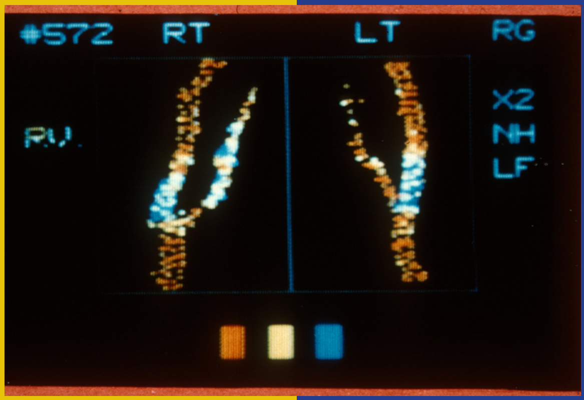
Rochester Center for Biomedical Ultrasound



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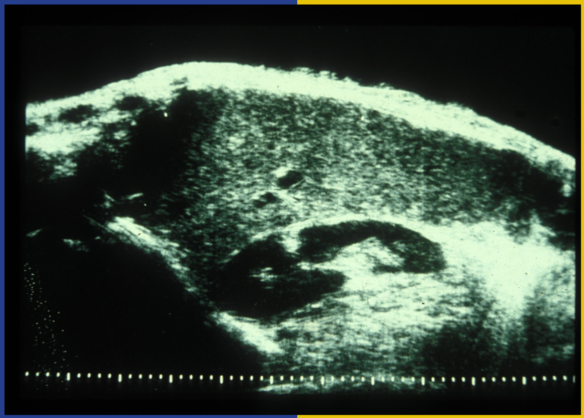

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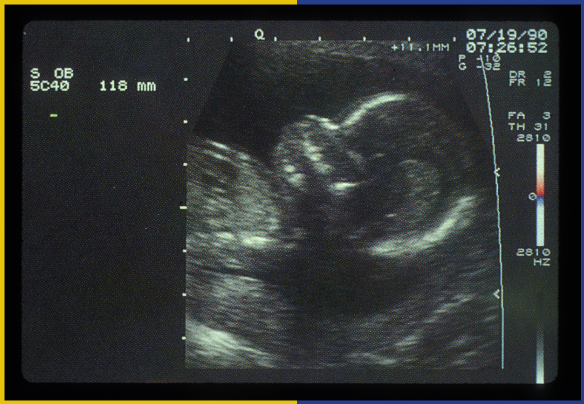

1990s

2000s

20th Anniversary Retrospective

On the cover:

Advances in ultrasound research have led to vast improvements in ultrasound images over the years, as shown:
1970s—Doppler image of carotid arteries
1980s—Liver and kidney image
1990s—Fetal image
2000s—3D fetal image, courtesy of GE

Rochester Center for Biomedical Ultrasound

Director: Kevin J. Parker, PhD, Associate Director: Deborah J. Rubens, MD | Executive Committee: Diane Dalecki, PhD, Vikram S. Dogra, MD, Morton W. Miller, PhD, Kevin J. Parker, PhD, and Deborah J. Rubens, MD | Provost: Charles E. Phelps, PhD | Vice Provost and Dean of The College Faculty: Peter Lennie, PhD | Dean, School of Medicine and Dentistry: David S. Guzick, MD, PhD | Editor and Designer: Betsy Christiansen

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Celebrating 20 Years of Ultrasound Research

The Rochester Center for Biomedical Ultrasound (RCBU) is celebrating 20 years of ultrasound research at the University of Rochester. In this special publication, we are pleased to present:

- Reflections from Kevin Parker and Deborah Rubens, our current directors
- Highlights of the past 20 years from Edwin Carstensen, founding director of the RCBU
- A look to the future from Diane Dalecki, Associate Professor of Biomedical Engineering

Reflections from our

Clinical Ultrasound at the University of Rochester

By Deborah Rubens, MD

Clinical ultrasound got a jump-start in the early 1980s with the advent of real-time imaging. When I arrived at the Department of Radiology at the University of Rochester in 1984, we had one real-time Toshiba, a mechanical-arm sector by Picker, and an Octason scanner in which multiple scanheads were immersed in a fluid bath behind a suspensory membrane, on which the patient lay, as on a waterbed. There were no sonographers. Physicians performed every scan. We saw, perhaps, eight patients a day. Our exams were limited to the abdomen (gallbladder, liver, kidneys, aorta), the pelvis (bladder, uterus, ovaries) and small parts (thyroid, scrotum, breast). We performed occasional ultrasound-guided needle biopsies. Our annual volume was less than 4,000 exams a year. Over the past 22 years, we have expanded to six regular scanning rooms, four pieces of portable equipment, and ultrasound equipment in two of five angio suites. We have 14 sonographers and the unit performs over 18,000 exams annually. We have progressed from real-time mechanical transducers through electronically steered arrays, from 3 MHz up to 18 MHz probes, and from B-mode imaging through tissue harmonic imaging, tissue compounding, digital encoding, and speckle reduction. Endorectal and endovaginal probes are used routinely, and specialized intraoperative probes have become commonplace for open as well as laparoscopic surgery.

