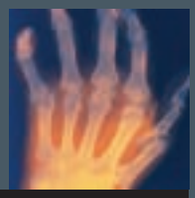
CASE

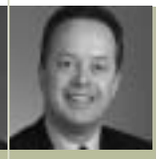
CASE WESTERN RESERVE UNIVERSITY

The Value of Research

2006 + 07



Case Western Reserve University is among the nation's leading research institutions. Founded in 1826 and shaped by the unique merger of the Case Institute of Technology and Western Reserve University, Case is distinguished by its strengths in education, research, service, and experiential learning.



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The Value of Research

The purpose of this book, now in its fourth edition, remains true to its original intent: to make tangible the scope and importance of the research taking place at Case Western Reserve University. Each year, the selection process to identify noteworthy research efforts is an inspiring exercise that brings into focus the remarkable accomplishments that take place on our campus.

Research success is often measured by final outcomes—a cure for a disease, an improved justice system, effective foster care reform, or technological advances that result in life-enhancing products. While you will read about many such achievements on the following pages, it is important to acknowledge that research is a process that is cumulative by nature; it does not always offer immediate applications. Because research universities are uniquely positioned to support this "pursuit of possibilities," they have been essential to the progress of humankind throughout history.

We commend the individuals who bring not only talent and creativity, but passion and vision to their disciplines. The many contributions being made by Case faculty—together with the outstanding teams they have formed across our campus, the community, and the world—are achieved while fulfilling the inherent obligation to train the next generation of researchers. Under the direction of Dr. Anne Hiltner, for example, an extraordinary grant from the National Science Foundation to create the Science and Technology Center for Layered Polymeric Systems will not only put Case at the forefront of this exciting new field of interdisciplinary macromolecular science and engineering, but will create innovative pre-college outreach programs for students in the Cleveland Municipal School District, and will strive to attract minority college students and prospective scientists who are underrepresented in the field.

From training today's Shakespearean actors to addressing the needs of the increasingly aging population; from bringing together the very best resources and minds for advancing the potential of stem cells to dealing with the intersection of religion and terrorism; from getting ever closer to a cure for colon cancer to improving the way we learn—this is but a sampling of the world-changing work that takes place at Case Western Reserve University every day.

We hope you enjoy reading about our contributions and we invite your support.

Human Life + Health

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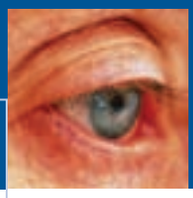


MEDICINE

6 Developing a Minimal Model for the Most Complicated Cellular Machine
7 A Weaker Subtype of HIV Results in Greater Proliferation of the Disease
8 Developing Stem Cell Therapies for Difficult-to-Treat Diseases
9 Age-Related Macular Degeneration: Closing the Door on Blindness
10 Defining the Links Between Inflammation and Cancer
11 New Uses for "Old Drugs": Targeting Brain Cell Inflammation in Alzheimer's Disease Patients
12 Identifying Genes That Are Key Targets for Mutation in Colon Cancer
13 Harnessing Genomic Information and Entering the Era of Personalized Medicine

NURSING

14 Helping a Vulnerable Patient Population: Adults Who Fail to Thrive
15 Improving Healing Rates in Chronic Wound Care

DENTAL MEDICINE

16 Linking Rheumatoid Arthritis and Periodontal Disease: Enhancing the Ability to Treat Both
17 Congenital Missing Teeth: A Complex Condition Requiring Lifelong Care

Society + Community

18

LAW

20 Arbitration: A Necessary Alternative in an Increasingly Litigious and Complex World
21 DNA Evidence: Changing the Dynamics of the Criminal Justice System
22 No Tax Refund for Fraudulently Inflated Corporate Income: Protecting Ohio's School Districts

DENTAL MEDICINE

23 Improving the Oral Health of Residents in Long-term Care Facilities

NURSING

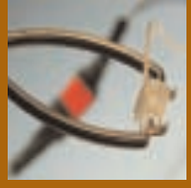
24 Improving Home Health Care: The Epidemic of Chronic Disease and an Aging Population

APPLIED SOCIAL SCIENCES

25 Engaging Families and Communities in the Care and Protection of Children

ARTS + SCIENCES

26 Religion, Terrorism, and the Law: Bringing New Understanding to a Critical World Issue
27 Preserving Tibetan Voices and Revising Modern Tibetan History



Technology + Innovation 28

ARTS + SCIENCES

30 Dancing Fluids in Magnetically-Controlled Gravity
31 Novel Technique Uses Data Mining to Prevent Pressure Ulcers
32 Understanding Cholesterol: How It Leads to Disease

MEDICINE

33 Connecting with the Nervous System: Integrating Engineered Devices into the Human Body

ENGINEERING

34 Bulk Metallic Glass: A Wonder Material with Many Potential Applications
35 Exercise, Diet, and Disease: Relationships Between Cellular Metabolism and Physiological Responses
36 Non-Invasive Imaging: Making Diagnoses at Cellular and Molecular Levels
37 Revolutionizing Medical Education through Virtual Reality
38 The Diamond Advantage in Implantable Biomedical Devices
39 Creating the Next Generation of Nanolayered Polymers
40 Biomimetic Materials: The New Building Blocks of Health

MANAGEMENT

41 Taking Risks While Avoiding the Risk of Failure: How Companies Profit

Mind + Spirit 48

APPLIED SOCIAL SCIENCES

44 Testing the Intelligence of Older Adults: Vision Linked to Cognitive Competence

MANAGEMENT

45 How We Learn: Using Experiential Learning Theory to Improve Higher Education

NURSING

46 Caring for the Caregivers: An Important Network for Improving the Lives of Older Adults

ARTS + SCIENCES

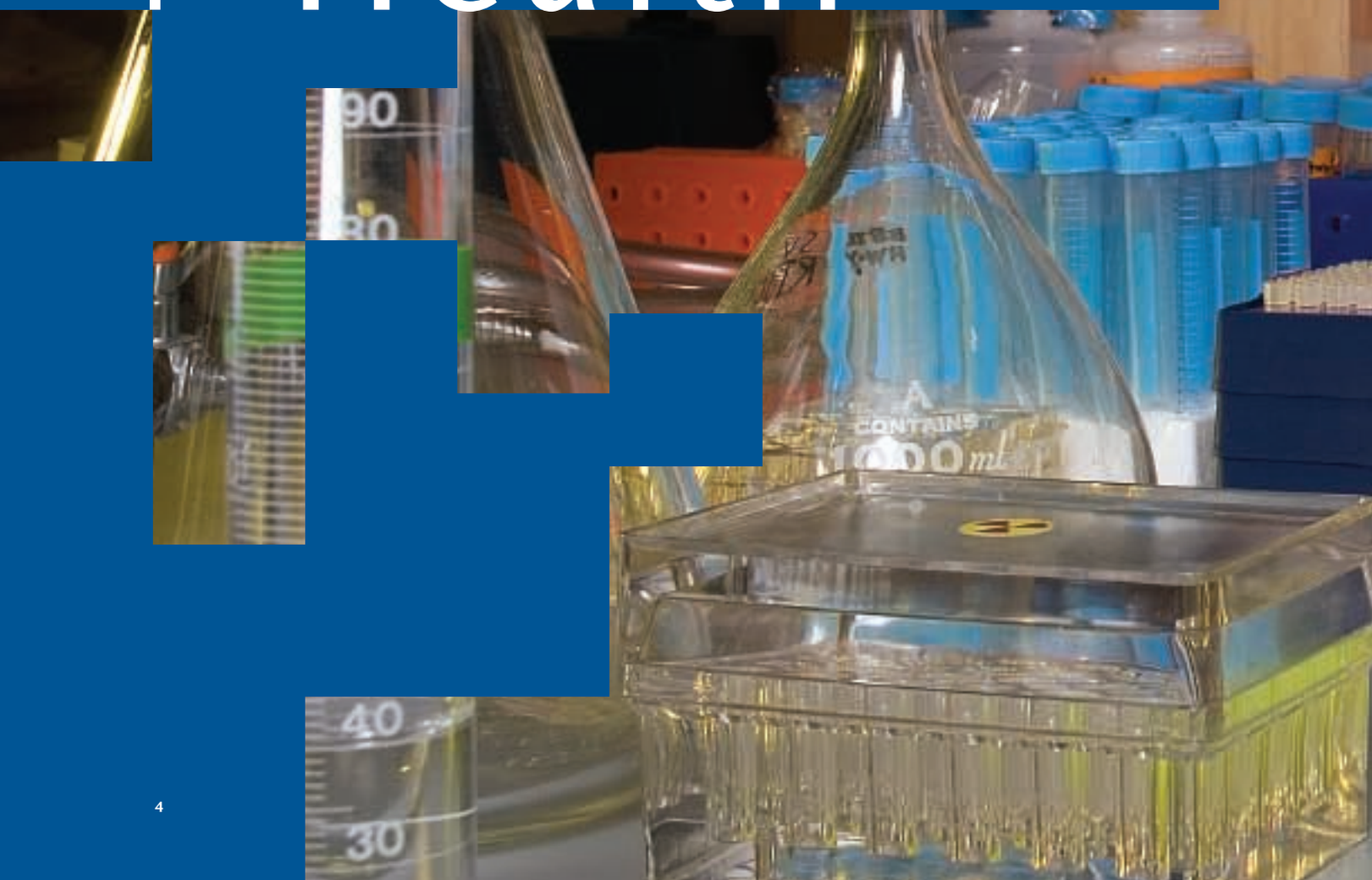
47 Much Ado About Language: Shakespeare's Words Written to Be Performed

49 Student Research
54 Selected Research Highlights
57 Research Fact + Figures
58 Case at a Glance

"The underlying cause of an astonishingly wide range of human disease is a small mistake in the process called splicing that enables the data stored in our genes to be used. Our research has opened the door to the inner workings of one of the most crucial molecular machines in the cell, allowing us to begin to understand the mechanisms of these disease-causing splicing mistakes."

SABA VALADKHAN

Human Life + Health



Medicine

Developing a Minimal Model for the Most Complicated Cellular Machine

A fascinating feature of the human genome is the abundance of regions that seemingly do not carry any useful information. These "non-coding" regions, also called intervening sequences or introns, frequently interrupt human genes and thus, pose a serious challenge to our cellular machinery. There are examples of human genes that contain more than a hundred introns. In order to be able to use the data stored in our genes, the boundaries of introns should first be correctly recognized, and then introns must be removed to generate an uninterrupted genetic message. The process of recognition and removal of introns, or splicing, is of such crucial importance that any mistake in it can lead to devastating human diseases: fifty percent of all human genetic diseases, a large number of cancers, and many neurodegenerative diseases such as certain types of Alzheimer's disease, are caused by small mistakes in the process of splicing. Large scale splicing mistakes are uniformly incompatible with life.

How do splicing mistakes happen? In order to ensure that splicing is performed accurately and in a timely fashion, human cells deploy an enormous and highly complex molecular assembly called the spliceosome to carry out splicing. While the complexity of the spliceosome with its many built-in safeguards guarantees the accuracy of the great majority of splicing events, at the same time it imposes severe limitations on scientific approaches that can be fruitfully applied to its study. Thus, despite more than two decades of intense research, many fundamental aspects of spliceosomal function including the underlying mechanism of disease-causing splicing mistakes have remained largely unknown.

To tackle this problem, **Saba Valadkhan, M.D., Ph.D.,** assistant professor at the Center for RNA Molecular Biology at the Case School of Medicine, and scientists in her lab are attempting to reconstitute the spliceosome from its basic components in order to create a functional, yet vastly simpler, splicing system. While such reconstitutions had been previously attempted in several laboratories without success, using a combination of molecular engineering and extensive optimization, scientists in the Valadkhan lab succeeded in creating a highly minimal but still functional spliceosome from only two of more than 200 spliceosomal components. Their newly-developed minimal spliceosome not only has provided a first glimpse of the inner workings of one of the most crucial molecular machines in the cell, but also has provided a model system that is amenable to study by current techniques; it has opened the door to a plethora of studies that otherwise would not be possible. Using the minimal splicing system, the Valadkhan lab has embarked on performing a detailed analysis of function of the human spliceosome in health and disease.

SABA VALADKHAN

http://www.rnaresearch.org/valadkhan.htm
http://filer.case.edu/org/valadkhanlab/

ERIC J. ARTS + ROBERT A. SALATA

Medicine

A Weaker Subtype of HIV Results in Greater Proliferation of the Disease

Human immunodeficiency virus type 1 (HIV-1), the virus causing AIDS, jumped from chimpanzees to humans between the 1920s and 1940s. The original HIV-1 strains remained isolated to various human tribes in the tropical and heavily forested regions of west central Africa for decades. Increased travel and migration into these areas, accompanied by Western colonization, may have resulted in the rapid spread of HIV-1 and diversification into multiple lineages, called subtypes. HIV-1 subtypes A through J now infect 40 million humans worldwide and have already led to at least 30 million deaths.

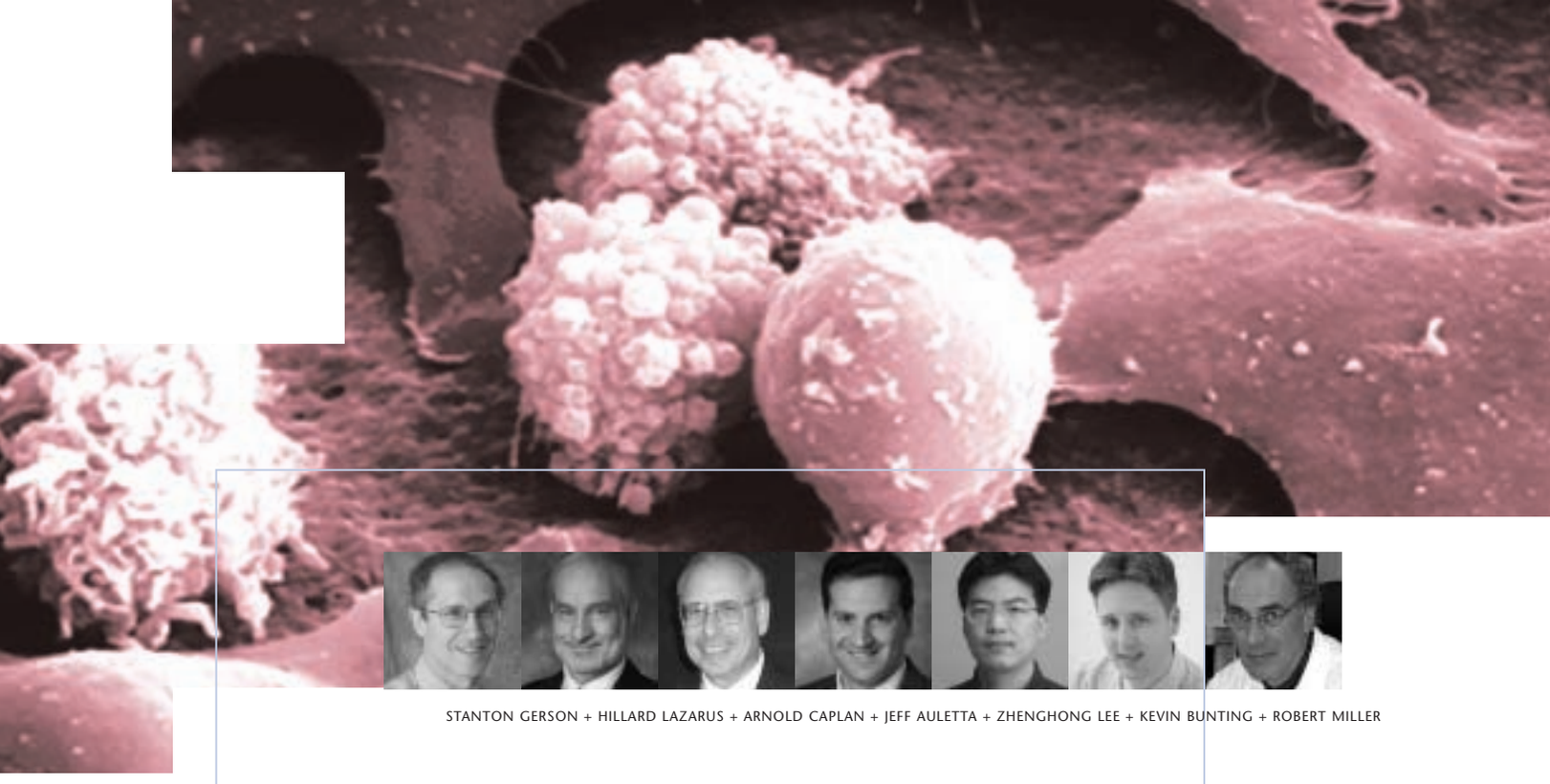
More lethal than the Ebola virus, HIV-1 kills everyone that it infects. However, history suggests that lethal pathogens do not "want" to kill their hosts because their survival is dependent on keeping the host alive for transmission. **Eric J. Arts, Ph.D.,** associate professor in the Division of Infectious Diseases and HIV Medicine at the Case School of Medicine, theorized that HIV-1 might be weakening and causing slower progression to AIDS. In collaboration with researchers at the Institute of Tropical Medicine in Antwerp, Belgium, he found evidence that the AIDS virus infecting humans in the early 1980s might be more virulent than the current day virus. With this knowledge in hand, Dr. Arts, in coordination with Division Chief **Robert A. Salata, M.D.,** and his research laboratories at both Case and the Joint Clinical Research Centre in Kampala, Uganda decided to tackle a much more difficult question: could various HIV-1 subtypes be evolving to less virulent forms?

Subtype C HIV-1 has come to dominate the epidemic in just ten years, accounting for fifty percent of the infections worldwide. Was this rapid expansion of subtype C HIV-1 in China, India, and southern Africa related to virulence? Women newly infected with subtypes A, C, and D HIV-1 in Uganda and Zimbabwe were identified in a cohort of more than 6,000 HIV-negative women. After following more than 260 HIV-infected women between two to five years, it became apparent that the subtype C infected women have a slower decline in CD4-positive lymphocytes that fight off infection in the body, including foreign pathogens such as HIV. In other words, the infection-fighting cells failed more rapidly in the women with subtypes A and D.

Slower loss in these cells suggests a slower disease progression to AIDS and a longer lifespan for subtype C HIV-1 infected women. Independent of this finding, the Arts laboratory also discovered that subtype C HIV-1 is approximately 100-fold less virulent than all other circulating forms of HIV-1. Accordingly, humans infected with subtype C HIV-1 may survive longer, resulting in more opportunity to transmit the virus and expansion of this HIV-1 form in the epidemic.

"Because HIV progresses more slowly in women with subtype C, they can go for years without symptoms. Unfortunately, unsuspecting victims can pass on the virus for a long time without realizing it," notes Dr. Arts.

http://www.case.edu/med/microbio/artslab/
http://www.cwru-id.org/
http://www.case.edu/med/microbio/arts.htm



STANTON GERSON + HILLARD LAZARUS + ARNOLD CAPLAN + JEFF AULETTA + ZHENGHONG LEE + KEVIN BUNTING + ROBERT MILLER

Medicine

Developing Stem Cell Therapies for Difficult-to-Treat Diseases

Translating a basic understanding of stem cell function into therapeutics requires a multifaceted team approach to science. Under the direction of **Stanton Gerson, M.D.,** Shiverick Professor of Hematological Oncology at the Case School of Medicine, an outstanding group of investigators at both the Center for Stem Cell and Regenerative Medicine and the Case Comprehensive Cancer Center are making great progress to develop cell therapies for difficult-to-treat diseases. To date, the best success has been in the treatment of leukemias, lymphomas, and aplastic anemia. **Hillard Lazarus, M.D.,** professor of medicine, leads this effort at University Hospitals Case Medical Center (UHCMC) as well as the innovative stem cell therapeutics program that includes the use of umbilical cord blood, purified stem cells, and the recent introduction of mesenchymal stem cells (MSC). More patients have received MSC therapy at UHCMC than anywhere else in the country for the investigational treatment of leukemia, genetic defects, and more recently for an immune disorder that evolves after a sibling transplant called Graft-Versus-Host Disease (GVHD).

Arnold Caplan Ph.D., professor of biology, originally described these cells in 1987 and now **Jeff Auletta, M.D.,** assistant professor of pediatrics, is defining how MSCs suppress the immune response that incites GVHD. An early study led by Dr. Lazarus showed a very low incidence of GVHD after blood stem cell transplantation, a very encouraging sign. Dr. Auletta's research indicates that MSCs reduce GVHD by secreting special immunosuppressive cytokines that block lymphocyte function. Furthermore, to determine exactly where MSCs go after infusion and to define how they impact on blood stem cell engraftment while reducing the immune effects causing GVHD, **Zhenghong Lee, Ph.D.,** assistant professor, is helping Drs. Auletta, Caplan, and Gerson genetically tag the stem cells with the firefly luciferase gene or a gene that helps retain a radioactive compound so they can be monitored using very sensitive imaging equipment in the state-of-the-art Case Center of Imaging Research located at UHCMC.

With a focus on the basic biology of various stem cells, **Kevin Bunting, Ph.D.,** associate professor of medicine, is defining the role of various signal transduction cascades in stem cell maintenance, focusing on the role of the STAT pathway that mediates signals from growth factor receptors. **Robert Miller, Ph.D.,** Allen C. Holmes Professor of Neurological Diseases, studies the sonic hedgehog pathway in neural stem cells that is important in their ability to reproduce and to migrate within the brain. Dr. Gerson is evaluating the importance of maintaining the DNA within the stem cell pool—he has found that many defects in DNA repair disrupt genomic instability and lead to loss of stem cells associated with the aging process and some diseases.

These studies will also promote a new research group in cancer stem cells, which may uncover the special properties of the most virulent forms of cancer cells. "The ability to translate these findings into better therapeutics using both new stem cells and replenishing those already in the body remains an important challenge for this team. Our hope is to develop new stem cell therapies in the not too distant future," comments Dr. Gerson.

http://ora.ra.case.edu/stemcellcenter/
http://www.ncrm.us

Medicine

Age-Related Macular Degeneration: Closing the Door on Blindness

One of the most devastating eye diseases associated with growing old is age-related macular degeneration (AMD), the leading cause of legal blindness in developed countries. More than 200,000 Americans become legally blind in one eye and 35,000 lose vision in the second eye each year. This number is on the rise, with the increase in life expectancy and population over the age of 60. However, the development of treatments for this devastating problem requires a better understanding of the pathophysiology of AMD. Through innovative research, it has clearly been determined that genetic background plays a significant role in the pathogenesis of the disease.

