HST connections

A special publication of the Harvard-MIT Division of Health Sciences and Technology

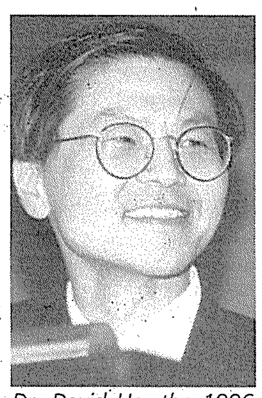
Supplement to *MIT TECH TALK* **June 5, 1998** **Cambridge, MA**

Whitaker College's Division of Health Sciences and Technology Integrates Research and Education Across Science, Engineering, Medicine

David Ho, '78 HST Graduate, is MIT Commencement Speaker

Renowned researcher and 1978 graduate of the Health Sciences and Technology Program, Dr. David Ho will address more than 2,000 graduates and their guests at today's Commencement.

Dr. Ho, TIME magazine's 1996 "*Man of the Year*" is the Scientific Director and Chief Executive Officer of the prestigious Aaron Diamond AIDS Research Center in New York, and Professor at The Rockefeller University. Dr. Ho is widely known for his position at the forefront of AIDS research in this country.



Dr. David Ho, the 1996 TIME magazine "Man of the Year" and a 1978 HST graduate.

Dr. Ho will precede President William J. Clinton, with whom he will share the podium at at today's ceremony. Dr. Ho was invited in February to address all of MIT after MIT President Charles Vest heared his speech at the HST Commencement last year. He graciously agreed to share the honor in April, when Clinton chose MIT as one of only three 1998 Commencement address sites. Clinton is expected to use the opportunity to make a policy statement.

A pioneer in AIDS research, Dr. Ho began his professional career puzzling over a new syndrome that seemed to be affecting gay men.

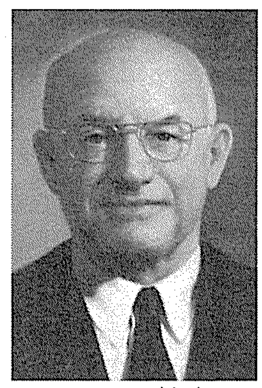
Just two years after his graduation from HST, Ho, chief medical resident at Los Angeles' Cedars Sinai Hospital, joined a very small number of scientists who believed that the strange group of symptoms in these patients was in fact caused by a virus.

By the mid 1980's, he began to question the way in which scientists were looking at the disease. Ho challenged the belief that the HIV virus enters the body and remains dormant, and instead focused on understanding the life cycle of the virus and directed therapeutic strategies at attacking the early stages of infection. This and his subsequent research substantially set today's more successful treatment of AIDS patients.

Dr. Ho's fundamentally different way of thinking about problems is illustrative of the goal of HST's educational programs. Approaches like Ho's are instrumental in achieving advances in medical science.

MIT's Whitaker College Formed While Ho a Student

In 1977, MIT established the Whitaker College of Health Sciences and Technology to provide a major academic and administrative focus for the extensive development of health-related activities at the Institute. The College represents a major commitment by MIT to marshal its resources and strengths to foster progress in the biological and health sciences to improve the quality of health care.



Uncas A. Whitaker

The concept of Whitaker College derives from MIT's belief that biomedical and health-related problems are complex in nature and require the combined efforts of a wide range of disciplines for solution. These disciplines include biology, chemistry, physics, mathematics, various branches of engineering, and computer science. Many faculty members involved in the educational and research programs of Whitaker College hold joint appointments in the College and/or HST and in other Schools, departments, and interdisciplinary laboratories at MIT.

The Whitaker College facility (Building E25) located on the East Campus of MIT was generously supported by Uncas A. Whitaker and AMP Incorporated. Mr. Whitaker was founder and CEO of AMP Incorporated, the world's largest manufacturer of electronic connectors and connecting devices. An inventor, engineer and philanthropist, Whitaker encouraged and supported collaborative medical research involving engineers, scientists and physicians. He and his wife, Helen, also contributed to the Uncas A. and Helen F. Whitaker Building for the Life Sciences at MIT. Whitaker also endowed two Professorships for HST, jointly administered by Harvard and MIT, and created the Health Sciences Fund that supported collaborative research between the faculties of MIT and Harvard Medical School, Boston University School of Medicine, and Tufts University School of Medicine. The Whitaker Foundation, a private nonprofit foundation dedicated to improving human health through the support of biomedical engineering, was established in 1975 upon the death of U.A. Whitaker.

"HST is where my clinical skills were honed, where my scientific interests were solidified, and where I truly learned to tackle research with a multidisciplinary approach not limited by arbitrary boundaries that separate medicine from the physical sciences, engineering, and mathematics. I will forever be indebted to HST."

– Dr. David Ho, HST Graduation Speech, June 1997

Building the Future

Integrated Solutions in Health

HST brings science and engineering to the solution of problems in science, biology and medicine. The Harvard-MIT Division of Health Sciences and Technology (HST) is the longest-functioning collaboration among the Massachusetts Institute of Technology, Harvard University, Harvard Medical School, teaching hospitals, and research centers to develop and conduct educational and research programs across interdisciplinary lines.

Through these relationships, HST trains students for research and leadership roles in medicine, biomedical sciences and biomedical engineering. HST's biomedical engineering and physician scientist training programs are among the largest in the United States, and have established an outstanding track record for advances in human health.

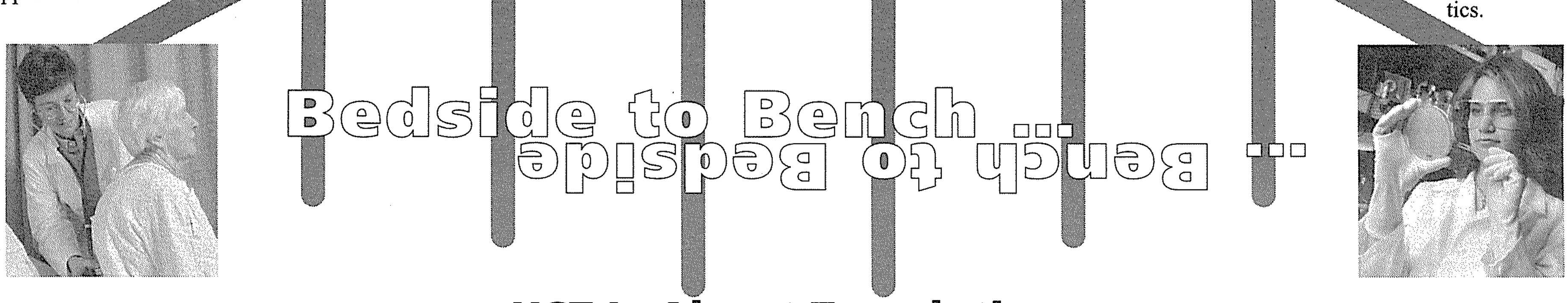
In 1966, MIT was urged by the US government to create a medical school based on its strengths in the natural sciences and engineering. Eleven years later, the HST joint program was launched to "break the mold" of the traditional academic department-centered approach.

