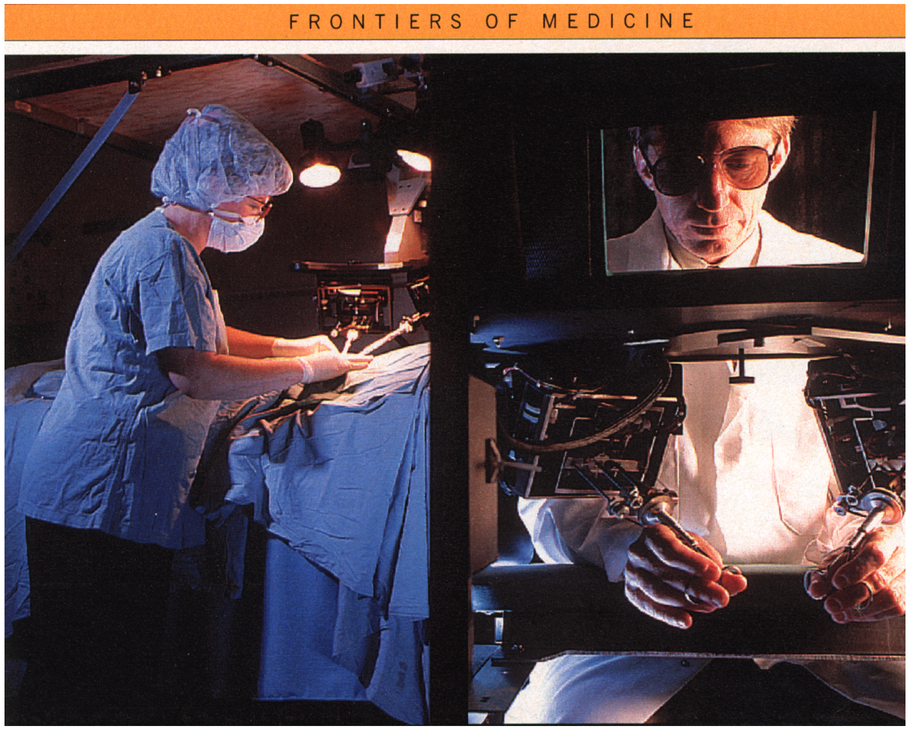


Figure 5-4. Examples of the surgeon's workstation and the effectors at the patient location. On the right is former military surgeon Jon Bowersox and the assistant on the left is Lynn Mortensen. (*Time Magazine,* Special Issue: The Frontiers of Medicine, p. 13, Fall 1996.)

In the meantime, Green began seeking investment money to commercialize the system. This effort went on during most of 1994 and 1995, but all of the major surgical instrument companies and the venture community turned him and SRI down. The concept was clearly sound and important to the future of surgical care, but a deal could not be struck.

One of the venture capital firms, in its due diligence pursuant to Green's inquiry, however, had retained Dr. John Freund, who was intrigued by the system. When the venture capital firm voted not to proceed, Freund came to SRI representing himself and a few other medical entrepreneurs and after negotiations obtained rights to SRI's system for all of surgery.[2] That was in September of 1995, and Freund soon joined with others from the medical community to form Intuitive Surgical Devices (ISD) of Sunnyvale, California, to manufacture the system shown in Figure 5-5.

The utility and importance of this kind of surgery are likely to be monumental. Use of ISD's da Vinci™ surgical equipment began in Europe, where it was first used on human patients with outstanding results. This work proceeded while awaiting approval from the more conservative U.S. Food and Drug Administration (FDA).

ISD's Web page (www.intuitivesurgical.com) provided a number of early examples of use of the equipment:

- Starting on May 7 (1998), Professor Carpentier and Dr. Didier Loulmet of the Broussais Hospital in Paris performed six open-heart surgeries using the Intuitive da Vinci™ system. Broussais Hospital, Europe's first cardiac surgery department, is renowned for performing Europe's first successful heart transplant and aortic

[2] At the time, SRI lacked a valuable patent position and so received just 7% of the stock at the seed round. U.S. patents on the overall system and four component parts had been applied for, but none had yet been issued. The first system issuance would be several foreign patents in 1997, and U.S. patents would be received on the components beginning the same year. The U.S. patent on the overall system is still pending after several revisions.

aneurysm repair procedures. This facility is also recognized as a world leader in the development of advanced valvuloplasty techniques. Professor Carpentier and Dr. Loulmet performed all or part of five surgical procedures with the Intuitive system:

  - Atrial septal defect repair
  - Commissurotomy and prosthetic ring annuloplasty
  - Papillary muscle shortening
  - Coronary artery bypass surgery

- Carpentier described his experience performing surgery with the Intuitive system as a major advance in minimally invasive technique, and commented that “the Intuitive system will bring minimally invasive cardiac surgery another step forward. This technology brings something not available in the past: much better visualization and more precise maneuvers of instruments inside the heart.” Commenting on the clinical study results, Dr. Fred Moll, founder and medical director of Intuitive Surgical said, “This is a key milestone for Intuitive Surgical. We’re proud to unveil the technology that made it possible to perform the world’s very first computer-enhanced open-heart operations.”