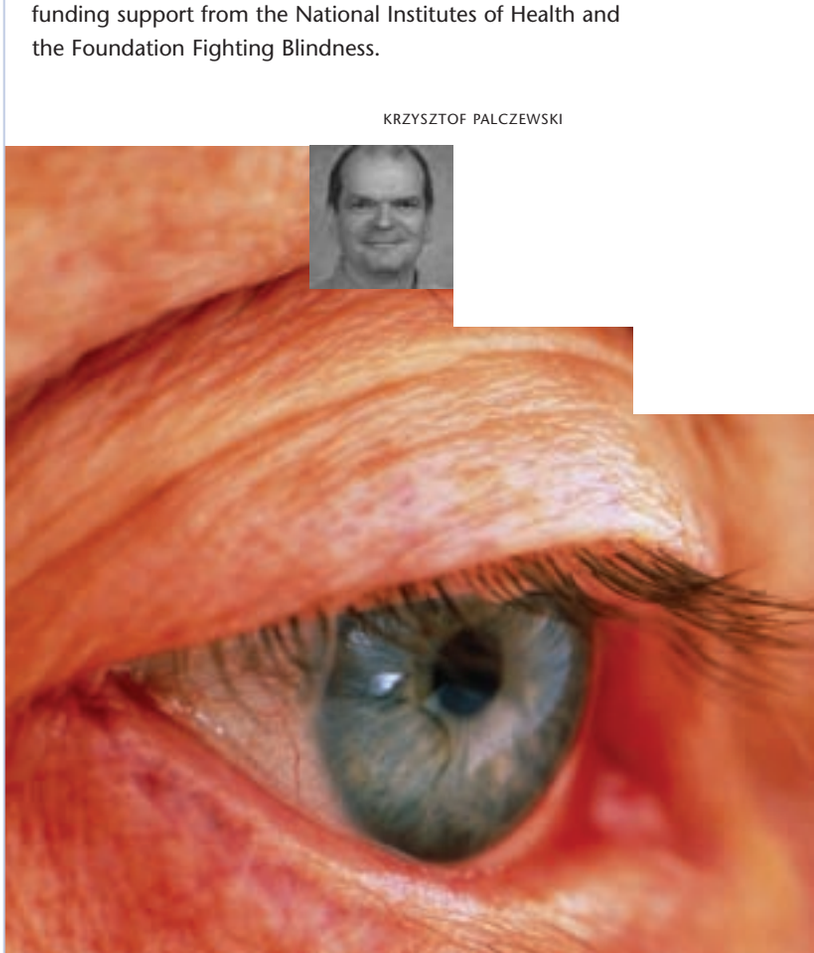
Krzysztof Palczewski, Ph.D., professor and chair of the Department of Pharmacology at the Case School of Medicine, has spent the last two decades working toward the prevention of blindness caused by various genetic defects. His research concentration is the retinal disease Leber congenital amaurosis, characterized by irreversible and severe congenital blindness. Dr. Palczewski and his team of researchers have successfully tested two new treatments in mice and found them to provide highly effective and complementary means for restoring retinal function in this animal model of human hereditary blindness. They anticipate that the combined treatments of orally administered retinoids, to avoid loss of vision in infants, and later, surgical intraocular gene therapy, as a long-lasting drug-free treatment, will converge to overcome eye disease.

However, in contrast to single gene-related diseases, the multifactorial and progressive nature of AMD requires a novel multidisciplinary team approach. Dr. Palczewski and his research team are investigating the hypothesis that a subtle change in the retinoid flow and rhodopsin regeneration, over time, results in the inability of the eye cells to eliminate waste products that build up within them. Rhodopsin is a receptor that is contained in the rods of the retina in the eye and is responsible for activating the translation of light into the biochemical signals which ultimately is recognized as vision. The succession of events would involve recruitment of immune system cells within the eye that would target retinal cells, leading directly to the development of AMD.

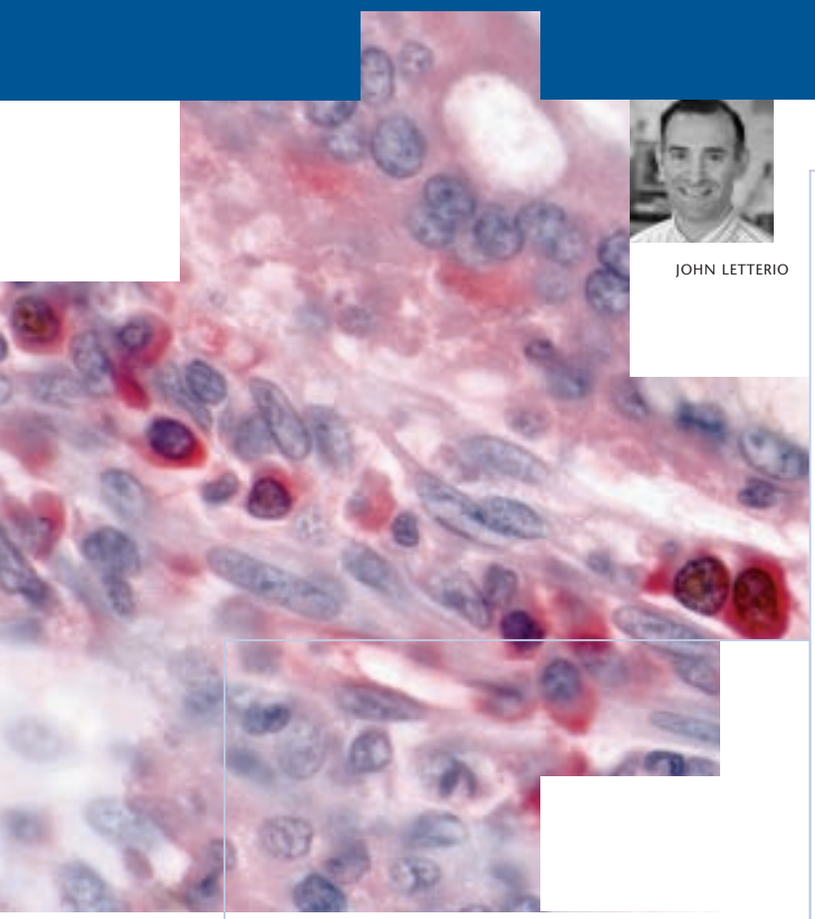
Dr. Palczewski's research is also focused on the structure of rhodopsin, which is by far the largest family of cell surface proteins involved in signaling across biological membranes. These proteins share a common seven alpha-helical transmembrane architecture and are targets for most of the current drugs. In addition, these proteins bind to the membrane-embedded receptors and cause them to undergo a conformational change, which regulate virtually all physiological processes in our body.

"My research team is focused on closing the door on blindness in the coming years. We have proven in mice that the prevention of blindness is no longer a dream, but a reality that can be achieved," notes Dr. Palczewski. His work receives funding support from the National Institutes of Health and the Foundation Fighting Blindness.

KRZYSZTOF PALCZEWSKI



http://pharmacology.case.edu/



JOHN LETTERIO

Medicine

Defining the Links Between Inflammation and Cancer

In the war on cancer, environmental awareness is important, particularly to the cancer cell. The pre-malignant cell can only realize its full potential by either finding the appropriate micro-environment to support its growth, or manipulating the environment to its advantage. This mysterious behavior of tumor cells has been appreciated for decades—studies in the 1970s demonstrated that the transforming oncogenic Rous Sarcoma Virus could only induce tumors in a "wounded" tissue environment. Local factors produced during the process of injury, inflammation, and tissue repair were not simply important, but required for the virus to induce a tumor.

Three decades later, the molecular basis that underlies the link between processes such as inflammation and cancer is being uncovered. A research team led by **John Letterio, M.D.** professor of pediatrics at the Case School of Medicine and chief of pediatric hematology oncology at Rainbow Babies and Children's Hospital (University Hospitals Case Medical Center), has just added an important piece to this puzzle. As a pediatric oncologist and physician-scientist, Dr. Letterio has devoted his career to research that has aimed to better define the basic mechanisms that underlie cancer pathogenesis, with a particular interest in the role of local micro-environment and tissue homeostasis in cancer observations that have challenged our view of how one protein, Transforming Growth Factor-beta (TGF-beta), regulates the processes of inflammation and cancer.

Dr. Letterio and his team focused on a disorder called familial juvenile polyposis (FJP). Patients with this genetic disorder inherit a defect in a tumor suppressor gene known as *SMAD4,* and are predisposed to developing gastrointestinal cancer, but are well known to have a "smoldering" infiltration of lymphocytes within the intestinal walls long before cancers of the overlying epithelial cells develop. Armed with this knowledge, the team decided to model this disease in mice, but utilized a strategy known as "conditional gene targeting" to restrict mutations in the gene *SMAD4* either to cells of the immune system (T-cells) or to the overlying epithelial cells that become cancerous.

The results were striking: only the mice with loss of *SMAD4* expression in T-cells went on to develop gastrointestinal cancer, developing the same pathology found in patients with FJP, including thickening of the epithelial lining, infiltration of antibody producing plasma cells, and ultimately cancer. The results support the concept that cancer, as an outcome, reflects the loss of the normal communication between the cellular constituents of a given organ, and indicate that *SMAD4*-deficient T-cells ultimately send the wrong message to the stromal cells that reside underneath the overlaying epithelial cells in the gastrointestinal tract. Accordingly, strategies that target the activation and function of T-cells may represent an effective form of preventive therapy that may obviate the need for surgical intervention.

"What we have discovered is that there is an important molecular basis that links chronic inflammation in the gastrointestinal tract and cancer. We need to focus on the development of therapeutics that aim to turn off the immune responses to this inflammation. If we can stop the activated T-cells and the cytokines they produce, this malignant transformation can be interrupted," observes Dr. Letterio.

http://pharmacology.case.edu/department/faculty/trainers/letterio.html

Medicine

New Uses for "Old Drugs": Targeting Brain Cell Inflammation in Alzheimer's Disease Patients

Many neurological diseases and disorders involve the death of neurons in the brain and spinal cord. The loss of these neural cells accounts for the devastating and irreversible loss of function that accompanies these disease processes. When brain cells die, the brain's immune cells, called microglia, sense the damage and activate the brain's immune system. This triggers a defensive response that results in the secretion of many inflammatory substances that are normally used to ward off infections, a response that causes further damage to the brain. Accordingly, drugs that act to suppress this inflammatory response are being investigated to slow disease progression and improve disease outcome.

Gary Landreth, Ph.D., a professor in the Department of Neurosciences at the Case School of Medicine, is focused on understanding how the microglia detect disease-related damage to the brain. In working to develop drugs that target these immune cells, his research team recognized that a class of anti-diabetic drugs, called PPAR-gamma agonists, had unusual and unexpected anti-inflammatory actions in the brain. Colin Combs, Ph.D., a postdoctoral researcher in the laboratory, discovered that these drugs worked effectively to block inflammation that occurs in Alzheimer's disease. Dr. Landreth and David Geldmacher, M.D., at the University Memory and Aging Center (a partnership of Case and University Hospitals Case Medical Center) then obtained funding for the first clinical trial of these drugs in Alzheimer's disease patients and have recently completed this study. Importantly, other clinical trials of these drugs have shown that they are very effective in improving memory and learning. The close collaboration between the Case scientists and clinicians has allowed the rapid translation of the basic science into new therapies for Alzheimer's disease.

Subsequent studies have shown that these drugs are also very effective in animal models of other diseases including Parkinson's disease, amytrophic lateral sclerosis, multiple sclerosis, and stroke, with clinical trials of the drugs currently in progress. Case was successful in obtaining patents on these new therapeutics and is now negotiating licensing them to the pharmaceutical industry so that they will be available to patients in the near future.

The Landreth laboratory continues to investigate the role of inflammation in brain diseases. With the underlying philosophy that a clear understanding of the biology of the brain's immune cells is a prerequisite for the development of new drugs and treatments, a very talented team of scientists is now pursuing the development of new classes of drugs that target inflammatory processes in the brain.

GARY LANDRETH

http://alzlab.cwru.edu/landreth/

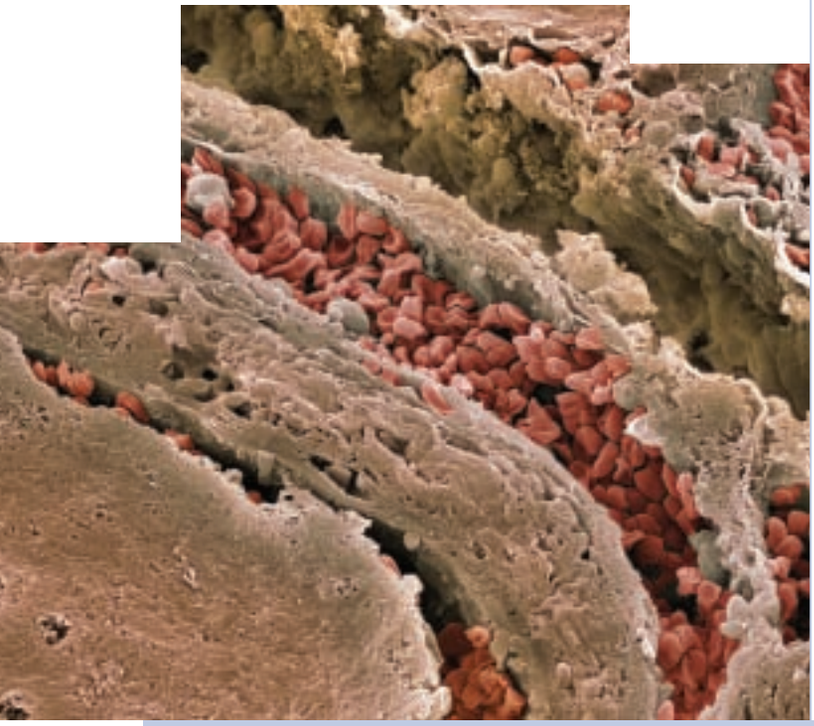
GEORGIA WIESNER + ROBERT ELSTON + WEI-DONG CHEN
SANFORD MARKOWITZ + JOSEPH WILLIS + DAWN DAWSON + MIN YAN

Medicine

Identifying Genes That Are Key Targets for Mutation in Colon Cancer

Colon cancer is the second leading cause of cancer death in America and throughout the industrialized world, claiming 145,000 new cases and 54,000 deaths annually. **Sanford Markowitz, M.D., Ph.D.,** the Francis Wragg Ingalls Professor of Cancer Genetics at the Case School of Medicine and the Ireland Cancer Center, and an investigator with the Howard Hughes Medical Institute, and his collaborators have led a series of investigations to use the power of molecular genetics to develop new tools for fighting this disease. A key concept that has emerged from these studies is that colon cancer results from alterations, or mutations, in human DNA.

Dr. Markowitz, along with **Joseph Willis, M.D.,** associate professor of pathology, and **Dawn Dawson, M.D.,** assistant professor of pathology, in collaboration with investigators at Johns Hopkins University, recently announced the successful sequencing of the "colon cancer genome"—13,000 different human genes were evaluated to identify 69 genes that are targets for mutations in colon cancer. These genes provide new targets for developing anti-cancer drugs and molecular methods for early cancer detection.



A key gene targeted for mutation (previously identified by Dr. Markowitz's laboratory) is the TGF-beta type II receptor (RII) that is required for suppressing colon cancer. Graduate student, **Min Yan, Ph.D.,** working together with Drs. Markowitz, Willis, and Dawson, has shown that a key tumor suppressor mechanism that RII uses is the activation of the "Celebrex-like" activity of the 15-PGDH gene. Like Celebrex (a non-steroidal anti-inflammatory agent), the activated 15-PGDH gene acts to oppose the build-up of tumor-promoting prostaglandins. The search is now on for drugs that can efficiently reactivate the 15-PGDH gene activity that is lost in human colon cancers.

Some individuals inherit cancer predisposing gene mutations, causing colon cancer to "run in the family." Dr. Markowitz, together with **Georgia Wiesner, M.D.,** director of the Center for Human Genetics and associate professor of genetics, and **Robert Elston, Ph.D.,** professor of epidemiology and biostatistics, has been searching for these elusive genes that cause familial colon cancer. With the help of news anchor Katie Couric, these investigators were able to sign up thousands of individuals with colon cancer from across the country to assist in this research. Recently, the team proved that forty percent of the families they have studied are harboring a new familial colon cancer gene that they have mapped to a small interval on human chromosome nine. The hunt is now on to complete the identification of the gene.

Colon cancer is completely curable when caught in the early stages. **Wei-Dong Chen, M.D.,** an instructor in the Department of Medicine, has recently succeeded in developing a molecularly-based test for non-invasive early detection by identification of abnormal cancer-associated DNA molecules in the feces of colon cancer patients. Case is now working with a biotechnology partner, Exact Sciences, to develop this test for application in the clinic. "It is the patients who have participated in these colon cancer research studies to whom the greatest credit is due. Continued advances truly do offer hope for discovery of better ways to prevent, treat, and ultimately cure this disease," comments Dr. Markowitz.

http://www.hhmi.org/research/investigators/markowitz_bio.html

CHARIS ENG

Medicine

Harnessing Genomic Information and Entering the Era of Personalized Medicine

Medicine has been practiced on the law of averages for centuries. While a twenty percent response rate for today's delivery of the standard-of-care combination chemotherapy to treat metastatic cancer would have seemed like a miracle to physicians of yore, it is still an unsatisfying eighty percent non-response rate. However, with the potential power to harness the knowledge from the Human Genome Project and accurately predict risk and outcome, as well as tailor treatment and preventative strategies based on genetic and genomic information, the modern era of personalized medicine has begun.

The ability to more accurately tailor medical treatment and prevention to subsets of patients based on objective means is being met with excitement and energy. The research of **Charis Eng, M.D., Ph.D.,** professor and vice chairman of the Department of Genetics, and founding chair and director of the Genomic Medicine Institute at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, seeks to identify and characterize genomic variation which can help make accurate diagnoses, assess cancer risks, and tailor medical care.

Dr. Eng's research program focuses on genetic risk assessment and management of solid tumors. Utilizing a single, very powerful model tumor suppressor gene called *PTEN* which prevents cell overgrowth, her team is translating laboratory discoveries to evidence-based personalized medical care. Germline (found in every single cell of the body) gene mutations represent faults or alterations in DNA, which is the stuff of genes. Germline mutations of *PTEN* cause Cowden Syndrome (CS), a condition characterized by multiple non-cancerous, tumor-like growths called hamartomas, usually found on the skin or mucus membranes of those with the syndrome. A more troubling aspect of CS is an increased likelihood of developing breast and thyroid cancers, and perhaps cancer of the uterus.

Because of Dr. Eng's work, a highly accurate molecular diagnostic test based on *PTEN* can be utilized in the clinical setting to make a diagnosis, predict age-related cancer risks, and tailor clinical screening for breast, thyroid, and uterine cancers. CS is under-recognized, particularly by non-cancer genetics professionals, and therefore, diagnoses are not made. As a result, individuals with the syndrome (and the associated increased likelihood of developing these cancers) do not seek pre-emptive monitoring for cancer development. Thus, one of the projects in the Eng lab is to objectively define, based on genomic and epigenomic analyses, the simplest set of symptoms that would help health care providers recognize CS for referral to cancer genomic medicine physicians. The future challenge is to determine how *PTEN* interacts with other genes and the environment to modulate cancer and other risks.

The utilization of genetic and genomic information to practice a broad spectrum of personalized medicine occurs in the clinical arm of the Genomic Medicine Institute, the Center for Personalized Genetic Healthcare, also directed by Dr. Eng. In this Center, teams of genetic counselors and genomic medicine physicians see patients and families where diagnosis, risk assessment, and management based on genetic and genomic information are performed.

http://www.lerner.ccf.org/gmi/

PATRICIA A. HIGGINS + BARBARA J. DALY

Nursing

Helping a Vulnerable Patient Population: Adults Who Fail to Thrive

Chronic critical illness develops when adults survive the immediate, life-threatening phase of critical illness, but continue to require intensive technological support for extended periods of time. Two hallmark characteristics, which differentiate the chronically critical ill (CCI) from other intensive care unit patients, are prolonged dependence on mechanical ventilation and significant in-hospital mortality rates. Adult failure to thrive syndrome (FTT) is defined as a less than expected level of functioning associated with nutritional deficits, altered rest-activity patterns, depressed mood state, and social isolation—all factors that frequently develop in adults with chronic medical conditions, including those who become chronically critically ill. Under the direction of **Patricia A. Higgins, Ph.D., R.N.,** associate professor of nursing at Case's Frances Payne Bolton School of Nursing, research is being done to better understand and treat the multiple problems and symptoms associated with both CCI and FTT syndromes.

Currently, it is not possible to predict which adults will develop either syndrome or the precise time of onset. In a series of studies that began in the mid-1990s, Dr. Higgins began assessing FTT factors in CCI patients—early pilot work concentrated on patients' mood state and nutritional status. As one of the first researchers to interview a small sample of mechanically ventilated patients while they were in the process of weaning from ventilator support, she found that they expressed feelings of fatigue, tension, sadness, and uncertainty. In addition, it was discovered that the vast majority of CCI patients were discharged with low levels of serum proteins despite implementation of specialized nutritional feedings early in their hospitalization.

A subsequent federally-funded longitudinal study focused on FTT factors in a sample of 807 patients. Dr. Higgins, along with co-investigator, **Barbara J. Daly, Ph.D., R.N., F.A.A.N.,** professor of nursing, confirmed the significant physiological and psychological stress of CCI, with mortality rates of approximately 40 percent, an 11-day average of ventilator time, abnormally low serum biological markers (despite adequate nutritional therapy), and continued patient reports of mood disturbances. Also, significant disruption of the patients' 24-hour rest-activity rhythms was documented.