The explosion in vascular imaging has been no less dramatic. With the advent of real-time color Doppler imaging followed closely by power Doppler imaging, vascular studies of everything from carotids to deep veins became a common everyday experience. Today we do over 5,000 dedicated vascular studies annually including transcranial Doppler for vasospasm subarachnoid hemorrhage, carotid studies for stenosis or thrombosis, upper and lower extremity for deep venous thrombosis (DVT), plus on average, at least five abdominal Doppler exams for every liver transplant recipient. Ultrasound guidance is used in multiple therapeutic arenas, including prostate brachytherapy, ablation (pseudoaneurysm), biopsies in neck, chest, abdomen, pelvis and extremities, aspirations and drainage procedures, and in guidance for tumor ablation (RFA, ethanol, and cryosurgery). Ultrasound contrast media is approved for cardiac use in the United States, but is gaining rapidly in hepatic and renal imaging in Europe, Canada, and Japan where it has been approved for several years. In our laboratory, we use it off-label to treat patients with endoleaks following aortic prosthesis and to assess patients with tumors who are unable to receive iodated contrast (CT or angio) and who cannot undergo an MRI examination.

Three-dimensional (volumetric) and real-time 3D (4D) ultrasound is emerging in the market and in our practice already with the niche applications in ob-gyn ultrasound and breast imaging. With faster processing and greater memory, fused ultrasound volumetric imaging to CT and/or MRI will become a reality. Given the growth and progress we've seen in the last twenty-five years, ultrasound is far from a mature technology, and we have much growth and new technical capabilities to expect in the years to come.

Current Directors

The Future of Biomedical Ultrasound

By Kevin J. Parker, PhD

One of the best prognostications on the future of ultrasound was given by Anne Hall of GE, in a presentation to the RCBU on August 12, 2005. Dr. Hall covered a number of recent and likely future innovations, and we are grateful for the many insights that she conveyed. (A DVD recording of that talk is available from the RCBU office). I can add only a few highlights to Dr. Hall's vision. First, let's look at the environment that contains all of medical imaging and healthcare. Second, let's examine the trajectory of trends in technology that accelerate the utility of medical ultrasound.

Imaging within healthcare: it may not be an overstatement to say that there is an epic four-way struggle underway over the economics of healthcare, including imaging. The payors and patients want cheaper, faster, and better imaging, however, the payors want less of it, and patients generally want more of it. The medical specialties engage in turf battles over who controls imaging and under what circumstances. The imaging manufacturers and innovators want wider dissemination and greater utility for imaging, while researchers continually push the leading edge of clinical applications and novel physics, bioengineering, and biotechnology.

Trends in technology can exacerbate or minimize these difficult conflicts. Ultrasound can benefit the most from Moore's law. Ultrasound does not require permanent installations for superconducting magnets, as does MRI, nor does it require a cyclotron for creation of isotopes as does PET. Therefore, ultrasound has a rapid path towards miniaturization (radiology on a chip!) with all the inherent advantages that Moore's law brings to the demands of cheaper, faster, better. This means that ultrasound imaging can be the most portable and have the widest dissemination at the lowest cost. However, that exacerbates the aforementioned issue of control and turf battles, along with payors reluctance to multiply the billing codes. Beyond Moore's law, ultrasound has benefited from, and will continue to benefit from surprising leaps in our understanding of what is possible. The past has shown revolutions in our understanding of Doppler signals, nonlinear signals, contrast behavior, and elasticity effects; all of which can be exploited in ultrasound systems for increased diagnostic utility. Emerging molecular imaging strategies, 3D, and 4D are examples of the continuing advances that routinely produce "unexpected" leaps in our imaging armamentarium.

The role of the RCBU

Rochester has played a unique and prominent role in the evolution of medical ultrasound, both diagnostic and therapeutic. Many of today's developments—contrast agents and nonlinear techniques—have a scientific history that includes benchmark experiments at the University of Rochester. The 20 years of the RCBU have launched many insights, both clinical and scientific, and have trained a distinguished group of MS, PhD, and MD graduates. The future of the RCBU will likely continue the dynamics of great clinical and scientific collaboration and innovation, but at a greater pace. New "unexpected" leaps in gene transfection, contrast enhancement, cancer diagnosis and treatment, and imaging enhancement and many other areas, await in the RCBU labs, and we look forward to the evolution and promulgation of these innovations yet to come.

A History of Medical Ultrasound at

By Edwin Carstensen, PhD

Introduction

Medical ultrasound had its University of Rochester beginnings in the Department of Radiology in the early 1960s with the pioneering work of **Raymond Gramiak**. It became interdepartmental in the late 1960s with **Frederick Kremkau's** Electrical Engineering Master's thesis. In Gramiak's laboratory, Kremkau demonstrated that the bright echoes that appeared in the heart with the injection of radio-opaque dyes were from bubbles. This, together with independent discoveries by Marvin Ziskin at Temple University, foretold today's routine use of microbubble contrast agents in many aspects of diagnosis.