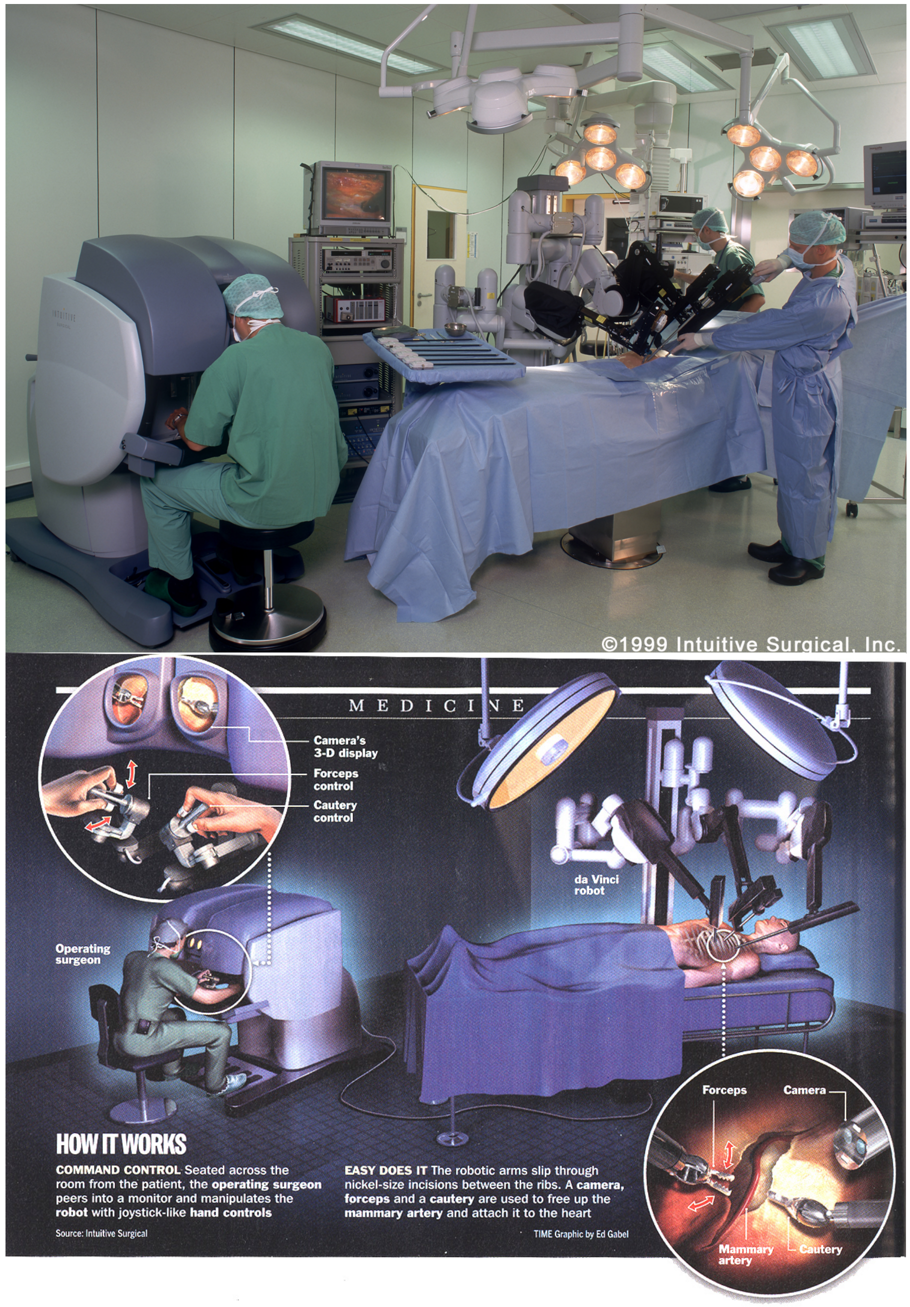


Figure 5-5. ISD’s minimally invasive da Vinci™ surgery system as (top) installed in a Dresden operating room in 1999, and (bottom) depicted in *Time Magazine* in 2001 (Anita Hamilton, “Forceps! Scalpel! Robot!, *Time Magazine*, pp. 64–65, June 4, 2001).

- The first videoscopic coronary by-pass procedures were performed 23-28 May 1998 at the Leipzig Heart Center in Germany using the Intuitive minimally invasive equipment. Prof. Mohr said, “The computer-enhanced precision, high resolution 3-D vision system, and the dexterity of Intuitive’s instruments allowed our team to perform the world’s first videoscopic anastamosis.” Dr. Falk commented on the surgeries by saying, "We believe this technology will enable cardiac surgeons to perform coronary bypass surgery through tiny ports."

- In early January 2000 the Leipzig Center and the Cardiovascular Institute, University of Dresden, performed the first series of closed-chest, endoscopic beating heart cases earlier this month. The procedures were completed solely through 4-5 ports, each less than 1 cm in diameter: 3 ports for surgeon access, 1 port for the stabilizer, and in some cases, 1 port for the assistant surgeon. This is the first time in medical history that patients have enjoyed the clinical benefits of cardiac bypass surgery performed solely through incisions of less than 1 cm without being placed on cardiopulmonary bypass (CPB) during the procedure. The ability to perform this surgery through tiny incisions significantly reduces pain, trauma, and recovery time for the patient. The avoidance of CPB eliminates post-operative neurological complications and reduces the risk of stroke for older patients. The result of this combination of clinical benefits means a short hospital stay, quick return to daily activities, and lower medical expenses. To date the University of Dresden has performed more than 90 closed-chest CABG procedures including single and double TECABs using the Intuitive Surgical System.
- In March 2000 the world's first totally endoscopic mitral heart valve repair was successfully completed by a cardiac surgical team at the Deutsches Herzzentrum Munich. The morning after surgery, the 48-year-old patient was extubated and reported little to no pain, and the intra-operative trans-esophageal echocardiogram (TEE) revealed that her mitral valve was no longer leaking. Dr. Hormoz Mehmanesh commented: "This is a significant milestone in minimally invasive intra-cardiac surgery. For the first time, we were able to perform a mitral valve repair without a mini-thoracotomy or chest wall retraction. We happily report that the day after surgery, our patient had only minimal pain from the chest tube and the four tiny ports."

Thus, ISD began commercializing the da Vinci™ Surgical System in December 1998. In the United States, the FDA approved the da Vinci™ system in July 2000 for abdominal surgeries such as gall bladders and colons; in March 2001 for chest surgery, excluding the heart; and in July 2001 for prostate surgery. More general permission has since been extended for laparoscopic and thoracoscopic (chest) surgery. As of the end of 2003, 200 systems have been installed worldwide, and more than 13,000 operations of approximately 200 different types, including cardiac, have been performed.

The importance of this SRI innovation seems almost impossible to overestimate. Though the system's capital cost is moderately high, about $1.25 million, it offers surgical advantages that are revolutionary:

- A less invasive, less traumatic means for an extremely wide range of surgical procedures
- A shorter operating time, reduced hospital stay or higher out-patient potential, and a more rapid healing process
- Intuitive operation that reduces or eliminates the need for specialized surgical training such as that required for laparoscopy
- A limited ability (defined by signal delay) to allow the surgeon to conduct procedures outside the operating location, thus enabling remote access
- Scale-up of surgery dimensions, including microsurgery, to allow the use of normal dexterity
- Stabilization of the surgeon's hand in delicate and dangerous situations.

Here are two brief observations on this subject. Curiously, only a few SRI people joined ISD, but none of those who invented the technique. One who did join ISD was Gary Guthart, now the Senior Vice President for Product Operations. Second, the market for this kind of surgical equipment is obviously young and open to competitive skirmishes. In May 2000, a month or so before ISD's IPO, its major competitor, Computer Control of Santa Barbara, California, filed suit for patent infringement. As the case dragged on for a long time and at great expense, the two parties decided that, rather than contesting such matters, they should merge under the ISD name. The resulting company is now the world's largest in this new and promising field.

The SRI Eyetracker

Its Genesis

Hew Crane is one of SRI's most prolific inventors. He has the uncanny ability to delve into the core of a technology and find the insight necessary there to open new horizons for its use. One such case was the SRI eyetracker, which is briefly described here. In the early 1960s, Crane had been working on a new means for automatically focusing a camera. At the same time, he had been looking into the "channel capacity" of various human sensory systems. He chose to concentrate on the human eye and found that, under certain circumstances, the eye oscillates slightly in its focal length. What if, he thought, those oscillations were the basis for the eye's ability to autofocus?

An opportunity to explore that hypothesis came when NASA expressed an interest in ascertaining whether the buffeting sometimes experienced in flight would affect a pilot's ability to focus. Such an inability to focus would be particularly troublesome in high-speed, low-altitude flight. SRI was awarded a contract to explore this condition, and its published findings—that a relationship existed between small, rapid movements of the eye and its adaptive focusing—caused excitement in the vision community. NASA continued funding SRI's work in the visual accommodation area and that funding led to SRI's development of an accurate optometer and the eyetracker. How the eye muscles focus in selecting different distances for viewing (a process called "accommodation") was known, but the neurological basis for the process was not.

A second and supplemental source of eyetracker funding came from an unlikely source that resulted from a chance meeting between Crane and Stanford social psychologist Leon Festinger (who eventually shared his National Science Foundation [NSF] grant on visual perception with SRI). Crane recalls how it occurred as a humorous, but not totally atypical, instance in research: Festinger, having learned of SRI's interest in vision research, paid a visit to Crane's laboratory. At the conclusion of a long, animated meeting where Festinger stated his need for an eyetracker, Tom Cornsweet, a vision researcher who had just joined SRI, said something like, "Well, one way or another, we could probably have something to demonstrate in at least crude form within a few months." When they were alone Crane exclaimed, "Tom, are you out of your mind? We don't have the faintest idea yet of how to build an accurate, noninvasive eyetracker!" But Tom did, and their competence prevailed.

The Approach[D]

The work on the eyetracker began in earnest in 1965, but to understand the approach it is necessary to back up a bit to SRI's study of how the eye focused. Their hypothesis was that accommodation depended on the axial position of a tiny area in the center of the fovea, the central, high-resolution part of the retina. To confirm that hypothesis, however, required a "means for stimulating and measuring eye focus in real time as well as the ability to place and hold a target image accurately within this small area." To do this required a major instrumentation effort that included the construction of:

- An accurate optometer to measure eye accommodation in real time
- An accurate eyetracker to measure the two-dimensional components of eye movement in real time
- A stimulus deflector that could, under the control of the eyetracker, stabilize a target at selected retinal positions.