In this study, the team also documented an intriguing finding that has implications for future research: CCI patients were consistently exposed to low ambient light levels, regardless of the time of day or patient location (intensive care unit or general ward room). Based on these findings, and the known contribution of illness-related factors to the desynchronization of circadian rhythms, Dr. Higgins and her team are focusing their next studies on investigating CCI patients' rest-activity patterns, melatonin rhythms, and light exposure patterns (circadian and ambient light) with the intent of developing a low-risk, safe intervention that will help this vulnerable patient population during their recovery and rehabilitation period.

http://fpb.case.edu/chronicallycriticallyill/index.shtm

Nursing

Improving Healing Rates in Chronic Wound Care

Chronic wounds are a health problem affecting hundreds of thousands of individuals, most of them elderly, and costing billions of dollars annually in the United States alone. More than ninety percent of all chronic wounds fall into one of three categories: venous, diabetic, and pressure ulcers. Although recommendations for general wound management have been identified and included in clinical practice guidelines and systematic reviews, chronic wounds remain difficult to treat and recurrence is common.

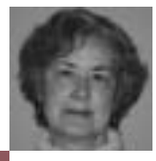
There have been few studies of wound care practices being used in daily practice, delivered by typical clinicians to typical patients, to help to identify best practices that could lead to better healing rates across sites of care delivery. **Katherine R. Jones, Ph.D., R.N., F.A.A.N.,** Sarah Cole Hirsh Professor at Case's Frances Payne Bolton School of Nursing, and her colleagues at the Yale School of Nursing, conducted a retrospective longitudinal study across four geographically disperse sites to determine actual wound care practices, and to analyze which practices were associated with better chronic ulcer healing rates. In a study of 400 subjects, trained research assistants collected detailed information on patient characteristics, wound characteristics, treatment approaches, and outcomes.

Two sites achieved healing rates comparable to benchmarks identified in the literature, while the other two sites had significantly lower healing rates. Multiple factors appeared to influence this result. Clinicians in the two sites with better healing rates more consistently matched characteristics of the wound with the dressing selected for application, and were more likely to use modern dressings. Patients being cared for at the two sites with lower healing rates were more likely to have Medicaid as their health insurance, and to have histories of substance abuse and malnourishment. In addition, clinicians in the lower performing sites were more likely to use gauze or antibacterial dressings. Organizational factors also seemed to play a role—the site with more infrequent clinic visits had the highest number of wounds that actually deteriorated over time. Lastly, the researchers were surprised to note continued use of cytotoxic cleansing agents and wet-to-dry dressings for many patients across all of the sites given the existing strong evidence that both practices damage healthy tissue and delay healing.

Multiple factors contribute to successful chronic wound healing. These findings suggest that interventions need to be targeted at clinicians, to improve their knowledge of recommended practices; at patients, to improve adherence to prescribed care; and at the system, to improve monitoring and management of patients.

"Non-healing wounds represent a significant burden to patients and the health care system. Adherence to just a few best practices, including the use of appropriately selected moisture-management dressings, could greatly improve chronic wound outcomes and, accordingly, patient quality of life," adds Dr. Jones.

KATHERINE R. JONES



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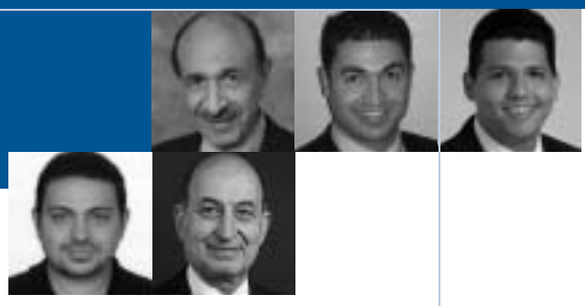
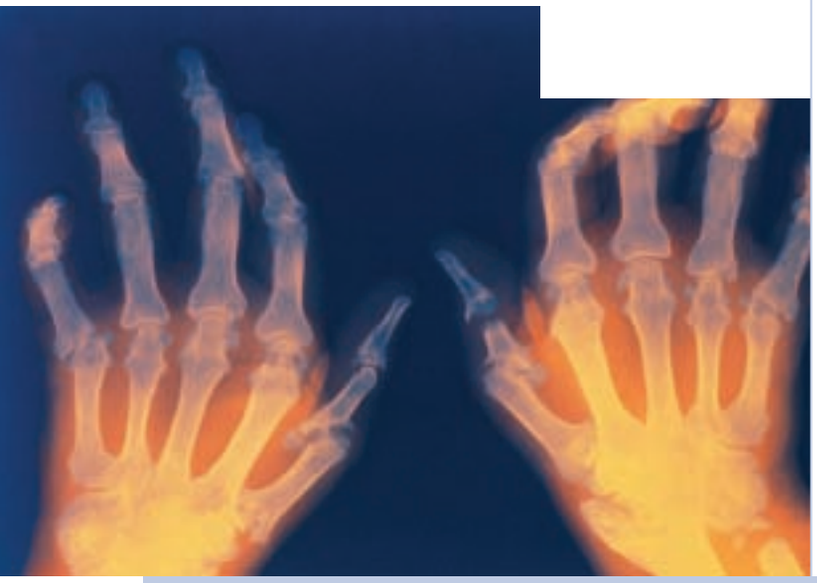


ALI ASKARI + OMID KIARASH + JOSE ARAUZ-DUTARI +
KHALDOUN AL-KATMA + NABIL F. BISSADA

Dental Medicine + Medicine

Linking Rheumatoid Arthritis and Periodontal Disease: Enhancing the Ability to Treat Both

A multidisciplinary research team at Case is making great strides in proving that there is a link between periodontal disease and rheumatoid arthritis—and that the treatment of one disease enhances the treatment of the other. A recent study led by **Khaldoun Al-Katma, D.D.S., M.S.D.,** together with **Nabil F. Bissada, D.D.S., M.S.D.,** professor and chair of the Department of Periodontics at the Case School of Dental Medicine, and **Ali Askari, M.D.,** professor and chair of the Division of Rheumatology at the Case School of Medicine and University Hospitals Case Medical Center, followed a group of patients with both active rheumatoid arthritis and periodontal disease. For eight weeks, some of the patients received standard gum disease treatment while others did not. A rheumatology examination at the end of this period clearly showed that the severity of the arthritis in the patients receiving gum treatment was reduced. The team also evaluated the effect of treatment of rheumatoid arthritis on periodontal disease and found that the disease modifying anti-rheumatic drugs (DMARDs) to treat arthritis appeared to ameliorate the severity of the gum disease.



In addition, the team completed a study that showed that the strain of bacteria in the synovial fluid of one patient with rheumatoid arthritis matched the bacteria found in the dental plaque of the same patient. While the bacteria was present in rheumatoid arthritis, it was not present in osteoarthritis, and the rest of the patients with rheumatoid arthritis.

The possibility of similarities between the inflammatory state in the rheumatoid lining of the joint and the gum inflammation in periodontal disease is being pursued further. **Omid Kiarash, D.M.D., M.S.D.,** working with **Jose Arauz-Dutari, D.M.D., D.D.S.,** assistant professor in the Department of Periodontics, Dr. Bissada, and Dr. Askari, recently completed a study that furthers the findings that these two disease entities have much in common. Sixty rheumatoid arthritis patients were examined by a rheumatologist and Dr. Kiarash according to the standard parameters of arthritis and gum disease: the amount of gingival inflammation, depth of the periodontal pocket, clinical attachment loss, presence of plaque, rheumatoid arthritis disease activity score, and the amount of systemic inflammation. Comparing the periodontal status of the patients receiving DMARDs plus anti-tumor necrosis factor therapy (anti-TNF) to those receiving similar DMARDs but no anti-TNF showed that the patients on anti-TNF therapy had healthier periodontal status independent of oral hygiene. The significant differences in the oral health of the two groups showed that the anti-TNF medication to help control the destructive activities within the joints may also prevent the loss of attachment of the periodontal tissues which support the teeth.

"Based on our findings, we encourage dentists to observe the periodontal status of patients with rheumatoid arthritis more diligently and respond decisively. This is also an opportunity for physicians to refer rheumatoid arthritis patients for prescreening to prevent the commonly high rate of tooth loss in these individuals, often a result of periodontal disease," comments Dr. Kiarash. "It may also mean a new future treatment for periodontitis," notes Dr. Askari.

http://dental.case.edu/admissions/gradstudies/perio/
http://www.case.edu/CWRU/Med/medicine/turq/divrhue.htm

MANISH VALIATHAN + ROBERT C. ELSTON + KATRINA A.B. GODDARD

Dental Medicine + Medicine

Congenital Missing Teeth: A Complex Condition Requiring Lifelong Care

The normal number of permanent teeth in humans, both upper and lower jaws, is 32, while deciduous or primary dentition (often called "baby teeth"), totals 20. By the age of three, the deciduous teeth have erupted in most children, and by ages 12 to 14, these primary teeth have been replaced by permanent ones. Departure from the usual number of teeth is one of the more common abnormalities affecting the formation of teeth. When the number of teeth is fewer than the normal complement, the condition is known as hypodontia or dental agenesis. In some extremely rare cases, patients have a complete absence of teeth, which is called anodontia.

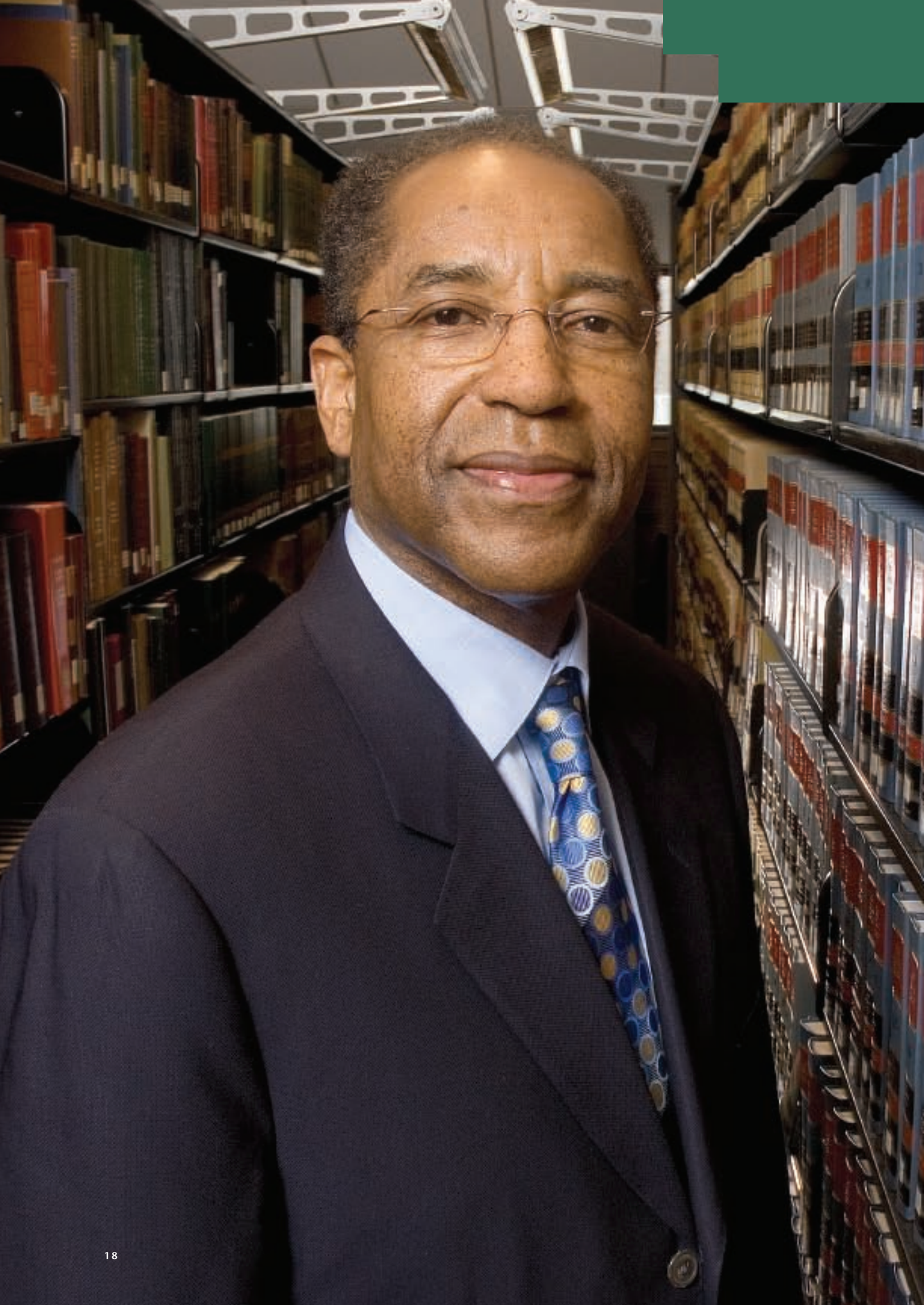
While hypodontia of the primary dentition is fortunately uncommon, it is usually followed by hypodontia of the permanent teeth in the same region. Hypodontia of the permanent dentition has a prevalence rate of six to ten percent in the general population. The treatment of patients affected by this condition is complex, expensive, and lifelong, and typically requires a combination of pediatric dentistry, orthodontics, prosthodontics, and tooth implantation. Such advanced work requires long-term maintenance and periodic revision. Working to address this dental anomaly is the interdisciplinary research team composed of **Manish Valiathan D.D.S., M.S.D,** assistant professor in the Department of Orthodontics at the Case School of Dental Medicine, together with **Robert C. Elston, Ph.D.,** professor, and **Katrina A.B. Goddard, Ph.D.,** associate professor, both from the Department of Epidemiology and Biostatistics at the Case School of Medicine.

After examining a group of 2,619 affected individuals, the most common missing teeth were mandibular second premolars followed by maxillary lateral incisors (third molars, known to be the most commonly missing teeth, were excluded). Other anomalies that were found to be associated with the phenomena of missing teeth were smaller than normal tooth size (microdontia) and anomalies in tooth shape, most commonly found were tapering or "peg-shaped" teeth.

A large number of the hypodontia patients surveyed had one or more affected relatives. Approximately 270 individuals were recruited from the larger group to join a family study for which a substantial database has been created with extensive dental and medical histories, radiographic information, and molds of each participant's teeth. While environmental factors can affect tooth development, it appears that the majority of cases have a genetic basis—hypodontia is most frequently associated with the autosomal dominant gene, although autosomal recessive and X-linked gene models of inheritance are also possible, as well as patterns of polygenic and multifactorial inheritance.

"Although the precise nature of the genes underlying congenitally missing teeth is not well understood at this time, uncovering this link is an important goal that is both timely and significant to the practice of dentistry," comments Dr. Valiathan.

http://orthodontics.case.edu/



"In our increasingly complex world, society's ability to render justice and achieve peaceful settlements will require greater interdisciplinary thinking and the design of appropriate systems to address a broad range of disputes. We can begin by making effective arbitration an optimal choice and working to gain a better understanding of the very nature of conflict to help us discover more suitable alternatives for resolving disputes peacefully."

CALVIN WILLIAM SHARPE

Society + Community

Law

Arbitration: A Necessary Alternative in an Increasingly Litigious and Complex World

As social interaction has grown in complexity, disputes have proliferated both domestically and globally. These range from simple transactions between individuals to multinational corporate and international governmental disputes. Likewise, the sources of rules governing these transactions range from contracts to statutes to international treaties. Among the peaceful alternatives for resolving such disputes, litigation is increasingly ineffective and often inappropriate to the transaction. Hundreds of thousands of civil cases filed in a single year in the federal judicial system, and more than a million in the state of California alone, make impossible the resolution of any significant number of these cases through court adjudication. Moreover, because of such concerns as party autonomy, conflict of laws, and national bias, more than ninety percent of international business agreements contain arbitration clauses.

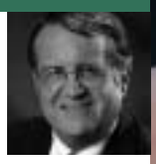
CALVIN WILLIAM SHARPE

Responding partially to the need to relieve the judicial system from this burdensome and unwieldy caseload, the United States Supreme Court in a famous case decided in 1991, Gilmer v. Interstate Johnson Lane Corp., made it easier to enforce arbitration agreements in disputes, including suits filed under statutes designed to protect important civil rights. The decision was based in part on the cost, speed, privacy, finality, and informality advantages of arbitration over the more formal, costly, and protracted litigation process. However, many critics have challenged the propriety of a mandatory private system of adjudication to handle the array of public policy issues that arise under statutes. These include Title VII protecting employees against employment discrimination and other laws protecting little guys such as insurance clients, hospital patients, credit card holders, and shareholders. Many ask how our society would look today if the 1954 decision of Brown v. Board of Education outlawing segregation in public schools had been decided in arbitration rather than the courts.

The research of **Calvin William Sharpe, J.D., M.A.,** the John Deaver Drinko-Baker & Hostetler Professor of Law, Director of the Center for the Interdisciplinary Study of Conflict and Dispute Resolution at the Case School of Law, and a seasoned professional in dispute resolution examines the theory and practice of effective arbitration. This work focuses on the circumstances that make arbitration instead of court litigation optimal, such as multiplicity of claims, private ordering, special expertise, costly alternatives, continuing relationships, and the realistic possibility of deterrence. It also examines the optimizing effects that can move arbitration toward rendering justice where our civil justice system has failed.

Professor Sharpe's larger project in this area is an ongoing interdisciplinary study of conflict and dispute resolution. It draws upon the insights of other disciplines such as psychology, sociology, anthropology and religion that systematically treat the problem of conflict in social interaction. The study is expected to move us closer to designing systems that better understand and respond to disputes. In a world characterized by global conflict, the very survival of the species as well as the planet may depend upon making and applying such discoveries.

http://law.case.edu/faculty/faculty.asp



PAUL C. GIANNELLI

Law

DNA Evidence: Changing the Dynamics of the Criminal Justice System

With accelerating advances in technology, increasingly sophisticated forensic techniques are making a significant impact on the outcome of many criminal trials, as well as the dynamics of the criminal justice system. The most prominent technology in the forensic context is the ability to identify DNA—it has changed the way that scientific evidence is accepted and relied upon in both investigative and judicial systems. **Paul C. Giannelli, J.D., LL.M., M.S.F.S.,** and Albert J. Weatherhead III & Richard W. Weatherhead III Professor of Law, an acknowledged expert on criminal and scientific evidence, focuses on these issues through his work with the American Bar Association (ABA).

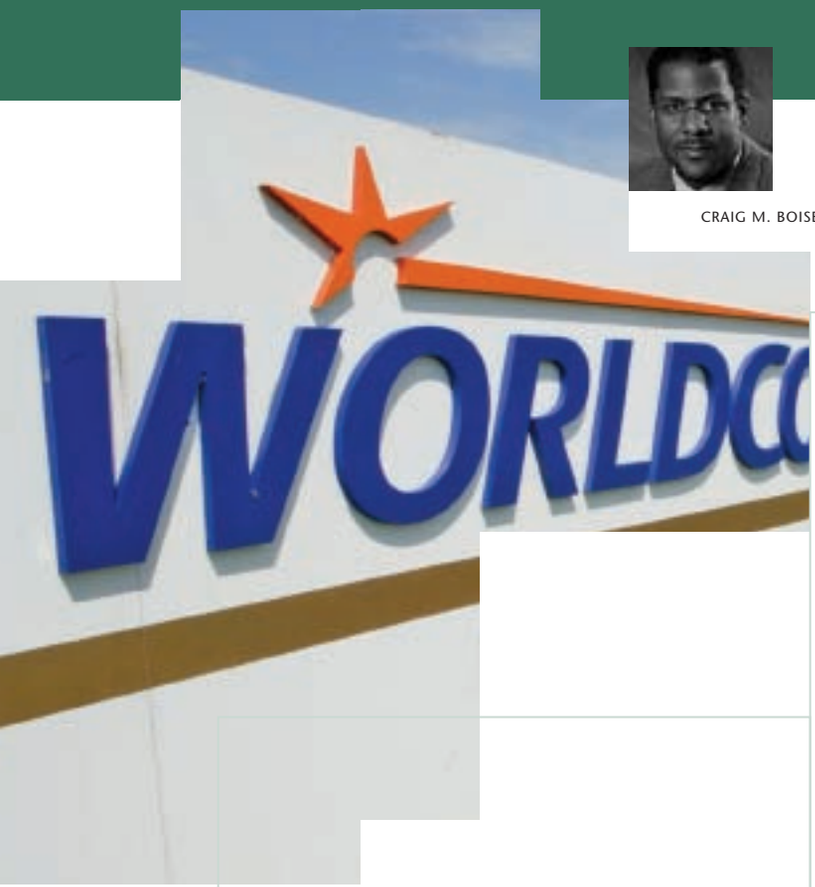
While DNA evidence has exonerated numerous convicts, the more recent ability to combine DNA information with database technology has produced hundreds of "cold hits" that have identified murderers and rapists in cases where the police had no suspects. By taking a DNA sample from a crime scene, and comparing it to a growing database of DNA profiles kept by law enforcement agencies, the power of technology and science trumps the need to rely on other forms of evidence.

"DNA exonerations have sent shock waves through the legal profession, which has long taken justifiable pride in the procedural safeguards accorded those accused of crime," notes Professor Giannelli. He points out that the Innocence Project, an independent, nonprofit organization affiliated with the Benjamin N. Cardozo School of Law, has used DNA analysis to exonerate 194 wrongly convicted individuals to date, some of whom had been on death row. Another study, *Exonerations in the United States: 1989 through 2003* (University of Michigan), that was updated in 2005, identified 340 exonerations, 196 of which did not involve DNA evidence. As a result of the exonerations, commentators and legal scholars began to examine the causes of these false convictions, including mistaken eyewitnesses, police misconduct, prosecutorial misconduct, tainted or fraudulent science, ineffective defense counsel, false confessions, and jailhouse snitches.

As co-chair of the ABA's Ad Hoc Innocence Committee, Professor Giannelli has shepherded numerous resolutions that include recommendations for the videotaping of all custodial interrogations; double blind procedures in pretrial lineups and photographic identifications; corroborating evidence when jailhouse informers testify; and providing adequate compensation and re-entry support for those who are exonerated.