Edwin Carstensen

By the early 1980s, personnel from sixteen departments of the University were involved in biomedical ultrasound. In 1986, seeing the potential for increased interaction among the approximately 40 active investigators in the University and sister Rochester institutions, **Sidney Shapiro**, Chairman of Electrical Engineering, sponsored the creation of the Rochester Center for Biomedical Ultrasound (RCBU). **Edwin Carstensen** was chosen to be the first director. The RCBU was originally conceived more as a local scientific society than an administrative unit and it has retained that character throughout its first twenty years. In contrast with national meetings, however, in its monthly meetings, investigators described ongoing, incomplete research taking advantage of vigorous criticism and comment from the local membership. **Kevin Parker** became RCBU director in 1990 and holds that position today, together with deanship of the School of Engineering and Applied Science (SEAS). RCBU membership today is close to 70 people.

Diagnostic Ultrasound

Twenty years may seem like yesterday to some of the old timers in the business, but biomedical ultrasound has developed a great deal since the RCBU was created. At that time, Radiology's unit under Gramiak had two commercial machines, one an articulated arm scanner. Only a few years earlier, physicians performed all of the scanning in the Radiology Department. Images were recorded on film and videotape. Rochester Institute of Technology (RIT) had recently inaugurated a sonographer training program and **Eileen Wexler** from that program became Radiology's first clinical ultrasound technician. A quarter of the charter membership of the RCBU was from the Radiology Department.(**Jarle Holen, Neil Johnson, Nina Klionsky, Robert Lerner, Thomas Miller, Sandra Roe, Deborah Rubens, Stanley Weiss,** and **Beverly Wood**).

Early studies of the moving heart with an articulated arm scanner were a challenge. With some effort, Gramiak collected a series of B-mode scans and made a flip-card movie of them to demonstrate the motion of the heart throughout its cycle. When **Robert Waag** arrived in Electrical Engineering in the late 1970s, his collaboration with Gramiak quickly led to a state-of-the-art computer facility to automate and extend cardiac motion studies. That collaboration continued until Gramiak's retirement. Waag's work has included very extensive research on tissue characterization with ultrasound and studies of the effects of phase aberration on image quality caused by tissue inhomogeneities in realistic propagation paths.

Progress in commercially available instruments over the past twenty years has been spectacular. Real-time machines with steered, electronic arrays are now standard. Color Doppler replaced duplex Doppler in finding and tracing vessels and locating areas of stenosis. Coded excitation and compound imaging also improved signal to noise ratio and permitted higher resolution. Similarly, post-processing algorithms such as speckle reduction also improved image signal and diagnostic quality. Greater computer memory permitted acquisition of cineloops, which display motion and also permit acquisition of an image volume in

Robert Waag and Raymond Gramiak

real-time. Patient records are read on workstations, which allow copying and manipulation of images digitally and, in general, reduce examination time for our patients. Today, **Vikram Dogra** heads Radiology's ultrasound unit.

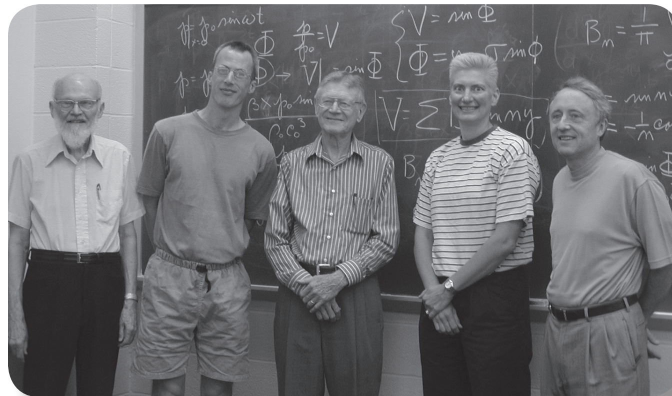
Image Analysis

Image analysis has taken a major step forward because of the collaboration between Parker and his colleagues in Electrical and Computer Engineering (ECE) and the Department of Imaging Sciences (formerly the Radiology Department). Not only are ultrasound data processed to provide 3D images that can be viewed from any angle, but these images can be superimposed upon CT, PET, and MRI images to give unparalleled, quantitative insight to tissue and organ structure. The techniques have such wide-ranging potential that Parker and his former graduate student, **Jose Tamez-Pena**, created VirtualScopics, LLC in 2000 to develop and market software for this function. With more than forty employees, the company has some 40 patents and is now public, with 2005 sales of $3.5 million. Parker's "Blue Noise Mask," which grew out of his ultrasound image processing studies, is now used in a majority of digital printers sold today.

Harmonic Imaging

Harmonic imaging, now commercially available as a technique for reducing clutter and improving resolution of deep targets, has a long history at the University of Rochester. Much of the theory of acoustics assumes that sound propagation is a linear phenomenon. It turns out that, at the frequencies and pressures used in medical diagnosis, ultrasound propagation is highly nonlinear. As a result, a wave emitted as a single frequency has many harmonics in the returned signal. In the early 1960s, when **David Blackstock** was a full-time member of the Department of Electrical Engineering, he developed the first comprehensive, analytical theory of nonlinear sound propagation. In 1980, the first implications of nonlinear propagation for medical ultrasound were demonstrated in a series of collaborations between Blackstock's colleague, Tom Muir, at the University of Texas and Ed Carstensen at the University of Rochester.