Legacy of Leadership

Bridging Disciplines, Technologies

Recognizing that the future requires leaders who can effectively bridge the cultures represented by medicine, science, and engineering, HST accomplishes its mission by providing truly multidisciplinary training in these three areas to both M.D. and Ph.D. candidates. HST trains physicians to have a deep understanding of the underlying quantitative and molecular science of medicine and biomedical research. Ph.D. students merge scientific or engineering training with an in-depth exposure to a foundation of medical courses and hospital care.

HST seeks to explore the fundamental principles underlying diseases, to discover new pharmaceuticals and devices to ameliorate human suffering, and to train the next generation of physicians, scientists, and engineers to do the same. By applying the appropriate tools of medicine, engineering and science, HST integrates patient care and laboratory research in these five areas: Biomedical Engineering/Biological Physics; Medical Sciences and Molecular Medicine; Imaging Science and Technology; Bioinformatics and Medical Informatics; and Experimental Therapeutics.



HST Is About Translation...

Among humankind's greatest achievements are advances in caring for the body and in extending and improving life. On the threshold of a new millennium, we can see that technology's accelerating march will likely yield greater changes for the benefit of the human condition than in any other area.

Technology in itself is but a tool. It's the great minds of a few individuals who explore with the technology, test and retest theories with technology, and reach where none could reach… using this technology.

It is these unique people who can apply the scientific method to their unbounded creativity and curiosity with discipline and training and association with other great minds and institutions – they will change the world like never before.

It's these hard-working, dedicated scholars, scientists, students, and teachers that the Division of Health, Sciences and Technology calls upon to be the "translators," challenging them to take findings in the lab and translate them directly into real therapies. Similarly, it's taking the real world health needs and translating those directly into the most meaningful and focused research possible.

Solving problems in healthcare is the HST mission. HST bridges disciplines and brings together people from all walks of science, engineering, and medicine to find real benefits for human health, to convert discovery into treatment and prevention.

Almost 30 years ago, HST was formed to organize the resources of Harvard and MIT toward this goal. We already have seen the benefits of this joint venture with many prominent graduates and faculty. The students laboring in laboratories right now are the ones we'll be hearing from in the not-too-distant future – our next leaders in biomedical science, biomedical engineering, and translational research!

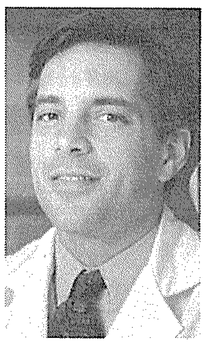
HST Faculty, Alumni and Students Integr

Biomedical Engineering/Biological Physics

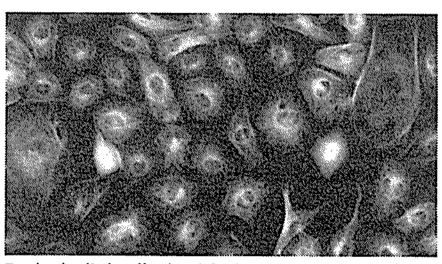
A revolution is happening in the technology of health care driven by remarkable discoveries in molecular and cellular biology. Engineering design principles are being used to measure and model molecular and cellular processes. Biological design principles are being used by engineers to develop new technologies that can be applied to non-living systems.

New instrumentation and signal processing, medical devices, artificial tissues and organs are the basis for unprecedented diagnosis and therapies. A central concept is the fundamental understanding and manipulation of how cells, organs, and the body as an integrated whole respond to their local environment, providing a better understanding of physiology and disease, and alternative therapeutic strategies.

PREVENTING AND CONTROLLING CARDIOVASCULAR DISEASE

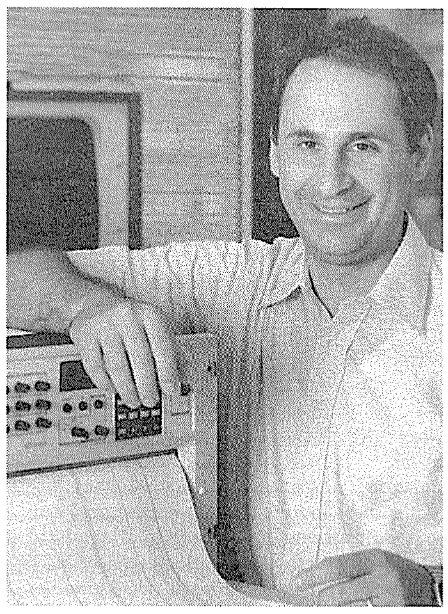


Elazer R. Edelman, M.D., Ph.D., HST '83, uses elements of continuum mechanics, digital signal processing, and polymeric controlled release technology to examine the cellular and molecular mechanisms that transform stable coronary-artery disease to unstable coronary syndromes. Tissue-engineered cells, for example, deliver growth factors and growth inhibitors for the study and potential treatment of accelerated arterial disease following angioplasty and bypass surgery. Edelman is motivated by a tough clinical problem: more than half of blocked blood vessels that are cleared by a procedure called balloon angioplasty become blocked again. His discoveries have lead to patents for endovascular stents, drug-delivery devices, tissue-engineered implants and new drug formulations.



Endothelial cells double-immunostained for F-actin and tubulin. These cells form the critical lining of the blood vessel and their integrity dictates the course of vascular health or disease. The image was produced by Dr. Edward Koo and Professor Elazer R. Edelman in the Harvard-MIT Biomedical Engineering Center.

Frederick J. Schoen, M.D., Ph.D., has made major investigative contributions in identifying, elucidating the mechanisms of, and solving the critical problems associated with the biomaterials and devices used clinically to replace diseased heart valves. His approaches have used basic biology, evaluations of clinical implants that have failed, and industrial developmental studies.



Richard J. Cohen, M.D., Ph.D., HST '76, is studying the electrical and mechanical regulation and stability of the cardiovascular system. Dr. Cohen's laboratory has developed a noninvasive means of identifying individuals at risk for dying of sudden cardiac death – from which 400,000 adults die each year in the US. For those at risk, there is an effective preventive therapy – an implantable cardioverter/defibrillator.

