

UMDNJ RESEARCH

FOR THE RESEARCH COMMUNITY FROM THE STATE UNIVERSITY OF THE HEALTH SCIENCES

Special Issue: NIH - Supported Clinical Trials



Translational Research in Prostate Cancer

by **Robert DiPaola**

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Vaccine therapies have become attractive for translational study in prostate cancer. The development of immune therapies for prostate cancer includes the study of viral, dendritic, DNA, peptide and carbohydrate vaccines, which have promising results in initial studies. Viral vaccines are particularly promising, since they mimic natural infection and can induce potent immune responses. Replicating and non-replicating members of the poxvirus family have been widely studied for expression of tumor antigens and other immunomodulatory genes, such as cytokines and co-stimulatory molecules. A large number of tumor-associated antigens are available for insertion into viral vectors for future development. In this regard, our team — and other investigators — have completed initial studies of a smallpox virus containing the gene sequence for prostate specific antigen (PSA) in patients with prostate cancer. For example, an Eastern Cooperative Oncology Group (ECOG) study demonstrated safety and efficacy in patients with PSA progression after local therapy for prostate cancer (Kaufman H, DiPaola RS, et al. *J Clin Oncol.* 2004 Jun 1; 22(11):2122-32). The safety of a second generation PSA vaccine was recently tested with three additional co-stimulatory molecules (called TRICOM) along with the gene sequence for PSA in the viral vector (DiPaola et al. *Proceedings of the American Association for Cancer Research* 45:1035 Abs#4485, 2004). Based on these initial data, we proposed and have received approval from the ECOG and the NCI to begin a phase III study

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- New Jersey Medical School
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The University of Medicine and Dentistry of New Jersey is a statewide network of eight schools on five campuses in Camden, New Brunswick/Piscataway, Newark, Scotch Plains and Stratford. The schools include New Jersey Medical School, Robert Wood Johnson Medical School, School of Osteopathic Medicine, New Jersey Dental School, Graduate School of Biomedical Sciences, School of Health Related Professions, School of Nursing and School of Public Health. The University has more than 5,400 students in more than 50 degree and certificate programs, 14,884 employees, including 2,566 faculty members, 20,258 alumni and more than 200 education and healthcare affiliates throughout New Jersey. The University is dedicated to pursuing excellence in the education of health professionals and scientists, conducting research, delivering health-care, and serving the community. UMDNJ is ranked among the 100 top research universities in the country.

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UMDNJ RESEARCH
Volume 6, Number 2, Fall 2005

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UMDNJ Research is published by the University of Medicine and Dentistry of New Jersey, University Affairs Department, Publications Office, Stanley S. Bergen Building, 65 Bergen Street, Suite 1328, P.O. Box 1709, Newark, NJ 07101-1709.

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NIH - Supported Research at UMDNJ

One of the most crucial, yet demanding and complex, steps in medical discovery is the testing of new treatments and devices on human subjects. With nearly 3,000 active human research studies, UMDNJ supports one of the nation's largest clinical research operations. The last issue of *UMDNJ Research* described some of the key industry-sponsored clinical research programs at UMDNJ. As a sequel, this current issue features clinical trials supported by funding from the National Institutes of Health. As it is not possible to include all of the University's government funded research in a single issue, select programs have been highlighted to portray the scope and quality of NIH-funded clinical research being conducted.

Last year was a stellar one for UMDNJ's research programs. In fiscal year 2004, UMDNJ-Robert Wood Johnson Medical School received nearly \$58 million in NIH awards, placing it 61st among the nation's medical schools. UMDNJ-New Jersey Medical School ranked 67th with more than \$46 million of NIH funding. UMDNJ's School of Osteopathic Medicine placed first among the nation's schools of osteopathy, receiving \$3,253,906 in NIH awards. In 2003, the most recent year for which data are available, the National Science Foundation ranked UMDNJ 74th nationally among research universities in federally funded expenditures.

Becoming a national leader in biomedical, clinical and healthcare research is one of the primary goals set forth by UMDNJ's strategic plan. The many forms of support provided by the University have already produced significant progress toward that goal. Over the past five years an aggressive construction campaign added 600,000 square feet of new facilities and laboratories and the University Professor program recruited 16 internationally recognized researchers to our faculty. The following articles — focusing on such areas as vaccine strategies for cancer, when to administer blood transfusions after surgery and treatment consequences in HIV-infected children with prior single-dose nevirapine exposure — provide evidence of our achievements.

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of the optimized smallpox vaccine with PSA, TRICOM and the addition of GM-CSF, an additional growth factor that has been demonstrated to enhance immune responses. The study is titled "a phase III study of PSA vaccine in androgen refractory PSA progression with absence of metastatic disease and GM-CSF," or PARADIGM. This phase III national study will determine the true benefit of a vaccine in prostate cancer and is planned to begin in 2006.

Targeting Apoptosis

In addition to the translational studies of new immune paradigms on a national level, we have been studying methods to improve standard chemotherapy in prostate cancer by targeting apoptosis, the regulated pathway of tumor cell death. Advanced prostate cancer is only temporarily controlled by hormonal therapy or chemotherapy. The current standard chemotherapy is the agent docetaxel, which has been demonstrated to improve survival in men with advanced hormone resistant prostate cancer (HRPC). Despite initial benefit in many patients, docetaxel has improved the median survival by only 2.5 months, promoting efforts to discover agents that will overcome the molecular mechanisms of resistance that develop to docetaxel. To overcome tumor resistance, we used an epithelial cell line model developed in the laboratory of Eileen White, PhD, a resident faculty member of the Center for Advanced Biotechnology and Medicine, a joint program of UMDNJ and Rutgers University, to dissect out mechanisms of resistance such as mutations in p53 and overexpression of the anti-apoptotic protein bcl-2. In an attempt to sensitize these cells to taxol, a cousin of docetaxel, we found that 13-cis retinoic acid and alpha interferon (CRA/IFN) reduced the expression of bcl-2 and are capable of overcoming resistance. We hypothesized that drugs which could overcome bcl-2 mediated resistance would improve chemotherapy response or duration of response in the clinic. We then translated these results to the clinic in a series of clinical trials with funding from the National Cancer Institute (DiPaola, R.S., et al. *Clin Cancer Research*, 3:1999-2004, 1997; DiPaola et al. *J Clin Oncol* 17:2213-2218, 1999; Thalasila, DiPaola, et al. *Cancer Chemother Pharmacol*, 52: 119-124, 2003). Recently, a phase II randomized study with CRA/IFN with taxol was accepted as a national trial. Initial results demonstrated that CRA/IFN was able to reduce bcl-2 expression in the blood of patients (Elsayed, DiPaola, R. S. et al. *Proceedings of the American Society of Clinical Oncology* 23:431 (4707), 2004).

Based on these studies with CRA/IFN combined with taxol, we have now obtained funding through the Department of Defense to complete studies with CRA/IFN combined with docetaxel. We hypothesized that CRA/IFN will improve the response rate, or duration of response, of docetaxel in patients with HRPC. These studies are nearing completion at CINJ. Within the same scientific theme of understanding mechanisms of resistance to docetaxel chemotherapy and developing strategies to overcome such resistance, we have also studied additional agents that affect tumor cells resistant to taxol and docetaxel. One of these agents, epothilone, was studied in our laboratory and was found to potentially occur by different mechanisms of resistance compared to taxol (Ioffe, DiPaola, et al. *The Prostate*. 2004 Nov 1;61(3):243). We are currently completing a trial with epothilone in patients with prostate cancer that progressed despite treatment with docetaxel. This study is being conducted by ECOG supported through NCI.

We have also tried to overcome tumor resistance to chemotherapy by treating patients earlier in their course, prior to the development of resistance mechanisms. Some of these studies have already been published and are being used to support further study of agents in early prostate cancer (DiPaola et al. *Cancer*. Oct 15; 92(8):2065-71, 2001; Rao, DiPaola et al. *The Prostate*, 61:2004; Kumar, DiPaola et al. *J. Clin Oncol*, 2004; Goodin, DiPaola et al. *J. Clin Oncol* May 20, 2005). Other ongoing clinical trials of earlier agents include a prevention study of calcitriol, a vitamin D derivative, in patients with prostatic

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intraepithelial neoplasia, a marker of high risk for prostate cancer; this study is based on laboratory studies in mouse models conducted in the laboratory of Cory Abate-Shen, PhD, co-director of the prostate program at CINJ.

Targeting Metabolism

We have also published preliminary data that supports a novel approach targeting metabolism to bypass tumor resistance. Prior studies demonstrated the dependence of early tumor growth on anaerobic metabolism through glycolysis. In fact, the greater preference of tumor cells than normal cells to utilize glycolysis is the basis for the successful development of FDG-PET imaging. More recent studies have also demonstrated that abnormal growth factor and apoptotic pathways, required by tumor cells to resist multiple insults, can drive tumor cells to even further dependence on glycolysis. For example, studies have recently demonstrated that activation of Akt kinase, which occurs commonly in tumors such as prostate cancer, increases dependence on glycolysis. We set up a laboratory co-culture model that could detect the growth effect of autocrine stimulation by tumor cells independent of the changes in anti-apoptotic proteins such as over-expression of bcl-2. Using two dimensional (2D) gel analysis in this co-culture model, we found that seven proteins increased most significantly with autocrine stimulated growth in LNCaP cells and identified all these proteins as specific glycolytic enzymes, suggesting that this was a critical early event (Dvorzhinski, DiPaola et al. *Proteomics*. 4:3268-3275, 2004). We then began to test 2-deoxyglucose, an inhibitor of glycolysis, and found decreased expression of these enzymes in this co-culture model and inhibition of cell growth at concentrations below what can be obtained safely in humans. In collaboration with Eileen White, we found that Akt activation increased sensitivity to this agent (DiPaola, White et al. *Proceedings of the American Society of Clinical Oncology*, 2005). These laboratory data supported a recent proposal to conduct additional laboratory studies and a clinical trial in patients with prostate cancer that received funding by the Department of Defense.