Professor Giannelli also served as reporter for the *ABA Standards for Criminal Justice on DNA Evidence* to create proposed standards for federal, state, and local governments to balance the societal benefits of this powerful technology with the right to privacy and due process concerns. The *Standards* addressed the collection, preservation, testing, and presentation of DNA evidence in court; provisions on DNA databases; post-conviction testing for convicts asserting their innocence; methods for extending the statute of limitations for serious crimes; accreditation of crime laboratories performing DNA analysis; and indigent defendants' right to expert assistance when confronted with DNA evidence at trial. The ABA House of Delegates adopted the *Standards* as ABA policy in August 2006.

http://www.abanet.org/crimjust/home.html



CRAIG M. BOISE

Law

No Tax Refund for Fraudulently Inflated Corporate Income: Protecting Ohio's School Districts

The law is fundamentally concerned with notions of equity and justice. If a taxpayer inadvertently pays too much tax, tax rules provide that the overpayment must be refunded. The law is intended to insure that the taxpayer is treated equitably—that justice is done. Suppose, however, that a corporation willingly pays too much tax to disguise the fact that it has fraudulently inflated its earnings. Is equity served by permitting the corporation to benefit from tax rules that require a refund to be granted? The work of **Craig M. Boise, J.D., LL.M,** associate professor of law and associate director of the Center for Business Law and Regulation at the Case School of Law, is influencing the way that tax administrators think about that question.

Following the implosion of Enron in 2001, dozens of corporations were found to have fraudulently inflated their income. The appeal of earnings inflation is obvious. By means of various accounting gimmicks, or by simply manufacturing transactions that never took place, a company can create a steadily rising earnings curve that will boost its share price, producing lucrative rewards for management.

The largest case of income inflation was WorldCom, which added billions of dollars in fictitious earnings to its financial statements. To disguise its fraud, WorldCom also purposely inflated the value of its Ohio properties and, as a result, paid more Ohio property tax than it owed. WorldCom now seeks a refund of the taxes that it willingly overpaid. The refund, however, would have to be paid by the school districts across the state that have already received and spent property tax revenue that was based on WorldCom's false tax returns. Many of those districts are already facing funding deficits and forcing them to carve hundreds of thousands of dollars from their operating budgets would create severe hardship.

The refunds may never be paid, however, if the Ohio Board of Tax Appeals adopts a legal theory advanced by Professor Boise in a recent *Minnesota Law Review* article in which he asserts that tax refund claims are essentially "claims in equity." Equitable canons that date to sixteenth century England provide that such claims may be denied if they result from illegal or unethical acts of the person making the claim. Professor Boise argues that Ohio may deny WorldCom's refund claim because it arises from the company's own fraud. Professor Boise's article was cited in the Ohio Tax Commissioner's brief in the WorldCom refund litigation last summer and his arguments will play a significant role in similar litigation involving HealthSouth this year.

"The problem with permitting such claims is that reporting phony income is as much a tax fraud as is failing to report real income. The application of equitable doctrines to gaps in the positive law can insure that the law serves the ends of fairness and justice," notes Professor Boise.

http://ssrn.com/author=345018
http://law.case.edu/faculty/faculty.asp

Dental Medicine

Improving the Oral Health of Residents in Long-term Care Facilities

Preserving the oral health of individuals when their general health begins to fail is an enormous challenge. National epidemiological data substantiates the low priority placed on oral health care for the elderly residing in long-term care facilities. **Marsha A. Pyle, D.D.S., M. Ed.,** associate professor at the Case School of Dental Medicine has studied oral health priorities in long-term care environments from several perspectives. The most recent study investigated institutional priorities for oral health care in Ohio's nursing homes. Working with **T. Roma Jasinevicius, D.D.S., M.Ed.,** associate professor in the Department of Comprehensive Care and **Danny R. Sawyer, D.D.S., Ph.D.,** chair of the Department of Oral Diagnosis and Radiology, Dr. Pyle explored what executive directors of nursing homes thought of the quality and delivery of the oral health care in their facilities.

Three hundred thirty-eight executive directors of long-term care facilities responded to a survey designed to assess their perceptions regarding the value placed on oral health in the facility as well as other variables that influenced the daily delivery of oral care within the facility. The results of the survey showed that most executive directors rated their residents oral health as fair or poor, yet were still satisfied with the oral care provided at their facilities. The apparent discontinuity between perceived levels of oral health and satisfaction suggest that their roles may prevent them from direct knowledge of oral health levels or lack of acknowledgement of oral health care needs. Dr. Pyle notes that this, coupled with negativity expressed about the topic, may suggest the larger issue of continued low priority for oral health in the long-term care setting.

Previous work looked at perceptions of nursing assistants who were charged with the duty of daily oral care of long-term care residents. For the staff that had direct responsibility for patient care on a daily basis, an adequate level of knowledge and values about oral health was evident. However, considerable concern about being very busy with a variety of other important caring activities and fear of being bitten by patients unable to cooperate during oral care was expressed.

It is apparent that many factors impact how oral health is valued in long-term care facilities where patients frequently must depend on caregivers to provide daily oral care among a number of other services. The challenge will be to assist future generations of patients with natural teeth in maintaining oral health when they become frail and require significant levels of assistance. With the growth of the aging baby boom generation that has had the benefit of preventive lifestyles, new strategies will be required to ensure the continued quality of life that oral health imparts.

MARSHA A. PYLE + T. ROMA JASINEVICIUS + DANNY R. SAWYER

http://dental.case.edu

ELIZABETH A. MADIGAN

Nursing

Improving Home Health Care: The Epidemic of Chronic Disease and an Aging Population

The epidemic of chronic diseases in the United States is causing an upheaval in the health care system while, at the same time, the country is faced with a projected explosion in the number of older Americans. The country's health care system provides many sites and forms of care for older Americans with chronic diseases: nursing homes, hospices, assisted living, and adult day care. Most older adults, however, prefer to remain at home. According to **Elizabeth A. Madigan, Ph.D., R.N., F.A.A.N.,** associate professor of nursing at Case's Frances Payne Bolton School of Nursing, home health care services are widely available, but their effectiveness and the best approaches to providing care are not well understood. "Part of the problem," she says, "is that the community-based care system is complicated with various kinds of providers that all have different requirements for service eligibility. In addition, there can be gaps in communication between physicians, hospitals, and home health care agencies."

As part of her 10-year study of home health care patient outcomes, Dr. Madigan has been working with local and national groups of home health care agencies to determine the best approaches to providing care that achieve the best outcomes for their patients. One of the most pressing issues is that of repeated hospitalizations among some patient groups. Using a health services research approach, Dr. Madigan and colleagues are studying national populations of home health care patients to try to determine the factors that place patients most at risk for repeated hospitalization. In this way, the agencies that provide care can more easily identify the patients at most risk for repeated hospitalization and provide more home visits at the times of highest risk. The National Institutes of Health are interested in translational research—translating results from bench science and randomized clinical trials into actual health care settings. Unlike a tightly controlled experiment designed to evaluate an intervention on a select group of patients, translational science takes science directly to the bedside, including the home.

"Translational science is a challenge because it can be very difficult to change actual clinical practice within the constraints of the real health care system," Dr. Madigan notes. Adding to the complexity is the attempt to change practice outside a traditional health care setting: home health care nurses are experts at adapting patient homes for health care, but there are limits as to what is possible. Despite the challenges, Dr. Madigan acknowledges that the best use of investments in health research are with patients being cared for by providers informed of the research, adapting the science to a particular patient situation.

http://fpb.case.edu/faculty/madigan.shtm

Applied Social Sciences

Engaging Families and Communities in the Care and Protection of Children

In the most severe cases of child abuse and neglect, child welfare professionals remove children from their parents' care to protect the children from additional harm. Rather than leaving a social worker to make these choices in isolation, an alternative approach called Team Decision-Making (TDM) was developed in Ohio and is now used throughout the United States. TDM includes a meeting of community representatives, family members, and social workers who review every decision to remove a child from his or her parents, or make any change of placement, including reunification or adoption. Led by a skilled facilitator, team meetings allow the members to make the best decision possible in each case with the last resort being the removal of the child from the home.

Recognizing the serious challenges facing the country's child welfare system, the Annie E. Casey Foundation developed the reform initiative called *Family to Family* to identify strategies and tools to confront these very real problems. With TDM as one of the program's core strategies, the foundation selected **David Crampton, Ph.D.,** assistant professor of social work at Case's Mandel School of Applied Social Sciences to join a national research team that is evaluating *Family to Family's* implementation. Dr. Crampton, the lead investigator for the analysis of TDM, is working with Tom Crea, a doctoral candidate from the University of North Carolina at Chapel Hill, and Anne Abramson Madden, a doctoral student at the University of California at Berkeley. Together they visited Cleveland, Ohio; Denver, Colorado; Louisville, Kentucky; and Orange County and San Francisco in California and conducted 74 focus groups and interviews involving 180 administrators, caseworkers, community partners, supervisors, and TDM facilitators across these five *Family to Family* sites.

The study articulates the strategies that these five communities used to implement TDM and to overcome the challenges it presented. For example, while child welfare staff members were generally supportive of TDM, they were concerned about the amount of time needed to organize and attend meetings, adding the time demands of TDM to work that is already very time-intensive. In order to address this concern, the child welfare agency's leadership must provide sufficient resources to support TDM and demonstrate its benefits by providing data that shows how it improves the lives of the children and families the agency serves. Dr. Crampton will continue to work with the national research team to evaluate the *Family to Family* strategies that will help strengthen these efforts.

"Team Decision-Making is an effective way to increase family and community input into the most critical decisions made by child welfare staff. Our goal is to help identify how child welfare agencies can improve their use of TDM—not only in Cleveland, but across the United States," said Dr. Crampton.

DAVID CRAMPTON

http://www.aecf.org/initiatives/familytofamily/tools.htm

AMOS N. GUIORA + JESSIE HILL + WILLIAM E. DEAL + TIMOTHY K. BEAL

Arts + Sciences / Religion + Law

Religion, Terrorism, and the Law: Bringing New Understanding to a Critical World Issue

In the aftermath of September 11th, age-old questions about the relationship between religion and violence presented a new urgency. How does religion serve to inspire, ordain, and sanctify terrorist violence, from radical Islamists in Pakistan, to followers of Aum Shinrikyo in Japan, to Christian white supremacists in Ohio? Is religious terrorism fundamentally different from other forms of terrorism? Does religion motivate terrorist violence, or does it simply serve to justify it?

Moreover, how should legal and political institutions respond? Can a deeper, more complex understanding of religion and its relationship to radicalism, sectarian violence, and the forces of nationalism and globalization help law and policy makers address the crisis more effectively? What are the means and limits of intervention within religious groups? When does intervention go too far, threatening the rights of religious freedom, or not far enough, threatening the security of others?

These questions are not simply "academic." The effectiveness of local, national, and global law and policy in deterring religious terrorism will depend on how they are answered. Because they cannot be addressed adequately from any single perspective, they call for new and unprecedented forms of collaboration between scholars in the fields of law and religious studies.

Responding to this call, faculty members in the Case School of Law have partnered with religious studies faculty in the Case College of Arts and Sciences to form a research initiative on religion and terrorism. The goal of this initiative is to put law and policy into closer conversation with religious studies and other humanities disciplines in order to inform policy makers so that they may develop more effective means of addressing the problem of religious terrorism. The leadership team is headed by **Amos N. Guiora, J.D.,** professor of law and director of the Institute for Global Security Law and Policy, and **Jessie Hill, J.D.,** assistant professor of law, along with the co-directors of the College's Interdisciplinary Initiative on Religion and Culture, **William E. Deal, Ph.D.,** Inamori Professor of Ethics, and **Timothy K. Beal, Ph.D.,** Florence Harkness Professor of Religion.

In keeping with their goal of bringing together scholars from many disciplines to address these pressing issues, the team hosted an opening roundtable conference to identify the relationship between law, policy, and religion. Participants included experts from the Case faculty, physicians, a senior law enforcement official, and a Presbyterian minister. Prior to the roundtable, Professor David Little of the Harvard Divinity School gave the inaugural *Distinguished Lecture in Global Security Law and Policy.* The roundtable and subsequent meetings have led to a major interdisciplinary conference, "Sacred Violence," to be held at the Law School this spring. The keynote speaker is Professor Bruce Hoffman, one of America's foremost experts on terrorism. Other participants include leading academics from several different fields.

"This team represents the very best in an interdisciplinary approach to a highly complex, 'hot-button' issue by combining academics with practitioners from different fields, enabling Case to make a unique contribution to the public debate," notes Professor Guiora.

http://www.law.case.edu/centers/igslp/
http://www.bakernord.org

MELVYN C. GOLDSTEIN

Arts + Sciences / Anthropology

Preserving Tibetan Voices and Revising Modern Tibetan History

Fifty-three years after Tibet was incorporated into the People's Republic of China, the status of Tibet vis-à-vis China remains a contentious issue, as does our understanding of what Tibetan society was like before and after its traditional system was ended by the Chinese Communist Party in 1959. Despite the enormous interest in Tibet and the Dalai Lama in the West, our understanding of modern Tibetan history and society has been severely distorted by politically slanted representations and by a lack of firsthand field research with Tibetans.

To fill this knowledge gap, the *Tibet Oral History and Archive Project* was established in 2000 to collect a large corpus of oral histories from everyday Tibetans from all walks of life. Led by **Melvyn C. Goldstein, Ph.D.,** the John Reynolds Harkness Professor in Anthropology and co-director of the Center for Research on Tibet at the Case College of Arts and Sciences, the project received initial funding from the Henry Luce Foundation. At the time the project began, the cohort of individuals who were adults at the end of the traditional era in 1959 was dwindling, meaning an impending loss of a crucial dimension of the history of the Tibetan people—the voices of ordinary Tibetans—speaking to the continuities and changes they had experienced over the past five decades.

Since the project's beginning, more than 1,000 hours of taped interviews have been conducted with more than 500 individuals, creating a corpus of nearly 15,000 pages of transcripts (in translation) that together present a remarkable new and exciting window on modern Tibetan society and history. These interviews are being analyzed and incorporated into new publications, including Dr. Goldstein's *A History of Modern Tibet, 1951-55: The Calm Before the Storm* (Spring 2007, University of California Press), which is volume two of a planned four-volume set, as well as in his new monograph on Trinley Chodron, a Buddhist nun who emerged during the Cultural Revolution in Tibet and became a "Tibetan Joan of Arc."

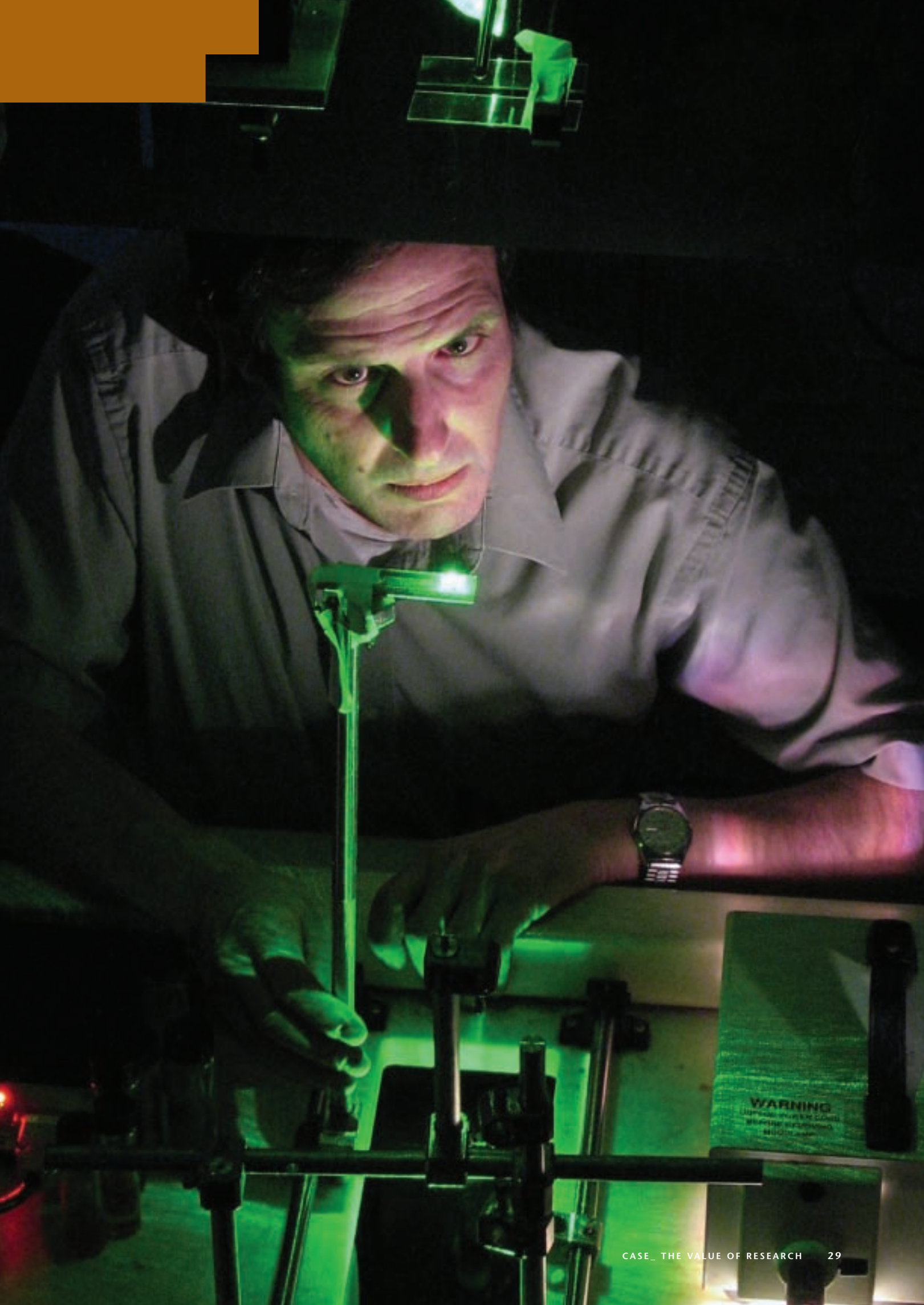
The *Tibet Oral History and Archive Project* is also creating a substantial Web-based archive to preserve this interview corpus together with hundreds of previous interviews conducted by Dr. Goldstein with Tibetan government officials. When completed, users anywhere in the world will be able to access the archive on-line and instantly search the archive, listen to interviews in Tibetan, and read the English translations that include an integrated glossary for specialized vocabulary. The *Tibetan Oral History On-Line Archive* will eventually become part of the Digital Collection of the Asian Division of the U.S. Library of Congress.

http://www.case.edu/affil/tibet/

"The use of magnetic fields to levitate fluids in a simulated reduced or zero gravity environment is scientifically fascinating, and may provide clues for solving a number of concrete problems. The application of our discoveries to controlled nuclear fusion for energy production, to water recovery on interplanetary space missions, or to a more prosaic problem such as resolution control of inkjet printers are just three possibilities."

CHARLES ROSENBLATT

Technology + Innovation

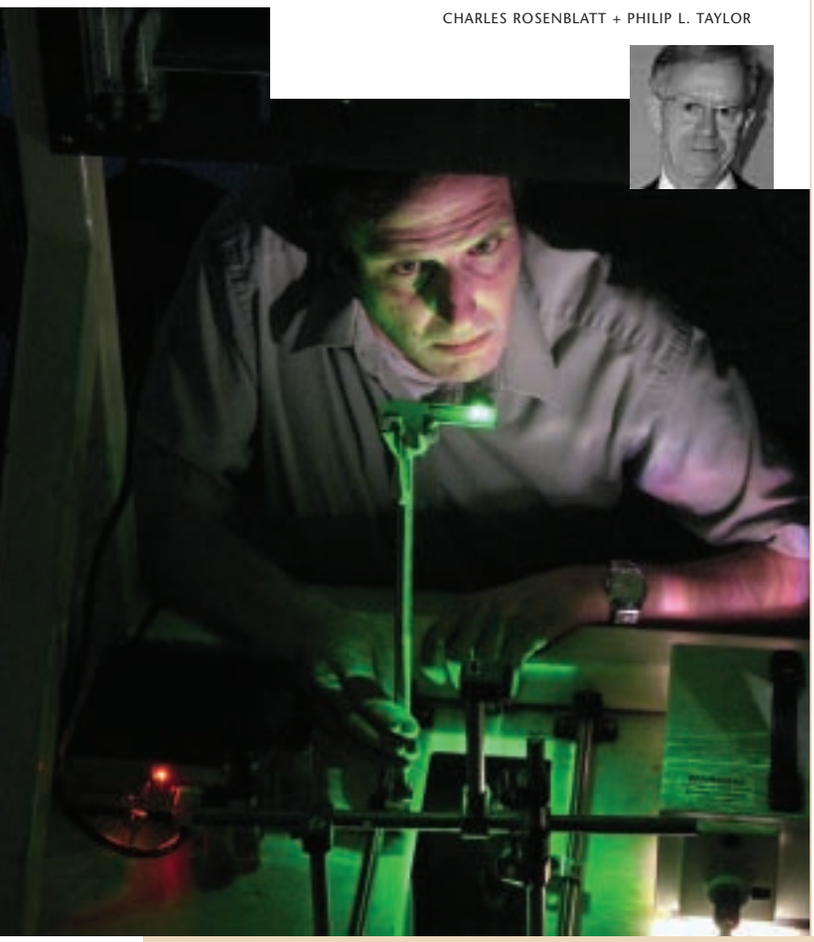

WARNING

Arts + Sciences / Physics

Dancing Fluids in Magnetically-Controlled Gravity

During the past two decades, **Charles Rosenblatt, Ph.D.,** professor of physics at the Case College of Arts and Sciences, has been a pioneer in the use of magnetically-simulated micro-gravity to study the behavior of fluids. Using an electromagnet to levitate fluids in order to simulate the spectrum of gravitational force, he can determine the fluid's physical properties from the resulting motion and shape, which are captured on computer-recorded images. This technique has important implications for understanding how materials act under a variety of gravitational conditions. For example, magnetic levitation may be used to simulate the vibrational effects of earthquakes, the motion of fluids that build up in the lungs with heart failure, or what may happen aboard a spacecraft during a lunar landing.

CHARLES ROSENBLATT + PHILIP L. TAYLOR



The research of Dr. Rosenblatt, who shares a NASA grant with **Philip L. Taylor, Ph.D.,** Perkins Professor of Physics, can be illustrated by the vigorous shaking of a bottle of vinegar and oil salad dressing to mix the liquids. What happens if one attempts to float the more dense vinegar on top of the less dense oil? The interface is metastable: a tiny perturbation will disturb the interface and cause the vinegar to fall to the bottom, which is known generically as an "acceleration-driven fluid instability." It lies at the heart of myriad industrial applications and diverse phenomena, including liquid impact and atomization, which is important in the optimization of rocket motors or diesels; nuclear fusion by inertial confinement as an energy source; the explosion of supernovae; and even the resolution control of ink-jet printers.