Cohen's group at MIT analyzes tiny, microvolt level fluctuations in the electrocardiogram to identify individuals at risk. However, the pattern is so subtle that it can be detected only with sophisticated computer-based analysis.

The technology developed in Dr. Cohen's laboratory has been licensed by Cambridge Heart, a company founded by Dr. Cohen, that is commercializing this technology for routine clinical use.

LASERS AND MEDICINE

Prof. Michael S. Feld heads the MIT Laser Biomedical Research Center, an NIH Biotechnology Resource Center housed in the MIT Spectroscopy Laboratory, which develops basic scientific understanding, new techniques and technology for advanced biomedical applications of lasers.

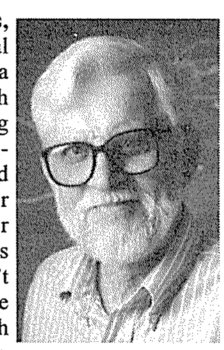
He has developed techniques for biochemical analysis of tissues and blood, and early diagnosis of cancer, atherosclerosis and other diseases. The idea is to introduce a fiber-optic probe or catheter into the body, deliver excitation light, collect spectroscopic signals remotely, and analyze the data outside the body as the test is being done.

One new and exciting result is HST Ph.D. student Vadim Backman's development of a light-scattering technique for detecting early cancer which is not visible to the eye. The first application studied a condition known as Barrett's esophagus, which is very difficult to diagnose.

WHY CATARACTS FORM

George B. Benedek, Ph.D., and colleagues have found the molecular factors that produce lens opacification in cataracts. They have developed instrumentation for the early detection of cataract formation and are developing agents designed to inhibit cataract formation. Also, he and colleagues at MIT and Harvard Medical School have developed methods to assay and control the growth of fibrils of the protein beta amyloid. Plaques made up of these fibrils are believed responsible for neuronal damage in the brains of patients suffering from Alzheimers's disease.

NEW INSIGHTS IN SPEECH AND HEARING



Kenneth N. Stevens, Sc.D., has made several contributions in the area of speech and speech perception, integrating the thinking from linguistics, acoustics, and signal processing. "For linguists," Professor Stevens says, speech is discrete! But that doesn't sit well with what we know of analog speech production." Out of Dr. Stevens laboratory have come the quantal theory of speech production, sophisticated models of sound production by the vocal tract and the pioneering work in speech synthesis and recognition. In recent years, students have driven

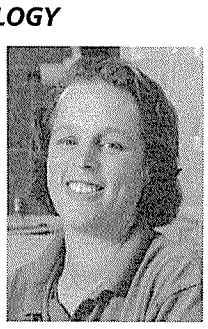
Continued on page four

Imaging Sciences and Technology

Medical and biological imaging have grown explosively during the century since Roentgen's discovery of x-rays. The contribution of imaging technology to medical science promises to be even greater in the next century as imaging expands to demonstrate function as well as anatomy. The advance of structural and functional imaging includes imaging technology for disease, brain function, auditory and speech process, gene expression, and cardiac imaging. Revolutionary research has propelled imaging technology for active treatment planning and monitoring.

HST is launching the Harvard/MIT Imaging Center to house new faculty and their imaging and image processing teaching and research facilities, and to create a critical link devoted to developing imaging technology.

MRI IMAGING TO ASSESS CARTILAGE PHYSIOLOGY



Martha L. Gray, Ph.D. HST '86, co-director of HST, and collaborator **Deborah Burstein, Ph.D., HST '86** use magnetic resonance for measuring composition and functional integrity of cartilage.

Over the last century, clinicians and researchers have had to struggle to understand and treat diseases they couldn't "see" until a lot of cartilage destruction had occured. This situation has the potential to improve dramatically with the method that Gray and Burstein have pioneered.

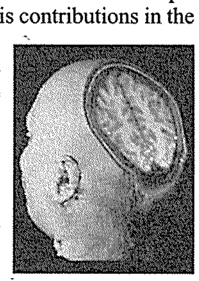
3D VISUALIZATIONS FOR SURGERY

W. Eric L. Grimson, Ph.D., conducted research in computer vision for more than 20 years. He is internationally known for his seminal work in stereo vision, object recognition, formal models of visual processes, image indexing and visual surveillance. His current research interests include applications of computer vision to medical image analysis, especially the topics of image guided surgery, construction of anatomical and functional models of tissue from medical imagery, and surgical simulators.

Grimson and colleagues are developing three-dimensional visualization tools that will give surgeons the equivalent of X-ray vision so they can see inside a patient before the first cut. The tools can help a surgeon tell the exact location of blood vessels and tumors, thus minimizing damage to surrounding structures during surgery. Another application is tracking the growth of tumors and Multiple Sclerosis lesions. One system based on these tools is currently being used at Brigham and Women's Hospital in Boston.

ADVANCING FUNCTIONAL IMAGING

Bruce Rosen, Ph.D., HST '84, Director of the NMR Imaging Center at Mass. General Hospital. He is well known for his contributions in the area of "functional" imaging – that is, magnetic resonance images of the brain in which areas having some functional activity (e.g., visual cortex) are highlighted by receiving increased blood flow.



The techniques Rosen and colleagues have developed are now being used by hospitals throughout the would in evaluating patients with acute stroke, and by neurosurgeons to non-invasively provide a "road map" of the functioning brain prior to surgery. Functional imaging tools are also being used by cognitive scientists and psychiatrists to study normal brain functions such as language and memory, and a host of mental illnesses including Alzheimer's disease, schizophrenia, and drug abuse.