In summary, these efforts to translate laboratory discoveries into clinical trials have led to new insights in immune therapies and modulation of resistance mechanisms present in prostate cancer. This work has been supported by governmental agencies including the NCI and the Department of Defense. Our efforts in early clinical trials have led to the movement of results into high priority national clinical studies.

Robert DiPaola, MD, is a professor of medicine at UMDNJ-Robert Wood Johnson Medical School. He is currently co-director of the prostate cancer program at The Cancer Institute of New Jersey, the state's only National Cancer Institute-designated Comprehensive Cancer Center, and executive director of the Dean and Betty Gallo Prostate Cancer Center. His research efforts are based on the translation of laboratory discoveries to clinical trials. Dr. DiPaola's success is evidenced by being recently elected as chair of the Genito-urinary Committee of the Eastern Cooperative Oncology Group, one of only a few national clinical trials groups funded by the NCI. He has served on both NCI and Department of Defense grant study sections and The American Society of Clinical Oncology Program Committee. His work has been published in the most prominent journals, including The Journal of Clinical Oncology, Clinical Cancer Research, Proteomics, and The New England Journal of Medicine. Examples of his ongoing funded research include the development of vaccine therapies for prostate cancer and bypassing cancer resistance through targeted approaches of the apoptotic pathway and cell metabolism. 🍷

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Evaluating a prevention strategy for maternal-to-infant HIV transmission worldwide

by **PAUL PALUMBO**

Prevention of maternal-to-infant HIV transmission has been one of the major success stories in the fight against this relatively new infection. New Jersey Medical School (NJMS) investigators and associated clinical trials programs have made major contributions to this effort, beginning with the landmark PACTG 076 trial in 1994, which demonstrated that the sequential use of AZT during pregnancy, labor, and in the newborn reduced transmission by two-thirds. The '076' prevention strategy has become a public health standard in the developed world and is a key component in the dramatic reduction of new pediatric HIV infections. The remarkable success of 076, combined with the inability to implement such a complex regimen in resource-poor countries, where most of the infection burden resides, led to a search for simpler, more feasible strategies, culminating in the HIVNET 012 trial. This study, conducted in Uganda, demonstrated in 1999 that a single dose of the drug nevirapine, administered to an HIV-infected mother in labor, and a single dose to her newborn, can reduce transmission risk by about half. Both trials were conducted in NIH-funded HIV Clinical Trials Networks in which our local group of NJMS investigators participates, and like 076, HIVNET 012 has resulted in sweeping public health policy changes in the global setting.

The euphoria following the announcement of the 012 results was tempered modestly one to two years later by the realization that a large percentage of women developed viral resistance to nevirapine after just the single dose. In addition, the subset of infants exposed to single dose nevirapine who became HIV-infected also demonstrated a high rate of viral resistance to the drug. While the viral resistance generally wanes to a non-detectable level over a six- to 12-month time period (using standard, relatively insensitive assays), this phenomenon raised serious concerns about the effectiveness of subsequent treatment strategies should a mother and/or her baby qualify for and have access to treatment. Although multiple antiretroviral (ARV) agents and drug classes are available in the developed world, limited treatment options are available in resource poor settings. In particular, first line treatment regimens feature the non-nucleoside reverse transcriptase inhibitors — nevirapine and efavirenz — both of which will be hypothetically compromised by prior single dose nevirapine exposure. Preliminary studies of a cohort of Thai mothers who began treatment after prior receipt of single dose nevirapine suggested that treatment responses were modestly inferior compared with control mothers, but rigorous follow-up studies are clearly warranted. There are additional hypothetical concerns for infected babies in this situation, given that their initial infection is established with mutated, resistant viruses as the majority viral species.

Many research groups were quick to take up the challenge posed by this very effective, but potentially seriously flawed prevention modality. One such group was organized by the NIH Division of AIDS, which convened a think tank meeting in 2003. It resulted in four interrelated trial concepts — two to probe innovative approaches to prevent the emergence of resistant virus in mothers and neonates in the prevention setting and two to study the consequences of single dose nevirapine exposure on subsequent treatment efforts in women and children.

I have been fortunate to lead the formation of a trial team charged with investigating treatment consequences in HIV-infected children with prior single



PAUL PALUMBO, MD, PROFESSOR OF PEDIATRICS, BIOCHEMISTRY AND MOLECULAR BIOLOGY, UMDNJ-NEW JERSEY MEDICAL SCHOOL

dose nevirapine exposure. Together with my associate chair — Avey Violari, MD, from Johannesburg, South Africa — we have assembled a group of domestic and international experts, including pharmacologists, biostatisticians, and community representatives, and developed a clinical trial entitled: *PACTG 1060 — Parallel Randomized Clinical Trials Comparing the Responses to Initiation of NNRTI-based versus PI-based Antiretroviral Therapy in HIV-Infected Infants Who Have and Have Not Previously Received Single Dose Nevirapine for Prevention of Mother to Child Transmission*. This trial will be conducted at international sites within the Pediatric AIDS Clinical Trials Network (PACTG) funded by NIH. It has two major goals: 1) to compare treatment responses of single dose nevirapine-exposed and unexposed infants who qualify for HIV treatment by World Health Organization criteria and who are between six months and three years of age; and 2) to compare the relative efficacy of NNRTI-based versus PI-based ARV regimens for initial therapy in this age group, for which there is plenty of investigator bias but a lack of data. The trial plans to enroll 480 children, is rigorously designed biostatistically, and is currently targeted for implementation in three South African sites (Johannesburg, Cape Town and Durban) and possibly in Uganda, Zimbabwe and Botswana.

Serial challenges have presented themselves, not the least of which has been negotiating with three individual pharmaceutical companies to serve as collaborators for trial design and provision of trial drugs. Special issues, such as breast versus formula infant feeding, maintenance of a local cold chain for drug storage, and trial indemnification, have had to be addressed. In addition, multiple trial approvals have to be received from the Division of

AIDS at NIH, from local Institutional Review Boards and from Ministries of Health of each country involved. PACTG 1060 is projected to begin enrollment in the fall of 2005 and to require two years to complete enrollment and an additional half year for cohort follow-up. A new, independent International Data Safety Monitoring Board (iDSMB) has been convened by the Division of AIDS to oversee the progress, safety and outcome of the trial. The iDSMB has recently reviewed the protocol and plans serial, closed reviews during the course of the trial. Rigorous rules have been established for early study termination should safety or outcome issues warrant. The outcome of this trial is eagerly anticipated by the international community and it is hoped that substantial contributions to pediatric HIV treatment will be forthcoming.

Paul Palumbo, MD, is a professor of pediatrics, biochemistry and molecular biology at UMDNJ-New Jersey Medical School. He has been a long-standing participant in maternal and pediatric HIV clinical trials and in laboratory-based studies of pathogenesis. Dr. Palumbo participates in the leadership of multiple HIV clinical trials groups, including the Pediatric AIDS Clinical Trials Group (PACTG; NIAID-funded) in which he serves as the group vice-chair, the Adolescent Trials Group (ATN; NICHD-funded), and the newly formed IMPAACT Network, which is a collaboration of the PACTG and the Perinatal Working Group of the HIV Prevention Trials Network (HPTN; NIAID-funded).

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(LEFT TO RIGHT) RACHEL PRUCHNO, PHD, DIRECTOR OF RESEARCH, NEW JERSEY INSTITUTE FOR SUCCESSFUL AGING, UNIVERSITY PROFESSOR AND ENDOWED PROFESSOR OF GERONTOLOGY, UMDNJ-SCHOOL OF OSTEOPATHIC MEDICINE; FRANCINE CARTWRIGHT, PROGRAM ASSISTANT, OPTIONS STUDY; RICHARD MCCONAUGHY, JD, PHD, RESEARCH DATA ANALYST, OPTIONS STUDY

End-of-life treatment preferences of older nephrology patients and their spouses

by **Rachel Pruchno**

The aging of our population and the tremendous biomedical advances of the past several decades have raised a host of new ethical questions regarding initiating, withholding and terminating treatment at the end of life. While advances in medical technologies have enabled people with chronic illnesses to be kept alive in conditions never before possible, so too have they created the need for people to make life or death decisions that were unthinkable even as recently as a decade ago.

THE CENTRAL QUESTION THE STUDY SEEKS TO ADDRESS IS HOW PATIENT AND SPOUSE PREFERENCES FOR DIALYSIS

TREATMENT RELATE TO ONE ANOTHER AND HOW THESE PREFERENCES CHANGE OVER THE COURSE OF TIME.

Decision making at the end of life is often complex and full of emotion. The principal foundation guiding decision making at that time is patient autonomy, a standard suggesting that individuals have the right to make decisions about their healthcare treatment. Although our society values individual

autonomy, the reality is that many older people are unable to express their wishes about treatment at the end of their lives.

In the absence of patient competence, patient autonomy requires that the preferences of the patient be honored when treatment decisions are made.

Advance directives in the form of durable Power of Attorney for Health Care or Health Care Proxy and Living Wills are mechanisms that have been promoted to empower people with the capacity to maintain their voices in healthcare decisions should they later lose their capacity to do so. However, the reality is that most Americans do not have an advance directive, and even when an advance directive exists, it is frequently ignored.

When a patient's cognitive ability is compromised, healthcare professionals

typically ask family members to make health related decisions for them. The President's Commission for the Study of Ethics Problems in Medicine and Biomedical and Behavioral Research has endorsed "substituted judgment" as a means for promoting patient autonomy. Substituted judgment calls for

family members to make decisions in a manner that approximates the patient's wishes. It assumes that family members understand patient preferences and can correctly represent their wishes.