Although this instability was described by Lord Rayleigh more than a century ago, experimental work has been plagued by difficulties in establishing the initial condition of a dense fluid floating on top of a lighter fluid. Numerous techniques have been attempted, including separating the fluids with a membrane that can be removed quickly, analogous to a pulling a table cloth from beneath a setting of fine china. The resulting jitter, however, causes undesirable artifacts and obfuscates the results.

With his expertise in creating spatially-inhomogeneous magnetic fields to exert forces that counteract gravity—either partially or completely—Dr. Rosenblatt joined with theorist Pierre Carlès, professor of fluid mechanics at the University of Paris, to investigate the Rayleigh-Taylor and Richtmyer-Meshkov fluid interface instabilities. By using his magnetic technique to levitate the heavier fluid, control the shape of the fluid-fluid interface, and then release the fluid, he is able to investigate the instability over a far wider range of physical properties than is possible using conventional methods. In a recent modification he has found the 50-year old "Holy Grail" of fluid interface instabilities: the ability to impose arbitrary and controlled initial perturbations on the interface.

"This magnetic technique has three unique advantages—it facilitates investigations involving time-varying accelerations, allows one to study the evolution of the instability for very long durations, and permits exquisite control of the initial interface shape," explains Dr. Rosenblatt, who also maintains an active National Science Foundation and U.S. Department of Energy-funded research program on nanoscopic control and properties of "soft materials" such as liquid crystals.

http://liq-xtal.case.edu
http://liq-xtal.case.edu/videos.htm

KATH BOGIE + JIAYANG SUN + XIAOFENG WANG

Arts + Sciences / Statistics + Medicine

Novel Technique Uses Data Mining to Prevent Pressure Ulcers

For patients who are paralyzed, bedridden, or in wheelchairs, there is a great risk of developing pressure ulcers. Staying in one position creates constant pressure against the skin which cuts off circulation to certain areas, causing the affected tissue to die. For many people with reduced mobility, this devastating complication can lead to systemic infections, septicemia, and death. **Kath Bogie, D. Phil.,** a senior research associate in the Case Department of Orthopaedics and the Cleveland FES (Functional Electrical Stimulation) Center—a consortium that includes Case, MetroHealth Medical Center, and the Cleveland Louis Stokes Department of Veterans Affairs Medical Center—has been investigating the long-term use of gluteal electrical stimulation (GSTIM) to reduce pressure ulcers.

The GSTIM system uses implanted electrodes to exercise paralyzed gluteal muscles to improve the tissue health. The effects of GSTIM are determined using several outcomes measures, including assessment of the pressures between the user and the seat. Regular assessments over several years produce huge quantities of pressure mapping image data for each patient. In collaboration with data mining experts **Jiayang Sun, Ph.D.,** professor in Case's Department of Statistics, and **Xiaofeng Wang, Ph.D.,** assistant professor of medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, the Longitudinal Analysis with Self-Registration (LASR) was developed.

The key challenges in data mining include huge datasets, in either dimension or size, with a need for an efficient alignment between sessions for accurate analyses. LASR is a novel technique for mining spatial-temporal data that overcomes these challenges. Properly registering and analyzing the huge amount of image data is crucial to understanding if true differences at the same location can be obtained and if they are due to GSTIM usage or just experimental variation. With the diverse knowledge and expertise of the collaborating investigators, LASR was developed to automatically register a large sequence of images and to analyze both "static" (quiet sitting) and "dynamic" (weight-shifting) pressure map images and movies.

In this study, LASR showed that GSTIM provides statistically significant changes in regional pressure distributions over time. The dynamic response to gluteal stimulation also changed significantly over time with continued regular use. In addition to its effectiveness to help reduce the risk of pressure ulcers, LASR has wider implications for other clinical fields and has many potential applications, including monitoring swarm formation, crowd management, or tracking drifting oceanic icebergs.

Drs. Bogie, Sun, and Wang agree that the ever increasing image data acquired for each patient makes it more and more desirable to use multiple statistical tools to assist in extracting relevant clinical information. They further agree that it is also becoming increasingly necessary to develop new statistical techniques, which is exciting because it motivates and shapes new directions in fundamental statistical research with applications far beyond the original clinical problem.

http://stat.case.edu/lasr

JAMES D. BURGESS + JONATHAN D. SMITH + THOMAS J. KELLEY

Arts + Sciences / Chemistry + Medicine

Understanding Cholesterol: How It Leads to Disease

Cholesterol molecules are essential building blocks of cell membranes and, as such, are a required ingredient for human life. The word "cholesterol" has, however, become notorious as several diseases are linked to improper cellular processing of the molecule, particularly atherosclerosis (hardening of the arteries), a global health problem. **James D. Burgess, Ph.D.,** associate professor of chemistry at Case's College of Arts and Sciences, and his research team are focused on gaining a better understanding of how cells handle cholesterol.

Within each cell, complex trafficking pathways exist to maintain the appropriate distribution of cholesterol between intracellular compartments. Cholesterol-related diseases appear to involve dysfunctions in the cell's ability to properly shuttle cholesterol between specific locations in the cell or to export cholesterol from the cell. The largest sub-cellular cholesterol pool is the plasma membrane, the barrier that separates and defines the inside and outside of the cell. The cholesterol content of the plasma membrane is believed to be tightly regulated by the cell to ensure that this critical barrier maintains the physical properties required for life. On the biochemical level, many basic life functions, such as cell-cell communication and immune response, inherently involve events occurring at the cell surface. To achieve this multifunctional behavior, the cell plasma membrane contains a vast array of membrane-resident proteins that carry out specific functions. Indeed, growing experimental evidence indicates that biochemical functions of the cell plasma membrane are dependent on and coupled to intracellular cholesterol transport and cholesterol metabolism.

A primary limitation in gaining a clearer understanding of how cholesterol is processed by cells is uncertainty in evaluating the cholesterol content of the cell plasma membrane using currently available methodology. To address this technological problem, Dr. Burgess's team has developed a microelectrode-based strategy that allows measurements of plasma membrane cholesterol in live cells at physiological temperature. Through collaboration with other research groups at Case, the team is now implementing the microelectrodes to evaluate altered cell plasma membrane cholesterol in disease state.

The initial progression of atherosclerosis involves accumulation of cholesterol in cells found in artery walls. The inability of these cells to export cholesterol by forming HDL particles, so-called "good cholesterol," plays a major role in triggering plaque buildup in arteries. Working with **Jonathan D. Smith, Ph.D.,** of the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, the team is performing experiments aimed at determining if HDL particles are produced inside the cell or on the surface of the cell. Basic knowledge about the mechanism by which healthy cells produce HDL is required for a better understanding of how disruption of cellular cholesterol metabolism can lead to disease. **Thomas J. Kelley, Ph.D.,** assistant professor of pediatrics at the Case School of Medicine, has discovered a link between cholesterol metabolism and airway inflammation associated with cystic fibrosis. The collaborative studies with Dr. Kelley are providing new insight into cellular cholesterol transport in lung related diseases.

http://www.case.edu/artsci/chem/faculty/burgess/

Medicine

Connecting with the Nervous System: Integrating Engineered Devices into the Human Body

Improving human health and function through the integration of engineered devices into living biological systems is the research focus of **Dustin Tyler, Ph.D.,** Nord Distinguished Assistant Professor in Case's Department of Biomedical Engineering and associate director at the Advanced Platform Technology (APT) Center. The APT Center and the Cleveland Functional Electrical Stimulation (FES) Center, where Dr. Tyler is an investigator, are both partnerships of Case and the Louis Stokes Cleveland Veterans Affairs Medical Center. The mission of the APT Center is to develop advanced technologies that serve the clinical needs of veterans and other patients with motor and sensory deficits, as well as limb loss, in order to reduce disability, improve daily functions, and enhance their quality of life.

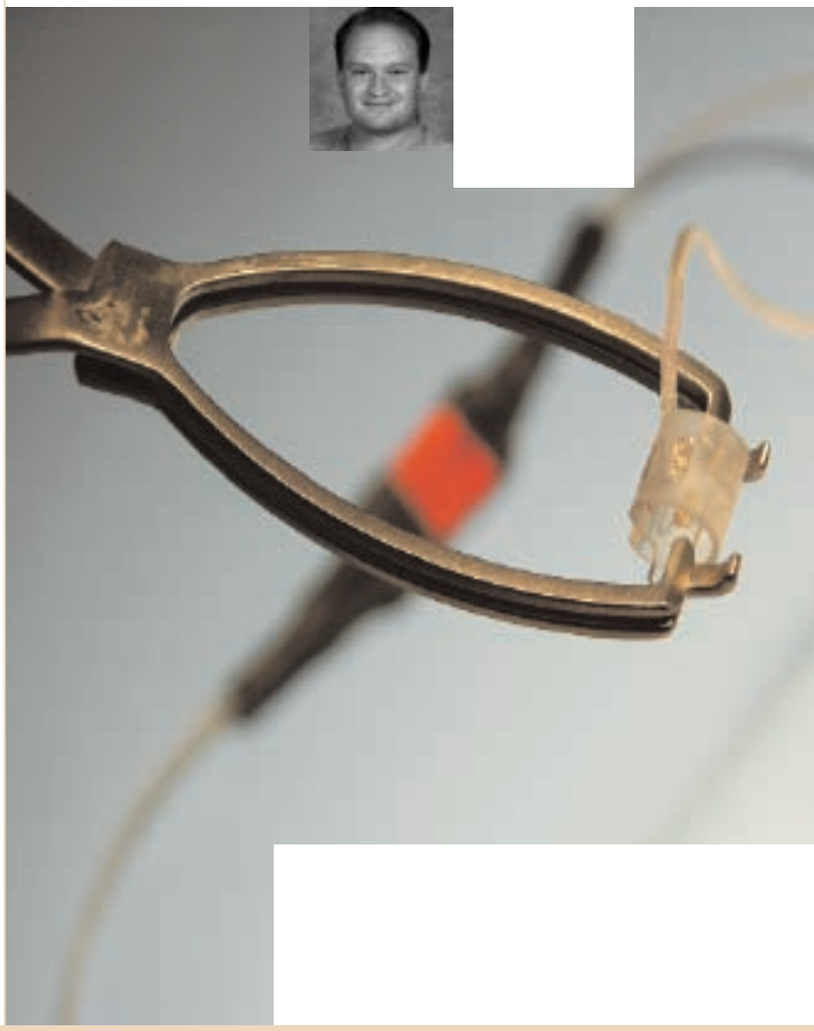
Dr. Tyler and his research team have successfully applied such technologies in a variety of clinical applications including restoration of hand, arm, and leg function in spinal cord injured individuals, as well as improvement of swallowing function following a stroke or central nervous system injury. They are beginning investigation with the technology as interfaces for natural communication between artificial limbs and the amputee. While the engineered devices employed in clinical trials have been successful, they do not yet behave as if they were natural neural tissue—they fall short of interacting with each individual neuron.

In developing neural interfaces to more efficiently connect engineered systems with biological systems, and specifically with the nervous system, there are many challenges that must be overcome. The nervous system is a dynamic, always evolving system that is sensitive to foreign materials. It consists of thousands of axons in each peripheral nerve and billions of neurons in the brain. More importantly, there are hundreds of connections for each neuron and hundreds of supporting cells—numbers that dwarf even our most advanced microprocessors.

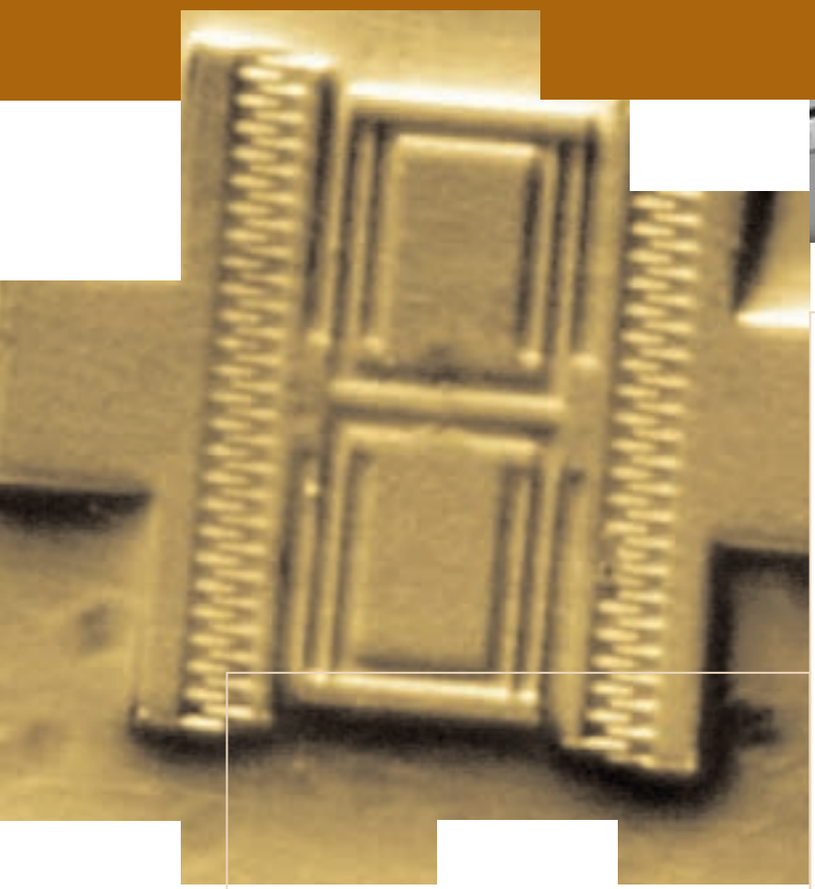
"The challenge is to develop next generation devices that integrate with rather than simply *interact* with the nervous system," notes Dr. Tyler. To this end, his multi-disciplinary research team is developing biomimetic materials with dynamic mechanical properties based on the structure of the sea cucumber. Biomimetics is a research field that incorporates properties that are found in nature into manufactured devices. Because the sea cucumber's skin is composed of collagen fibers in a matrix-like structure, it can go from a soft, liquid-like state to rigid stiffness. Using this model, the team's first application is to brain implantation devices that need to be stiff for insertion, but then soft to mimic the mechanical properties of the brain for long-term effectiveness. Continued work will incorporate molecular signals and cues to encourage neurons to attach directly to these devices.

"To design and build prototype devices that are clinically meaningful, a broad collaboration is required between biomedical engineering, macromolecular engineering, electrical engineering, chemical engineering, neuroscience, and many other disciplines," adds Dr. Tyler.

DUSTIN TYLER



http://www.aptcenter.research.va.gov/
http://bme.case.edu/faculty_staff/tyler/



JOHN J. LEWANDOWSKI + VIKAS PRAKASH + JOE H. PAYER

Engineering

Bulk Metallic Glass: A Wonder Material with Many Potential Applications

The Center for Mechanical Characterization of Materials at Case has sophisticated equipment that is capable of mechanically evaluating and deformation processing materials that range in size from the micrometer scale to bulk quantities. Center Co-Director **John J. Lewandowski, Ph.D.,** Leonard Case, Jr. Professor of Engineering in the Department of Materials Science and Engineering at the Case School of Engineering, is currently focusing his research on a particular class of fascinating materials that combines the property characteristics of metals, ceramics, and polymers: bulk metallic glasses.

There is a renewed interest in metallic glass, also known as amorphous metallic alloy, due to the recent success in producing it in a size that exceeds two centimeters. Most of the early metallic glass systems were produced in thin ribbon form, typically less than 200 micrometers thick, due to the high critical cooling rate required to obtain the amorphous structure. Unlike conventional metals that have a crystalline structure, the atoms of metallic glass must be cooled quickly to freeze their random atomic patterns. New metallic glass systems have a significantly lower critical cooling rate, enabling the production of thick sections. The low critical cooling rate has been attributed to the high glass-forming ability and excellent resistance to crystallization.

The recent availability of bulk metallic glasses enables the determination of the unique mechanical properties of these novel materials that include very high strength and hardness, malleability, increased energy absorption, and superplasticity. With superplasticity and flow characteristics similar to that of some polymeric systems at intermediate temperatures, metallic glass can be easily formed into complicated shapes at relatively low temperatures. Returning the material to room temperature returns the high strength characteristics, while exposing them to intermediate temperatures has been used to create nano-crystalline materials.

The photo shows a magnified replication of a MEMS (micro-electromechanical systems) device where simple metal forming techniques were used to replicate the sub-micrometer features—its fine scale features are on the order of one micrometer. Each total MEMS device is about 250 micrometers (in comparison, a human hair is on the order of 50 micrometers).

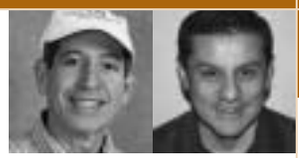
Case works collaboratively with industry, government, and other research teams to exploit some of these unique characteristics. **Vikas Prakash, Ph.D.,** professor of mechanical and aerospace engineering, is investigating the effects of high strain rate on the flow and fracture behavior of these materials. The unique corrosion resistance of some of these materials is being investigated by **Joe H. Payer, Ph.D.,** professor of materials science and engineering, and collaborators.

Most recently, in conjunction with researchers at the University of Cambridge, the Case team developed nano-scale temperature-sensitive coatings with high spatial and temporal resolution in order to detect the temperature rise that locally occurs as these materials deform and fracture via very thin, shear bands. A recent paper 'Temperature Rise at Shear Bands in Metallic Glasses' detailing their techniques and results was published in *Nature Materials* and was selected as an 'Editors Choice' paper in *Science.*

http://www.engineering.case.edu/research/

Engineering

Exercise, Diet, and Disease: Relationships Between Cellular Metabolism and Physiological Responses



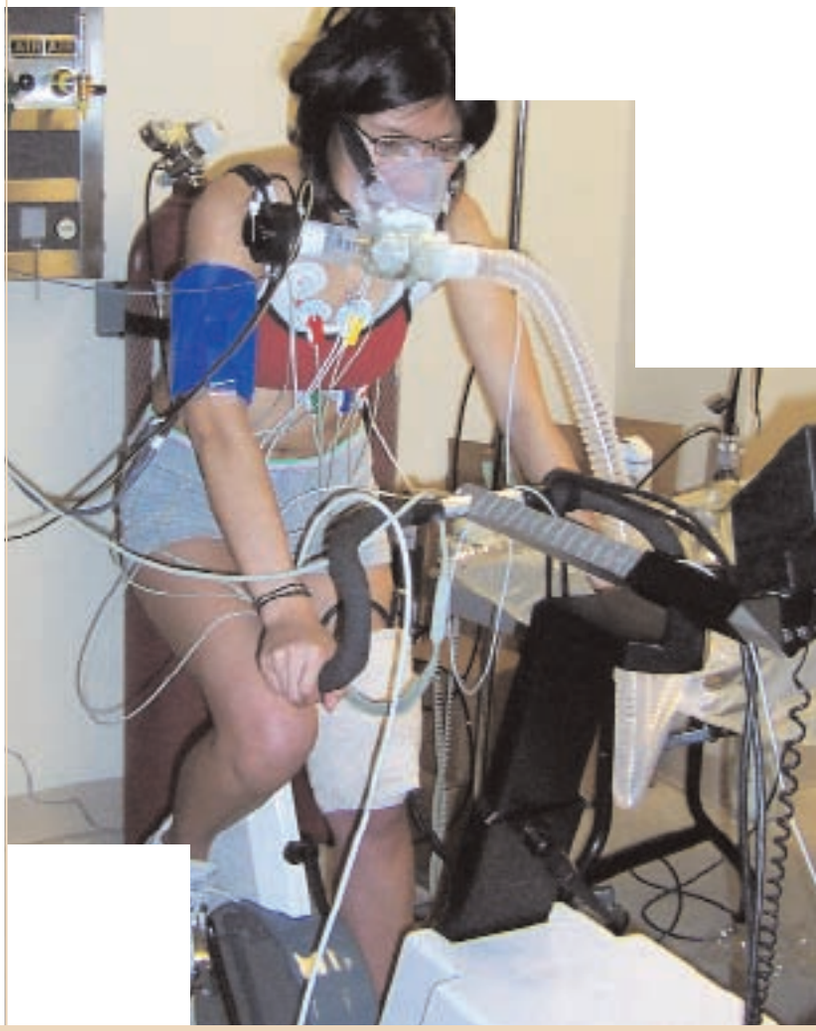
GERALD M. SAIDEL + MARCO E. CABRERA

The goal of the Center for Modeling Integrated Metabolic Systems (MIMS) is to apply computational methods for quantitative analysis of metabolic mechanisms of the heart, skeletal muscle, brain, liver and adipose tissue, as well as their integrated effects in the human body. The ultimate purpose and mission of the MIMS Center is to identify molecular targets or control points in metabolic pathways for therapeutic interventions. Using mathematical modeling and computer simulation to analyze cellular metabolism *in vivo,* research teams of the MIMS Center examine metabolic changes associated with exercise, diet, and disease. The MIMS Center is distinctive because of its multi-level, multi-scale approach to *in vivo* metabolic system dynamics. With this approach, MIMS research teams develop and apply quantitative tools to analyze complex biological mechanisms related to obesity, aging, diabetes, liver diseases, and neuro-degenerative processes.

The MIMS center achieves its goals with distinctive collaborative teams that provide tight relationships between theoretical and experimental studies. Validated MIMS models not only simulate biochemical and physiological responses, but also predict responses for which insufficient experimental data exist. Computational dynamic models allow quantitative evaluation of metabolic pathways and regulatory mechanisms under normal or abnormal conditions and in disease states. Another goal of the MIMS Center is to develop a new generation of researchers who can deal with complex systems modeling with emphasis on metabolism. The MIMS Center offers research training at the undergraduate, graduate, and postdoctoral levels associated with biomedical engineering, mathematics, biomedical sciences, and related fields.

The MIMS Center's director, **Gerald M. Saidel, Ph.D.,** professor of biomedical engineering, and associate director, **Marco E. Cabrera, Ph.D.,** associate professor of pediatrics and biomedical engineering, work with nine Center teams. These teams of four to seven participants involve 10 other key faculty collaborators and more than 20 research associates, graduate students, and staff. They come from many fields including biomedical engineering, pediatrics, physiology and biophysics, anatomy, biochemistry, molecular medicine, mathematics, and chemical engineering. These participants are associated with Case and Cleveland State University. Key investigators have research laboratories also at the University Hospitals Case Medical Center and Cleveland Clinic.