In 1987, Parker came up with some angular spectrum-based nonlinear beam modeling ideas and initiated the local modeling efforts. During a meeting with Parker, Blackstock turned to **Ted Christopher** and in a period of about 30 seconds (and 4 sentences) laid out a grid-based picture of how nonlinearity could fit into the beam propagation business. This gave Christopher a picture he could start to work with. Between the persistent efforts at the University to investigate the possible bio-influence of nonlinearity and the efforts to understand the influence of



Ed Carstensen, Ted Christopher, David Blackstock, Diane Dalecki, and Kevin Parker in July 2006

tissue aberration, it appeared that nonlinearity found a productive and safe home in reducing the latter.

During his dissertation research with Parker in the 1990s, Christopher developed a unique, comprehensive computational procedure for the prediction of nonlinear propagation for medical sources, including not only diagnostic transducers but also lithotripters. During that period, he recognized the potential advantages of the use of the harmonics generated in the tissue for imaging and patented the concept. Christopher's third patent on harmonic imaging was issued recently, coinciding with the 20th anniversary of the RCBU and the 40th anniversary of Blackstock's weak shock theory.

For many years, Blackstock has divided his time between the University of Texas in Austin during the academic year and Rochester in the summer. His graduate acoustics course is standard fare for students associated with the RCBU, and during the summer of 2006, he presented the first nonlinear acoustics course at the University. In July 2006, the RCBU celebrated the 40th anniversary of the publication of Blackstock's paper on weak shock theory. (See photo above.)

Sonoelasticity

Robert Lerner received an MD and a Ph.D. in Electrical Engineering, the only combined degree to have come from Rochester's ultrasound program. He joined the Radiology faculty in 1981 and soon carried much of the responsibility for body ultrasound, thus freeing Gramiak to devote more time to heart and vascular examinations and research. At a 1982 radiological society meeting, Lerner and Gramiak introduced endocavitary ultrasound for rectal cancer staging, pelvic lymph node detection, and distal ureteral stone diagnosis.

Among many research projects during his work at the University, Lerner initiated a procedure that has come to be known as sonoelasticity. He found that standard protocols for endocavitary ultrasound of the prostate were less successful in localizing tumors than the urologists' digital rectal examinations, in spite of the fact that only a fraction of the prostate can be probed digitally. It was Lerner's hypothesis that the elastic properties of prostate tumors differed from normal tissue much more than the corresponding ultrasonic parameters. His proposal: perturb the prostate tissue and observe relative tissue movement with ultrasound, thus combining the best of both techniques. The initial proof of concept was carried out with Waag using correlation length of the speckle pattern to measure tissue displacement. Parker then showed that with the application of low frequency vibrations or shear waves, a pre-production quantum color Doppler instrument could provide an ideal detection tool. Mode patterns in the color Doppler images confirmed that the effective tissue distortion was produced by shear waves produced by the low-frequency source. Of course, it is the relatively large shear stiffness, not compressional stiffness of the tumor that is detected digitally. So, sonoelasticity measures a physically different property of inhomogeneous tissues than conventional diagnostic ultrasound, which uses compressional waves. The first public presentation of sonoelasticity as a diagnostic tool came in 1987. The technique is now nearing commercial realization.


Eva Pressman

The basic concept has spawned several related approaches, all designed to detect tissue inhomogeneities based on their shear elastic properties. In Biomedical Engineering, **Stephen McAleavey** probes the tissue with acoustic radiation force and monitors the resultant tissue displacement with very sensitive pulse echo ultrasound. Other techniques are under development in other laboratories throughout the world.


Morton Miller

In October 2006, the fifth annual International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity, sponsored by the RCBU and the University of Texas Health Science Center, will be held in Snowbird, Utah. Researchers from around the globe will make over 120 presentations.

Ob/Gyn Ultrasound

Because of its inherent assumed safety, ultrasound has been the primary imaging modality for obstetrics from its first practical availability. **James Woods** was the primary sonologist in the Obstetrics Department at the University of Rochester from 1986 to 1990. While he continued to scan patients after that, he was joined, in 1990, by **Jacques S. Abramowicz** as Director of Ob/Gyn Ultrasound. The number of machines, sonographers, and scans increased dramatically over the years. Endovaginal ultrasound became routine because of the possibility of using higher frequencies, hence better resolution and more accurate diagnosis of fetal anomalies and pelvic disorders. While ultrasound guided amniocentesis (obtaining amniotic fluid for cell analysis) was routine, invasive fetal procedures (such as cordocentesis (umbilical cord blood sampling or injection) or placement of bladder shunts were initiated. Ultrasound also became widely used in the field of reproductive endocrinology to examine ovaries during ovulation induction or to assist in ovum pick-up for in vitro fertilization.