Patients with end stage renal disease (ESRD) make end-of-life decisions on a daily basis. ESRD is an incurable, life-threatening disease marked by permanent cessation of kidney function, forcing patients to receive some form of dialysis to survive. The decision to discontinue dialysis means that the patient will die within days. Moreover, because patients with ESRD often have additional co-morbid conditions that limit their ability to make decisions, family members are often called upon to make substituted judgments for patients with ESRD.

The OPTIONS study, funded by a grant from the National Institute of Nursing Research (R01 NR 05237), examines the lives of patients with ESRD and their spouses. The central question the study seeks to address is how patient and spouse preferences for dialysis treatment relate to one another and how these preferences change over the course of time. Eligible couples include a patient diagnosed with ESRD who has been on hemodialysis for at least six months and is at least 55 years old. To be eligible to participate in the study, couples had to have been married for at least five years. Each patient and spouse are interviewed at intake to the study and then annually for three years. Interviews are conducted by telephone.

A total of 315 couples living throughout the U.S. have been participating in this research. The average age of patients and spouses is 69.9 and 67.8 years, respectively. The majority of patients are Caucasian (85.5%), while 10.7% are black/African-Americans, 1% Native Americans, and 2.7% identify themselves as being of other or mixed races. The average length of patients' treatment for ESRD at intake was 6.7 years. Patients and spouses had been married for an average of 41.4 years.

Patients and their spouses were presented with a series of hypothetical situations and typical conditions of people with ESRD (e.g., stroke, dementia, coma, terminal illness). Following the description of each health condition, patients were asked the following question: "If you had this condition, how likely would you be to want to continue your dialysis treatments?" (patient preference). Spouses were asked two questions after each hypothetical description. The first questions asked were "If the patient had this condition, how likely would you be to want his/her dialysis treatments continued?" (spouse preference) and "If the patient had this condition, how likely do you believe she/he would be to want his/her dialysis treatments continued?" (substituted judgment).

Analyses revealed that patients and their spouses have very different preferences about the desirability of the patient continuing dialysis. Across all hypothetical situations, spouses were consistently more likely to indicate a preference for the patients to remain on dialysis than were the patients themselves. Moreover, the substituted judgments that spouses indicated they would make fell between their own preferences and the patients' preferences on each of the hypothetical scenarios, suggesting that substituted judgments reflected both the patients' actual preferences and the spouses' preferences. More detailed analyses indicated that patients' preferences accounted for only minute proportions of the substituted judgments made by spouses. On the other hand, spouses' own preferences were highly significant predictors of their substituted judgments.

To understand the dynamics responsible for the above differences, a second set of analyses examined the factors predicting patient preferences and spouses' substituted judgments. Results indicated that patients' preferences to continue dialysis were positively related to their education, subjective quality

of life, and religious participation, and negatively related to months of ESRD treatment and fear of end-of-life suffering. Spouses' substituted judgments regarding patients' dialysis continuation preferences were positively related to being African-American and to spouses' perceptions of patients' quality of life, and negatively related to months of ESRD treatment, spouses' perceptions of patients' negative affect, and spouses' own fear of end-of-life suffering.

Information from the OPTIONS study provides a more comprehensive understanding of the preferences for end-of-life treatment held by patients and their spouses than previously existed. The tendency for spouses' own preferences rather than actual patient preferences to guide substituted judgments helps to confirm the inability of surrogate decision makers to accurately represent the wishes of the people whose perspectives they are presumed to represent. Results from this study suggest the need for better and more structured communication between patients and their surrogate decision makers. Healthcare providers can play an important role in facilitating this conversation. Explicit conversations between patients, family surrogates and physicians can help physicians and family members gain a better sense of the patients' preferences and values regarding life-sustaining treatment. This knowledge can become invaluable should the patient lose decision-making capacity.

Rachel Pruchno, PhD, received her BA from Michigan State University, her MA from Oakland University and her PhD from Pennsylvania State University. She joined the faculty of the New Jersey Institute for Successful Aging at the UMDNJ-School of Osteopathic Medicine in July 2004. Her research over the past two decades has focused on older people and their families. In addition to the OPTIONS study, she has funding from the National Institute on Aging to study women who are in the labor force while simultaneously taking care of an older person. 🍷

Primary care: a new frontier for mental health research

by **Javier I. Escobar**

I recently received a \$3 million grant from the National Institutes of Health (NIH) to lead a new, developing center for services research at UMDNJ-Robert Wood Johnson Medical School (RWJMS). Based in the Department of Psychiatry, this research consortium includes other investigators from RWJMS, UMDNJ's University Behavioral Healthcare (UBHC) and Rutgers University, who will examine new research strategies to assess and manage patients with mental health problems in primary care.

A new center grant for RWJMS, "Medically Unexplained Physical Symptoms (MUPS) in Primary Care Research Center," \$2,911,462 total costs, was competitively funded this July as a Developing Center for Intervention and Services Research (DCISR) by the National Institute of Mental Health (NIMH). I will lead the center and serve as principal investigator. Michael Gara, MD, professor of psychiatry, is co-principal investigator. Other RWJMS investigators include Denise Rodgers, MD,

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associate dean for community health and associate professor of medicine, Eric Jahn, MD, assistant professor of medicine, and Lesley Allen, PhD, Paulette Hines, PhD, Edward Kim, MD, Paul Lehrer, PhD, Shula Minsky, William Vega, PhD, Betty Vreeland, MSN, Robert Woolfolk, PhD, and Doug Ziedonis, MD, MPH, from the Department of Psychiatry at RWJMS.

A key mission of this developing center is to forge research collaborations to devise strategies and design projects to improve the understanding and management of primary care patients, particularly those from low-income minority groups. It will also evaluate a set of cost-effective, practical therapeutic interventions within primary care settings to manage medically unexplained

the majority do not and prefer seeking treatment specifically for their MUPS in primary care as opposed to treatment for their depression/anxiety in mental health clinics. While stigma and limited resources contribute to this trend, there appears to be a preference on the part of many consumers to seek primary care services. Unfortunately, despite the availability of efficacious interventions for depression/anxiety suitable for use in primary care, these interventions have not been widely disseminated in these settings.

In a previous NIH-funded study of patients presenting with MUPS to primary care providers (Chandler Clinic and other sites), we learned that their clinical management could be practically enhanced if they were approached at the

WORLDWIDE, PEOPLE WITH COMMON MENTAL DISORDERS SUCH AS ANXIETY/DEPRESSION TEND TO FIRST SEEK HELP

FROM PRIMARY CARE PROVIDERS, NOT FROM BEHAVIORAL HEALTHCARE SPECIALISTS.

physical symptoms (MUPS) and associated depression and anxiety syndromes.

The main site for the clinical studies will be the Chandler Clinic, an RWJMS facility and federally qualified center that offers comprehensive services to an underserved, ethnically diverse, low-income urban population in New Brunswick. At Chandler, 70% of patients speak languages other than English as their primary language; and Latino patients constitute one half of the patient population, with a predominance of recent immigrants from 11 Latin American countries.

Worldwide, people with common mental disorders such as anxiety/depression tend to first seek help from primary care providers, not from behavioral healthcare specialists. These patients tend to emphasize their MUPS in the way they present to their doctors. Some may acknowledge psychological issues, but

primary care site, often in a non-traditional manner, by addressing their physical symptoms first, and not the “depression” or “anxiety” per se. That study (1-RO1 MH 60265-01, “Treatment of Somatization in Primary Care,” Javier I. Escobar, MD, principal investigator; Michael Gara, PhD, co-PI; \$1,600,000 total costs) began in late 2000 and recruited 180 primary care patients presenting with symptoms such as persistent fatigue, pain or gastrointestinal, cardiovascular or musculoskeletal symptoms that remained medically unexplained. A majority of patients had mild to moderate anxiety/depressive disorders. Ten sessions of an intervention incorporating cognitive-behavioral principles together with a relaxation component were compared to “treatment as usual.” The results were statistically significant and quite impressive in that more than 65% of the patients who received the intervention attained good outcomes (clinical ratings of “very

much improved” or “much improved”) whereas about one third of the patients in the “treatment as usual” group demonstrated this kind of outcome.

We also learned in that first study that patients with MUPS and co-morbid anxiety/depression syndromes fare better if we “take them as they come,”

addressing their MUPS symptoms first and their psychiatric symptoms next. When we tried the reverse sequence, we ran considerable risk of losing the patient altogether, in the sense of unacceptable increased rates of patient drop-out and non-compliance. We also learned that the “one size fits all” approach is not an appropriate strategy for most MUPS patients and that a more flexible, progressive (one step at a time) approach must be considered. Therefore, one of the goals of our new center grant is to develop and refine an innovative approach that comprises a number of interventions (pharmacological and non-pharmacological).

Research emanating from our developing center will devise and test new ways to assess and treat these MUPS patients in a culturally relevant manner, determining which approaches/methods work well with each population and which do not, and developing products such as treatment manuals and multimedia to facilitate diffusion of effective interventions in primary care settings nationwide.

Setting up such a center has required tightening the rather loose and informal infrastructure that linked psychiatric and medical specialties with primary care in our University-RWJMS system. A critical new link that had to be added to this infrastructure is between primary care and behavioral healthcare, represented by UMDNJ’s University Behavioral HealthCare (UBHC). The hope is that eventually such a link can be self-sustaining as well as transferable to other settings outside UMDNJ. The success of such a transfer is more likely if ingenuity is harnessed to forge new and replicable communication structures (including computerized ones), financial structures (including revenue sharing), culturally competent behavioral healthcare services rendered at primary care sites, training, research mentoring and so on.

The center will also provide the needed research infrastructure to take advantage of these newly forged links between medicine, psychiatry and UBHC. This research infrastructure would include data management, with the ability to merge the center’s databases with UBHC’s highly sophisticated administrative database, statistical support, and a methods core to develop new, streamlined and biometrically sound ways to assess MUPS and cultural competence in primary care.