The MIMS Center is one of seven national Systems Biology Centers supported by the National Institute of General Medical Sciences, an arm of the National Institutes of Health, established to develop new methods for studying complex biological systems. "Our ability to analyze complex biological mechanisms is of critical importance because they are at the root of many serious health problems," notes Dr. Saidel.



http://www.csuohio.edu/mims/
http://bme.case.edu/faculty_staff/saidel/

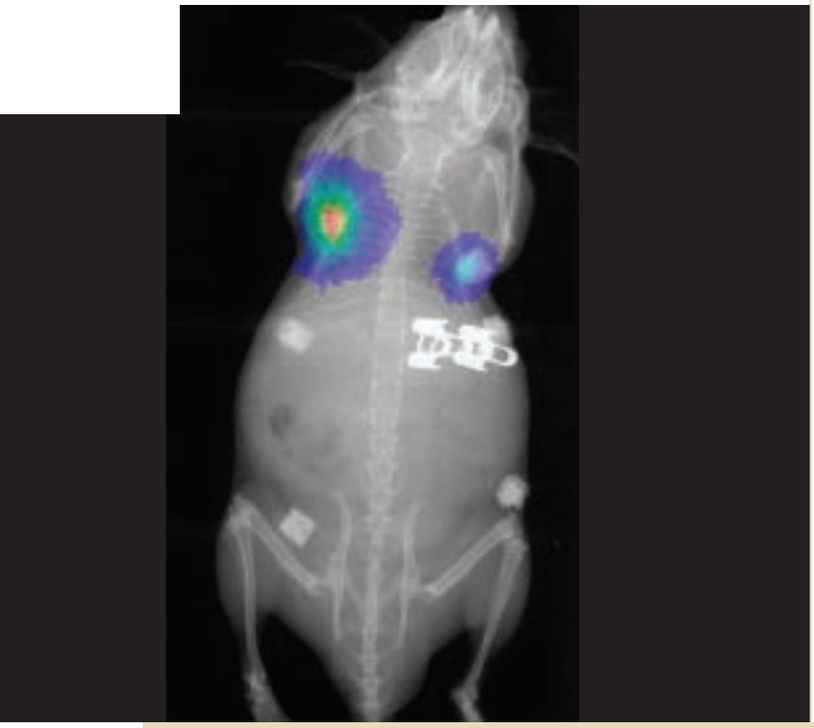
DAVID L. WILSON + JAMES BASILION + XIN YU + MARTY PAGEL + ANDREW ROLLINS

Engineering

Non-Invasive Imaging: Making Diagnoses at Cellular and Molecular Levels

Biomedical imaging has revolutionized health care by providing non-invasive diagnoses of anatomical shapes and sizes within the human body. New research paradigms are being developed to provide non-invasive diagnoses at the cellular and molecular levels—this new information can provide diagnoses at the earliest stages of a disease and can provide rapid assessments of many different therapies. Providing an exciting foundation for personalized medicines that are specific to a patient's cellular or molecular composition, these emerging paradigms are the focus of several biomedical engineering research endeavors at the Case School of Engineering, including the Molecular Imaging Program of the National Foundation for Cancer Research (NFCR) which is a joint venture among the Department of Radiology at the Case School of Medicine, University Hospitals Case Medical Center, the Case Center for Imaging Research, and the Department of Biomedical Engineering.

David L. Wilson, Ph.D., professor, is developing cryo-imaging techniques to provide ultra-high resolution and contrasts that will enable one to find a "needle-in-a-haystack"—single fluorescently-labeled stem cells, metastatic tumor cells, and infectious bacteria. Currently, instrumentation, software, and applications are being developed to this end. The lab of **James Basilion, Ph.D.,** associate professor of radiology and biomedical engineering and director of the NFCR Center for Molecular Engineering, is engaged in defining "molecular signatures" of disease, developing paradigms to image multiple markers of disease simultaneously, developing methods to image intracellular disease markers in breast cancer, and developing molecular imaging technologies that allow for intraoperative assessment of disease progression.

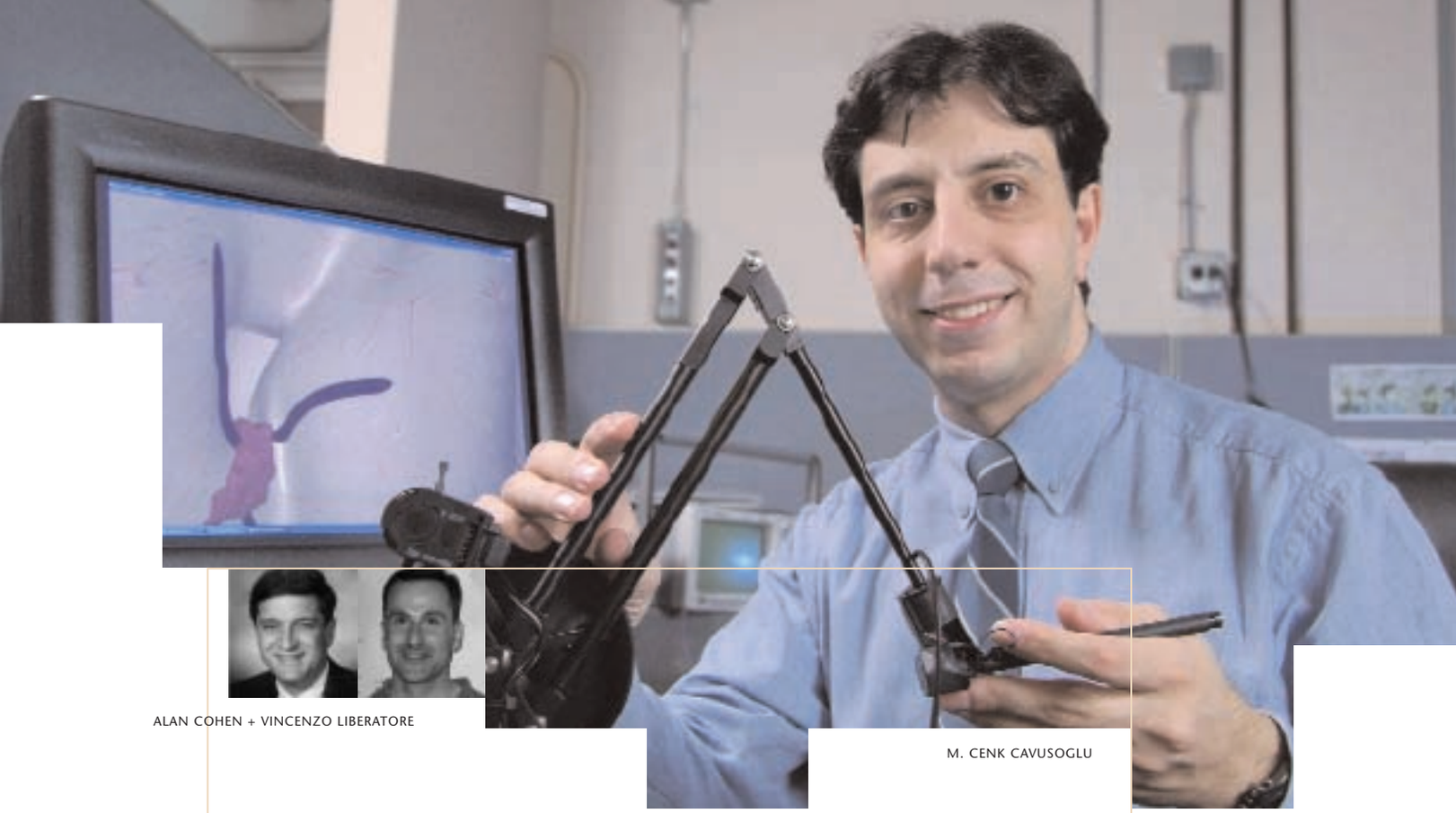


Using state-of-the-art MRI technology, **Xin Yu, Sc.D.,** associate professor, is exploring the links between cardiac mechanical function and structural and metabolic abnormalities in transgenic mouse models with cardiovascular diseases. In addition, MRI is being used in her lab to assess stem cell treatments of heart disease in mice. She is also collaborating with clinicians to apply the technologies developed in her lab for better and more sensitive detection of functional abnormalities in patients with cardiac disease. This interdisciplinary research integrates MRI, cardiology, and cell biology. Also using MRI technology, **Marty Pagel, Ph.D.,** assistant professor, has recently invented a fundamentally new type of molecular imaging chemical agent that can detect enzymes. By applying these chemical agents to detect enzymes that are responsible for breast cancer metastasis and cystic fibrosis, he can evaluate chemotherapies that stimulate enzymes to kill cancer cells.

Andrew Rollins, Ph.D., Warren E. Rupp Assistant Professor, is developing new methods of Optical Coherence Tomography (OCT) and fluorescence imaging of voltage sensitive dyes to assess cardiac development in avian and mouse models. This project will elucidate basic developmental cardiology and the etiology of congenital heart defects. In addition, Dr. Rollins has also been using OCT to detect early cancer in the esophagus and colon. This translational research involves the integration of biomedical optics and endoscopic methodologies.

Case's Biomedical Imaging Program is ranked among the top 12 pre-clinical imaging resources in the nation and its interdisciplinary teams currently support more than 80 biomedical research projects. Together with the state-of-the-art facilities at the Case Center for Imaging Research that is continuously evolving, along with the fast pace of imaging research developments, the collaborative achievements in the creation of novel imaging technologies at Case has made it a leader in fostering the next biomedical imaging revolution in health care.

http://bme.case.edu/research/imaging.html



ALAN COHEN + VINCENZO LIBERATORE

M. CENK CAVUSOGLU

Engineering + Medicine

Revolutionizing Medical Education through Virtual Reality

Despite the recent widespread popularity of minimally invasive surgical interventions, the steep learning curve of this technique has posed a major problem in the training of resident and attending surgeons. Minimally invasive surgery requires unique spatial perception and motor skills that are difficult to master. Traditional methods of surgical training that were previously adequate are not as effective in training these substantially new techniques.

Virtual environments present a complement to the contemporary apprenticeship-based training scheme of surgery. The idea, similar to using a flight simulator to train pilots, will lead to a quantum leap in surgical training. Virtual environments make it possible to create an interactive three-dimensional simulation environment, where surgeons, using haptic interfaces, can manipulate, cut, or suture dynamically and geometrically correct models of organs simulated on a computer. Providing a milieu in which there is no risk to patients, virtual environments are interactive and three-dimensional in contrast to text materials, and relatively inexpensive compared to training in the operating room or in animal laboratories. A unique advantage of this virtual training is that it is possible to generate arbitrary anatomies and pathologies, thus allowing surgeons to be trained for cases that they will encounter only infrequently in their entire careers.

An interdisciplinary research team led by **M. Cenk Cavusoglu, Ph.D.,** assistant professor at the Case School of Engineering, Department of Electrical Engineering and Computer Science, in collaboration with **Alan Cohen, M.D.,** professor at the Case School of Medicine, Department of Neurosurgery, and **Vincenzo Liberatore, Ph.D.,** associate professor at the Case School of Engineering, Department of Electrical Engineering and Computer Science, is developing the enabling technologies for the next generation of surgical training simulators that will revolutionize surgical training. The research focuses on several key enabling technologies ranging from human interfaces and computer networks, to an open source software development framework for medical simulation.

The research is driven by a clinical application of the technology for the development of a training simulator for endoscopic neurosurgery. Three-dimensional geometric models of the anatomical structure are constructed from segmentation of magnetic resonance images. They are then augmented with realistic computer graphics and simulation of the dynamic behavior of the manipulated tissue, and embedded into a virtual environment-based simulation. While the initial prototype is being developed for endoscopic third ventriculostomy, it will be followed by simulations of more complex procedures. Magnetic resonance images acquired from actual patients will be used to construct a library of patient-specific models of various pathologies and anatomical variations to provide a rich set of training cases.

http://robotics.case.edu/
http://gipsi.case.edu/

HEIDI B. MARTIN + CHRISTOPHER G. WILSON

Engineering

The Diamond Advantage in Implantable Biomedical Devices

The word "diamond" inevitably brings to mind the coveted jewel. In the 1940s, DeBeers introduced the highly successful "A Diamond is Forever" campaign, making diamonds the gem of choice for engagement rings. Scientifically, a diamond is also "forever" in terms of its extreme chemical and mechanical stability. For several decades, researchers have synthesized diamond either as a single-crystal or as a film coating, with anticipation that these high-quality gems with fascinating engineering properties will promise more than their sparkle. **Heidi B. Martin, Ph.D.,** assistant professor of chemical engineering at the Case School of Engineering, has been one of the leading researchers on characterization of conductive diamond for electrochemical applications since the research area emerged.

While industrial tool makers use diamond as an ultra-hard coating to increase tool lifetimes, Dr. Martin and her team work to apply the same advantage to implantable medical devices and to create conductive, diamond-based films that can be used as robust sensors and stimulators in the human brain. Diamond electrodes have potential as biosensors for electrochemical detection of neurotransmitters—the chemical messengers between neurons within the brain and nervous system. Neurotransmitters play a critical role in healthy brain function; abnormal increases or decreases in neurotransmitter levels have been linked to Alzheimer's, Parkinson's, and Huntington's diseases, as well as schizophrenia and drug addiction. Diamond provides a unique opportunity to integrate stimulation and sensing in the same implantable device. If implanted diamond electrodes can be used to continuously monitor and manipulate the concentration of neurochemicals in real time, doctors might better understand the processes that regulate communication between neurons. For example, such an electrode could help guide treatment in Parkinson's patients, by allowing doctors to measure the levels of dopamine, a deficiency of which is found in people with Parkinson's, or to control patients' random movements with deep-brain stimulation.

In collaboration with **Christopher G. Wilson, Ph.D.,** assistant professor of pediatrics at the Case School of Medicine, Dr. Martin's research team has developed diamond micro-disk electrodes that are implanted into the group of nerve cells in the brain that control the frequency of breathing, known as PreBötzinger Complex. This makes it possible to explore the role of adenosine, a compound released by the brain that modulates neural activity, in modulating respiratory rhythm. Because this compound's activity is linked to insomnia, apnea, and other sleep problems, the diamond electrode's capability to detect adenosine will assist in the development of more effective medicines to regulate it.

"Case has a strong, 40-year reputation in diamond research. Our interdisciplinary team is showing how diamond electrodes can provide real-time neurological sensing capability with greatly improved sensitivity, selectivity, and stability, as well as an expanded range of operation over present materials," notes Dr. Martin. Working together with colleagues from biomedical and electrical engineering, as well as biology, the team seeks to incorporate diamond electrodes as part of a wireless, implantable device combining chemical and electrical recording with neural stimulation, providing the basis for robust, diamond-based devices that can extend into broader areas of biomedical research.

http://www.case.edu/cse/eche/people/faculty/martin/

Engineering

Creating the Next Generation of Nanolayered Polymers

An exciting new field of interdisciplinary macromolecular science and engineering has rapidly emerged over the past decade at the crossroads of polymer science, engineering, chemistry, physics, and biology. This field of "polymers plus" enjoins natural biological materials systems (lessons from biology), revolutionary new synthetic polymers with greater control of macromolecular and supermolecular architecture, and innovative processing of polymeric assemblies. A recent breakthrough in the laboratories of **Eric Baer, D. Eng.,** the Leonard Case Professor of Engineering, and **Anne Hiltner, Ph.D.,** the Herbert Henry Dow Professor of Science & Engineering, both in the Department of Macromolecular Science and Engineering at the Case School of Engineering, extends layer-multiplying co-extrusion technology to the nanoscale, making it possible to fabricate films with many thousands of layers. This extremely flexible process relies on forced-assembly to achieve nanoscale structure.

With Dr. Hiltner serving as director and Dr. Baer as research chair, Case's new National Science Foundation *Science and Technology Center for Layered Polymeric Systems* (CLiPS) promotes this nanoscale technology and facilitates its translation to the commercial sector through innovative research and education partnership. Its three research platforms focus on different aspects of the technology.

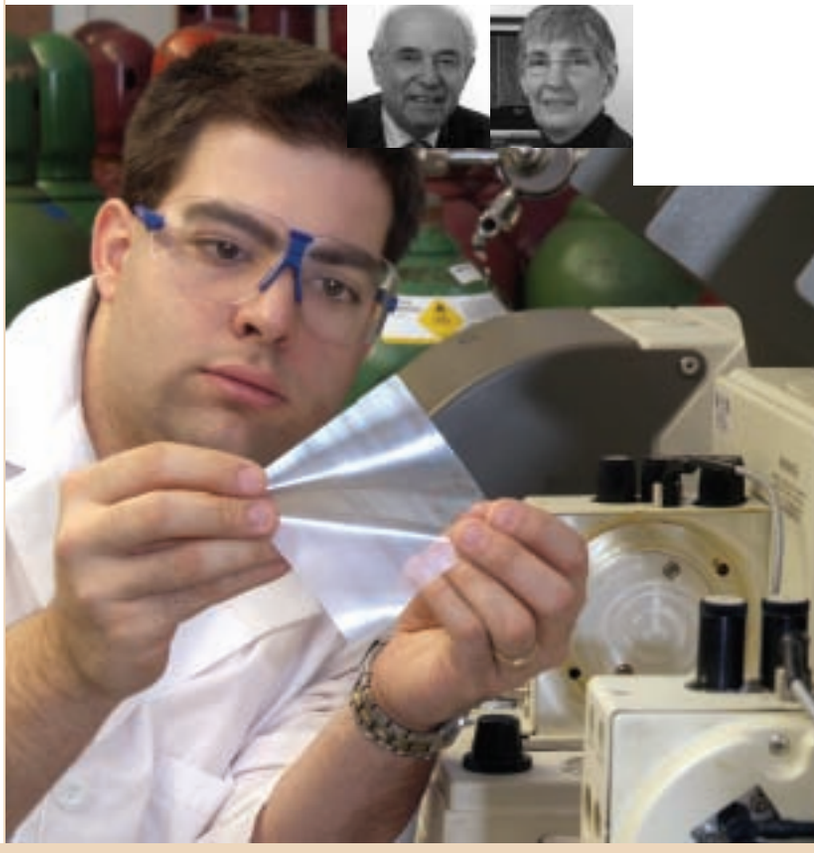
The first platform focuses on process innovations for creating the next generation of nanolayered polymer-based structures and systems. It directly extends the research of Drs. Hiltner and Baer and concentrates on enhancing existing co-extrusion facilities to improve uniformity of nanolayers, to increase the flexibility of the system, and to improve the overall quality of co-extruded film. Current research involves further improving layer uniformity through novel processing techniques.

Additionally, this platform identifies and characterizes the unique properties of the polymer interface in nanolayers. The extremely large interfacial area of these structures makes it possible to probe the interface-dependent phenomena using conventional methods of polymer analysis. This interfacial area will additionally be exploited to develop new material systems, which may require incorporation of active species into the layers that will undergo physical self-assembly or chemical reaction at the interface.

The second platform deals with the discovery and exploitation of membrane and barrier phenomena that lead to material systems with unique transport properties. Activities include studies of membranes with unique selectivity and thermal responses, and open-cellular structures. A fundamental understanding of transport phenomena in nanolayered systems is being developed and will be used to design and optimize unique layered systems for food and electronic packaging, drug delivery, environmental control, and diagnostic devices.

In the third platform, the novel optical properties associated with one-dimensional photonic bandgap structures are exploited and combined with other property enhancement strategies to impart superior optical responses on a new generation of photonic devices. Such strategies include the synthesis of highly nonlinear optical responsive chromophores, and inclusion of metallic and semiconducting nanoparticles, nanorods, and carbon nanotubes. Unique properties of nanolayered polymer structures are being investigated with the aim of enhancing the efficiency of photovoltaic devices and designing various terahertz-frequency photonic components.

ERIC BAER + ANNE HILTNER



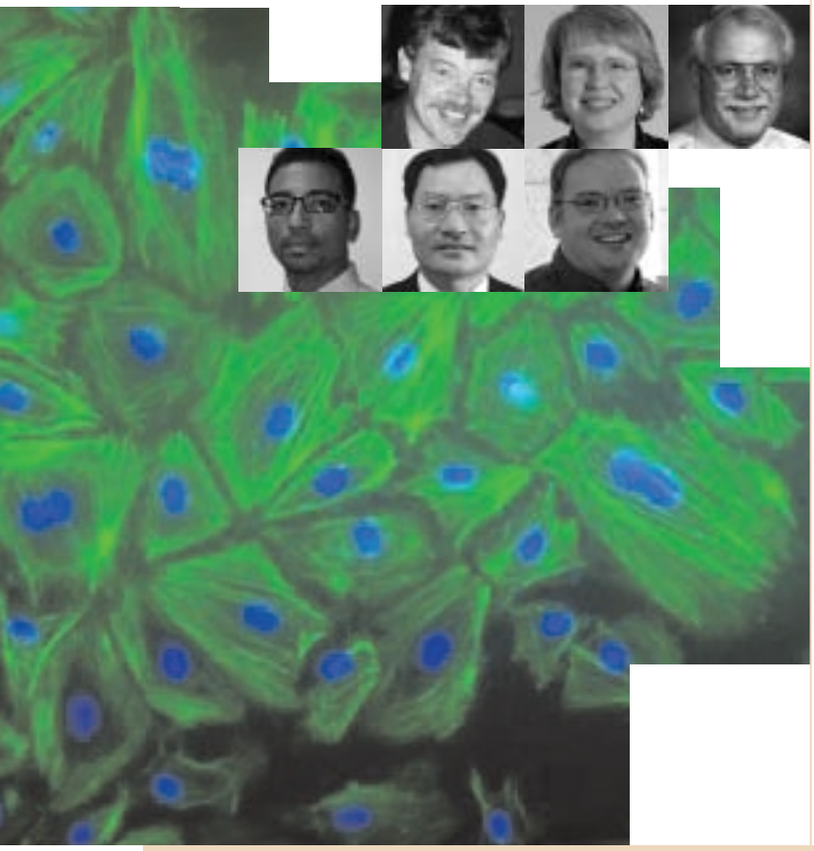
http://clips.case.edu/

Engineering

Biomimetic Materials: The New Building Blocks of Health

Thrombosis, excessive healing responses, and bacterial infection, are significant clinical problems associated with blood- or soft tissue-contacting medical devices, such as arterial prostheses, endovascular stents, catheters, and drug delivery systems. To address these clinical problems, the research of **Roger Marchant, Ph.D.,** professor of biomedical engineering at the Case School of Engineering, is concerned with the design and engineering of new "biomimetic" materials that will make implanted devices biocompatible in contact with blood and soft tissues. Biomimetic (or biomimicry) describes a research approach for designing new biomaterials that are based on understanding and exploiting the mechanisms that the body uses to solve clinical problems. Understanding how biological molecules can assemble in a cell membrane for example, provides a wealth of concepts for creating new building blocks for bioengineered materials that will also assemble and display biological properties.