The use of color and spectral Doppler for analysis of fetal and maternal vascular beds was introduced around 1990 and the department continued to be a major referral center for complicated pregnancies and complex pelvic pathologies. With the addition of a mini-PACS (picture archiving communication system), all images became digitally recorded. In 1997, the Section of Ob/Gyn Ultrasound became accredited by the American Institute of Ultrasound in Medicine (AIUM), the first unit to get such recognition in upstate New York. Besides clinical research and applications, Abramowicz pursued many research efforts in the use of ultrasound contrast agents in placental imaging (with **Richard K. Miller**) as well as bioeffects of ultrasound (with **Morton Miller**). In 2000, **Eva Pressman** became Director of Maternal-Fetal Medicine and Director of Ob/Gyn Ultrasound and continues in that position today.

Cardiology

Although Gramiak's primary clinical research in the Radiology Department was devoted to studies of the heart, it was inevitable that the Cardiology Department would develop its own independent facilities. Navin Nanda was the department's first sonologist. Nanda moved to the University of Alabama and, when the RCBU was formed, the ultrasound unit was headed by **Richard Meltzer.** Other charter members from Cardiology included **Gerson Lichtenberg**, **Michele Nanna**, **Karl Schwarz**, and **Feng Xie**. Meltzer had experimented with the use of microbubbles as contrast agents before coming to Rochester and continued those studies here using "home made" bubble preparations before the contrast industry had produced stable, uniform agents. Schwarz became head of Cardiology's Echocardiography Lab in 1992.

Biophysics and Bioeffects

Like speech, ultrasound is used as a communication tool, sending signals into the body and digesting the information in the returned signals. Unlike speech, the pressures and intensities used in medicine are large enough to produce significant effects in the propagating media. Work in the latter aspect of the subject at the University of Rochester has involved collaboration among the departments of Biochemistry and Biophysics, Biomedical Engineering, Biostatistics, Cardiology, Chemistry, Electrical and Computer Engineering, Genetics, Mechanical Engineering, Microbiology, Obstetrics, Pathology, Pharmacology and Physiology, Vascular Medicine, and Urology.

Charles Linke

Knowledge of the basic acoustic properties of tissues is required for any work in biomedical ultrasound. RCBU personnel have made a number of both fundamental and incremental contributions to the techniques of measuring absorption, attenuation, and scattering of tissues. Parker and his coworkers extended a thermocouple technique for measurement of true absorption of ultrasound (originally introduced by William Fry at the University of Illinois), minimizing the artifact of local viscous heating of the thermocouple. Several independent contributions to problems of measuring attenuation of inhomogeneous tissues have come from RCBU investigators. Errors in many of the published tissue attenuation data were shown to result from phase distortion of the probing signals (Marcus and Carstensen). In principle, radiation force detectors can avoid these difficulties. **Jack Mottley** introduced a qualitatively new absorption measuring technique to solve these problems using an acoustoelectric hydrophone. A significant fraction of Waag's research career has been devoted to evaluation of the impacts of tissue inhomogeneities on diagnostic ultrasound and to acoustic scattering as a way of identifying and evaluating tissue structures.

Nonlinear Absorption

Nonlinear propagation of ultrasound, which generates harmonic frequencies that are useful in diagnostic imaging, gives rise to a form of true absorption (as opposed to simple attenuation) that depends more on the pressure dependence of the sound speed than on linear absorption coefficients of the tissues. As sound propagates away from the source, the positive phase moves faster than the negative phase. If the combination of acoustic pressure and propagation distance is great enough, a shock front forms at the point where the displacement would become double valued. Instead, mechanical energy in the wave is converted into heat by absorption of the high frequencies in the shock wave by the medium. To a first order, however, the loss depends on the properties of the sound wave and only weakly on the linear absorption of the medium. If the medium has a small linear absorption coefficient, higher frequencies are generated in the shock front leading to higher energy loss. Thus, at high intensities, the absorption coefficient of water can be nearly as great as liver.

The effects of nonlinear absorption in a medical setting surfaced first in ultrasonic thermal surgery studies initiated by **Charles Linke** (Urology) in collaboration with Carstensen and co-workers in Electrical Engineering. Investigation of the thermal implications of nonlinear propagation involved members of the same team who eventually applied it to harmonic imaging. In addition, **Diane Dalecki** made a thorough application of Blackstock's weak shock theory to the heating problem. David Bacon's (National Physical Laboratory, UK) study during a summer visit demonstrated striking effects of nonlinear absorption in liver. Christopher's numerical predictions of nonlinear absorption have been used in commercial applications of high intensity focused ultrasound (HIFU) in a variety of medical applications.

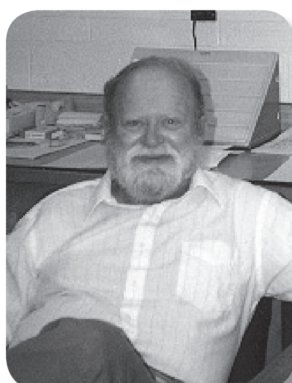
Thermal Studies

Although never carried to the point of clinical application locally, Linke's investigation of ultrasonic thermal surgery demonstrated that localized tissue destruction in the kidney could be performed noninvasively with ultrasound and that the necrotic lesion would be resorbed almost completely over a period of roughly six months. Linke was motivated in these early studies of thermal surgery by a desire to avoid the extensive bleeding that characterizes excision surgery of the kidney. The program was completely successful in that goal.