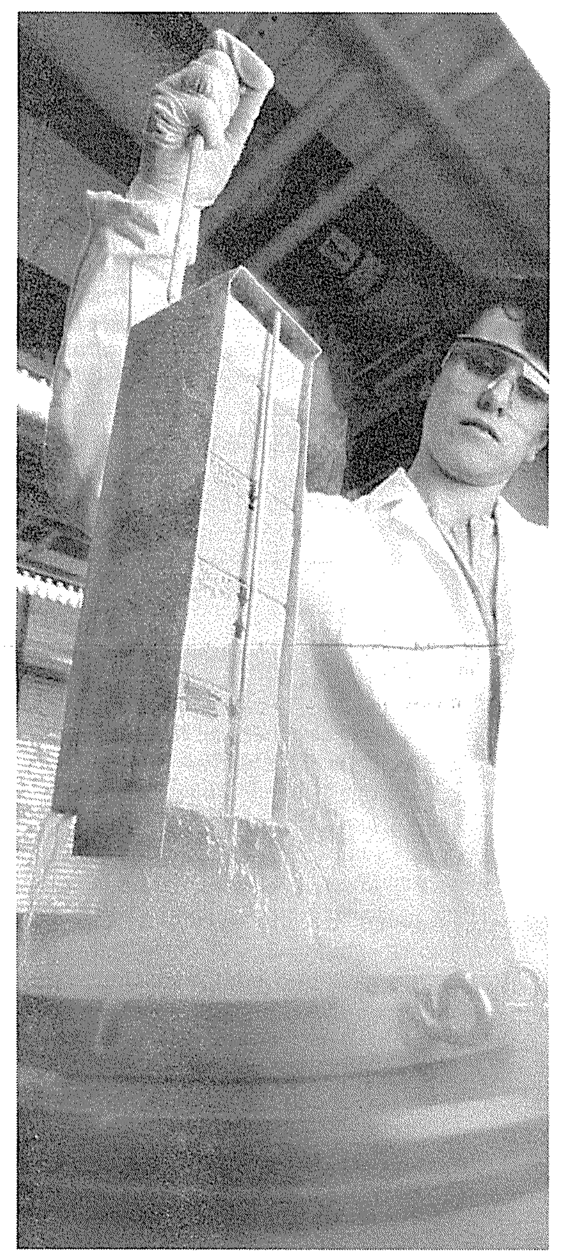
SEEING THE EYE IN A NEW LIGHT

James G. Fujimoto, Ph.D., performs research on laser diagnostic and therapeutic applications in medicine. A central theme of the group's research is the development and application of optical coherence tomography (OCT), a new technique which can take high-resolution cross-sectional images of tissue microstructure. Working with the New England Eye Center, the group is investigating the clinical application of OCT for the diagnosis and monitoring of retinal diseases including macular disease and glaucoma. With MGH, the group is also developing techniques for intraarterial imaging and optical biopsy to diagnose disease. Other research interests include new optical diagnostics, new optical technology in medicine in general, laser-tissue interactions, and laser applications to surgery.

Integrated Res

From its inception, HST has fostered the institutional collaborative research among research of the HST faculty, staff, and st medical areas including: auditory p pathophysiology, epidemiology, and thera tic instrumentation); biological response o chemical and electrical factors; regulatio rus replication and assembly; hyperthe instrumentation; tissue engineering; syst ological signal processing; vascular biolo and fundamental pathophysiology of bon

This research takes place on the Harvard Medical School teaching hospitals in the a sampling of faculty and their research o focus areas.



Integrated Educa

Medical Sciences (MD) Program

The Medical Sciences (MD) program is oriented towards students with a background in the quantitative sciences. In the preclinical curriculum, taught by Harvard and MIT faculty, students are expected to develop some understanding of the scientific and engineering underpinnings of normal and abnormal human physiology and clinical medicine. All students engage in research, which often includes a year of full-time research, and 3+ years of part-time research. Some 30-40% of students ultimately pursue a Ph.D. degree.

Medical Engineering and Medical Physics

The Medical Engineering and Medical Physics (MEMP) Ph.D. program builds on students engineering and physical sciences background. In addition to an engineering or physics curriculum and thesis research, students take preclinical courses with HST-M.D. students, and have hands-on experience in the clinic, learning how to take a history and conduct a physical examination, serving as medical students in a hospital medical unit, and participating in a preceptorship, where they explore in-depth an area of their choice.

Speech and Hearing Sciences Doctoral Program

The Speech and Hearing Sciences Doctoral program is the only program of its type in the country and the only training program funded in this area by NIH. It prepares its students to be leading research scientists who can apply quantitative and biological methods to problems relating to speech and hearing. The highly multidisciplinary character of the program is reflected by the range of research projects undertaken by students and faculty and in the program's core curriculum.

ate Patient Care & Laboratory Research

earch Program

development of interdisciplinary, inter-
; the faculties of MIT and Harvard. The
udents covers a wide spectrum of bio-
hysiology (including therapeutics);
y of atherosclerosis (including diagnos-
f tissue such as cartilage to mechanical,
n of gene expression; gene therapy; vi-
rmia for cancer therapy; biomedical
ems physiology and modeling; physi-
gy and pathophysiology; biomechanics;
e.
 and MIT campuses and at all Harvard
Greater Boston area. Presented here is
rganized according to HST's five main

Medical Sciences and Molecular Medicine

We are living in an incredible age of innovation, particularly as it relates to biology and medicine. The physicians of tomorrow are going to have to be competent with emerging technologies in molecular biology, computer technology, advance imaging technology, to name a few. HST spans the spectrum from basic science research in human health to the application of new technologies to clinical care.

CELLULAR AND TISSUE INJURIES

Joseph V. Bonventre, M.D., Ph.D., HST '76, co-director of HST, studies a group of proteins called phospholipases A_2, to understand their role in kidney failure and stroke. His laboratory wants to understand the factors determining the recovery of the kidney in order to design strategies to enhance and hasten these processes. These goals require multiple experimental approaches. Animal experiments are carried out on normal or genetically altered animals in order to test potential drug treatments or to test the hypothesis that a particular protein is important to the injury or repair process. Gene ablation has been carried out to produce a mutant mouse that does not make a particularly important protein. Since recovery of the kidney recapitulates renal development, the group uses tissue engineering to facilitate regeneration and create support devices which will carry out some of the functions of the kidney for patients with acute and chronic renal disease in need of dialysis.

ANTI-VIRAL RESEARCH

Lee Gehrke, Ph.D., studies the replication and assembly of viruses that use RNA as their genetic material. Key biochemical processes that allow viruses to replicate depend on docking interactions between RNA and protein molecules. Gehrke's laboratory is focused on identifying these docking signals, an effort that will facilitate therapeutic approaches for blocking virus replication and assembly. The research has led to the molecular identification of amino acids and nucleotide sequences that are crucial for forming the RNA-protein interactions; moreover, the work also suggests the shape or conformation of the molecules changes upon binding. Another aspect of Gehrke's work is understanding how viruses are able to gain an advantage over the infected host cell in expressing their own genetic information. Nucleotide signals in a viral messenger RNA have been identified that give the virus a competitive advantage, and the lab is now working to elucidate the detailed mechanism.

MOLECULAR BIOLOGY OF HEMOGLOBIN SYNTHESIS AND HUMAN GENE THERAPY

Irving M. London, M.D., Founding Director of Health Sciences and Technology and Professor of Biology, Emeritus, is studying the regulation of hemoglobin synthesis at both transcriptional and translational levels. His laboratory has discovered and characterized the main enhancer elements that control the transcription of the human ß-globin. In collaboration with Dr. Philippe Leboulch, he is also focusing on novel gene transfer strategies for the gene therapy of human diseases.