The SRI team of Crane and Cornsweet quickly concluded that the only feasible approach to a noncontact eyetracker was to use Purkinje reflections, which are reflections from various layers at the visual entrance to the eye when it is exposed to a beam of light. It turned out that tracking the two-dimensional reflections from the surface of two particular layers could provide information on where the eye was looking. But because one of the important reflections (the one from the back of the lens) was weak, tracking it reliably was a challenge.

The two reflections used were known as the first and fourth Purkinje reflections—the first from the cornea and the fourth from the rear of the lens. The configuration of the eye, shown in Figure 5-6, produced virtual sources for these two reflected images, which separated from each other with eye rotation but not with eye lateral movement (or translation). Thus, the two-dimensional separation of the virtual sources was an expression of where the eye was pointed. This fact, then, became the basis for designing an eyetracker to monitor that separation continuously (see Figure 5-7).

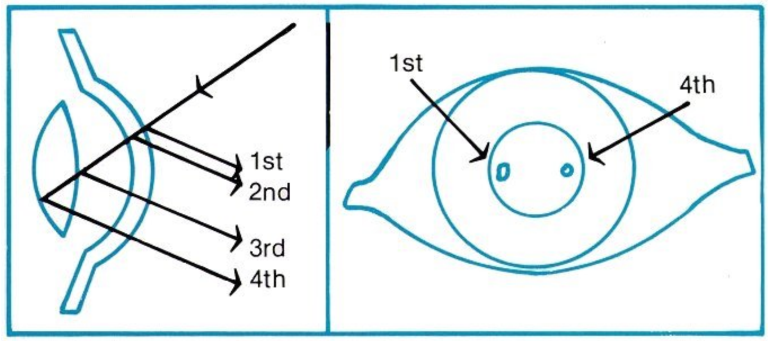


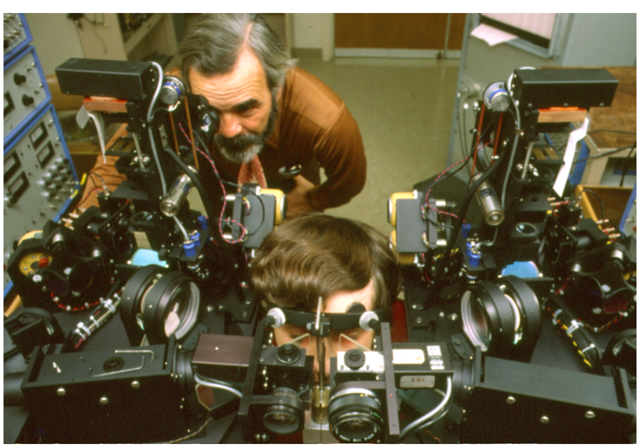
Figure 5-6. On the left are shown the four Purkinje reflections. On the right the virtual sources of the first and fourth reflections are depicted as being in the same plane (from Fourward Technologies' Web page, www.fourward.com).

As might be expected, years of work were involved in realizing the promise of this concept. System artifacts that unintentionally altered the relative position of the two Purkinje images had to be eliminated. SRI built five generations of eyetrackers, with each successive generation delivering better, more accurate measurements or greater ease of use. Development of the first generation lasted from 1965 to 1971 and, over the following 6 years, SRI built and delivered 30 Generation I, II, and III instruments. During that time and continuing through the development and sale of 11 Generations IV and V instruments, NIH's National Eye Institute provided additional funding, with the grants spanning about 12 years. Such manufacturing numbers were getting to be larger than SRI could efficiently handle and in 1987 the Institute licensed the technology to Fourward Optical Technologies on a worldwide basis. That company created a sixth generation with the following characteristics, which make it perhaps the most accurate eyetracker available:

- 400 Hz bandwidth
- 1 minute of arc accuracy
- Response time of less than 1 millisecond
- Slue rate of 2000º per second
- Less than 1 minute of arc resolution
- Enhanced auto staging
- Large two-dimensional field (± 20º).

Applications for the Fourward Optical eyetracker include:

- Image stabilization
- Analysis of visual perception
- Strabismus therapy
- Accommodation tracking
- Drug evaluation
- Reading analysis
- Vergence (binocular system)
- Stabilized photocoagulation
- Mapping retinal features
- Scotoma simulation
- Neurologic investigation
- Man-machine interactions
- Analysis of advertising material



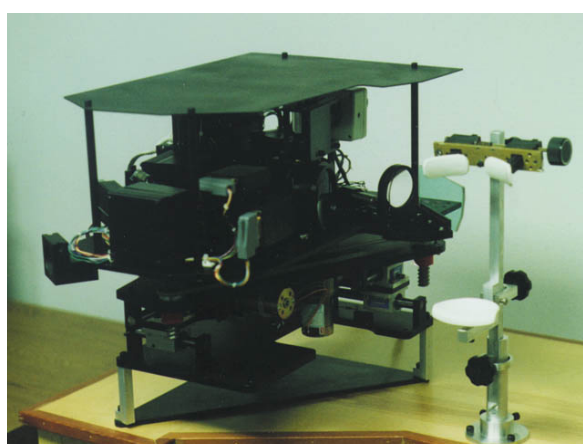


Figure 5-7. (a) Laboratory complexity of the early eyetracker and (b) the present commercial product.

More than 80 of the instruments are in use around the world in eye research and other applications requiring an accurate knowledge of eye movement.

SRI also built a related instrument called an optometer about the same time.[3] It could instantaneously measure the plane of focus of the eye, and its speed enabled it to track the most rapid changes in focus. Because of it speed, it was capable of tracking the goodness of focus on a target as it moved closer or further away from a patient, revealing at what distance the eye ceased to focus correctly. This was an alternative to the normal method of overlaying different lenses and asking the patient for judgments about clarity.[E] But it would also be more costly so the use for the optometer remained as the sensor providing the third dimension (distance) to SRI's 3D eyetracker.

Figure 5-8. The prototype stabilization system for laser photocoagulation with Hew Crane and Mike Clark (right).

A final note about SRI's eyetracker work: In early 1979, the technology enabling this instrument to stabilize targets in the visual field was used to stabilize the instrument-eye relationship in the use of the laser photocoagulators, which are discussed next. Figure 5-8 provides an illustration of a prototype of that stabilization equipment. In addition to Crane and Cornsweet, other SRI staff added greatly to the development of the eyetracker—Carroll Steele, Lloyd Alterton, My Van Njuyen, and Mike Clark.

[3] The optometer measures eye focus with an accuracy of 0.1 diopter and with rapid response. Merging the optometer with the eyetracker resulted in a three-dimensional tracker. Other devices developed by Crane in conjunction with Carroll Steele can be added to the eyetracker including a stimulus deflector that the subject looks through and that can move the viewed scene horizontally, vertically, and in varying degrees of depth under rapid servo control, and a means for accurately simulating, in a patient with normal vision, a scotoma (a spot where the retina has ceased to function) of arbitrary shape, size, and position.