Hugh Flynn

Morton Miller and his coworkers in Obstetrics confirmed and extended observations that ultrasound at intensities great enough to produce a 3 - 5 °C rise in tissue temperature produced teratological changes in rodent fetuses.

Bioeffects studies at Rochester began in the 1970s with collaborative studies of nonthermal effects of continuous wave ultrasound on the growth of plant roots involving teams headed by Morton Miller in Radiation Biology and Carstensen in Electrical Engineering. The first effect from diagnostically relevant exposure conditions (1980) was a confirmation of a report that pulsed ultrasound killed fruit fly larvae. By 1990, the Electrical Engineering team had demonstrated that mammalian lung was also susceptible to hemorrhage under diagnostically relevant conditions. The bulk of evidence is consistent with a purely mechanical mechanism for lung hemorrhage. Although lung tissue is particularly fragile because of the anatomy of its air containing structures, there is no support for either cavitation or heat as the mechanism for lung hemorrhage. Upon completion of her studies of nonlinear heating, Dalecki, with technical support from **Sally Child** and **Carol Raeman**, assumed primary responsibility for bioeffects studies in ECE and in the newly created Department of Biomedical Engineering (BME).



Eric Schenk

Acoustic Cavitation

Although there are exceptions, acoustic cavitation is involved at a basic level in most of the reported nonthermal biological effects of ultrasound. For this reason, many bioeffects are greatly enhanced through the use of microbubble contrast agents. Whereas diagnostically relevant ultrasound causes negligible hemolysis in normal blood, Morton Miller and **Andrew Brayman** found significant lysis of red cells in vitro and Dalecki in mice when microbubble contrast agents were present. **Claudio Rota** and Dalecki observed a high incidence of premature ventricular contractions (PVCs) and persistent changes in the heart cycle when mice with contrast agents in their blood were exposed to diagnostic ultrasound.

In the early 1990s, Meltzer returned from a cardiology meeting with reports of the use of ultrasound in enzymatic lysis of blood clots. He catalyzed the interaction of teams under **Charles Francis** in Vascular Medicine and Carstensen in ECE, who first confirmed and subsequently extended the investigation of the phenomenon. Although ultrasound alone had negligible effect on clots in vitro, it significantly increased the rate of action of enzymes such as tissue plasminogen activator (tPA). The initial work was performed largely by Páll Önundarson, a post-doctoral investigator from Iceland, and later by Aleš Blinc from Slovenia. Ultrasound appears to increase diffusion of tPA into the clot. Other studies in the Vascular Medicine laboratories showed that ultrasound alone changed the structure of the fibrin in the clot. **Farhan N. Siddiqi** and **Valentina Suchkova** demonstrated that mid-kilohertz frequency ultrasound not only minimized heating that characterized the original megahertz studies but was somewhat more effective in clot lysis for a given intensity. Francis and colleagues have collaborated with other academic and industrial groups in applying their findings to the treatment of ischemic stroke and myocardial infarction.

During studies of clot lysis in rabbits, Suchkova discovered that 40 kHz ultrasound increased perfusion in tissue that had become ischemic. Vasodilation appears to be a purely mechanical action of ultrasound. The effects of heat and cavitation are eliminated in these experiments. Francis and Suchkova have shown that the mechanism of action of ultrasound involves release of nitrous oxide from endothelial cells lining the blood vessels.

Lithotripsy

By the mid 1980s, lithotripsy had obtained FDA approval and quickly gained popularity in the treatment of both kidney stones and gallstones. The Urology Department acquired one of the original Dornier HM-3 lithotripters and their caseload in the late

Sally Child, Edwin Carstensen, Carol Raeman, and Diane Dalecki

1980s was around 700 - 800 per year. Research in Germany, notably that of Michael Delius in Munich, had shown that lithotripsy was not without side effects—hemorrhage in the target organs and lungs and premature contractions of the heart. Although most kidney stones responded to treatment, difficulties in fragmenting gallstones were apparent from the beginning. The RCBU addressed these problems with one of its broadest research teams: **Christopher Cox** (Biostatistics); Blackstock, Carstensen, Child, Christopher, Dalecki, **Carr Everbach**, Raeman, **Hugh Flynn**, and Parker (ECE); **Nimish Vakil** (Gastroenterology); **Asish Basu** (Geology); **Stephen Burns** and **Sheryl Gracewski** (Mechanical Engineering); **David Penney** and **Eric Schenk** (Pathology); and Linke and **Robert Mayer** (Urology). That both cavitation and purely mechanical action of the shock waves are involved in stone destruction was shown through the analytical, numerical, and experimental studies of Gracewski and graduate students Girish Dahake and Zhong Ding.