LOOKING INTO LEUKEMIA

George Daley, M.D., Ph.D., HST '91, a Whitehead Fellow, is looking into how the bcr/abl gene product stimulates blood cell growth, and has begun work toward a possible new therapy for leukemia. He has made great progress in the search for genes involved in other blood cell disorders.

"Right now, we're tremendously excited about the development of two new systems for identifying genes involved in blood cell proliferation," Daley says.

"Nowhere are the ties between Whitehead science and medical practice more evident than in Dr. George Daley's work on leukemia and blood cell development," says the Whitehead Institute for Biomedical Research's 1998 annual report. He "moves back and forth between the clinical and experimental worlds without the pause for repatriation typical of such interdisciplinary journeys."

DIAGNOSTIC IMAGING

Robert S. Lees, M.D., focuses on atherosclerosis, its causes, prevention, diagnosis and treatment. His broad range of contributions include the design and implementation of an ultrasound system for accurate noninvasive assessment of progression and regression of atherosclerosis, and the discovery of key oligopeptides (short polymers of amino acids which resemble a small portion of a protein) that functioned in a manner analogous to the full length protein and so, when radiolabeled, served as a diagnostic probe visualized by a special imaging procedure. These patented techniques developed in Dr. Lees's laboratory have been successfully incorporated into multiple diagnostic drugs which are in clinical trial for imaging not only cardiovascular disease but also cancer and infection.

TRANSPLANT REJECTION

Richard Mitchell, M.D., Ph.D., researches the mechanisms underlying acute and chronic rejection in solid organ allografts, and more specifically in heart transplants. The work spans from mouse heart transplant models (and all the technical difficulty involved with transplanting hearts half the size of a little fingernail) up to human hearts, and is focused on understanding the specific immunologic mediators that drive the rejection and failure of these allografts. His lab is particularly interested in the mechanisms that induce the process of "chronic vascular rejection" whereby the vessels in transplanted hearts become progressively more occluded until the grafts get starved for blood and die. This is critically important in heart transplantation where "chronic vascular rejection" remains the single most important limitation to long-term survival, this even in an era in which there is terrific immunosuppressive agents that effectively block most short-term rejection. Moreover, the research may have much broader applicability, since the inflammatory mediators that drive the occlusive process in transplanted hearts may also be involved in mediating the vascular wall thickening that characterizes more "typical" atherosclerosis.

Mitchell's lab uses a number of genetically-engineered mice (so-called "knock-out" mice) that are either deficient in particular mediators (called "cytokines") or deficient in the receptors for those cytokines. In collaboration with other members of the HST community (such as Dr. Elazer Edelman), Mitchell has been trying new interventions to prevent the chronic vascular pathology. They have also developed collaborations with a number of pharmaceutical firms (Schering-Plough and Bristol Myers-Squibb) to evaluate new drugs that may reduce the vascular narrowing.

Bioinformatics & Medical Informatics

Knowledge discovery and its dissemination in health care have been deeply influenced by recent advances in computer science and engineering. Medical and Biological Informatics (MBI) is the use of computer technology to extract, transport, and manage information from medical and biological data, and to model and support human decision-making in clinical and biological domains. The field is a scientific and engineering activity which is inherently multidisciplinary. Research challenges include: deducing and mapping genomic structure, predicting structure and function of proteins, representing medical knowledge for modeling diagnostic and prognostic decision-making processes, extracting new information from large clinical and biological datasets, building comprehensive electronic medical records (EMR) and clinical information systems, interfacing monitoring devices and the EMR, assuring privacy and confidentiality in medical transactions, analyzing and manipulating images, recognizing patterns of disease progression, analyzing costs and benefits related to medical use of information technology, computer-aided instruction, and utilizing the Internet for providing education and health care services.

TECHNOLOGY FOR HEALTHCARE

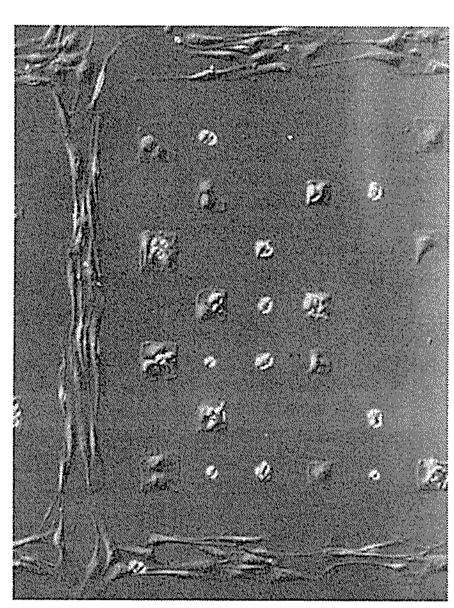
Robert Greenes, M.D., Ph.D., Director of the Medical Informatics Training Program, established the Decision Systems Group (DSG) in 1978, to pursue methodologies for physician education and decision support. Dr. Greenes has had a 34-year history of work in the area of medical informatics.

The DSG lab includes physicians, computer scientists, database experts, graphics and multimedia specialists, with primary focus on development of means for enhancing decision support and education in medicine, and for integrating these capabilities into clinical practice. For the past ten years, emphasis has been on the development of component-based approaches to implementing applications that provide a framework for integration of diverse information resources in a cohesive manner.

MEDICAL DECISION-MAKING

Peter Szolovits, Ph.D., and colleagues study the intellectual processes in medical decision making and build systems that help improve them. One example is Guardian Angel, a lifelong personal health-information system which, among other things, collects all health-relevant information about its subject, communicates with health-care providers, payers, etc., and helps the patient manage ongoing medical problems. He is also developing a World Wide Web-based electronic medical-record system that permits sharing of clinical information among health-care providers while assuring confidentiality of patient data. Another tool in development, Geninfer, computes the risk of genetic disorders based on analysis of an individual's pedigree and results of genetic tests. Geninfer is to be used by genetic counselors. Szolovits is also developing and testing a program that diagnoses and evaluates possible therapeutic interventions in heart disease.

Lucila Ohno-Machado, M.D., Ph.D., investigates machine learning techniques to extract information from clinical databases, especially in the form of predictive models for prognosis. She has used special methods to predict survival for patients with AIDS, to assess the probability of myocardial infarction in certain populations, to predict ambulation for patients with specific kinds of spinal cord injuries, and to predict outcomes in other clinical domains. Her research is focused on the development and evaluation of models involving binary outcomes. She is also interested in deploying practical models for direct use by patients, physicians, and health care managers, so that they can make more informed decisions. An example in this area is a project that uses artificial intelligence techniques for dealing with uncertainty to select suitable clinical trials for patients with certain types of breast cancer.