In related work, I have for the past five years led a NIH-funded mentoring program (1-R13 MH 66308-01, “Critical Research Issues in Latino Mental Health,” Javier I. Escobar, MD, Principal Investigator, \$354,800 direct costs) aimed at training new investigators to conduct research on Latino mental health issues. This program has been adopted nationally as a model for developing similar programs.

Javier I. Escobar, MD, MS, is chair of psychiatry at RWJMS. He received his medical degree from the University of Antioquia Medical School. After postgraduate training at the Complutense University in Madrid, he came to the U.S. He completed a psychiatry residency and research fellowship on psychiatric genetics and received a Master’s degree in psychiatry/medical genetics at the University of Minnesota. He served as Senior Advisor to the Director of NIMH, and as a member of NIMH’s National Advisory Mental Health Council, FDA Advisory Committee and several NIH and VA IRGs and national task forces. An advisor to the World Health Organization, he is past president of the American Society of Hispanic Psychiatry. 🍷

When should patients receive blood transfusion?

by Jeffrey L. Carson

More than 11 million units of blood are transfused each year in the U.S. Between 60% and 70% of blood transfusions are given to patients undergoing surgery, with the majority of blood transfusions given to older patients. Despite the common use of red blood cell transfusions, physicians are not sure how much blood people need after surgery. This study is being conducted to determine when blood transfusions should be given to patients after surgery for a broken hip. The purpose of this study is to compare two plans for giving blood transfusions to patients. Some physicians give a blood transfusion to keep the blood concentration at about 10 grams, whereas other doctors wait until the blood count is less than 8 grams before giving a transfusion. Healthy people have blood counts above 12 grams. Doctors are unsure how much blood patients need for optimal recovery after surgery. With more knowledge and understanding of how blood transfusions improve recovery from surgery, we hope to provide a more effective and timely treatment so that a greater number of patients can recuperate appropriately.

Despite the enormous number of red blood cell transfusions in the U.S, we have very little high quality scientific data to guide us as to when blood should be administered. Most of the efforts during the past 20 years have been directed at improving the safety of blood transfusions. Back in the 1980s the risks from blood transfusions were high, since HIV had contaminated the blood supply. New screening procedures and tests, such as nucleic acid testing for HIV and hepatitis C, have greatly reduced the risk of transmission of viral diseases. The current risk of acquiring HIV or hepatitis C is now only one in two million. New risks, such as West Nile virus and variant Creutzfeldt-Jacob disease, are extremely rare. Overall, the risks related to blood transfusion appear to be very low.

What is needed is new information to serve as a guide for when blood should be transfused. Most research on the indications for blood transfusion is flawed and potentially biased. Only one adequately powered clinical trial has been performed in intensive care unit patients. This trial found that patients receiving a restrictive transfusion approach (7 g/dL trigger) do as well as patients receiving a liberal transfusion approach (10 g/dL trigger). However, it is unknown if these results generalize to surgical patients. Furthermore, we have previously demonstrated in an NIH-funded study of nearly 2,000 patients who declined blood for religious reasons that the odds of death in patients with underlying cardiovascular disease is greater than for patients without cardiovascular disease. This is due to a decline of the preoperative hemoglobin in patients with cardiovascular disease. Thus, it is unclear if it is safe to withhold transfusion in patients with underlying cardiovascular disease.

With this knowledge in mind, the National Heart, Lung, and Blood Institute has funded a new clinical trial called Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS). This study is a randomized clinical trial designed to test the hypothesis that a higher blood transfusion threshold improves functional recovery and reduces morbidity and mortality in patients with underlying cardiovascular disease. In the study, 2,600 patients from 25 medical centers in the U.S. and Canada who undergo

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(RIGHT TO LEFT) JEFFREY L. CARSON, MD, RICHARD C. REYNOLDS PROFESSOR OF MEDICINE, CHIEF, DIVISION OF GENERAL INTERNAL MEDICINE, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL, HELAINE NOVECK, MPH, DEPUTY DIRECTOR, CLINICAL COORDINATING CENTER, FOCUS CLINICAL TRIAL, AND KAREN DRAGERT, RN, HEAD RESEARCH NURSE, FOCUS CLINICAL TRIAL

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surgery for hip fracture, have a history of cardiovascular disease, and have a postoperative hemoglobin level less than 10 g/dL within three days of surgery, are eligible. Patients will be randomized to receive enough blood to raise the hemoglobin level above 10 g/dL. If at any time the hemoglobin level is detected to be below 10 g/dL during the hospitalization or if symptoms of anemia develop, the patient will receive a transfusion. Transfusion is permitted but not required if the hemoglobin level is less than 8 g/dL. The primary outcome is the ability to walk 10 feet (or across a room) without human assistance at 60 days. The most important negative outcome is postoperative

strategy. On the other hand, if the 10 g/dL strategy does not have greater efficacy in this highly sensitive population of patients with cardiovascular disease, then the question of transfusing to greater than 8 g/dL will be closed. The results of FOCUS should be available in about four years.

Jeffrey L. Carson, MD, is the Richard C. Reynolds Professor of Medicine and chief of the division of general internal medicine. He is the principal investigator and study chair of the FOCUS clinical trial at RWJMS. Dr. Carson completed a fellowship in epidemiology and biostatistics at the University of Pennsylvania and was a

THIS STUDY IS DESIGNED TO TEST THE HYPOTHESIS THAT A HIGHER BLOOD TRANSFUSION THRESHOLD IMPROVES FUNCTIONAL RECOVERY AND REDUCES MORBIDITY AND MORTALITY IN PATIENTS WITH UNDERLYING CARDIOVASCULAR DISEASE.

unstable angina, myocardial infarction or death. Myocardial infarction will be diagnosed based on four blood specimens, three electrocardiograms, and a medical history. Medical records will be reviewed while the patient is in the hospital. Patients will be telephoned at 30 and 60 days after entry into the study to determine functional capacity and vital status. Long-term mortality will be determined by searching vital statistics registries in the U.S. and Canada.

The results of this trial should have a profound impact on the use of blood transfusions in patients with cardiovascular disease. If the FOCUS trial demonstrates that higher blood counts improve functional recovery, or reduce the risk of postoperative complications such as myocardial infarction, then clinicians will have a compelling reason to use a liberal transfusion

resident and chief resident at Hahnemann Medical College, also in Pennsylvania. He is a board-certified internist and his practice includes the care of pre- and postoperative surgical patients. His research in blood transfusions began more than 17 years ago with the initiation of a cohort study involving Jehovah's Witness patients. Dr. Carson has published more than 125 peer reviewed papers, book chapters, and editorials. He has been awarded five teaching awards, including the 2002 Alpha Omega Alpha Faculty Recognition Award.

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New immune-based gene therapy approaches to cancer

by **Edmund C. Lattime**

One of the greatest advances in healthcare has been the development of vaccines for infectious disease. The immune system efficiently recognizes an unlimited array of disease causing agents and has developed highly effective mechanisms for their destruction. Despite having this broad repertoire, the immune system has learned to distinguish self from non-self and usually it does not attack its own tissues. The last

regulated. Second, we are just now realizing that we have underestimated the ability of the tumor to directly compromise the immune response and thus escape immune destruction. Combining advances in both areas has led to a new generation of vaccine strategies for the treatment of cancer. Studies being carried out by the Immunotherapy Group at The Cancer Institute of New Jersey are focused on developing next-generation approaches to immune-based gene therapy by combining expertise in basic immunology, medical oncology, surgical oncology, and urology.

The development of an immune response requires the highly regulated interaction of a number of different types of white blood cells (WBC) (See Fig. 1). When exposed to a potential target (antigen), cells called antigen-presenting cells or dendritic cells (DC) take up antigenic material, are activated, and then travel to the lymph nodes. There they interact with T

THE IMMUNE SYSTEM EFFICIENTLY RECOGNIZES AN UNLIMITED ARRAY OF DISEASE-CAUSING AGENTS

AND HAS DEVELOPED HIGHLY EFFECTIVE MECHANISMS FOR THEIR DESTRUCTION.

feature makes difficult the harnessing of the immune system as a means of treating cancer, although it remains an attractive strategy and has been a goal of scientists for decades. While there have been some encouraging results, this goal has for the most part gone unrealized. Despite this lack of success, there is currently renewed enthusiasm for the potential of cancer vaccines. The reasons are twofold: First, we have become more knowledgeable about the complexity of the immune system and how it is

and B lymphocytes, resulting in the generation of antibodies and lymphocyte populations that can kill cells bearing the antigen. In addition to effector populations, regulatory cells that enhance or inhibit the end stage effector response are activated.

Our studies have focused on analyzing the tumor microenvironment in patients with a variety of tumors to determine the presence or absence of a tumor-specific immune response, and of immune regulatory molecules that

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EDMUND C. LATTIME, PHD, PROFESSOR OF SURGERY AND MOLECULAR GENETICS, MICROBIOLOGY, AND IMMUNOLOGY, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL (RWJMS) AND ASSOCIATE DIRECTOR FOR EDUCATION AND TRAINING, THE CANCER INSTITUTE OF NEW JERSEY; AND (RIGHT TO LEFT) ROBERT E. WEISS, MD, ASSOCIATE PROFESSOR, SURGERY, RWJMS; RODERICH SCHWARZ, MD, PHD, ASSOCIATE PROFESSOR, SURGERY, RWJMS; SCOTT R. SCHELL, MD, PHD, ASSOCIATE PROFESSOR, SURGERY, RWJMS. NOT PICTURED; MARK STEIN, MD, ASSISTANT PROFESSOR, MEDICINE, RWJMS.



would provide targets for manipulation. This information, coupled with the growing knowledge of the regulatory pathways involved in the development of an effective immune response, allowed us and others to identify a series of immune regulatory cytokines overexpressed in tumors that have the potential to suppress the development of antitumor immunity. We have primarily focused our studies on interleukin 10 (IL10), a cytokine normally elicited in the process of the development of an immune response as a means of dampening the response and preventing runaway inflammation. Using pre-clinical tumor models in mice, we found that the tumor-associated IL10 completely inhibited the ability of mice to develop effective antitumor immunity. Our experimental tumors uniformly grew in IL10 wild type mice without development of an anti-tumor response. In addition, the tumor-bearing mice were completely non responsive (anergic) to immunization with traditional vaccines. When IL10 was inhibited using either neutralizing antibody or IL10 knockout mice, a significant number of mice developed effective immunity and rejected the tumor challenge. We have gone on to show that IL10 was exerting its suppressive activity by inhibiting the

intra-vesical fowlpox-GMCSF vs. intra-vesical fowlpox-TRICOM (immune co-stimulatory molecules) in patients with advanced bladder cancer.