Dalecki's team reported a threshold for lung hemorrhage with shock waves of approximately 1 MPa in 1990. Subsequently, they showed that although mouse kidneys were only slightly damaged with 60 MPa shock waves from a piezoelectric lithotripter, when the animals were infused with microbubble contrast agents, the kidneys and almost every other organ in the body was hemorrhaged at pressures as low as 1 MPa. The implication, of course, is that cavitation can be highly damaging to tissue but, in addition, one can conclude that the normal mammalian system is remarkably free of cavitation nuclei. Were that not true, lithotripsy would be out of the question. Commercial products such as Albunex® have an effective lifetime as contrast agents of only a few minutes. The RCBU studies demonstrated that small fragments of the agents surviving in the circulating blood for several hours after injection were still very effective nuclei for cavitation. Michael Bailey from the University of Texas, in a summer project in the RCBU, showed that positive and negative shock waves were equally effective in their damage to mouse lung and to fruit fly larvae. Dalecki's group subsequently demonstrated that organs infused with microbubbles were far more susceptible to damage from negative than positive shocks as one would expect from cavitation. This, together with several other experimental investigations in the laboratory was consistent with a purely mechanical model of lung hemorrhage.

Almost all of the bioeffects, which were discovered originally in studies of shock waves, have a corresponding effect with pulsed ultrasound. Among these effects are those noted above for heart function. Among the surprises that occurred during the studies of shock waves was hemorrhage near bones in fetal mice (subsequently observed with pulsed ultrasound). Thresholds for this effect are of the order of 1 MPa!

Audible Frequencies

Studies of biological effects of acoustic fields on lung in the RCBU have now been extended over five decades of frequency and have demonstrated hemorrhage in mouse lung at acoustic pressures as low as 2 kPa at ~300 Hz. The extreme sensitivity can be explained with a model of the lung oscillating at its resonance frequency. The damping of the oscillation is not much greater than would be predicted for a free air bubble in water. The amplitude oscillation of the lung at threshold is only a few one hundredths of the radius. This small strain is great enough to damage the fragile structure of the lung tissue. Since normal breathing amplitude is much greater than this, the dynamics of the excitation, not the strain itself, must be responsible for damage. Completely unexpected, however, is the fact that this small amplitude of motion of the lung surface is enough to produce hemorrhage in the adjacent liver!

In memorium:

Hugh Flynn, 1913 - 1997

Raymond Gramiak, 1924 - 2002

Charles Linke, 1926 - 2002

Eric Schenk, 1927 - 1993

A Look to the Future

Twenty Years of Collaborative Innovation at the RCBU

By Diane Dalecki, Ph.D.

In 1986, Professor Edwin L. Carstensen founded the Rochester Center for Biomedical Ultrasound (RCBU) with the vision of uniting engineers, physicians, clinicians, and basic scientists to advance innovations in the use of ultrasound in medicine and biology. For the past twenty years, that vision has provided a unique foundation for scientific and clinical collaborations among RCBU members. Through this dynamic collaborative environment, RCBU scientists, physicians, and engineers have led advances in the clinical use of ultrasound in diagnostic imaging and therapy, and expanded our fundamental understanding of the interactions of acoustic waves with biological systems.

The RCBU has played a prominent role in clinical and technological advances in diagnostic ultrasound imaging. Nonlinear imaging techniques, novel imaging modalities and clinical imaging techniqes, and the use of microbubble ultrasound contrast agents all have foundations in discoveries and innovations within RCBU laboratories. Sonoelasticity imaging of tissue material parameters (discovered and advanced by RCBU members Kevin Parker, Robert Lerner, and Deborah Rubens) promises to extend the clinical utility of ultrasound in diagnosis. Today, collaborative projects between RCBU clinicians and engineers continue to advance novel scanning techniques, three- and four-dimensional imaging, ultrasound contrast agents, and image fusion techniques. To fuel these new innovations, RCBU laboratories allow students and postdoctoral fellows to work with state-of-the-art diagnostic ultrasound devices, and provide unique opportunities for students to investigate the translation of their research to clinical practices. Furthermore, productive collaborations between RCBU researchers and industry colleagues have been instrumental in forging new discoveries and advances in diagnostic ultrasound imaging.

Ultrasound also now has important applications in noninvasive therapies. Extracorporeal shock wave lithotripsy has dramatically changed the treatment of kidney stone disease. During the early days of lithotripsy, collaborative efforts of RCBU members, spanning physicians in Urology and Gastroenterology, electrical and mechanical engineers, and basic scientists in Pathology, Biostatistics, and Geology, advanced our understanding of shock wave propagation, mechanisms for stone breakage, acoustic cavitation, and bioeffects of lithotripter fields on soft tissues. Now, exciting new therapeutic applications of ultrasound in medicine are on the horizon, including high intensity focused ultrasound (HIFU), gene transfection, drug delivery, clot lysis, and new roles for ultrasound in tissue repair and cell and tissue engineering. Once again, exciting discoveries in these therapeutic applications of ultrasound will be primed through the collaborative teamwork of basic scientists, engineers, and clinicians afforded by the RCBU.

Through the leadership and vision of Founding Director Carstensen, and Directors Parker and Rubens, the first twenty years of the RCBU have provided groundbreaking advances in the use of ultrasound in medicine. As we head to the future, RCBU laboratories will continue to work together to discover and develop exciting new technological innovations in ultrasound imaging and therapy.

Selected Theses and Photos

Many MS and PhD students in the departments of Electrical and Computer Engineering, Mechanical Engineering, and Biomedical Engineering have explored ultrasound in their dissertation research. Listed below are some selected theses.