It was at a local tennis club, but not one of your normal club tennis matches. Don Scheuch, then head of the SRI Electronics and Radio Sciences Division, was in the pool tossing a wet tennis ball around with his son. One such toss came at Scheuch from out of the sun and struck him directly in the eye. Dazed and hurt, he tried to brush it off, but a day or so later began to see the impact of the injury on the sight in that eye. He called his tennis friend and ophthalmologist, H. Christian Zweng, who urged him to come immediately to the Palo Alto Clinic where he worked. After diagnosing the injury as a torn retina, he showed Scheuch a brand new device that used a laser for retina repair. The treatment worked, at least temporarily, but Zweng took the opportunity to grumble about the many disadvantages of this handheld ophthalmoscope into which a ruby laser had been incorporated.[4] He was considering alternatives and looking for an environment in which to develop a more clinically useful device. Scheuch replied that SRI had very competent engineers and that if he wanted to pursue a better system why not come to SRI and explore that possibility. Zweng took Scheuch's advice, and in late 1963 a long and fruitful SRI relationship with Zweng and his fellow ophthalmologists at the Stanford Medical Center began. Some 5 years later that collaboration resulted in SRI building what was probably the first clinically useful instrument for laser photocoagulation.[5]

The transparent openings to the eye, the cornea and the lens, offer a natural entrance for visible laser light. The spherical inner backside of the eye, called the chorioid, supports the retina, a light-sensitive film containing rods, cones, nerve endings, and blood supply. Images falling on the retina are converted to electrical impulses that are interpreted in the brain as what we see. The center of the retina, that region responsible for our central vision is called the macula, and it is the most critical element in our visual field. When we look at an object and focus on it, we are positioning the image on the macula. When any portion of the retina detaches from the back of the eyeball, it loses its spherical shape and vision is disrupted in that area. Because the retina is so inaccessible, lasers offer excellent means to reach and treat the retinal area.

Since the early 1950s, powerful light sources have been used in a process called photocoagulation to repair injured retinas by binding retinal tissue together or cauterizing diseased blood vessels in the eye. The earliest approach was the use of a white-light xenon arc-lamp source. While a large and powerful source, it required an exposure between 0.5 to 1.5 seconds to produce a lesion. Therefore, to avoid injury, the patient's eye often had to be anesthetized. Nonetheless, lesions were often mislocated or proved too large to treat. Because the most critical areas of the retina are quite small, the inaccuracies of the white-light photocoagulator meant it was unsuitable for the most important operations. The coherent power of visible-wavelength lasers offered a new approach.[F] The first laser used was the low-power, handheld ruby laser mentioned above, but it was frustratingly difficult to use and somewhat dangerous.

When the program began at SRI, the leading cause of blindness in the United States was diabetic retinopathy, a disease for which the laser proved to be ideally suited and for which the treatment need was great. The procedure was noninvasive and simple for trained ophthalmologists. By choosing a suitable wavelength and exposure time, the ophthalmologist could readily cauterize the diseased blood vessels in the retina or reattach certain forms of torn or detached retinas. The laser's contribution has been enormous.

Soon after Zweng's visit to SRI, grant applications to NIH's National Center for Neurological Disease and Blindness were made through Stanford University to explore new uses of the laser in ophthalmology. In 1964, the group, which included some of Zweng's colleagues at Stanford, received initial internal funding[G] to look into medical applications of the laser. In 1966 a $1.5 million grant was awarded to Stanford, with appropriate funding

[4] The device, which was built by a local firm, Optical Technologies Inc., was one of the early laser photocoagulators. As mentioned in the preface of Zweng's book, *Laser Photocoagulation and Retinal Angiography,* Scheuch was the first patient on whom Zweng used the device, and he notes the date as Aug. 27, 1963. An important member of Optical Technologies staff, Norm Peppers, left there to become a member of the SRI project team with whom Zweng would work on a new laser photocoagulator.

[5] From comments by ophthalmologist Hunter Little, "clinically useful" means that it was powerful enough to be rapid and focused enough to be precise.

coming to SRI, and the two institutions embarked on a multiyear development program.[H] Figure 5-9 shows the SRI team, along with Zweng.

What impact has SRI's work had? As mentioned, out of this effort came the first clinically useful and commercially successful argon laser photocoagulator. This technology became the basis for an important local company, Coherent Radiation. It proved to be not only a highly successful clinical tool, but also a significant commercial asset for the company. Art Vassiliadas left SRI to join Coherent and helped transfer the technology. Today, Coherent, as it is now known, is a corporation engaged a wide range of laser applications and has revenues exceeding $400 million a year. Figure 5-10 shows its main ophthalmologic product.

This instrument can repair torn retinas or help prevent detached retinas by "welding" them back in place. The SRI team continued to work with the Stanford Medical Center in other ocular uses of the laser: puncturing a tiny hole in the iris to relieve the fluid overpressure in patients with acute glaucoma and coagulating hemorrhaging blood vessels in diabetic retinopathy. Other areas explored were the use of lasers as microprobes in the spectroscopic analysis of cells and dermatology. The laser even became important in the removal of tattoos—an improvement over existing methods, which involved incisions, scraping, or other trauma to the skin and which left broad scars or, in some cases, required skin regrafting. A higher intensity, Q-switched version of the ruby laser turned out to be not only effective in removing a range of tattoo pigments, but left minimal damage to the surrounding skin when the light energy density was correctly applied. SRI engineers designed and built a special excitation chamber for the ruby laser to gain the required power levels.[I] The treatment produced minimal pain but, because of the high cost of lasers at that time, treatments didn't catch on right away. One of those who volunteered to have a tattoo removed from his arm was the police chief of Menlo Park whose office was across the street from SRI.

Figure 5-9. The laser photocoagulation team at SRI. From left to right and front to back, Art Vassiliadis, Christian Zweng, Dick Honey; Norm Peppers, Ann Hammond, Lloyd Alterton; Earl Scribner, James Hayes, and Bob Myers.

Figure 5-10. Coherent 2000 Series photocoagulator.

In more recent years, SRI also obtained continued support for the development of nonlinear optical limiters that can automatically increase their opacity to protect the eye, or other sensors, from inadvertent exposure to lasers. The eye damage thresholds developed concurrently for the Air Force led to safety standards for Air Force personnel, and eventually were a major contributor to the American National Standards Institute (ANSI) laser safety standards adopted by all the armed services and industry.

Meanwhile, Scheuch's eye needed continuing attention as a result of his injury, and he became the first patient to use the SRI-developed system; a true pioneer, on more than one occasion he lent himself for tests as the development proceeded. Today, his eyesight is fine. To conclude this section of this phase of SRI work, two stanzas are presented of a poem written by a diabetic Lutheran minister who was treated in the testing phase at SRI and whose life was changed by the benefits of this collaborative work. Here is SRI meeting its chartered purpose.

Obviously, laser interaction with an eye can also be dangerous. Given the widening use of lasers in the workplace and the military, another concurrent effort was SRI's work on the eye's vulnerability to damage from lasers.[6] SRI wanted estimates of retinal and corneal damage thresholds, as well as a means to protect the eye from dangerous exposure. Retinal thresholds were measured for Rhesus monkeys and some humans, and corneal thresholds were determined using rabbits. Funding for this work came from the Air Force and the NIH. In parallel with the clinical program, and with support from the Air Force, SRI explored the thresholds for eye damage from a wide variety of lasers and laser pulse lengths.

[6] The work on laser vulnerability to the eye actually preceded that on photocoagulation, starting at SRI with Air Force sponsorship in 1965. (SRI Project 5571 July 1, 1965 for $91,368.)

FROM "VISION'S TIME EXTENDED

Come with me
Share a moment with me
Scanning at a nearer distance
The Marks of Beauty
One here near her lip
Another there on her shoulder
Each in its just-right place
And noting the symphony of light
The soft blending
Of her hair
Her eyes
Her skin
The harmony of her body
Knowing she is a woman
All Woman
Knowing this by looking
And beauty is sensual
With vision's time extended
Through the touch of a blue-green light
The beauty of her face
Will not be a mere memory
Not yet!

Come with me
Share a moment with me
Scanning through iron-grilled doors
Down corridors and into cubicles
Having signed ones name
And noted the time
A team is observed
Searching and researching
A therapeutic team
A compassionate team
People with heart
An unassuming and undaunted team
A beautiful team of Beautiful People
Caring and sharing
Their crafts have merged
They have cohered
Ophthalmology and physics
Mechanics and mathematics
Biology and electronics
The name of their game
Is coherent Argon Laser
With vision's time extended
Through the touch of a blue-green light
The Argon Laser Team
Will never be a mere memory
Never!