As an extension of our pre-clinical studies that demonstrated the activity of recombinant virus encoding both GMCSF and antigen, we have recently shown that the level of immunity induced is significantly increased when the

vaccine is given at the tumor site. We hypothesize that the combination of tumor antigen with the positive cytokine overcomes anergy by expanding tumor-specific T cell populations already present in small numbers in the draining lymph node. We are in the process of translating these findings to clinical trials where we will administer these combination vectors intra-tumorally in patients with breast and pancreatic cancer. In addition to determining direct anti-tumor effects of such therapies, we have designed correlative laboratory studies evaluating how these therapies are influencing the development of anti-tumor immunity.

We hope that the information gained from the early trials and their correlative studies will be critical to the design of the next generation of clinical trials.

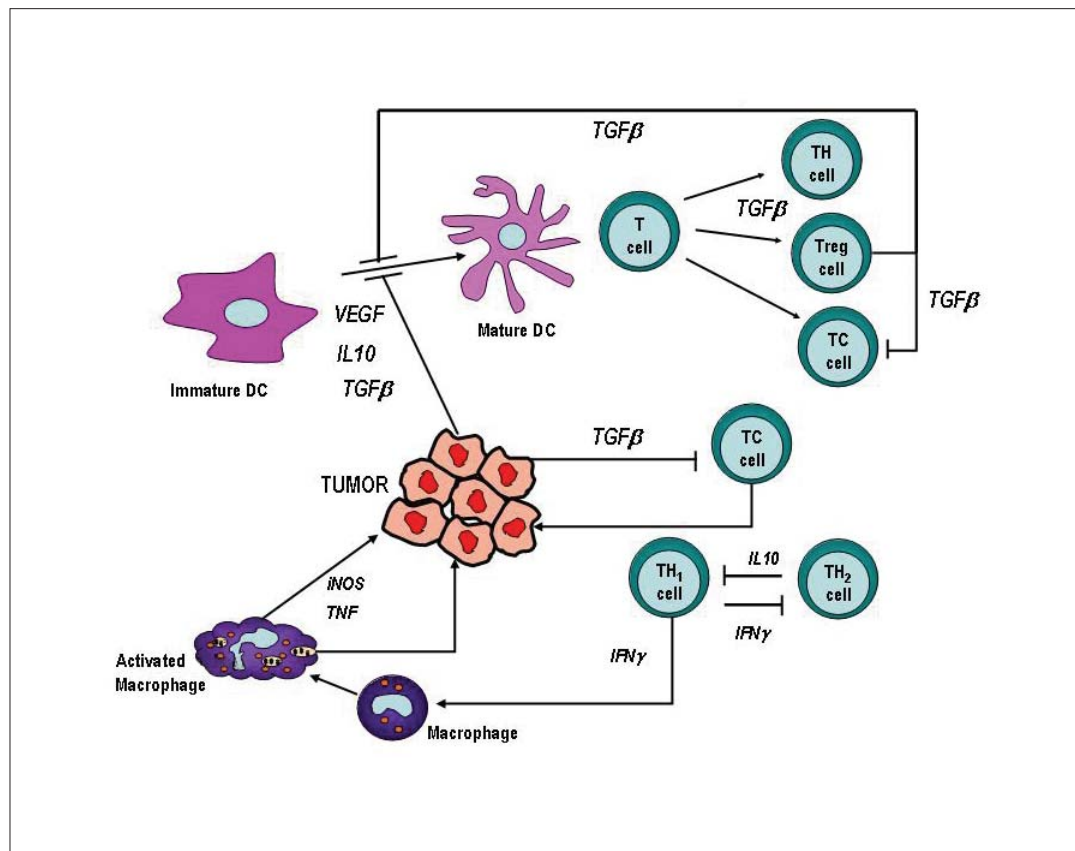


Figure 1. **Tumor-associated cytokines inhibit anti-tumor immunity.** The generation of cytokines by tumor cells directly or by non-tumor cells under the influence of tumor has a profound effect on the development of anti-tumor immunity and the responsiveness to tumor vaccines. Factors such as interleukin 10 (IL10), transforming growth factor beta (TGFβ), and vascular endothelial growth factor (VEGF), can inhibit the maturation and activation of antigen-presenting dendritic cells (DC) as well as regulate the generation of effector and/or regulatory T cells, with the end effect of allowing the tumor to escape immune recognition and surveillance.

OUR STUDIES HAVE FOCUSED ON ANALYZING THE TUMOR MICROENVIRONMENT IN PATIENTS WITH A VARIETY OF TUMORS TO DETERMINE THE PRESENCE OR ABSENCE OF A TUMOR-SPECIFIC IMMUNE RESPONSE, AND OF IMMUNE REGULATORY MOLECULES THAT WOULD PROVIDE TARGETS FOR MANIPULATION.

maturation of antigen-presenting dendritic cells. This observation led us to develop (a combination vaccine by engineering) a recombinant vaccinia virus that encoded both the gene for granulocyte-macrophage colony stimulating factor (GMCSF), a factor that stimulates DC function, and tumor antigen. Use of this vaccine allowed us to break the anergy and effectively immunize tumor-bearing mice.

Having identified the association between tumor induced IL10 and its downstream effects on antigen presentation, we have developed a novel strategy of using recombinant poxvirus, administered intra-tumorally in the case of accessible solid tumors or intra-vesically (instilled into the bladder cavity) in bladder cancer, to transfer the GMCSF gene, as well as genes encoding a number of immune co-stimulatory molecules, to tumors. We hypothesize that this approach will overcome the tumor-associated inhibition of DC activity leading to a productive antitumor response. Initial clinical trials of intra-tumoral vaccinia-GMCSF produced encouraging responses in patients with metastatic melanoma. We are currently accruing to a trial of

Edmund Lattime, PhD, is a professor of surgery and molecular genetics, microbiology, and immunology at RWJMS. He obtained his PhD from Rutgers University, followed by postdoctoral training at the Memorial Sloan Kettering Cancer Center, where he was a member of the faculty for 10 years. Dr. Lattime has served on a number of NCI and ACS study sections. He is associate director for education and training and the director of surgical oncology research at The Cancer Institute of New Jersey. He currently serves on the editorial boards of Cancer Research and The Journal of Clinical Oncology.

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SUNIL WIMALAWANSA, MD, PHD, PROFESSOR OF MEDICINE, CHIEF OF THE DIVISION OF ENDOCRINOLOGY, METABOLISM & NUTRITION, AND DIRECTOR OF THE REGIONAL OSTEOPOROSIS CENTER, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL

Development of a cost-effective novel therapy for osteoporosis

by **Sunil J. Wimalawansa**

Osteoporosis — literally “porous bone”— is the most common metabolic bone disease. Characterized by bone loss and deterioration of bone quality, it leads to bone fragility and an increased risk of fractures. It is responsible for approximately 1.6 million fractures, primarily of the hip, spine and wrist each year, and for medical expenses of \$20 billion annually in this country. Not only do a high percentage of patients who experience a

of highly effective medications that reduce the risk of osteoporotic fractures by half are available to help treat osteoporosis. However, these agents are very costly and have significant adverse effects, such as upper gastrointestinal irritation/ulceration, constipation, enhanced arterial and venous thrombosis, and increased fracture incidence with over-treatment. Some studies have shown that nitroglycerin, a commonly used heart medication, may preserve bone density. Our group is currently investigating whether a nitroglycerin-based ointment would be effective in reducing bone thinning in menopausal women.

Unlike some diseases, osteoporosis can be easily diagnosed and treated. The keys to preventing fractures are a bone-healthy lifestyle, early detection of the disease by bone mineral density (BMD) testing, elimination of secondary

causes of bone loss and prevention of falls. In the past, many women relied on hormone replacement therapy (HRT) after menopause to reduce the risk of heart disease and osteoporosis. However, the Women’s Health Initiative (WHI) study recently demonstrated that, although effective in fracture prevention,

STUDIES CONDUCTED OVER THE PAST 18 YEARS IN LABORATORIES AND CLINICS HAVE SHOWN THAT NITROGLYCERIN

MAY PRESERVE THE SKELETAL SYSTEM, AND THUS SLOW OR PREVENT THE BONE-THINNING PROCESS.

broken hip require permanent nursing care, these fractures are also a significant cause of morbidity and mortality in elderly people. Until recently, little could be offered to these individuals to slow or halt the progression of osteoporosis, and it was accepted as part of the aging process. Today, an increasing number

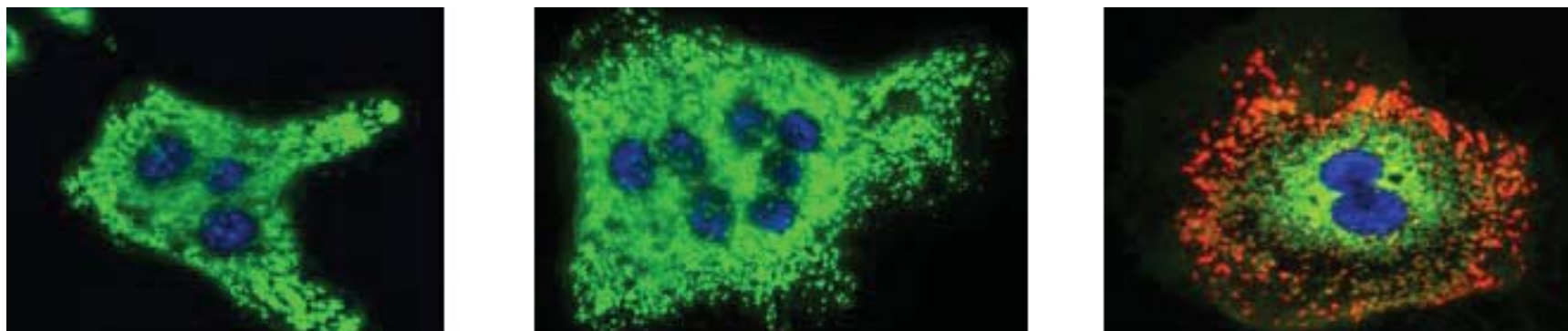
causes of bone loss and prevention of falls. In the past, many women relied on hormone replacement therapy (HRT) after menopause to reduce the risk of heart disease and osteoporosis. However, the Women’s Health Initiative (WHI) study recently demonstrated that, although effective in fracture prevention,

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HRT may actually increase the risk of stroke, heart disease and breast cancer. In addition, some postmenopausal women have additional side effects, and others cannot afford HRT or other expensive medications that combat osteoporosis. Thus, finding a cost-effective alternative therapy is essential.