ROGER MARCHANT + KANDICE KOTTKE-MARCHANT + JAMES M. ANDERSON + ANIRBAN SEN GUPTA + JUNMIN ZHU + STUART ROWAN

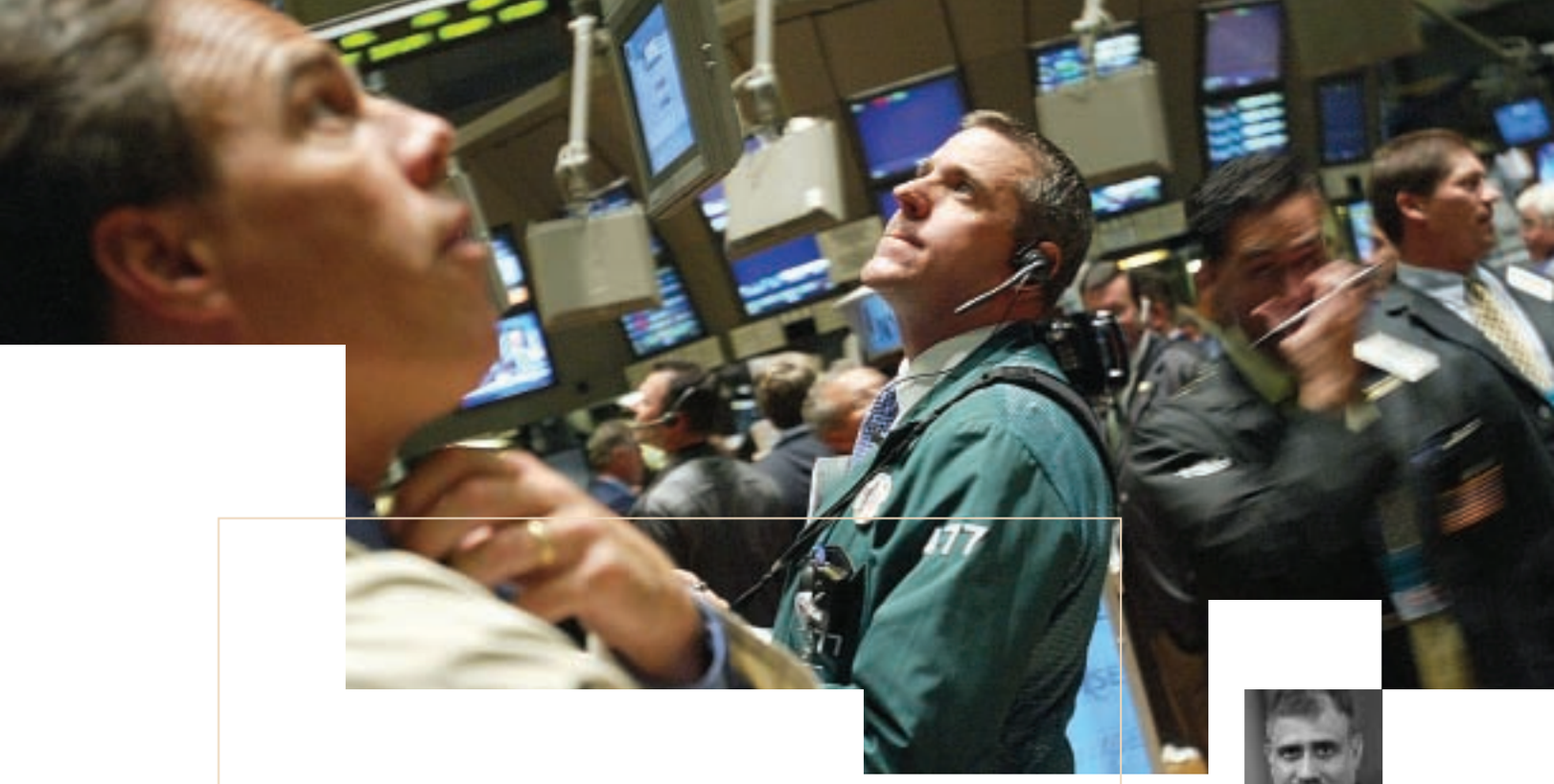


Dr. Marchant, together with his principal collaborators, **Kandice Kottke-Marchant M.D., Ph.D.,** Division of Pathology and Laboratory Medicine at Cleveland Clinic; **James M. Anderson M.D., Ph.D.,** professor of pathology; **Anirban Sen Gupta, Ph.D.,** assistant professor of biomedical engineering; **Junmin Zhu, Ph.D.,** senior research associate in biomedical engineering; and **Stuart Rowan Ph.D.,** associate professor of macromolecular science, work towards mimicking and adapting structural concepts from Nature to create new biomaterials that incorporate molecular recognition and self-assembly. The research first involves designing the biomimetic molecules using computer modeling, followed by detailed synthesis and analysis. The building block molecules are then assembled into a final biomimetic material, and its biological properties in cell cultures are studied using advanced imaging techniques such as fluorescence microscopy and atomic force microscopy.

One biomimetic design that benefits from understanding the structural and functional properties of the corresponding system in Nature is the external region of a cell membrane, known as the glycocalyx. The glycocalyx is a dense canopy of carbohydrate molecules that covers every cell, and helps protect the cell from many undesirable reactions that initiate thrombosis or infection. Based on this concept, Dr. Marchant designed carbohydrate polymers that suppress undesirable protein interactions and thrombosis on cardiovascular implant devices. Local companies, Biomec Inc. and Nanomimetics Inc. are commercializing this design for applications on blood pumps/extracorporeal circuits, catheters, and small diameter vascular grafts.

Similarly, within the glycocalyx are specialized protein molecules that enable the cell to stick to the surrounding tissues and the extracellular protein matrix. Based on this understanding of how cells adhere to surfaces, Drs. Marchant, Kottke-Marchant, and Zhu have developed new biomimetic materials on which endothelial cells can grow and mimic a blood vessel. Biomimetic approaches are also being explored in the development of targeted cell selective drug delivery, and for water-swollen gels, called hydrogels, which are needed for tissue engineering applications.

http://bme.case.edu/faculty_staff/marchant/



SAYAN CHATTERJEE

Management

Taking Risks While Avoiding the Risk of Failure: How Companies Profit

The whole reason business exists is to take risks, yet most strategy frameworks are focused on analyzing returns and addressing risk only as an afterthought. When analyzing industries to determine whether they are attractive, attractiveness typically equates to profits. However, using that measure, companies such as JetBlue and Southwest should not exist: they are thriving in an industry where most of the established players are barely getting by. The research of **Sayan Chatterjee, Ph.D.,** professor of management policy at Case's Weatherhead School of Management, takes a different perspective. Profit is paramount, but only after adjusting for risk, because profit is the result of a firm's ability to take risks while avoiding the adverse impacts of those risks.

Throughout the 1990s, business models that increased risk were hailed to be "revolutionary." Yet following the Enron debacle, it suddenly became fashionable to eschew the revolutionary approach as being too risky, and there was a swing back to a more incremental approach. According to Dr. Chatterjee, this behavior is a classic response firms tend to exhibit when confronted with unexpected risk, and it is also exactly the wrong kind of response.

His research suggests a different approach is needed. Instead of running away from risk, profits are viewed as the residual return after avoiding the risk of failure. There are three dimensions for avoiding these failure risks: clarity, choice, and trade-offs. Clarity involves understanding exactly where the risks lie; choice involves identifying more options than competitors to avoid the risks; and trade-offs are the decisions the manager has to make in order to manage the risks.

Dr. Chatterjee further identifies three basic risks that can derail any strategy. Demand risk is the risk that the value proposition a firm is trying to sell will not be accepted by the market or that the demand proves to be higher than anticipated, making a firm vulnerable to competitors capturing its market before it can scale up capacity. The inability to cope with unexpected demand may make a firm vulnerable to competitive risk, which is the risk that competitors will take its customers away. Finally, capability risk is the risk that a firm is not able to deliver the value propositions that customers will pay for or the capabilities cost so much that it is unable to make a satisfactory profit. Typically, companies choose between demand and competitive risk when developing a new strategy and then deal with capability risk at the operational level—a major source of execution failure is not having the appropriate capabilities to deliver a value proposition while capturing some of the value for the firm's shareholders.

"Simply put, my research shows that profit comes from taking risks—profitable firms are profitable because they can manage risks better than the competition. Further, the way to manage risks is to design a business model that plays to a firm's strengths. Most firms fail because they do not understand the risks and they overestimate their capabilities in mitigating the risks," points out Dr. Chatterjee.

http://wsomfaculty.case.edu/sayan/


disease (AD) and
participants
contrast
repetition
that the
patients,
subject
than

"The widely accepted assumption that intellectual capacity diminishes in older adults is challenged by our research results—we have shown that it is age-related impaired visual perception that greatly affects this group's ability to perform well on intelligence tests. In other words, their competence is better than their performance. As the population becomes increasingly older, we must be dedicated to understanding such issues to improve life quality."

GROVER C. GILMORE

Mind + Spirit

Applied Social Sciences

Testing the Intelligence of Older Adults: Vision Linked to Cognitive Competence

As people grow older, do they really lose intelligence or is something else happening that lowers their IQ scores over time? This was the question that **Grover C. Gilmore, Ph.D.,** dean of Case's Mandel School of Applied Social Sciences and professor of psychology and social work, wanted to answer. Heeding his training that had taught him "to look for the simpler explanation first," Dr. Gilmore's research found that the competence of older adults is better than their performance. In other words, they are smarter than they seem.

GROVER C. GILMORE

To test his hypothesis that visual perception problems in older people impaired their ability to perform well on intelligence tests, Dr. Gilmore and his team conducted an experiment that tested both college students and older adults for their ability to encode, remember, and search for visual symbols. The results showed that when the impaired visual perceptions associated with old age were simulated on the same material, the college students exhibited the same diminished cognitive skills as the older adults. The research further showed that even subtle deficits, such as a reduction in spatial contrast sensitivity, can also impair performance on intelligence tests. Such deficits are often missed because they occur gradually over time and are not identified by regular eye examinations. Accordingly, Dr. Gilmore refers to them as "hidden deficits."

"As people grow older they are entering into a literally dimmer world. For Alzheimer's disease patients, that effect is even more pronounced," notes Dr. Gilmore. His research results not only proved the critical role that vision plays in cognitive competence, but allowed the team to actually improve the performances of Alzheimer's disease patients. One of the major findings showed that people with dementia can better and more safely navigate their environments when there is a higher contrast between furniture, floors, and walls. Adults with dementia also increase the amount of food eaten when the tableware is in high contrast to the table, such as using a white plate on a dark wood table.

"One of the desired outcomes of our research is to create an awareness of such changes so that older people can take steps to accommodate their visual deficits by using brighter lights, large print, and sharper contrasts in their surroundings, such as on the edges of steps," adds Dr. Gilmore. Currently, his work focuses on developing visually fair neuropsychological tests and in developing methods to enhance the visual environments of Alzheimer's patients.

http://msass.case.edu/faculty/ggilmore/index.html

DAVID A. KOLB

Management

How We Learn: Using Experiential Learning Theory to Improve Higher Education

David A. Kolb, Ph.D., professor of organizational behavior at the Case Weatherhead School of Management, has been studying human learning for more than 35 years. In the early 1970s he created Experiential Learning Theory (ELT) based on the work of foundational experiential learning scholars—Kurt Lewin, John Dewey, Jean Piaget, William James, and Carl Jung. Dr. Kolb coined the term "learning style" to describe individual differences in preference for the phases of learning and developed the Kolb Learning Style Inventory to help people assess their unique way of learning from experience. The central concept of the theory describes how individuals construct knowledge through a cycle or spiral of learning with four phases—experiencing, reflecting, thinking, and acting.

Recent efforts to improve higher education have focused on improving the learning process in education through the application of what has been called "the new science of learning." Dr. Kolb's application of ELT to the enhancement of learning in higher education is a noteworthy component of this movement. Such application in educational institutions emphasizes an institutional development approach that integrates curriculum development, faculty development, student development, and resource development around a vision and mission that is learning focused. At Case, ELT played a significant role in the creation of the new undergraduate curriculum, the active and inquiry-based Sages, that offers a seminar approach to learning.

A tangible example of ELT's application is found in the research of Guy K. Hutt, associate dean of business, mathematics and technology at Cuyahoga Community College. As a graduate student working on his dissertation under Dr. Kolb, he implemented an experiential "learning-to-learn" course designed to reduce math anxiety and increase student performance in developmental mathematics courses. Results showed that the experiential course reduced students' mathematics anxiety—the students felt safer, and more self confident about learning. Subsequently these students on average performed nearly a whole letter grade better than other students in the regular math course. Typically in mathematics courses, students with the abstract "thinking" learning style preference that tends to match their instructors teaching style perform better than students with other learning style preferences. This learning style effect was erased for students in the experiential course where students of all styles earned better grades than those who had not taken the course.

Dr. Kolb's work, which has sparked much research interest in the subject of learning, has resulted in the current *Bibliography of Research on Experiential Learning* that includes more than 2,200 journal articles, books, and dissertations on the subject. "Learning is the major determinant of human development. How individuals learn shapes the course of their personal development," notes Dr. Kolb.

http://www.learningfromexperience.com/
http://weatherhead.case.edu/faculty/faculty.cfm?id=5389

CAMILLE WARNER + EVANNE JURATOVAC +
DIANA LYNN MORRIS + ELIZABETH O'TOOLE + ALOEN TOWNSEND

Nursing

Caring for the Caregivers: An Important Network for Improving the Lives of Older Adults

Statistics regarding the growth of aging populations in the United States and worldwide are well known. In the United States, approximately ninety-five percent of older adults live in the community, while the remaining five percent reside in nursing homes. According to the U.S. Administration on Aging (an agency of the U.S. Department of Health and Human Services), 4.5 million older adults have some problem with activities of daily living such as bathing and feeding, while 6.9 million have difficulties with instrumental activities of daily living—food preparation and banking, for example.

Care for older adults is provided by a network of formal caregivers who are paid for their services, as well as unpaid informal caregivers such as family and friends. Formal long-term care services, including home care and nursing homes, have come under increased economic stress and scrutiny while trying to meet the increasingly complex health and social needs of older adults and their families. Concurrently, informal caregivers provide the majority of long-term care to older adults with an estimated cost savings of $45 to $94 billion per year, according to the Administration on Aging.

The Prentiss Care Network Project, based in Case's University Center on Aging and Health, was established to enhance the quality of life of older people by educating their caregivers. The project is led by **Diana Lynn Morris, Ph.D., R.N., F.A.A.N., F.G.S.A.,** associate professor of nursing at Case's Frances Payne Bolton School of Nursing, and co-directors **Elizabeth O'Toole, M.D.,** associate professor of medicine, and **Aloen Townsend, Ph.D.,** associate professor of social work, with the support of **Camille Warner, Ph.D.,** core faculty, and **Evanne Juratovac, M.S.N., R.N., C.S.,** project coordinator. A unique characteristic of the project is that its education and training programs are designed to be taken into the community and to worksites where caregivers are living, working, and going to school. This extensive outreach is achieved through collaborations with community partners who are the foundation of the network—education programs are based on the kinds of programs that both the community partners and caregivers say are needed. Further, the content of each program is based on current evidence from research and guidelines for best practices in the care of older adults. A primary goal of the educational programs is to help caregivers take care of themselves and stay healthy.

A key component of the project is an ongoing evaluation of the effectiveness of the educational programs to improve caregiver effectiveness that results, in turn, in improved care of the elderly. In addition, the staff is currently testing a questionnaire called the *Community Caregiving Capacity Index,* which was initially developed at the Rosalyn Carter Institute for Caregiving. "This questionnaire will help communities determine what resources are available and how useful each resource is to formal and informal caregivers. The well-being of elderly persons is inextricably linked to the well-being of their caregivers, and we are focused on both," notes Dr. Morris.

http://caregiving.case.edu/

Arts + Sciences / Theater

Much Ado About Language: Shakespeare's Words Written to Be Performed

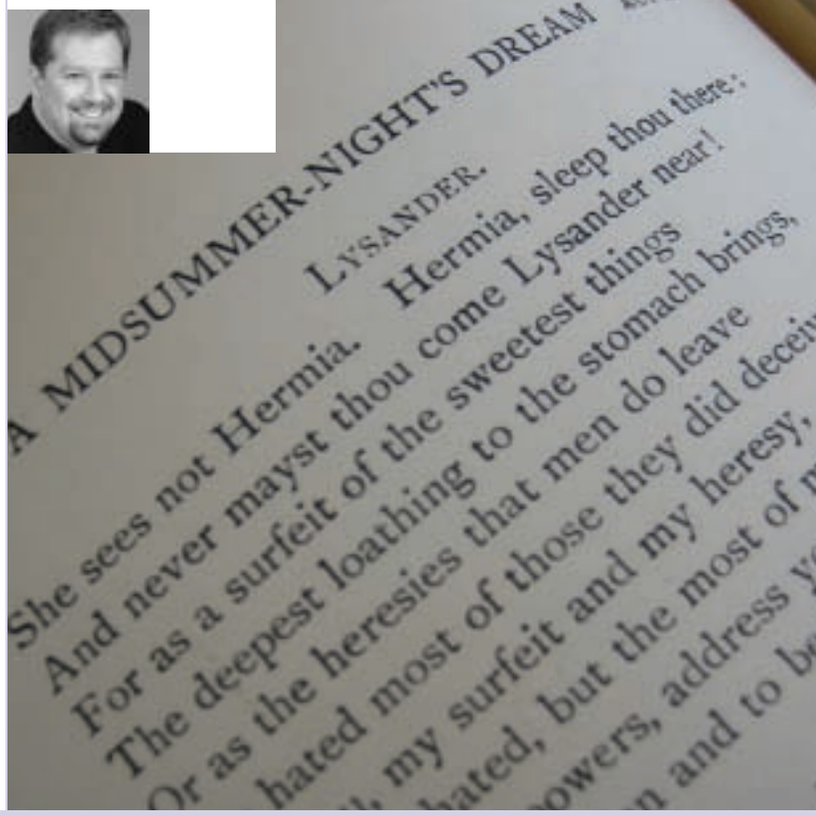
Mastering the heightened language style of classical playwrights is a well-known challenge in the theater. The most frequently performed of all English language playwrights, William Shakespeare, presents particular obstacles for contemporary theatrical performance due to his poetic style and archaic language usage. When Shakespeare's language is unlocked and understood by actors, however, he is the most naturalistic of all playwrights, according to **Jerrold Scott, M.F.A.,** associate professor of theater at the Case College of Arts and Sciences. Professor Scott's research in classical theater performance involves understanding how today's actors can overcome these challenges to become more linguistically skilled performers.

At the heart of the problem, Scott suggests, is that actors in the twenty-first century live in a world that constantly projects glossy images across a screen, suggesting that its splendor lies in flashy cars and flashier bodies, not in the sophisticated use of phonemes. In an article published in the *Voice and Speech Review,* Professor Scott outlines how to deal with these issues in the rehearsal hall and classroom. Using tactics drawn from his own work as a director, actor, and speech consultant, he integrates the three fields into a single pedagogical and professional approach.

In his research, Professor Scott examines how the teaching of dramatic text as a literary form rather than dramatic form can emotionally detach acting students from the play. "Asking actors to connect verbally to the images of the language is very difficult when their past perception of Shakespeare has been that it is written in a language that is best to be read silently," he says. By using a combination of emotional word-response techniques and training in the International Phonetic Alphabet language articulation set, he helps these students develop skills in handling classical text as a living, spoken language.

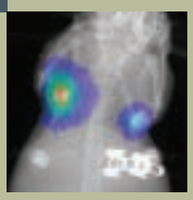
"Shakespeare's genius lies partly in his understanding of sound and word interconnectivity. He was writing to be spoken and heard, not read. Essentially, words are just sounds, and speech is just muscle memory. If we, as performers, understand how the individual sound is formed, and joined with other sounds to create a word, we process the text on a visceral level," Professor Scott adds. "Then, when we speak the language aloud, the meanings of the words have a connection from the intellect to the emotion." The result is the development of more linguistically skilled actors, and subsequently, more accessible productions of classical drama in performance.

JERROLD SCOTT



http://www.case.edu/artsci/thtr/scott.htm

Selected Research Highlights



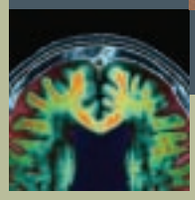
"These major research awards are a reflection of the many noteworthy strengths at Case Western Reserve University. They allow us to fulfill one of our primary goals—to see that an increasing number of technologies developed by our researchers will reach the public."

MARK E. COTICCHIA
VICE PRESIDENT
RESEARCH AND TECHNOLOGY MANAGEMENT

Case Western Reserve University Awarded Science and Technology Center by National Science Foundation

The National Science Foundation (NSF) established a multimillion-dollar research center at Case, effective August 1, 2006. The NSF Science and Technology Center, the first at Case, is named the Center for Layered Polymeric Systems (CLiPS) at the Case School of Engineering. It will be a powerful national presence for research at the crossroads of polymer science and engineering with the physical sciences, and for education of a diverse American workforce that can meet the challenges of emerging multidisciplinary polymer-based technologies. CLiPS will receive approximately $19 million from NSF over the first five years. With a center's average lifetime of 10 years and total funding of $40 million, Case and its partners will have the opportunity to reapply after four years to renew funding for a second five-year period. One of only six centers funded (and the only one in the physical sciences and engineering), Case was chosen from 160 competitors across all disciplines. There are currently 17 Science and Technology Centers operating at academic institutions in the United States.