From "Vision's Time Extended" by SRI patient
Paul C. Imschweiler, July 31, 1971

Ultrasonic Imaging

Because of its safety and ability to image soft tissue, ultrasound has become a mainstay worldwide in medical diagnostic tools. Not only has it become the primary sensor for obstetrical and gynecological examinations, but it also has great utility in a variety of other soft-tissue imaging applications such as cardiac and vascular disease and breast cancer screening. In addition, it is the principal diagnostic tool used whenever X-rays are deemed too hazardous, such as in screening newborn infants with congenital deformations. The development of the technique has spread over decades and is global in its origins. While the use of sound for therapeutic reasons predates World War II, its use as a medical imaging modality began in the late 1940s, largely stimulated by the military development of sonar following the War. Contributions to its development came from Europe, the United States, and Japan. Though the 1950s and 1960s saw rapid increase in employing the real-time, intensity-modulated, two-dimensional imaging systems in use today, those early systems were static, and their sensitivity and resolution were poor.

Accordingly, work on more sophisticated acoustic sources and processing systems continued into the 1970s and 1980s. In the 1980s, the sale of ultrasonic imaging systems began to accelerate. Though SRI is not a visible part of today's marketplace in ultrasound systems, such as those from Picker, Siemens, and Diasonics, it has played an important role in the design of improved ultrasound imaging systems and in research into the biological effects of ultrasound. Let's see how.

Ultrasonics Begins at SRI

In 1967, when the utility of ultrasound was just becoming broadly appreciated, Earle Jones, head of the Electronics and Optics Group,

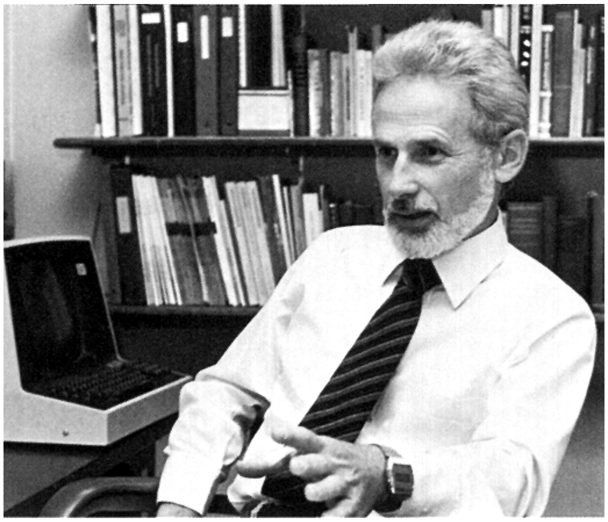


Figure 5-11. Phil Green, at the time director of SRI's ultrasonic imaging program.

brought in Phil Green (Figure 5-11) to open a new, exploratory SRI program in ultrasonic imaging. Green's goal was to make SRI a significant player in this developing field. Usually, such a statement was SRI administrative code-speak for an individual who had fresh ideas about how to develop a particular technology—and ultrasound, at that time, needed a lot of innovation to make it more clinically useful.

The first ultrasonic instrument to be built at SRI was a precision mechanical two-dimensional scanner that scanned a single transducer (i.e., an instrument that coverts input energy in one form into output energy in another) or opposed (facing) pair of transducers in a water tank containing the object to be imaged. The system permitted imaging in three modes: reflective, transmissive, and holographic.[7] A two-dimensional image was created by moving an acoustic detector in a raster pattern (as in a TV picture) that spanned the target. The output of the detector was then modulated onto an attached, point light source, moving in synchrony with the detector, that was in turn photographed as a time-exposure in the darkened room. This system produced exquisitely detailed transmission and reflection images, phase-contrast images, and ultrasonic holograms of a wide variety of objects, including excised animal organs. One of the images—that of an *ex vivo* human fetus—is shown in Figure 5-12(a). Its detail was unprecedented. It received widespread press coverage and dramatically raised the level of expectation for future diagnostic uses of ultrasound. Yet these images took many minutes to acquire, and true diagnostic ultrasound would have to show tissues and organs moving and thus be capable of real-time imaging.

An Ultrasonic Camera and Real-time Imaging

The next important development in SRI's pursuit of ultrasound systems was the building of an ultrasonic camera, which began in 1971. At the outset, this approach also used a tank of liquid but with an improved lens system and a highly sensitive electronic image detector. Figure 5-13 provides a schematic diagram, and Figure 5-14 shows a picture of the camera being used.

The camera system was sponsored by a 3-year grant from the NIH (subsequently renewed). At the heart of this instrument were two components. The first was a 192-element curvilinear piezoelectric transducer array with a curved plastic cylindrical lens. Each array element had an associated amplifier and detector that fed a multiplexer. The second component consisted of a large cylindrical chamber, whose faces were double-concave plastic lenses, 20 cm in diameter. Between the lenses was a pair of circular 15-cm-diameter, 4.7 deg. prisms, which were counter-rotated at a 15-Hz rate by a motor. The prism system, invented by Green, repeatedly swept the focused image field past the 192-element linear transducer array. The chamber was filled with a totally fluorinated hydrocarbon fluid. The 4:1 ratio of acoustic refractive indices of the fluid and plastic resulted in a very short focal length and a wide sweep angle. All of the computer-designed refractive surfaces were coated with quarter-wave impedance-matching layers for minimum reflection.[J] This flexible system had a number of advantages over then existing ultrasonic imagers:

- Real-time imaging, showing anatomical structures in motion
- High sensitivity with lower transducer power for equivalent depth of penetration
- High resolution of 0.75 mm

[7] Acoustical holographic images detect a optical or acoustic wave interference field that is created by interaction between a plane reference wave and waves scattered from the target object(s). This lensless scheme can simultaneously acquire multiple image planes but has both sensitivity problems and image noise caused by artifacts characteristic of coherent wave interaction.

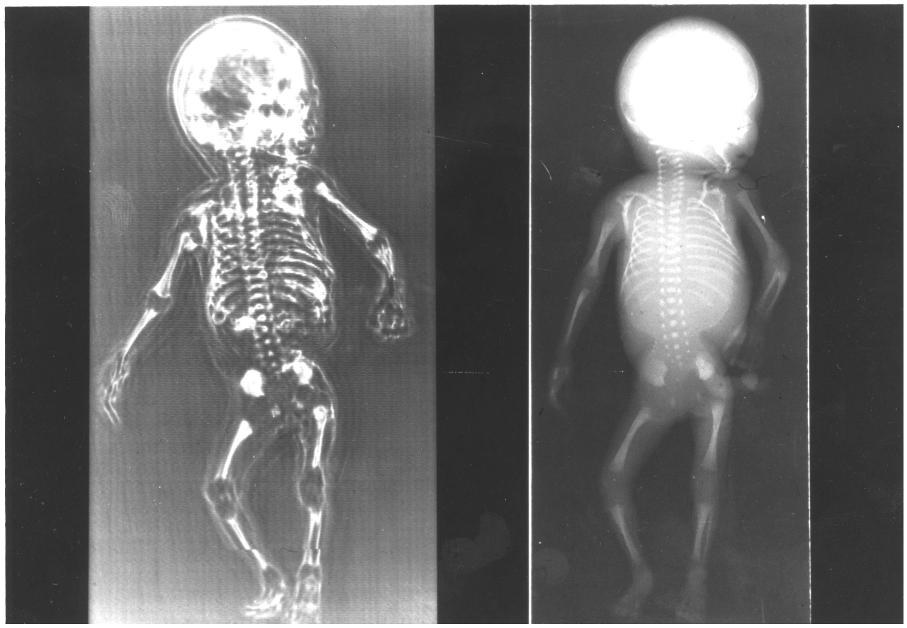


Figure 5-12. The (left) ultrasound and X-ray images of an ex vivo human fetus. The detail of the ultrasound image was unprecedented and markedly raised the awareness of what diagnostic ultrasound could do.

- A variable focal-plane position within the body
- Dual modes of operation—reflective as well as transmissive imaging.