Nitroglycerin is a common heart medication used to dilate blood vessels, decrease blood pressure, improve circulation and control angina. Studies conducted by our group over the past 18 years in laboratories and clinics have

As a nitric oxide (NO) donor, nitroglycerin has a beneficial effect on controlling bone destruction while improving bone formation. In addition, at physiological doses, NO decreases the stickiness of platelets, which is responsible for clogging arteries. Evidence is also accumulating that, at physiological doses, NO may also prevent cell death in vital organs such as heart, brain and pancreatic beta cells. The most common, only significant, adverse effect of nitroglycerin is the occurrence of mild headache in about



Figures 1 through 3: Maturation of an Osteoclast

shown that nitroglycerin may preserve the skeletal system, and thus slow or prevent the bone-thinning process.

The Regional Osteoporosis Center at UMDNJ-Robert Wood Johnson Medical School (RWJMS) provides state-of-the-art bone mineral density testing, which is an integral part of a new clinical trial known as the NOVEL study. [The acronym NOVEL stands for “Nitroglycerin as an Option: Value in Early Bone Loss.”] This five-year study is funded by the National Institute of Arthritis and Musculoskeletal Diseases at the National Institutes of Health. The RWJMS site has a unique focus. We asked the questions: Can Nitro-Bid® ointment, which contains nitroglycerin, stop bone thinning in menopausal women?

10% of the subjects who use this ointment. The dose of nitroglycerin used in this study is about one quarter of that routinely used in angina patients. Since menopause leads to NO deficiency, there is a plausible biological basis for use of NO replacement therapy (NO supplementation). Well-established exogenous NO sources, such as nitroglycerin ointment, constitute a practical way to supplement NO when the body cannot generate enough for normal biological functions.

For postmenopausal women who cannot tolerate or afford costly HRT and other FDA-approved medications, nitroglycerin treatment could be utilized for less than \$5 a month. Our preliminary human studies demonstrated

STUDIES CONDUCTED OVER THE PAST 18 YEARS IN LABORATORIES AND CLINICS HAVE SHOWN THAT NITROGLYCERIN

MAY PRESERVE THE SKELETAL SYSTEM, AND THUS SLOW OR PREVENT THE BONE-THINNING PROCESS.

Can this be an alternative to estrogen and HRT therapy?

Treatment consists of a daily application of Nitro-Bid® ointment (manufactured by E. Fougera & Co., a division of Altana Pharmaceuticals) or a placebo ointment to the arms or legs. Nitroglycerin (NTG) is 1,2,3-propantriol, an organic vasodilator nitrate. Nitroglycerin ointment has been on the market for more than 25 years and its adverse effects are well documented. In addition to a patent (US patent # 5,898,038; PCT pending), an IND application has been filed with the Food and Drug Administration for the administration of this ointment under this protocol for the indications of osteoporosis prevention and treatment. It is supplied as USP 2%, is in 60-gram tubes and should be stored at 15-30°C (59-86°F). The average NTG dose used in clinical practice to treat angina ranges from 15 to 30 mg, 2 to 3 times a day (>60 mg of NTG/day, or bio-equivalent for other nitrates); however, the NTG dose used in this NOVEL study is only 20 mg per day.

All participants receive 630 mg of elemental calcium and 400 IU of vitamin D daily (Citracal-D®, Mission Pharmacal), providing an estimated total daily intake of 1,400 mg calcium and 800 IU vitamin D per day. In this randomized, double-blind, controlled clinical study, the results of bone mineral density tests of women using only calcium and vitamin D will be compared with those using the active nitroglycerin ointment and taking calcium and vitamin D supplements. This ointment is far less expensive than the U.S. Food and Drug Administration approved drugs for osteoporosis.

that the efficacy of nitroglycerin in preventing postmenopausal bone loss is equivalent to Premarin®, and that nitroglycerin has beneficial additive effects on bone mineral density when co-administered with some established anti-osteoporosis therapies. This is yet another exciting area to be explored.

Sunil Wimalawansa, MD, PhD, MRCP, FRCP, DSc, is a professor of medicine, chief of the Division of Endocrinology, Metabolism & Nutrition, and director of the Regional Osteoporosis Center at UMDNJ-Robert Wood Johnson Medical School. He also holds the distinction of University Professor. Dr. Wimalawansa received his MD from the University of Sri Lanka (1975) and his PhD from the University of London (1988), and diploma in Business of Medicine from the Johns Hopkins School of Business (1999). He has received several awards from national and international societies. He has been involved in many volunteer humanitarian and social development activities over the past 35 years. He serves on several national review committees, including NIH, DEA and NASA, and several other national and international committees and advisory panels. His main focus of research is metabolic bone disease, in particular osteoporosis and biochemical and molecular approaches to basic cardiovascular disease, including gene therapy.

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NANCY S. REDEKER, PHD, RN, PROFESSOR AND ASSOCIATE DEAN OF RESEARCH,
UMDNJ-SCHOOL OF NURSING

Sleep and functional performance in heart failure

by Nancy S. Redeker

Disturbed sleep and sleep disordered breathing are common among the 5 million Americans who have heart failure, a devastating chronic illness that is associated with death, disability and poor quality of life. Disturbed sleep consistently ranks among the most frequently reported symptoms in these patients, and may occur in as many as 70%. Sleep disordered breathing, including Cheyne-Stokes breathing and/or obstructive sleep apnea, occurs in 30-60%

of heart failure patients and is associated with repetitive apneic and hypopneic events, frequent nocturnal arousals from sleep and excessive daytime sleepiness. However, there is evidence that some heart failure patients may have disturbed sleep that is unrelated to sleep disordered breathing.

Heart failure patients live with impaired functional performance — the ability to accomplish normal activities during the course of daily life. Although reported prevalence rates vary based on measurement methods and stage of heart failure, as many as 50% also suffer from clinical depression and the majority of heart failure patients report fatigue. Studies conducted with cardiovascular populations and patients with sleep apnea, and our own preliminary data with heart failure and cardiac surgery, suggest that sleep disturbance is common and contributes to decrements in functional performance, as well as fatigue and excessive daytime sleepiness.

Sleep is a multidimensional biobehavioral phenomenon. The contributions of specific characteristics of sleep disturbance (e.g., sleep duration, depth,

fragmentation) and sleep disordered breathing to functional performance in heart failure have not been previously examined. Heart failure patients who are fatigued, depressed or excessively sleepy as a consequence of disturbed sleep may be unable to accomplish normal activities of daily living. The

OUR PRELIMINARY WORK WITH HEART FAILURE PATIENTS DEMONSTRATED THAT FRAGMENTED SLEEP WAS

ASSOCIATED WITH DECREMENTS IN PHYSICAL FUNCTION AND MENTAL HEALTH.

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purpose of this research is to examine the contributions of both sleep and sleep disordered breathing to functional performance and to evaluate the extent to which this relationship is mediated by depression, fatigue and excessive daytime sleepiness. Understanding the specific attributes of sleep and the nature of the relationships between these aspects and functional performance is particularly important because functional performance is linked with mortality. Interventions to improve sleep may improve functional performance, and may also contribute to reductions in mortality.

Funded by the National Institute of Nursing Research of the National Institutes of Health, this ongoing four-year multi-site observational study involves recruitment of 400 patients who have stable heart failure. The protocol includes completion of a polysomnographic study, including EEG, chin EMG, eye movement recordings, ECG, and measurement of respiratory effort, nasal airflow (pressure transducer and thermistor) and oxygen saturation, obtained in the home environment with a miniaturized sleep recorder. Obtaining these measures in the home, a more comfortable environment, is likely to provide a more accurate picture of the patients' typical sleep pattern than is possible in a sleep laboratory setting. In addition to polysomnography, questionnaires and three-day behavioral sleep recordings obtained with wrist actigraphs are used. This battery of measures has been selected to permit evaluation of physiologic, behavioral and subjective attributes of sleep disturbance, each of which contributes information about important attributes of sleep.

Wrist actigraphs are computerized electronic accelerometer-based monitors that record activity/rest patterns. The activity/rest data are downloaded into a personal computer. Using commercially available software, inferences are made about the timing, duration, and extent of fragmentation of sleep throughout a 24-hour time period. The algorithm upon which this software is based has been validated against polysomnography, the gold standard of sleep measurement. Unlike polysomnography, actigraphy is non-intrusive and permits evaluation of sleep-wake over extended periods of time in natural environments. In my extensive work with this technology over the past 15 years, actigraphy has proved to be highly reliable and sensitive to clinically important changes in sleep patterns over time, as well as to clinically significant group differences.