Modulation of growth and apoptosis (programmed cell death) are essential to tissue structure. The balance between growth and apoptosis is regulated by soluble growth factors and extracellular matrix (ECM). Combining microfabrication technologies with surface chemistry engineering, HST student Christopher S. Chen developed surfaces micropatterned with regions of ECM surrounded by nonadhesive regions, thus controlling the geometry presented to cells. Chen discovered that ECM regulates a transition from growth to quiescence to apoptosis. This micropatterning technology may be useful for a range of applications in biotechnology, including automated single cell analysis, drug screening, toxicology, and tissue engineering.

tional Programs

Radiological Sciences Joint Program

The Radiological Sciences Joint
ogram is a joint doctoral pro-
am with MIT's Nuclear
ngineering Department. These
udents complete a doctoral pro-
am within the Nuclear
ngineering Department, but
ve in addition, a focused clini-
l experience comprised of three
sic biomedical courses and a
e-month clinical practicum.
e research and education of ra-
ological sciences students
pically revolve around radiation
erapy or imaging (including
agnetic resonance imaging,
mputer-aided tomography,
sitron emission tomography,
d single photon emission to-
ography).

Medical Informatics Program

The Medical Informatics program provides graduate and postgraduate research training opportunities in three primary areas of study: informatics as related to health and health care delivery (e.g., clinical information structures, decision making, etc.); biomedical science (modeling and simulation, data banks, etc.); and imaging (e.g., acquisition, processing, correlative imaging, etc.)

Clinical Investigator Training Program

The Clinical Investigator Training program trains post-doctoral physicians from a variety of clinical disciplines in the techniques and processes used in patient-oriented research. The curriculum allows trainees to develop expertise in clinical investigation while they take courses in computational and statistical sciences, biomedical ethics, principles of clinical pharmacology, in vitro and in vivo measurement techniques, and aspects of the drug development process. This four-year-old program is funded by an unrestricted grant from Pfizer, Inc.

HST Connections

JUNE 5, 1998

This special graduation edition of *HST Connections* was produced by the Harvard-MIT Division of Health Sciences and Technology for the MIT commencement exercises.

For more information on HST, please see our World Wide Web site at:

www.harvard-mit-hst.org

or write to the division at: MIT E25-519; Cambridge, MA 02139; or call (617) 258-8759.

Our thanks to the *Tech Talk* staff and many others who helped in the writing, design and production of this special section.

Congratulations to all the 1998 graduates of MIT, HST, HMS, and their families.

Experimental Diagnostics/Therapeutics

One of the most visible and obvious arenas in which the bench-to-bedside transfer is a two-way bridge is with regard to therapeutics. Drugs and therapies not only may treat disease by serving as probes, they can provide important insights into disease mechanisms and offer diagnostic opportunities. Most faculty in HST are involved at some point in clinical human studies. The support of a clinical research center at MIT and the teaching hospitals, and the recently launched Clinical Investigator Training program have significantly enhanced the infrastructure, further enabling translational efforts.

AWAKENING THE STUDY OF INSOMNIA

It's well recognized now that melatonin, the hormone secreted by the pineal gland, has the important role of telling us when to fall asleep, and helping us to remain asleep. This recognition, as well as the knowledge that giving people low doses of melatonin can be used to treat insomnia, have their origins in research done during the past two decades by **Richard Wurtman, M.D.** and his associates.

Wurtman showed that melatonin is a true hormone, that it is normally produced at night, and that the reason for this daily rhythm is that environmental light, acting via the eyes, inhibits melatonin synthesis. Wurtman's studies in HST's MIT Clinical Research Center showed humans, like animal subjects, also produce the hormone at night, but not during the day. Moreover, in humans, night-time melatonin production was found to decrease markedly with age.

Wurtman suspected that the night-time rise in blood melatonin levels might allow it to serve as a time signal to the brain. He and his associates showed that if young people received tiny doses of the hormone in daytime – when blood melatonin levels are very low – they became sleepy and often fell asleep. Sleep thus produced is normal, electroencephalographically. And the effect of the melatonin in producing sleep is independent of its ability to shift rhythm.

Older people often complain of insomnia, particularly having difficulty in staying asleep, and in falling back to sleep after they awaken at night. Doses of melatonin which give them "youthful" blood melatonin levels correct this insomnia.

LASERS AND TISSUE

John A. Parrish, M.D., developed a novel treatment of psoriasis (oral psoralen photochemotherapy, or PUVA) which is now used worldwide. His research group at MGH introduced laser lithotripsy of kidney stones, selective laser therapy of vascular birthmarks and lesions, and novel laser-based diagnosis and treatments of selective cardiovascular disorders and malignancies. Dr. Parrish has more than 300 publications, many of which describe new treatments and diagnostics. He has written eight books, most of which are textbooks, but include a book on baseball, a book on the Vietnam War, and a book on skin for the layperson.

Dr. Parrish organized the first, and now the world's largest, multidisciplinary research group to systematically study the basic nature of laser effects on tissue, the Wellman Laboratories of Photomedicine at MGH of which he is Director. Dr. Parrish is also Director of the MGH-Harvard Cutaneous Biology Research Center (CBRC), a research center committed to fundamental research in cutaneous biology as broadly defined. Dr. Parrish is also Director of Partners-MIT-Draper Center for Innovative Minimally Invasive Therapy (CIMIT), a multidisciplinary research and clinical effort to introduce new therapeutic and diagnostic procedures to improve health care.

PREVENTING TRANSPLANT INFECTIONS, REJECTION

Robert H. Rubin, M.D., has spent much of his clinical career studying and caring for transplant patients. Among his accomplishments are the development of new strategies for preventing the most important infections, particularly those due to viruses and fungi; the establishment of the link between certain viral infections and allograft injury and the development of certain malignancies; and the development of novel antimicrobial approaches that are effective not only in transplant patients, but also in such other immunocompromised patient populations as those with AIDS and cancer.

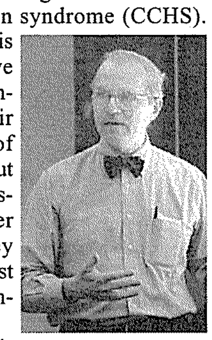
As director of the HST Center for Experimental Pharmacology and Therapeutics, Dr. Rubin has pioneered in the application of positron emission tomography, magnetic resonance imaging and spectroscopy and other measurement technologies to the development of new drugs, including those designed for the transplant patient.