But, as an instrument for clinical diagnosis, the camera also had significant problems:

- Images often contained spurious detail from diffraction by tissue outside the focal plane, which could be mistaken for real and valid structure. (In later versions, a more diffuse sounding source diminished this artifact.)
- Water-tank immersion was too inconvenient for most diagnostic applications.

The SRI ultrasonic camera was first presented in 1973 at the 5th International Symposium on Acoustical Holography, which

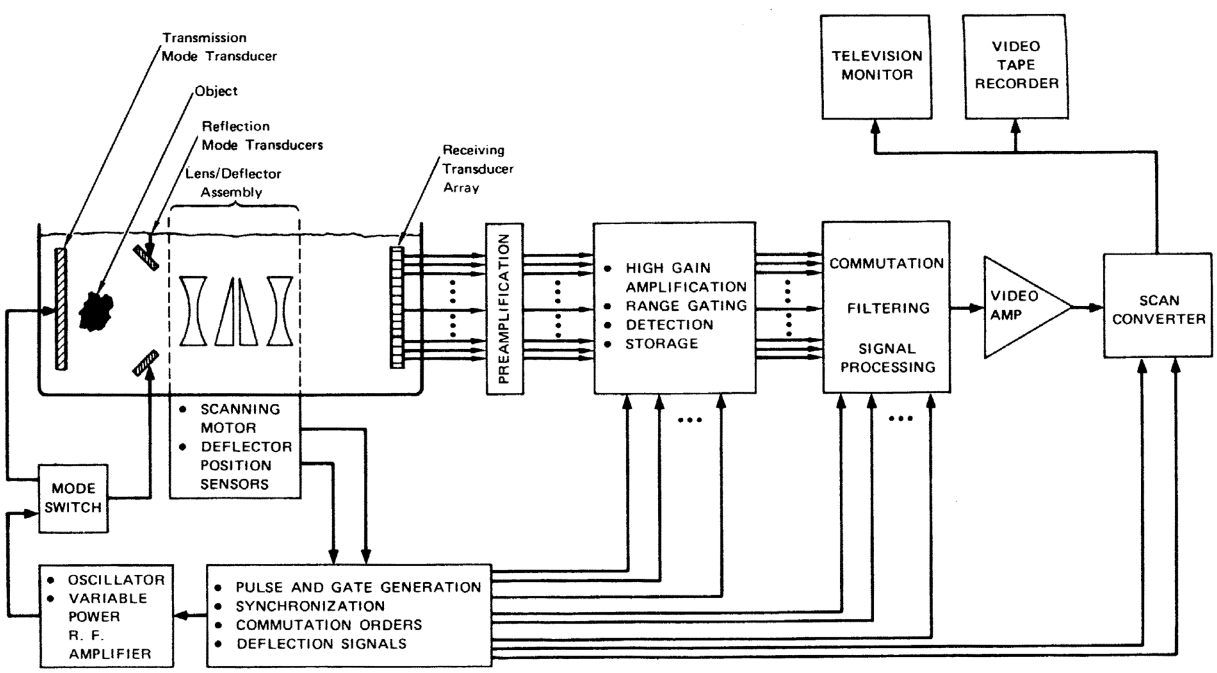


Figure 5-13. Schematic of the SRI ultrasonic camera.

Figure 5-14. The SRI ultrasonic camera in use.

SRI hosted.[K] It was acknowledged to be the most outstanding development in the field. A "water-pillow" version was also built that removed the need for the patient to be immersed in a tank; this version was intended mainly for abdominal imaging. This form of transmission imaging was successful in diagnosing several pathological conditions, including enlarged spleens, and large kidney stones or cysts. Late-pregnancy fetal imaging, earlier limited to extremities and torso, was also done. Several patents were granted on the camera systems, which were licensed to Picker, for which SRI did additional contract work. Picker chose to switch its interest to another SRI technology (see below), and the camera was subsequently licensed to Siemens, for which SRI built an elaborate clinical version that was used for orthopedic diagnostic studies at the University of Muenster. In collaborations with the Palo Alto Clinic and the Stanford University Medical Center, the camera was successfully used in depicting breast carcinoma *in vivo* and soft-tissue hand anatomy.[8]

While work continued on the camera, SRI began its first collaboration with the Mayo Clinic in 1977 under a major new contract secured from the NIH (also subsequently renewed.) The initial goal of this work was to develop and clinically evaluate a high-resolution real-time "B-scan" (pulse-echo, cross-sectional) imager designed especially to view tissue within the first few centimeters of the skin. Its major use was the examination of the site where the internal and external carotid arteries join in the neck—the site of arterial narrowing and clot formation that give rise to most strokes. With this work, an alternative was being sought to the use of X-ray angiography, the painful, sometimes risky injection of X-ray-opaque dye into the blood vessels of interest.

SRI developed a series of increasingly sophisticated scanners that operated at 10 MHz to provide the needed resolution. These instruments clearly delineated not only atherosclerotic plaque on arterial walls but its precursor—subtle thickening of those walls. Strikingly detailed images of the nearby thyroid gland demonstrated that high-frequency "small parts" scanning would have many other clinical applications as well. One SRI invention made on this project—a time-varied filter that compensated for variations in depth-dependent attenuation—proved later to be a major source of royalty revenue to SRI.[9] SRI licensed this system to Picker and developed a manufacturing prototype under contract to Picker. Picker produced and sold these systems as the *MicroView*®. In a special conversion made for the University of Düsseldorf's neurology clinic, SRI added a dynamically focused, annular-shaped transducer array and real-time Doppler blood-flow profiles that were superimposed on the image. Figure 5-15 shows a version of the SRI-Picker instrument. SRI and the Mayo Clinic continued collaborative research on arterial imaging for several more years, under a third NIH contract. This work

[8] Contributing significantly to the design and fabrication of the camera were John Holzemer, Jon Taenzer, Dave Murdock, Bill Mullen, Joe Suarez, Dave Ramsey, and Lou Schaefer.

[9] Because the attenuation of ultrasound in tissue increases linearly with frequency, the lower frequency components of a broadband pulse are stronger than its high frequency components at the same tissue depth. That action and the effective change in resolution with frequency suggested the introduction of a filter that varied as a function of depth, hence delay time.

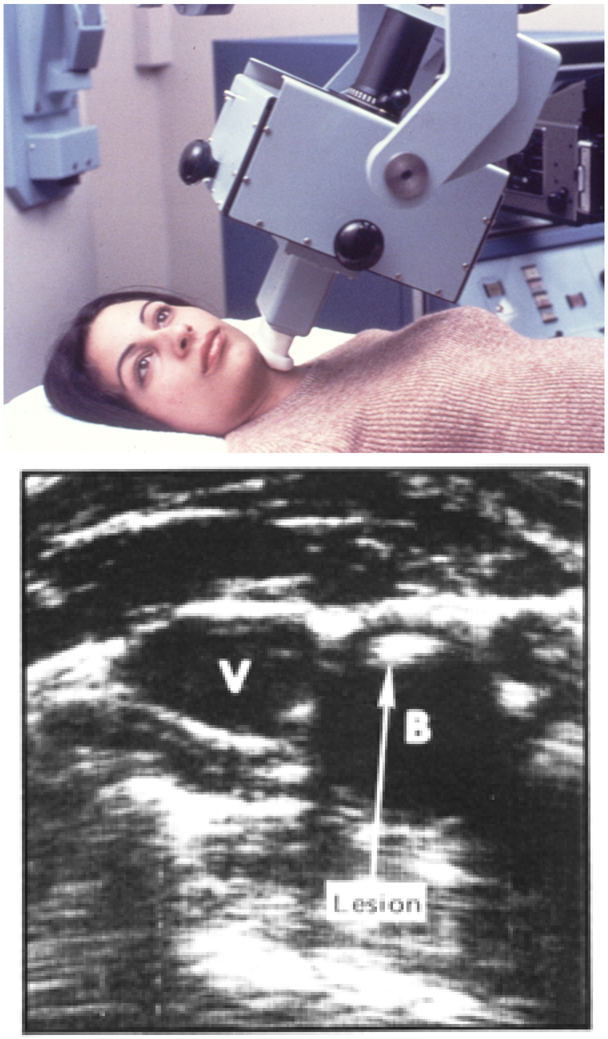


Figure 5-15. Ultrasonic examination of the cross-section of a carotid artery using the first of several such scanners developed at SRI. Atherosclerotic lesions (plaque) appear as a bright area within the otherwise dark interior of the carotid bulb (B)—the expanded region of the carotid artery just below just below where it branches. The jugular vein (V) is to the left of the artery.