We anticipate that data from the current observational study will be used as the basis for a future clinical trial designed to evaluate interventions to promote sleep in heart failure patients. Although recognition is emerging among scientists and clinicians about the high prevalence of sleep disordered breathing among patients with heart failure, and growing use of nasal continu-



Figure 1: Wrist actigraph

ous positive airway pressure (NCPAP) to treat it, less attention has been paid to other sources of sleep disruption, such as insomnia, among patients with heart failure. Behavioral strategies to reduce nocturnal arousals, such as cognitive behavioral therapy, music or massage, as well as judicious use of hypnotic medications, may be effective treatments for disturbed sleep among heart failure patients. The data obtained from the current study will provide baseline information from which to develop and test these interventions.

Our preliminary work with heart failure patients demonstrated that fragmented sleep was associated with decrements in physical function and mental health, and documented the severity of specific attributes of disturbed sleep among heart failure patients during daily life. Heart failure patients demonstrated poorer self-reported sleep quality and more fragmented sleep, but no shorter sleep duration, than a comparison group of adults who did not have heart failure.

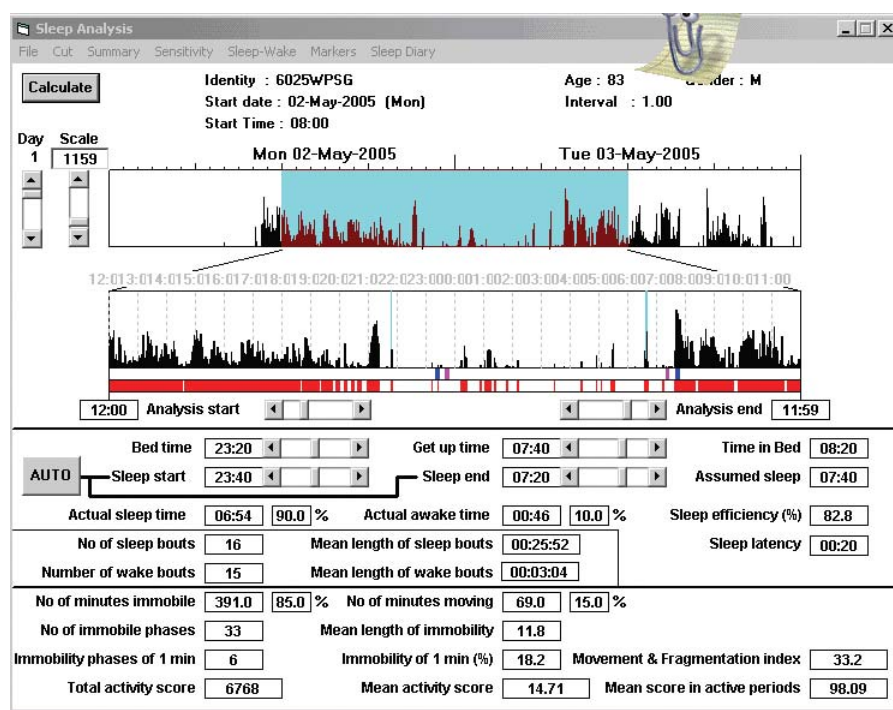
The current work with heart failure patients builds on a series of published studies in which we determined the nature of sleep disturbance over the course of recovery after coronary artery bypass surgery and the impact of sleep disturbance on physical function and emotional well-being — important quality of life concerns. Our finding that pre-operative sleep disturbance was an important predictor of post-operative sleep disturbance and physical function at four and eight weeks after surgery underscores the potential importance of pre-operative screening and intervention for sleep disorders among these patients. Our work also documented that post-operative sleep problems continued through the eighth post-operative week and thereby suggested the need for continued evaluation and management of sleep problems over the course of recovery.

I am also engaged in an ongoing collaborative series of studies to improve the sleep of adults during acute care hospital-

ization. The focus of this work is the development of sleep-promoting interventions for hospitalized patients.

Nancy S. Redeker, PhD, earned a BA in sociology from Rutgers University, BSN and MSN from Seton Hall University and a PhD in nursing from New York University. Dr. Redeker has completed NIH-funded training in sleep disorders. Her work has been funded by the National Institutes of Health, the American Nurses Foundation, American Heart Association, and the American Association of Critical Care Nurses. Until 2003, she was on the faculty of the College of Nursing at Rutgers. She is professor and associate dean for research at UMDNJ's School of Nursing.

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Data obtained from the Minimitter Actigraph. The top panel indicates the raw activity data for one study participant for one day. The middle panel shows the 24-hour period from 12 noon to 12 noon. The area marked with the aqua lines indicates time in bed. The remainder of the screen indicates calculated sleep and activity values.



BENJAMIN H. NATELSON, MD, PROFESSOR OF NEUROSCIENCES, UMDNJ-NEW JERSEY MEDICAL SCHOOL

Research on medically unexplained fatigue and pain

by **Benjamin H. Natelson**

While medicine usually progresses by identifying biomedical markers and indices of pathology, a large number of illnesses, ranging from autism and schizophrenia to migraine and chronic fatigue syndrome (CFS), do not fall within this model. CFS is characterized by extreme fatigue, producing a substantial decrease in activity accompanied by infectious, rheumatological and neuropsychiatric symptoms.

EVEN MILD EXERTION — AS SIMPLE AS PROLONGED STANDING — PRODUCES A DRAMATIC WORSENING OF THE CFS PATIENT'S FATIGUE AND MALAISE.

In 1991, the National Institute for Allergy and Infectious Diseases established a program of Chronic Fatigue Syndrome Cooperative Research Centers. I was fortunate enough to be awarded one of those Centers that continued receiving funding until the cessation of this program in 2004. That

program allowed me to assemble a cadre of researchers with different backgrounds, but common interests in medically unexplained fatigue and pain. This multi-disciplinary group was comprised of healthcare providers, including physiologists and psychologists.

The fact that medically unexplained fatigue is a component of major depressive disorder was recognized by the medical community. Consequently, it was believed that CFS was a *forme fruste* of depression. However, we and other groups have assembled a reasonable amount of data against this hypothesis. First, rates of major depressive disorder do not differ between CFS and multiple sclerosis, a neurological disease in which fatigue is prominent. Second, physiological measures, such as plasma cortisol and prolactin response to tryptophan, are reduced in CFS while increased in depression. Third, treatment with anti-

depressant drugs has little effect in CFS in contradistinction to its effect on depression. Finally, CFS patients have a symptom which is not seen in depression: namely, that even mild exertion — as simple as prolonged standing — produces a dramatic worsening of the patient's fatigue and malaise.

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We have done a number of studies that document and support this complaint. CFS patients show a decrease in activity and in neuropsychological performance following a standardized exercise challenge. The physiological concomitant appears to be a reduced capacity to respond to the stimulus. In other experiments, we have found that some CFS patients at rest have reduced stroke volumes and reduced global cerebral blood flow. This has led to the hypothesis that orthostatic challenge can further compromise cerebral blood flow to produce symptom exacerbation.

To test this hypothesis, we began assessing physiological parameters during orthostatic challenge. Prior reports had indicated that a substantial number of CFS patients had postural orthostatic tachycardia syndrome (POTS). We have found this in relatively few patients. However, substantially more patients show drops in end tidal CO₂ during orthostatic challenge. While mild hypocapnia is known to occur during postural challenge, the levels that developed in some patients were frankly abnormal. We hypothesized that perhaps posturally induced hypocapnia could further reduce cerebral blood flow in patients who already were on the low side of normal with symptom worsening as the outcome.

Bharat Biswal, PhD, of the NJMS Department of Radiology, and I are collaborating on studies based on this hypothesis. Dr. Biswal's major area

of research looks at control of cerebral blood flow as assessed by non-invasive neuroimaging methods. Thus, he can determine cerebral blood flow by using a form of functional magnetic resonance imaging. Studying orthostatic challenge in the 3-T magnet environment, where it is impossible to stand, was an obvious challenge. To deal with this challenge, predoctoral student Pratap Kunwar developed an apparatus that mimics a postural challenge by drawing blood from the head and thorax into the lower extremities. We are currently embarked on a major study of the effects of postural challenge on cerebral blood flow as modulated by changes in blood CO₂.

Medicine, we decided to assess cytokines broadly — in plasma using ELISA technology, in white blood cells using rT-PCR to capture cytokine message, and in living white cells using ELISpot technology stimulated both by herpes viruses and phytoagglutinin.

We applied to the National Institute of Allergy and Immunological Disorders and were awarded funding last October. Our experimental design requires blood sampling before, during and after sleep in CFS patients and in healthy controls whose total sleep time was matched to that of a CFS patient studied earlier. We are only recruiting women and excluding those with depression, which can affect both sleep and cytokines. A second experiment uses the same approach following a cardiac stress test. Since exertion is known to exacerbate fatigue and produce additional sleep problems, the purpose of this experiment is to determine if syndromic exacerbation is due to further unbalancing of the cytokine sleep network. Finally, we reasoned that if CFS patients had an underlying immunological disorder relative to healthy controls, a night of total sleep deprivation would magnify the differences because healthy subjects would show a cytokine shift in favor of sleep production whereas CFS patients would still show a predominance toward cytokines that disturb sleep.