With **Alan C. Moses, M.D.**, Dr. Rubin heads a two-year Clinical Investigator Training Program, a joint effort of the Beth Israel Deaconess Hospital, HST, and Pfizer, Inc. Trainees gain direct experience in clinical investigation and a strong foundation in the statistical and computational sciences, biomedical ethics, principles of clinical pharmacology, in vitro and in vivo measurement techniques, and aspects of the drug development process.

SAVING CHILDREN WITH RESPIRATORY PROBLEMS

Daniel Shannon, M.D., Chairman of the HST M.D. Admissions Committee, an admired original member of the Division, designed HST's first respiratory physiology course, and is a founder of the field of pediatric intensive care and pulmonology.

For more than two decades, Dr. Shannon has been furthering his breakthrough studies into the rare condition of congenital central hypoventilation syndrome (CCHS). Shannon and his colleagues have added incrementally to their framework of knowledge about the problem, using whatever new tool they could find to test specific hypotheses.

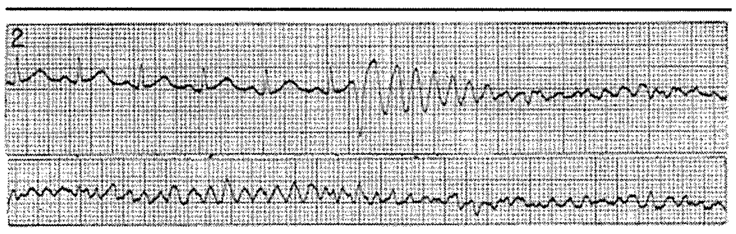


Still, the clinical problems – like a child's failure to breathe adequately when asleep – continue to stump clinicians and researchers alike. Shannon's latest research reflects his concern to use technology in the service of patients. He explains: "Applications of new technology are not without risk. Imaging techniques can uncover astounding, previously invisible, details. How do we see this detail without losing our focus on the patient? The more time spent with technology, the less spent with the patient."

DRUG DELIVERY

Robert S. Langer, Jr. Sc.D., a pioneer in biomedical and chemical engineering, is studying new ways to deliver drugs, including a skin patch/ultrasound treatment that allows large-molecule biotechnology drugs such as gamma-interferon (an immune system booster for cancer patients) and (erythropoetin (for severe anemia) to be absorbed easily into the body through the skin. Langer is also researching tissue engineering. He has developed biomaterials for medicine, including plastic that slowly dissolves and releases therapeutic drugs directly to tumors.

In 1996, this led to the first new treatment for brain cancer approved by the FDA in more than 20 years. The only active member of all three U.S. National Academies - sciences, engineering, and medicine - Prof. Langer was selected as the winner of the $500,000 Lemelson-MIT Prize for 1998, the world's largest cash prize for American invention and innovation.



This EKG from Professor Mark's lab illustrates cardiac fibrillation.

Biomedical Engineering & Biological Physics

Continued from page two

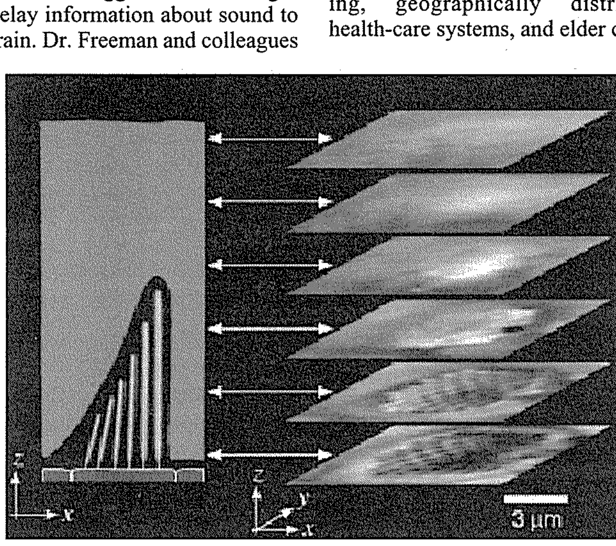
an increased effort in understanding and remediating disordered speech.

Dennis M. Freeman, Ph.D., focuses on hearing – the process of receiving and translating the sounds of speech, etc.

Via a bundle of microscopic hairs, sensory cells in the inner ear sense sound-induced motions of inner-ear structures and trigger neural messages that relay information about sound to the brain. Dr. Freeman and colleagues have devised video methods to measure the submicrometer motion of these sensory cells, which show for the first time how the microscopic hairs move in relation to other inner-ear structures. The studies should lead to a better understanding of our incredibly sensitive sense of hearing.

INTELLIGENT PATIENT MONITORING

Roger G. Mark, M.D., Ph.D., is devising intelligent patient monitoring systems. He also analyzes cardiac arrhythmias, or the rhythmic disturbances in the heartbeat often associated with heart ailments such as coronary heart disease. Other studies include physiological signal processing, geographically distributed health-care systems, and elder care.



The left part of this slide shows a schematic drawing of the bundle of microscopic sensory hairs that project from a single sensory cell into the overlying tectorial membrane. The right panels show video images from different planes of section that have been stacked up to produce a 3D image of the hair bundle. Stroboscopic illumination was used to create a slow-motion video of the motions that result when the ear "hears" a 513Hz tone.

HST 1998 GRADUATES

Graduates are listed by degree with their home town and thesis title.

Ph.D., Biological Engineering

James L. McGrath, B.S.E., S.M., S.M.T.P.
Mesa, Arizona
"Actin Dynamics in the Cell Cytoplasm and the Role of Actin Associated Proteins."

M.D., Medicine

Christiana G. Bardon, B.S.
Claremont, California
"The Role of CIS-Acting Elements in Regulating Accessibility of TCR α/δ Locus."

David Chen, B.A.
Pine Brook, New Jersey
"The Effect of Nitric Oxide Modulation During Ischemia on Functional Recovery of the Rabbit Retina."

Steven Chen, B.A.
Pine Brook, New Jersey
"The Role of Flap Endonuclease 1 (Fen1), Proliferating Cell Nuclear Antigen (PCNA), and p21$^{Cip1/Wat1}$ in DNA Replication and Repair."

George C. Cheng, A.B., S.B., S.M., Ph.D.
Rolla, Missouri
"Regulation of Vascular Smooth Muscle Cell Function by Mechanical Strain."

Harvey A. Greisman, A.B., Ph.D.
Brooklyn, New York
"A Strategy for Selecting Zinc Finger Proteins for Desired DNA Sequences."

Michael R. Hee, B.S., S.M., Ph.D.
Calabasas, California
"Optical Coherence Tomography of the Eye."