Frederick Kremkau, "Macromolecular Interaction in the Absorption of Ultrasound in Biological Material."

Leon Frizzell, "Ultrasonic Heating of Tissues."

Eveline Ayme, "Transient Cavitation Induced by High Amplitude Diagnostic Ultrasound."

Ted Christopher, "Modeling Acoustic Field Propagation for Medical Devices."

Diane Dalecki, "Mechanisms of interaction of Ultrasound and Lithotripter Fields with Cardiac and Neural Tissues."

Sung-Rung Huang, "Principles of Sonoelasticy Imaging and its Application in Hard Tumor Detection."

Theresa Tuthill, "Dominant Mechanisms of Ultrasound Tissue Interactions in Liver."

Clarence Reilly, "Finite Amplitude Propagation in Lossless and Absorptive Media."

Zhong Ding, "Numerical Simulation of Gas Cavity Responses to Shock Waves."

Girish Dahake, "Wave Propagation Problems in Solids Subjected to Plane and Radially Diverging Waves Incident in a Liquid: A Numerical and Experimental Approach."

Daniel Phillips, "Simulation of ultrasonic scattering from a fractal model of the liver."

Feng Lin, "Ultrasonic high-resolution and quantitatave imaging."

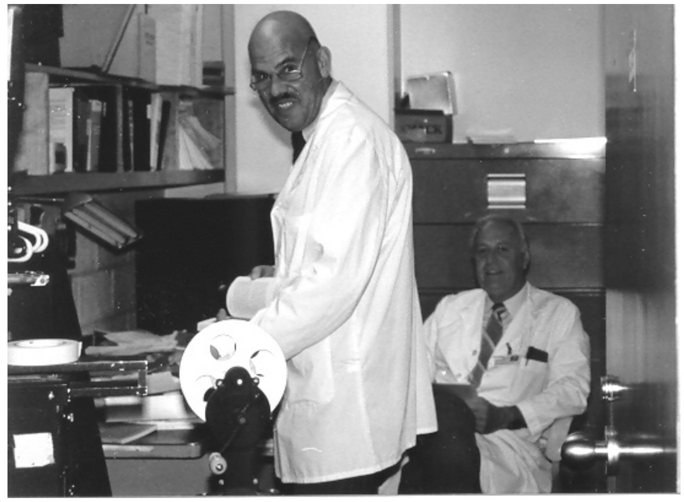
Lawrence Taylor, "Three-Dimensional Sonoelastography: Principles and Practices with Application to Tumor Visualization and Volume Estimation."

Claudio Rota, "Cardiac Arrhythmias Produced by Ultrasound and Contrast Agents."

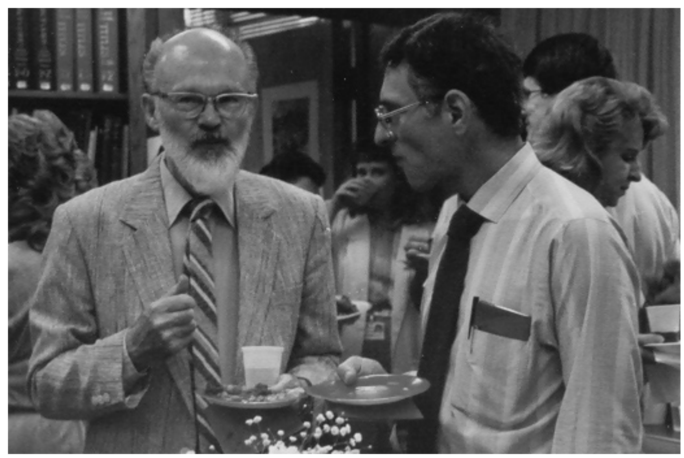
Wayne Pilkington, "Isoplanatic patch size for aberration correction in ultrasonic imaging."

Zhe Wu, "Shear Wave Interferometry and Holography, an Application of Sonoelastography."

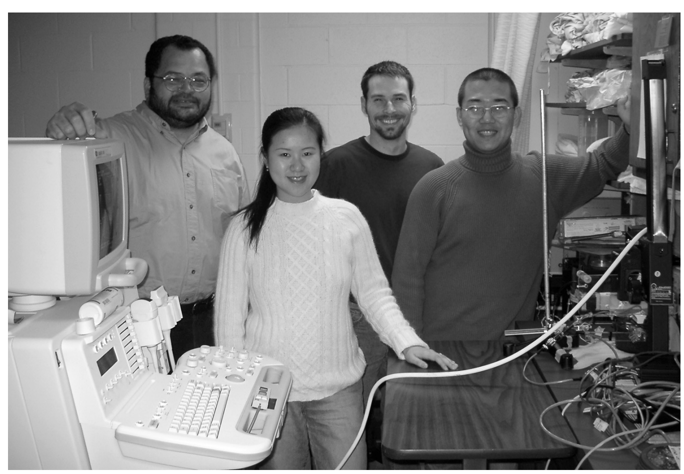
Jonathan Young, "The Relation Between Lung Damage Induced by Acoustic Excitation and the Subharmonic Response of Bubbles."



Jarle Holan and Raymond Gramiak



Edwin Carstensen and Robert Lerner



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