resulted in a new system, operating at 4 MHz, that yielded images of deep arteries (to 5 cm) such as abdominal aneurysms.[10]

By the 1980s, ultrasound diagnosis was in widespread use, and concern began to surface over the possibility that this form of energy might have undesirable side effects, especially when used in first-trimester pregnancies. SRI's Ken Marich secured a major grant from the NIH for an extensive bioeffects study.[11] The Ultrasonics Program, in cooperation with several laboratories in SRI's Life Sciences Division, conducted experiments in which pregnant mice and cellular suspensions were subjected to carefully calibrated ultrasound exposures and analyzed for short- and long-term effects, using a variety of analytical methods. These studies were carried out over many years and published in detail. Thanks to this program and to similar programs at cooperating universities, the mechanisms of ultrasound's interaction with tissue became better understood, and concerns over possible adverse side effects were abated. SRI made further use of its knowledge in bioeffects research and of its unique facilities by studying ultrasonic hyperthermia, then under consideration as an agent for cancer treatment.

Whereas SRI's "small parts" scanners showed anatomy in unprecedented detail, because of their high frequency (typically, 10 MHz) and high attenuation, they were limited to viewing only those tissues lying within a few centimeters of the skin. To extend this capability to organs lying deep within the body, SRI's James Buxton received a grant from the NIH in the late 1970s to develop a real-time ultrasound scanner with a transducer incorporated into the tip of a gastric endoscope—a device inserted into the esophagus, stomach, and duodenum to allow doctors to view those organs. Again, our clinical collaborator was the Mayo Clinic. A 3-cm-long, 64-element, lensed, piezoelectric transducer array was mounted within the tip portion of a 12-mm-diameter gastric endoscope, which retained all of its normal functions—optical illumination and imaging, forceps entry, suction, and irrigation; 64 subminiature coaxial cables conducted signals between the transducer elements and a novel, low-cost pulse generator, multiplexer, processor, and display. Multirange focusing ensured that the image was in good focus at all depths. The animal and human studies conducted with these systems at the Mayo Clinic showed, with great clarity, the ridges of the stomach lining and its thickness, the spleen and kidneys, abdominal blood vessels, and the heart's mitral valve. SRI also added a hand-held small-parts scan probe to the system to extend its utility (see Figure 5-16). SRI patented this technology and licensed it to Advanced Technologies Laboratories, which sponsored continued development at SRI. The

[10] Joining the team to work on artery scanners were Jim Havlice, Dave Wilson, Don Burch, and Dilip Saraf.

[11] While this work was initiated by Ken Marich, much of the bioeffects research was led for many years by Peter Edmonds. Pepi Ross, Virginia Rimer, and Lynn Mortensen also participated.

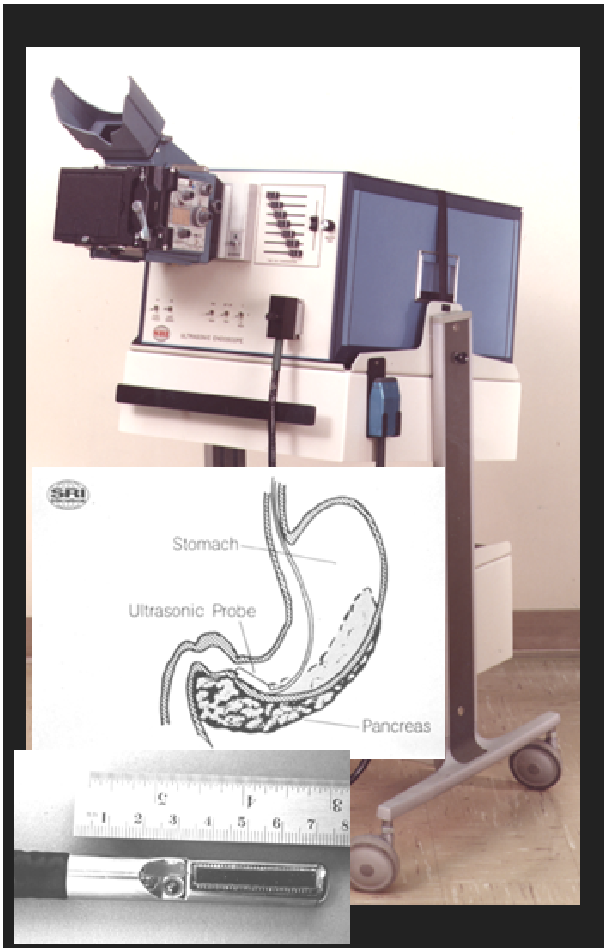


Figure 5-16. The SRI endoscopic ultrasonic imager showing the transducer at the bottom.

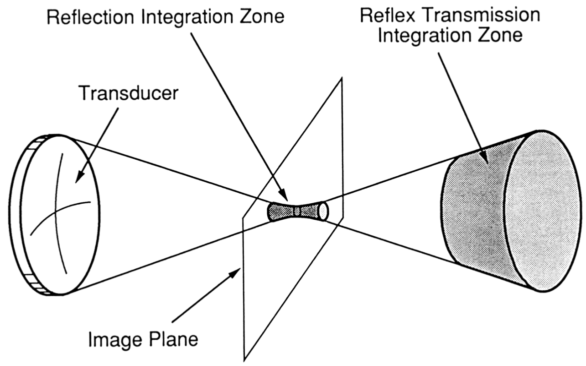


Figure 5-17. Basis for reflex transmission imaging. The large gray conic section on the right acts as a signal source for transmissive imaging.

National Cancer Institute also sponsored SRI to explore the utility of this imaging endoscope to detect pancreatic cancer through the stomach wall.[12]

Reflex-Transmission Imaging

As noted, SRI's early transmission-imaging work with the ultrasonic camera did not migrate into common clinical use owing to the difficulty of adequately imaging large areas on both sides of a body part without inserting the part into a water bath. The small, hand-held probe used in B-scan imaging, which displays reflections only from targets lying in the plane of scan, proved to be more convenient.[13] But, some anatomy is better delineated using the transmission mode; that is, the detector lies on the opposite side of the target or imaging plane from the transducer (see Figure 5-17). To incorporate transmission imaging into B-mode systems, in 1984 SRI devised reflex transmission imaging (RTI). In the RTI mode, a well-focused scanning transducer is used both to transmit energy into the body and to receive the echoes. However, in the RTI mode the echoes from a defocused (integrated) region beyond the focal plane become a source of sound waves directed back through the focal plane, thereby indicating the transmissivity of the tissue located there.[L] These sound waves are differentiated from the normal reflected image because they return to the receiver later. Thus, the displayed RTI image primarily depicts the variations in *attenuation* rather than reflection within the focal plane. SRI secured an NIH grant to develop a demonstration RTI system, which proved to be particularly effective for delineating kidney stones. RTI was licensed to Diasonics, Inc. for incorporation in its kidney-stone lithotripter, a noninvasive device for breaking up kidney stones using sound waves administered externally through water.[14]

SRI's Ultrasonics Program was active for more than 25 years. During that period, the Program also undertook many consulting and product-development projects for industry, including the development of a prototype ultrasonic eyescanner system for Asahi Medical, a prototype cardiac scanner system for Ansaldo Biomedica, and numerous design concept studies in nondestructive testing as well as in medicine using SRI's unique imaging systems.