Erling Ho, S.B.
West Bloomfield, Michigan
"Syndecan-1 Null Mice Exhibit Defective Skin Wound Healing Due in part to an Abnormal Keratinocyte Phenotype."

Edwin K. Joe, A.B.
New City, New York
"Regulation of Cardiac Myocyte Cyclic Nucleotide Levels and Contractile Function by inducible Nitric Oxide Synthase (iNOS): Methods of Contractile Depression by Nitric Oxide."

John R. Keltner, B.S., Ph.D.
Davis, California
"PRESS Single Voxel Proton Nuclear Magnetic Resonance Spectral Editing for the Detection of Human Brain GABA and Rat Brain GABA, Glucose and Lactate."

Harish S. Lecamwasam, B.S., S.M.
Battaramulla, Sri Lanka
"An Analysis of Detrusor Dynamics and Urethral Flow in the Canine Urinary Tract, under Obstructive and Non-Obstructive Conditions."

Karen L. Lee, S.B., S.B.
Lexington, Massachusetts
"The Phosphorylation of Thyroid Hormone Receptor Trβ-1 by Protein Kinase A."

Chiang J. Li, B.S., M.S.
West Roxbury, Massachusetts
"From Cell Cycle/Apoptosis to Human Diseases: T Cell Pathology in HIV Infection."

Vamsi K. Mootha, B.S.
Beaumont, Texas
"Regulatory Control in Mitochondrial Energetics."

Claribel G. Paguio, S.B., S.M.
San Francisco, California
"Derivation and Characterization of Swine Bone Marrow Stromal Cell Lines."

Rinaa S. Punglia, B.S., M.S.
Moraga, California
"Regulation of Vascular Endothelial Growth Factor Expression by Insulin-Like Growth Factor-1."

Joseph T. Rabban, III, Sc.B.
Bakersfield, California
"Clinical Efficacy of Surveillance Lower Extremity Venous Ultrasound for Prevention of Post-Traumatic Venous Thromboembolism."

Steven L. Stephanides, B.S., B.S., S.M.
Laguna Hills, California
"A Closed-Loop Fuzzy Controller for the Control of Oxygenation in Mechanically Ventilated Patients."

Marta K. Taylor, B.A.
North Hollywood, California
"IFN- and IL-4-Secreting Helper T-Lymphocyte Populations in Acutely Rejecting Murine Cardiac Allographs: Assessment by a Novel Intracellular Cytokine Staining Technique."

Conrad Wang, B.S.
Iowa City, Iowa
"Densitometric and Mechanical Testing in an Animal Model of Tumor-induced Osteolysis in Long Bones."

Thomas D. Wang, B.S., S.M., Ph.D.
Los Alamitos, California
"Fluorescence Endoscopic Imaging System for Detection of Colonic Adenomas."

Jun Wu, B.S., Ph.D.
Beijing, China
"Photon Migration in Turbid Media: Time-Resolved Optical Imaging in Tissue-Like Phantom."

M.D., Ph.D., Medicine

Sanjay K. Aggarwal, B.S.
Cincinnati, Ohio
"Analysis of the Voltage Sensor in the Voltage-Activated Potassium Channel."

Zoltan P. Arany, B.A.
Export, Pennsylvania
"E1A Oncoprotein-Targeted Transcriptional Activators."

Erik B. Finger, B.S.
Livermore, California
"Role of Leukocyte Microvilli in Selectin-mediated Adhesion to Endothelium."

Robert K. Hurford, Jr., A.B.
St. Louis, Missouri
"Analysis of E2F Activity in Primary Cells Deficient for pRB Family Member Proteins."

John S. Kuo, A.B.
Whitestone, New York and Kaosiung, Taiwan
"Early Steps in Xenopus Neural Determination: Cloning and Analysis of OPL."

Mathai Mammen, B.S.
Hartsdale, New York
"Contributions of Entropy and Electrostatics to Molecular Recognition."

Cindy C. Wang, B.S.
Norfolk, Virginia
"Molecular Analysis of the Mouse formin Gene."

Ph.D., Medical Engineering and Medical Physics

Paul A. Belk, S.B., S.B.E.E.
Belmont, Massachusetts
"Electrical Modeling of Myocardium and Development of Advanced Pacing Techniques."

Brian J. Benda, B.S., M.S.
Highland, Indiana
"Neural Correlates of Motor Learning/Memory in Primary Motor Cortex of Macaque Monkey."

Stephen A. Boppart, B.S., M.S.
Gibson City, Illinois
"Surgical Diagnostics, Guidance, and Intervention Using Optical Coherence Tomography."

Nada N. Boustany, S.B., S.M.
Beirut, Lebanon
"Characterization of Mucosal Dysplasia with Ultraviolet Resonance Raman Spectroscopy."

Howard A. Breinan, B.S., M.S.
Glastonbury, Connecticut
"Development of a Collagen-Glycosaminoglycan Analog of Extracellular Matrix to Facilitate Articular Cartilage Regeneration."

Timothy L. Davis, B.S., S.M., E.Eng., M.D.
Kokomo, Indiana
"Cerebral Hemodynamics and Oxidative Metabolism Dynamics Observed by Calibration of Functional MRI."

Hong-Kwang J. Kuo, S.B., S.B., S.M.
Flushing, New York
"Voice Source Modeling and Analysis of Speakers with Vocal-Fold Nodules."

Thomas J. Mullen, B.S., S.M.
Belmont, Massachusetts
"A System Identification Approach to Characterizing Intermediate Term Hemodynamic Variability."

Robert F. Padera, B.S.
Libertyville, Illinois
"Mass Transport in Implantable Medical Devices."

S.M., Medical Informatics

John D. Halamka, M.D.
Wellesley, Massachusetts
"Sharing Electronic Patient Records among Providers via the World Wide Web."

Ph.D., Radiological Sciences Joint Program

Li Zhang, B.S., S.M.E.E.
Beijing, China
"Near Field Three-Dimensional Coded Aperture Techniques: Theoretical and Experimental Exploration for Applications in Imaging and Detection Systems."

Ph.D., Speech & Hearing Sciences

Konstantina M. Stankovic, S.B., S.B.
Zagreb, Croatia
"Efferent Effects on Auditory-Nerve Responses to Tones: Substantial Inhibition Even at High Sound Levels and Tail Frequencies."

Thomas M. Talavage, B.S., M.S.
Lafayette, Indiana
"Functional Magnetic Resonance Imaging of the Frequency Organization of Human Auditory Cortex."

Susan E. Voss, B.S., S.M.
Somerville, MA
"Effects of Tympanic-Membrane Perforations on Middle-Ear Sound Transmission: Measurements, Mechanisms, and Models."