Anne Hiltner, Ph.D. the Herbert Henry Dow Professor of Science and Engineering, will serve as principal investigator and director of the center. See page 39 for more information about the research being done under her direction. In addition to The University of Texas at Austin, Fisk University, and the Cleveland Municipal School District, other CLiPS partners include the University of Southern Mississippi, Ohio Northern University, Rose-Hulman Institute of Technology, State University of New York at Fredonia; Rochester Institute of Technology, and the Naval Research Laboratory in Washington, D.C.



Case School of Medicine, Cleveland Clinic, and University Hospitals Case Medical Center Receive $13.5 million NIH Grant for Molecular Causes of Blood Clots

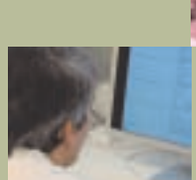
Researchers at the Case School of Medicine, Cleveland Clinic, and University Hospitals Case Medical Center (UHCMC), will join together to study the cellular and genetic causes of blood clots in a new Center for Thrombosis Research, made possible by a $13.5 million grant from the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health. The Center, to be based at the Clinic's Lerner Research Institute (LRI), is one of only three to receive funding from the NHLBI.

The five-year Specialized Center for Clinically-Oriented Research grant was received by a research team led by principal investigator Roy Silverstein, M.D., chair of the Clinic's Department of Cell Biology, vice chair of translational research at the LRI, and a professor of molecular medicine in the Lerner College program. The other project leaders include Kandice Kottke-Marchant, M.D., Ph.D., of the Clinic's Department of Pathology and Laboratory Medicine; Keith McCrae, M.D., associate professor of medicine at the Case School of Medicine and part of the Division of Hematology and Oncology in the Department of Medicine at UHCMC; Thomas McIntyre, Ph.D., of the Clinic's Department of Cell Biology and a professor of molecular medicine in the Lerner College program; and Edward Plow, Ph.D., chair of the LRI's Department of Molecular Cardiology and professor of molecular medicine in the Lerner College program.

Ohio Neurostimulation and Neuromodulation Partnership Awarded $8 million from Third Frontier Program

The Biomedical Research and Commercialization Program (BRCP) of the State of Ohio's Third Frontier Program (TFP) has announced that Case and its partners, the Cleveland Clinic, NDI Medical, Inc., and MetroHealth Medical Center of Cleveland will receive $8 million to extend and diversify the research capabilities of the Ohio Neurostimulation and Neuromodulation Partnership (ONNP). The partnership is dedicated to the commercialization of neurostimulation technologies that address critical neurological disorders.

Led by P. Hunter Peckham, Ph.D., Donnell Professor of Biomedical Engineering and Orthopaedics at Case, principal investigator and executive director of the Cleveland Functional Electrical Stimulation (FES) Center, the ONNP will use the funding to develop and market devices for peripheral nerve stimulation, cardiac function, motor function, and pelvic control. Research and development by the ONNP, established in 2003 with an initial TFP award of $7.8 million, benefits people with paralysis, spinal cord injuries, pain/palsy, sleep apnea, strokes, and urinary incontinence.



Center for Stem Cell and Regenerative Medicine Receives $8 Million from Third Frontier Program to Continue Adult Stem Cell Commercialization Programs

The Biomedical Research and Commercialization Program (BRCP) of the State of Ohio's Third Frontier Program (TFP) announced that Case and its partners, University Hospitals Case Medical Center (UHCMC), Cleveland Clinic, and Athersys, Inc., will receive $8 million to continue clinical commercialization programs in the Center for Stem Cell and Regenerative Medicine (CSCRM) for the next three years.

The Center, established in 2003 with an initial TFP award of $19.5 million, has united international leaders in stem cell biology, therapeutics, and clinical medicine to develop novel cell-based therapeutics for the benefit of patients throughout Ohio. All research at CSCRM uses non-embryonic stem cells derived from bone marrow, umbilical cord blood (after a child is born), or other adult tissue.

The Center's leadership is comprised of Director Stanton Gerson, M.D., who also directs the Case Comprehensive Cancer Center and the Ireland Cancer Center of UHCMC, Co-director Paul DiCorleto, Ph.D., who also directs Cleveland Clinic's Lerner Research Institute and Executive Director Debra Grega, Ph.D. The new award will support development of new therapies for heart, cancer, and neurological disorders, with funds targeted for early patient clinical trials. This builds on current strengths as cancer and cardiovascular disease are disciplines in which the two clinical centers (Cleveland Clinic and UHCMC) rank among the top five institutions in the United States.

Case Technology Transfer Reaches New Levels of Performance

In the fiscal year ended June 30, 2006, Case's technology transfer office completed 37 licensing and option deals, compared with 26 the previous year, a forty-two percent increase. According to Mark Coticchia, vice president for research and technology management, this record level of transactions will not only translate into meaningful revenue in three to five years, it also means more technologies developed by Case researchers will reach the public, the primary goal.

During the fiscal year, Case received 174 invention disclosures from its researchers and affiliate institutions, a new record and a thirty-six percent increase over the previous year. Dr. Joseph Jankowski, assistant vice president for technology transfer—biomedical sciences, notes that Case is performing above the national average in terms of inventions produced per million dollars in external research funding.

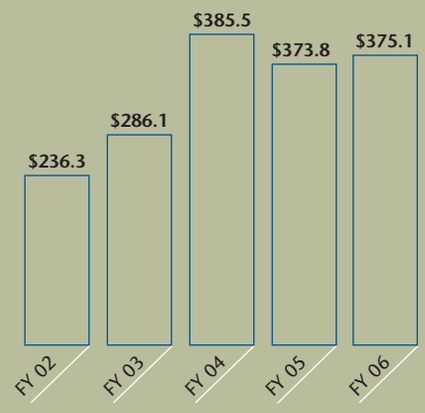
Licensing income for the fiscal year was $10.8 million, compared to $8.4 million in the previous year, an increase of twenty-nine percent, and a record for Case. In addition, four start-up companies were generated during the fiscal year, double that of the previous two fiscal years. Since the inception of the current technology transfer program in late 2001, approximately $21 million has been distributed to inventors at Case and its affiliate institutions; the balance of the proceeds have been used to support programs across campus.

Research Facts + Figures

	FY2006 COMPETITIVE SPONSORED PROJECT PROPOSALS (SUBMITTED BY SCHOOL)	FY2006 AWARDS BY SCHOOL (DOLLARS IN MILLIONS)
Applied Social Sciences	28	$ 6.1
Arts and Sciences	175	18.2
Dental Medicine	16	4.8
Engineering	333	41.8
Law	10	0.5
Management	13	0.7
Medicine	983	297.5
Nursing	42	2.3
University General	17	3.2

FY2006 AWARDS BY SPONSOR	(DOLLARS IN MILLIONS)	(PERCENTAGE OF TOTAL)
National Institutes of Health	$265.0	70.6
National Science Foundation	6.5	1.7
Department of Defense	4.2	1.1
Department of Energy	3.6	1.0
NASA	3.4	1.0
Other Federal Agencies	29.6	7.9
Foundations, Associations + Societies	20.4	5.4
State + Local Government	17.7	4.7
Other	13.6	3.6
Industry	11.1	3.0

FY2002-2006 SPONSORED PROJECT AWARDS
(DOLLARS IN MILLIONS)



		CASE RANKINGS
Among All Medical Schools	FY2005 National Institutes of Health Awards	12th
Among All Universities	FY2005 National Institutes of Health Awards	16th
	FY2004 Total Federal R+D Expenditures	43rd
Among All Private Universities	FY2004 Total R+D Expenditures	21st

Case at a Glance

Case is located in Cleveland's University Circle, the one-square mile parkland home of more than 40 cultural, medical, educational, religious, and social service institutions, with an additional 30 institutions nearby. These institutions include The Cleveland Museum of Art, The Cleveland Orchestra, The Cleveland Institute of Music, The Cleveland Institute of Art, The Cleveland Play House, University Hospitals Case Medical Center, and Cleveland Clinic, to name but a few.

The only independent, research-oriented university in a region bound by Pittsburgh and Rochester on the east, Nashville on the south, and Chicago on the west, Case holds membership in the Association of American Universities, and is fully accredited by the Higher Learning Commission of North Central Association of Colleges and Schools and by several nationally recognized professional accrediting associations.

PRESIDENT
Gregory L. Eastwood, M.D., Interim President
Barbara R. Snyder, President Elect (July 1, 2007)

SCHOOLS + COLLEGES
College of Arts and Sciences
Case School of Engineering
School of Graduate Studies
School of Dental Medicine
School of Law
Weatherhead School of Management
School of Medicine
Frances Payne Bolton School of Nursing
Mandel School of Applied Social Sciences

ENROLLMENT
Undergraduate 4,305
Graduate and Professional 5,622
Total 9,927
States represented 50
Countries represented 76

FACULTY AND STAFF
2,500 full-time faculty; 3,300 full-time staff

ALUMNI
101,000

CAMPUS
150 acres; more than 90 buildings

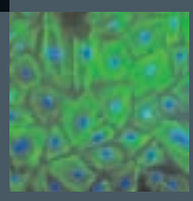
LIBRARY HOLDINGS
2,495,769 volumes
2,565,701 microform units
18,422 serials

RESEARCH
External Awards for Research, FY 2006
$375 million

ENDOWMENT FUNDS
$1.622 billion as of June 30, 2006

TOTAL NET ASSETS
$2.050 billion as of June 30, 2006

FIGURES AS OF FALL, 2006



The Value of Research

Number 4

Produced by the Office of Research and Technology Management in cooperation with the administrative and communications offices of the University's schools, college, and research centers, as well as the mentioned collaborating institutions.

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"I cannot think of a better place than Case Western Reserve University for a student to participate in research. As an undergraduate, I have been able to pursue my research interests with every advantage that a major research university has to offer, including the support of Case's scientists and scholars, all eager and excited to work with students."

SHAAN C. GANDHI

Student Research


April 22–
May 31
The Cleveland
Museum of Art
WBBG 1260AM
CIRCLE INSTITUTIONS
AFM LOCAL NO. 4
The Cleveland
Museum of Art
Nov. 24 through Feb. 2
Historical Society
Thru Oct 8
CWRU
Cleveland
Museum
of Art
NATURAL
HISTORY

Student Research

SHAAN C. GANDHI + CAROLYN J. MURROCK

Arts + Sciences / Biochemistry

Identifying the Biological Basis of Cancer

The biological basis of cancer has been a topic of in-depth investigation for years, with many research groups focusing on the cellular and genomic regulatory mechanisms underlying the progression of cancer. One particular area of great interest focuses on signal transduction pathways, cascades of interacting proteins that allow cells to regulate internal processes, such as cell division, and to communicate with the environment. The dysregulation of such pathways can lead to unchecked cell growth and proliferation, causing many cancers. For example, mutations in the Ras pathway have been correlated with the development of certain types of pancreatic, colorectal, lung, and breast cancers.

Shaan C. Gandhi's student research has strived to elucidate the particular mechanisms by which these cell signaling pathways can lead to cancer. As an intern at the National Institutes of Health during the summer of 2004, Gandhi clarified the Akt pathway as a key regulator of metastasis in Ewing's sarcoma. Other work he has done at the Memorial Sloan-Kettering Cancer Center and the Mayo Clinic have focused on the roles of other cascades, such as the Notch and Insulin-Like Growth Factor pathways, in promoting cell proliferation. Currently, Gandhi's research at Case is focused on understanding the protein binding properties of the transcription factor IX, a downstream participant in the Ras pathway that has been implicated in the progression of testicular cancer.

Shaan C. Gandhi is a senior B.S. (biochemistry) and B.A. (chemistry) undergraduate currently in the laboratory of Michael A. Weiss, M.D., Ph.D., chair of the Department of Biochemistry. In 2006, he was awarded the Barry M. Goldwater Scholarship for his achievements in research. This fall, he will begin his doctoral research in medical oncology at the University of Oxford as a Rhodes Scholar.

Nursing

Dance Intervention Increases Physical Activity in African American Women

Approximately 68 percent of African American women are sedentary and many of them experience debilitating, chronic illnesses and limiting functional capacities. With physical activity being a leading health indicator, Carolyn J. Murrock examined the effects of a culturally specific dance intervention designed to increase lifestyle physical activity and functional capacity in sedentary African American women, ages 40 years and older. The study was funded by the Ruth L. Kirschstein National Research Service Award.

Two African American churches were randomly assigned to either the treatment or control group protocols to control for diffusion of treatment for the repeated measures analyses. From these two churches, a sample of 126 participants was recruited. Variables measured included: lifestyle physical activity, functional capacity, efficacy expectations, outcome expectations, social support, body fat, age, and co-morbidity. Results of this study determined that a culturally specific dance was an appropriate intervention to increase functional capacity but did not increase lifestyle physical activity among the group who received the intervention compared to those who did not.

By incorporating dance into their lives, African American women can become more physically active, improve their functional capacity, and decrease their chances of developing chronic diseases and conditions.

Carolyn J. Murrock is a Ph.D. student at Case's Frances Payne Bolton School of Nursing. She has been a nurse for more than 20 years, working in various settings with diverse populations. Her primary interest is to develop interventions that promote healthy lifestyles and reduce risk of chronic diseases and other health conditions, especially among women and minority women.

Student Research

JODI THOMSON + RYAN M. MIZUMOTO

Medicine

Bacterial Infections: Overcoming Resistance to Antibiotics

Bacterial infections are a major source of morbidity and mortality in the U.S. and abroad. Compounding this problem are increasing levels of antimicrobial resistance, which are reaching epidemic levels in hospitals and long term care facilities. Jodi Thomson's research is focused on determining the mechanisms of resistance to antibiotics in an effort to guide future antimicrobial discovery, with a particular concentration on the beta-lactam family of antibiotics, which includes the penicillins and cephalosporins. Bacteria have evolved enzymes, called beta-lactamases, which degrade these antibiotics before they reach their targets, resulting in high-level resistance.

In an effort to combat this, specific beta-lactamase inhibitors have been designed that are used in combination with beta-lactam antibiotics. Together with her lab colleagues, Thomson's project has focused on the drug Augmentin®, commonly prescribed in the pediatric setting to treat inner ear infections, and to treat upper respiratory infections and pneumonia in adults. The first step in this research is to determine the molecular mechanism of inhibitor resistance. Next, along with several collaborators in academia and industry, the team will help design and test novel beta-lactamase inhibitors in early development. It is essential that new antibiotics not fall prey to the same resistance patterns as drugs currently on the market.

Jodi Thomson is currently in her sixth year of study in the Medical Scientist Training Program and is completing her Ph.D. in the Pharmacology Department. In addition to defending her thesis this spring, she is training to compete at Ironman Coeur d'Alene in June, and raising money for the Leukemia and Lymphoma Society.

Dental Medicine

The Effects of Individualized Prevention Plans on Oral Health Habits

Ryan M. Mizumoto is investigating the effects of individualized prevention plans on patients' oral health habits. The purpose of his study was to assess the degree to which patients with risk factors for periodontal disease followed their individualized prevention plans and to evaluate whether receiving such plans changed the subjects' attitudes and oral health habits. The project, a sub-study in Dr. Lance Vernon's investigation of the link between periodontal disease and vascular disease in an HIV-1 cohort, has provided a better understanding of prevention, patient compliance, and behavior change.

While most of the subjects stated that they had read their individualized prevention plan, the research team hypothesized that the degree to which they followed it may be predicted by specific, measurable factors—that patient compliance may be more successful with a hands-on approach (a coaching relationship), rather than simply telling them (a typical doctor-patient relationship). In terms of behavior change, the study demonstrated that subjects are more confident and motivated to modify an existing behavior, as compared to starting an entirely new behavior. Finally, the data revealed that a patient's motivation and confidence level were often strikingly similar—if their motivation for change was high, so was their confidence.

The findings not only support the importance of a dental professional's role in prevention, but also show the importance of educating patients in at-risk populations. Because HIV-1 infection is a risk factor for periodontal disease, good oral hygiene habits are crucial for those living with HIV. As part of the project, Ryan worked with 22 individuals in the study to encourage prevention through one-on-one discussions, hands-on demonstrations, and user-friendly pamphlets.

Ryan M. Mizumoto is currently a second-year dental student at the Case School of Dental Medicine, working under the guidance of Lance T. Vernon, D.M.D., M.P.H. His interests outside of school include playing soccer, golfing, and listening to music.

Student Research

NICK BERENTE + TRISTA PICCOLA

Management

Forms of Iteration and the Design of Complex Systems

Design activity is becoming more complex, with the convergence of software, mechanical, electrical, and service design activity, as well as modern requirements for sustainability and total life-cycle design. Nick Berente is studying the processes associated with next-generation complex system design.

"Iteration," or the progressive repetition of design activity, is the fundamental unit of analysis in Berente's study of innovation processes. He has developed a framework of iteration, which includes three types of cognitive iterations and two fundamental forms of iteration across representations. He found that while a great deal of iteration is essential to all complex design activity, different forms of iteration can be substituted for others under certain circumstances, and the control and visibility of various iterations are largely associated with the formal development methodology adopted by the design team.

Using multi-method case studies rooted in the theory of distributed cognition, Berente is tracking the design iterations of complex design processes. His findings show how information systems can supplement traditional forms of interorganizational governance, how certain forms of information systems are better suited to support design activity, and how different ecologies of information artifacts and individuals can bring about the knowledge creation necessary for modern complex design processes.

Nick Berente is a third-year Ph.D. candidate in the Information Systems Department of Case's Weatherhead School of Management. His dissertation research focuses on managing the design of next-generation automotive subsystems, partially funded by MIT's International Motor Vehicle Program (IMVP). He is also part of an NSF-funded team, led by Kalle J. Lyytinen, Ph.D., professor of information systems, studying the design requirements for complex, software-intensive systems.

Applied Social Sciences

Examining Differences in Foster Care Use in Ohio Counties

Why are there significant differences in foster care use across Ohio counties? This question formed the foundation for the research project undertaken by Trista Piccola, Ph.D. After examining the entry and exit patterns of children who entered foster care in Ohio over a three-year period, Dr. Piccola found that differences in county foster care entry rates, particularly in more densely populated counties, was most strongly related to social and economic conditions, including poverty and the density of single female-headed households, replicating prior research findings at the individual, family, and neighborhood levels.

Consistent with prior research, her study also showed disproportionate use of foster care for African-American children compared to other children in the majority of Ohio counties. In addition to this, though, a higher rate of use for this population was also correlated with overall higher county levels of foster care use.

Somewhat surprisingly, Dr. Piccola found significant differences in use in the least densely populated counties which tended to be more socially and economically homogenous. The variability in these counties was related to differences in foster care use for adolescents and children with behavior problems. These results are likely related to county differences in the child welfare system's role in responding to the needs of unruly and delinquent children.

Trista Piccola, a 2006 graduate of the doctoral program at Case's Mandel School of Applied Social Sciences (MSASS), is currently the Manager of Continuous Quality Improvement at Lorain County Children Services. She is also an adjunct faculty member at MSASS and Baldwin-Wallace College.

Student Research

ANDREW R. ALLEN + SHADYA YAZBACK

Engineering

Advancing Robotic Technology: DARPA Urban Challenge

Congress has mandated that by the year 2015, one-third of the operational ground combat vehicles will be unmanned. Consequently, the Defense Advanced Research Projects Agency (DARPA) is sponsoring the DARPA Urban Challenge: an autonomous robotic vehicle race in an urban environment to be held in November 2007. The race calls for vehicles to self-navigate common city roads with attention to traffic law abidance, obstacle avoidance, collision avoidance due to other vehicles, as well as traffic jam and parking lot handling. Team Case is entering the competition with their robotic car named Dexter.

Andrew R. Allen is developing the algorithms for which the vehicle gains situation awareness of its surroundings given the physical state of the robot, sensory data, a planned route, and description of the legal markings around the vehicle, thus enabling the robot to make strategic decisions about which augmentable, pre-programmed driving behavior it will perform. The decision process selects the optimal behavior that is safe, effectively moves the robot toward a goal, and is legal. A scoring system computed from the vehicle's speed, the speed of surrounding vehicles, the presence of obstacles, and distance to an intersection, among others, is used to evaluate the behaviors. Allen's research also includes developing the algorithms for right-of-way detection at intersections and choreographing the sensory-augmented driving behaviors.

Unmanned vehicle technology like that used in Dexter will eventually find its way onto non-military vehicles for commercial and private use. Advances will include minimizing traffic accidents caused by human error, optimizing traffic flow, and fuel new and exciting engineering solutions for increasing traffic efficiency and safety.

Andrew R. Allen is a Ph.D. student in the Department of Electrical Engineering and Computer Science at the Case School of Engineering. His research is supported by personal and commercial donations to Team Case and the Urban Challenge project, http://urbanchallenge.case.edu.

Law

School Financing in Ohio: Searching for a "Thorough and Efficient" System of Public Schools

School officials, students, and parents sued the State of Ohio in 1991 for failing to provide the "thorough and efficient" system of schools required by the state Constitution. The case, *DeRolph v. State,* sparked a 13-year battle over the state's school financing system. The Supreme Court issued four *DeRolph* decisions finding the system unconstitutional; with each decision, the justices issued widely divergent opinions. The case was ultimately dismissed in 2003, without any agreement on the definition of a "thorough and efficient" financing system.

In an attempt to define a "through and efficient" system, Shadya Yazback's research analyzes the *DeRolph* opinions and decisions from other states. Yazback proposes that in Ohio, a "thorough and efficient" system is one that provides schools sufficient funding to ensure that state proficiency and testing targets are met. The system need not, however, provide complete equality in funding.

By examining the state's school financing plans from 1991 through Governor Taft's 2006 reforms, Yazback concludes that the system remains unconstitutional. While the *DeRolph* litigation did result in significant funding level improvements for the state's poorest school districts, substandard scores on state proficiency tests as well as failures to properly account for inflation in the school funding formula remain problems.

Shadya Yazback received her J.D., *magna cum laude,* from the Case School of Law in 2006. Her research on school financing will be published in the fourth issue of Volume 57 of the *Case Western Reserve Law Review.* She currently works as a senior policy analyst for the Federal Reserve Bank of Cleveland and the views expressed here are those of the author and not necessarily those of the Federal Reserve System or the Federal Reserve Bank of Cleveland.