[12] Other contributors were Jerry Russell and Helmut Moessner.

[13] B-mode or B-scan (B stands for brightness) systems show two-dimensional cross sections of tissue with the intensity of the return at any point in the image proportional to the strength of the signal received there.

[14] Contributors to the RTI development were Joel Jensen, Peter Schattner, Marcel Arditi, and Yonael Gorfu.

Over the course of its history, the Ultrasonics Program patented more than 30 inventions, with many licensed to medical equipment manufacturers worldwide and returning about $60 million in royalties to SRI. It is important to note that such royalties did not flow from up-front licenses. Instead, the substantial returns from SRI's intellectual property in ultrasound were due to Green's efforts. He determined which manufacturers were encroaching on SRI patents, and then tried to persuade them to sign royalty agreements with SRI, which most did. The largest sum, about $30 million, came in one of the very few lawsuits SRI has filed against an infringer of its patents. Without Phil's insight and determination, these returns would never have been achieved.

Few of the Program's staff members came to SRI with experience in ultrasound. But the experience they garnered at SRI enabled many of them to take key positions with Diasonics and Acuson, the two Bay Area medical ultrasound startups that grew to hold commanding positions in the industry. At its peak, the Program employed 18 people.

Blood Pressure Monitoring

High blood pressure is a pervasive problem across the United States. This fact, together with redefinitions that have lowered the threshold of high blood pressure (now anything above 80/120), leaves many Americans vulnerable. Blood pressure is becoming one of our more important medical measurements.

Traditionally, the measurement is made using the familiar cuff-enabled sphygmomanometer, which compresses the artery to a point where the blood flow stops. Then, noting the so-called Korotkoff sounds of the beating heart, blood begins to flow, first marginally and then completely as the heart sound disappears. Although this method is universally used, it falls short in at least three areas: First, it is somewhat labor-intensive, and when many such measurements are made in screening, the person making the measurement may get sloppy. Second, since it closes off the return of blood through the veins, the cuff-enabled method can cause peripheral edema, or swelling in the arm, with prolonged use. The issue of prolonged use brings us implicitly to the third area, the need for *continuous* blood pressure monitoring during surgical procedures or in lie detector testing. It is for this third reason that SRI began its investigation.[15]

SRI's involvement in this field started in the early 1960s. While most researchers were concentrating on the Korotkoff sounds, to SRI they seemed too indirect across the range of people and environments that would be faced. Instead, SRI concluded it was better to measure the pressure directly. Under contracts with NASA and the NIH, Gerald Pressman and Peter Newgard in the Control Systems Laboratory began looking into ways to measure blood pressure continuously.[M] Some work had been done in the field of tonometry, which deals with the medical measurement of pressures such as that of arterial blood or in the eye. While conceptually more straightforward, tonometry was subject to all the vagaries of individual physiology, automatic calibration, and, by no means least, the technologies needed to create a useful product. Seeing the value and success of ocular tonometry, SRI researchers became the first to develop arterial tonometry using a piezoresistive (i.e., pressure resistant) method to measure the pressure exhibited by the artery at a point of convenience, the wrist. When the radial artery here is flattened somewhat (but not completely), it becomes an easily accessible source point for the entire pressure waveform.

Having decided on this location, the next challenges for perfecting this noninvasive method were to position the pressure sensor at exactly the correct location over the artery and to apply only enough pressure, or flattening, to yield a good continuous measurement. SRI's first models had only one sensor element, which made placement difficult. In the early 1970s, Newgard invented a way to ease the problem of location by fabricating larger, multiple-element sensors from silicon. But that development in turn introduced the need for algorithms to compute which elements should, in fact, be used to yield an accurate measurement. In 1979, Joe Eckerle, Steve Terry (a Stanford student), and Newgard tested an eight-element sensor that not only determined

[15] Although some have mistakenly attributed to SRI the automation of the cuff method now seen in workplaces and drugstores, those devices obviously do not provide continuous monitoring and are not part of this story.

the correct elements to use but also the correct amount of pressure to apply.[N] In 1984 for the FBI, Eckerle built a multi-element tonometer for use in polygraph testing. It also helped rectify polygraph inaccuracies stemming from movement of the subject being tested.

Figure 5-18. The Colin Electronics continuous blood monitoring instrument using the SRI sensor.

Continuing with medical applications, SRI obtained a development contract from a Japanese firm, Colin Electronics. Over the course of this work Colin licensed a multi-element tonometer method from SRI in 1986 and by 1988 placed the monitor in the Japanese medical electronics market. Innovations in this unit continued, included a motorized positioning of the sensor and a completely automatic adjustment of the flattening pressure. But several factors required that the tonometer output be calibrated using a cuff measurement. A year later SRI helped Colin upgrade its sensor to 31 elements and eliminate the need for calibration. The resulting instrument, shown in Figure 5-18, became widely used in operating rooms in Japan and has belatedly received FDA approval in the United States.

But the vagaries of the commercial world have now appeared. Oddly, though the SRI tonometer approach represents the state of the art in clinical continuous blood pressure measurement, Colin has not been able to penetrate the U.S. market where cuff measurement, albeit automatic, is still in use even in operating room settings. This lack of market development, plus Colin's own costly but unsuccessful investigation into the use of tonometry as a noninvasive diagnostic for arteriosclerosis added to increasing competitive pressures in Japan, recently sent Colin into bankruptcy. Without a required performance clause in the SRI license agreement, this inactivity now threatens SRI's interest in medical field tonometry since its relevant patents expire in 2005. Outside the constraints of the license, SRI continues to explore the uses of tonometry including the continuous measurement of heart rate using a watch-like device.

Endnotes

[A] SRI International, *Telepresence for Microscopy, Microsurgery, and Endoscopy*, Proposal EDU 89-214, September 29, 1989.

[B] Col. Irwin Simon, personal communication, September 14, 2000.

[C] Carl J. Levenson, M.D., letter to SRI, April 21, 1992.

[D] Some of what follows can be found in Donald H. Kelly, Visual *Science and Engineering—Models and Applications*, Marcel Dekker, 1994. Kelly was an SRI employee in the same laboratory.

[E] *SRI Investments in Tomorrow*, No. 6, Winter 1972-3

[F] *SRI Journal*, 22, 11-20, October 1968.

[G] SRI IR&D Project 186531-107.

[H] SRI Project 6282 for $116,652, on October 1, 1966 from Stanford University under its Grant NB 06341.

[I] Richard B. Yules et al., The Effect of Q-Switched Ruby Laser Radiation on Dermal Tattoo Pigment in Man, *Archives of Surgery*, 95, 179-180, August 1967. (This explains SRI's Q-switched laser approach.)

[J] L. M. Zatz, Initial clinical evaluation of a new ultrasonic camera, *Radiology*, 117, 399–404, 1975; K. W. Marich, L. M. Zatz, and P.S. Green, Real time imaging with a new ultrasonic camera. I. *In vitro* experimental studies on transmission imaging of biological structures, *Journal of Clinical Ultrasound*, 3, 5, 1975; and L. M. Zatz, K. W. Marich, and P.S. Green, Real time imaging with a new ultrasonic camera. II. Preliminary studies in normal adults, *Journal of Clinical Ultrasound,* 3,17, 1975.

[K] Green chaired the conclave and edited its proceedings: *Acoustical Holography*, Vol. 5, Plenum Press, 1974. The volume also contained a paper about the SRI system by Green, Louis Schaefer, Earle Jones, and Joe Suarez, *A New, High-Performance Ultrasound Camera*.

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[N] S. Terry, J. S. Eckerle, R. D. Kornbluh, T. Low, and C. M. Ablow, Silicon Pressure Transducer Arrays for Blood Pressure Measurement, *Sensors and Actuators*, A21-A23, 1070–1079, 1990.