We have assembled a research team consisting of Mayka Benitez, study

ANOTHER MAJOR PROJECT HAS TO DO WITH THE HYPOTHESIS THAT CFS IS AN ILLNESS OF IMMUNE DYSREGULATION. THAT HYPOTHESIS STEMS FROM THE FACT THAT APPROXIMATELY 40% OF CFS PATIENTS REPORT A SUDDEN ONSET. BECAUSE OUR OWN WORK HAS SHOWN THAT THE TEMPORAL PATTERN OF THESE ILLNESS ONSETS IS NON-RANDOM, WE BELIEVE THEY PROBABLY REPRESENT AN INFECTIOUS TRIGGER.

of research looks at control of cerebral blood flow as assessed by non-invasive neuroimaging methods. Thus, he can determine cerebral blood flow by using a form of functional magnetic resonance imaging. Studying orthostatic challenge in the 3-T magnet environment, where it is impossible to stand, was an obvious challenge. To deal with this challenge, predoctoral student Pratap Kunwar developed an apparatus that mimics a postural challenge by drawing blood from the head and thorax into the lower extremities. We are currently embarked on a major study of the effects of postural challenge on cerebral blood flow as modulated by changes in blood CO₂.

Another major project has to do with the hypothesis that CFS is an illness of immune dysregulation. That hypothesis stems from the fact that approximately 40% of CFS patients report a sudden onset. Because our own work has shown that the temporal pattern of these illness onsets is non-random, we believe they probably represent an infectious trigger. The high rate of infectious-type illness onset led patient advocates to label the illness "chronic fatigue and immune dysfunction syndrome" or CFIDS. The idea is that infection produces immune activation, leading to a chronic illness state. The fact that fatigue and diffuse aches are common side effects of cytokine administration supports this hypothesis.

Unfortunately, studies failed to provide evidence to support the immune dysfunction hypothesis, possibly due to their design. Specifically, samples were usually collected at one time of day and we used only one method to quantify cytokines. My colleague, Neil Cherniack, MD, and I reasoned that perhaps the research tactics used to date could be improved. We focused on sleep in CFS since a very common symptom of patients is unrefreshing sleep. Reduced total sleep time with frequent arousals has been reported in laboratory assessed sleep. A major regulator of normal sleep is a balance between Type 1 (sleep producing) and Type 2 (sleep disrupting) cytokines. We hypothesized that CFS might result from an imbalance in the cytokine sleep network in favor of sleep disrupting cytokines. Collaborating with Stephan Schwander, MD, PhD, assistant professor, NJMS Department of

coordinator, Jennifer FitzGibbons, research nurse practitioner, and Carmen Garcon, research sleep nurse. We have begun these studies in the medical school's prototype General Clinical Research Center. The study is really just getting started. Fifteen women have volunteered to date and we plan to study approximately another 65 research volunteers. Additional information about our work can be found at www.umdj.edu/cfs.

Benjamin Natelson, MD, received his BA from the University of Pennsylvania and his MD from the University of Pennsylvania School of Medicine. He completed his neurology residency at Albert Einstein College of Medicine in the Bronx and his post doctoral research fellowship in behavioral neurosciences at Cornell Medical Center. Dr. Natelson is currently a professor in the Department of Neurosciences at NJMS. He was the previous director of the War-Related Illness and Injury Study Center at VA New Jersey Health Care System in East Orange. Dr. Natelson has been on the editorial board of many journals, with his most recent appointments on the journals Psychosomatic Medicine and Current Psychosomatic Medicine. He has also authored two books: Tomorrow's Doctors: The Path to Successful Practice in the 1990s and Facing and Fighting Fatigue: A Practical Approach. 📖

Rehabilitating walking through virtual environments

by Judith E. Deutsch

Many stroke victims never fully regain their walking ability. In particular, they may not be able to walk as far or as fast as is required to function in a community setting. To improve walking, we have developed virtual reality devices that allow an individual to train at the intensity and duration necessary to achieve improvements in strength, coordination and endurance. We have shown that providing leg movement training in a virtual environment achieves increased walking speed outside the virtual environment. We are now in the process of testing a walking simulator, where one can stay in the clinic setting but practice in a variety of virtual worlds. We are also working on the remote delivery of rehabilitation and the transfer of technology from the laboratory to the clinic. Our work is an excellent example of interdisciplinary collaboration.

In our lab, a major focus is the rehabilitation of individuals post-stroke, as they strive to recover function, and in particular to improve their walking ability. We are pursuing several lines of inquiry to address the question of how to improve walking ability in individuals who are recovering from a stroke. These interventions include the use of motor imagery, awareness through movement training and virtual reality. This article will focus on the virtual reality work.

The clinical application of virtual reality to rehabilitation of walking is grounded in several areas of basic science. Animal studies have shown that training in enriched environments produces improvements in motor behavior. Furthermore, animals trained with specific goal-directed activities, in contrast to endurance and strength training, develop both behavioral improvements and neural plasticity. We have also learned from animal studies that a high degree of repetition and intensity is required for motor learning and brain plasticity. These principles form the foundation for pursuing virtual environments as an avenue to rehabilitation.

Virtual environments can be used to engage the patient in the intensive repetitive practice required to produce behavioral changes. Furthermore, the environments can be customized to address specific deficits of the individual patient. It is this promise of virtual rehabilitation (VR) that we are investigating in our lab.

In collaboration with Greg Burdea, PhD, and Rares Boian, PhD, at Rutgers University, we have developed and refined virtual reality technology for rehabilitation. In particular, we have been interested in creating systems to rehabilitate individuals post-stroke. These systems use a combination of hardware as inputs into the virtual environments that are displayed using software on a desktop computer. We use a combination of vision, sound and touch (haptics) to engage users in the virtual environments.

Our first system, the Rutgers Ankle Rehabilitation System, has a device that allows patients to use their foot to navigate in two virtual worlds. We have created an airspace and a seascape (for airspace see Figure 1) with

targets and obstacles to be navigated. As patients are occupied with moving in the virtual environment, they perform hundreds of repetitive foot movements without realizing it. We make the tasks more interesting by creating weather disturbances such as a thunderstorm. For example, one scenario is based on a virtual airplane that will shake in the

storm when it encounters turbulence. Using this system, we have shown that individuals post-stroke who trained three times a week for four weeks improved their walking speed, endurance and stair climbing speed. We confirmed that these gains were in part achieved through better control, coordination and strength of foot movements (see Figure 2).

Our second system (see Figure 3) is designed for walking in different virtual environments. This system has two platforms on which the person stands with a weight reducing device (the amount of weight the person bears on his feet is reduced by 40% of the person's body weight) to maintain balance. Our street crossing simulation has a flashing light signaling when it is time to stop and go. Cars encroach on the crosswalk and honk their horns. The length and surface of the street can be changed, making it slick or sticky to simulate ice or mud. We can also change the season. Currently, we are in the process of characterizing the gait of healthy individuals in these virtual environments. We are using motion analysis tools to



Figure 1. Airplane simulation: Users navigate through the targets while therapists monitor patients' performance. Target speed, pattern lighting, sound and turbulence can be modified.

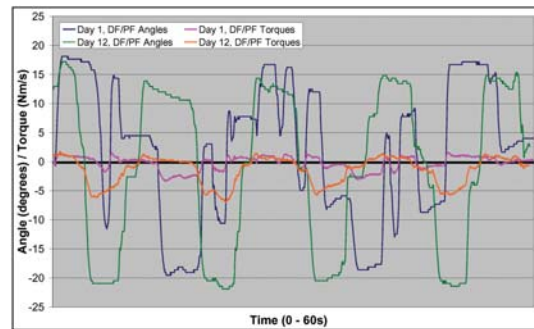


Figure 2. Ankle coordination before and after training. The patient's ability to generate torque (pink and orange) and displacement (blue and green) not only increase after training but become more synchronized (orange and green).

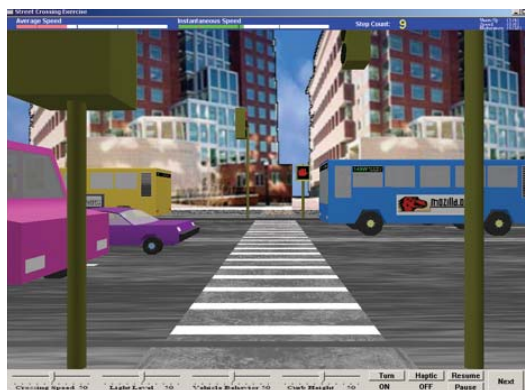


Figure 3. Street crossing simulation: users cross the street before the flashing light turns red. Therapists can change the speed necessary to cross the street, curb height, scene lighting and vehicle behavior.

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JUDITH E. DEUTSCH, PHD, PT, ASSOCIATE PROFESSOR AND DIRECTOR, RESEARCH IN VIRTUAL ENVIRONMENTS AND REHABILITATION SCIENCES LAB, UMDNJ-SCHOOL OF HEALTH RELATED PROFESSIONS, AND JEFFREY LEWIS, RESEARCH ENGINEER, SHOWN IN THE LAB. PATIENT WORKING WITH MOBILITY SIMULATOR IN BACKGROUND.

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describe the kinetics and kinematics of gait in different environments and are comparing it to regular walking. We will then begin to analyze the gait of individuals post-stroke.

The virtual reality systems are integrated with software that allows for remote delivery of rehabilitation, also called tele-rehabilitation. We have shown that individuals can train at a rehab site while being monitored by a physical therapist at a remote location.

Finally, to facilitate the transfer of our technologies to the clinic, we involve both therapists and patients in the development and refinement of the technology through an interactive process called a usability study. Users are trained in the technology and then practice with it to provide feedback on its ease of use. Ultimately, we hope to develop and validate the use of these technologies to augment rehabilitation. Our work is funded by the National Science Foundation.

Judith E. Deutsch, PhD, PT, is an associate professor of physical therapy and director of the Research in Virtual Environments and Rehabilitation Sciences Lab at UMDNJ-School of Health Related Professions. She received her BA in human biology from Stanford University, her MS in physical therapy from the University of Southern California and her PhD in pathokinesiology from New York University. She was a NIDRR post-doctoral fellow in rehabilitation research at Kessler Institute of Rehabilitation. She is the editor in chief of the Journal of Neurologic Physical Therapy (JNPT), which was recently indexed in Medline. Dr. Deutsch is also a member of the UMDNJ Master Educators Guild. 🍷

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