Federal Contract Leads to Larger Role in National Children’s Study

Children’s Hospital and Drexel University College of Medicine received a federal contract to manage two new study sites in the National Children’s Study, the first and largest long-term study of children’s health ever conducted in the U.S. The study, funded by the National Institutes of Health, will eventually follow a representative sample of 100,000 children from across the U.S. to gather information to prevent and treat some of the nation’s most pressing health problems, including autism, birth defects, diabetes, heart disease and obesity.

Two years ago, the National Children’s Study named Montgomery County, Pa., one of seven Vanguard sites in the nation charged with studying children’s health determinants. Children’s Hospital and Drexel are primary collaborators on this site.

Under the latest contract, the institutions will manage local participation, recruitment and data collection in Schuylkill County, Pa., and New Castle County, Del.

Investigators anticipate approximately 1,000 families each in Schuylkill and New Castle counties will participate in the study that will follow children from before birth until age 21.

“The children enrolled from these counties represent a snapshot of all of America’s children,” says principal investigator Donald F. Schwarz, M.D., M.P.H., deputy physician-in-chief of the Department of Pediatrics and chief, Craig-Dalsimer Division of Adolescent Medicine at Children’s Hospital. “The National Children’s Study provides us with a great opportunity to contribute to improving the health of children and families in Schuylkill and New Castle Counties and across the nation for generations to come.”

In the two new counties covered by the Children’s Hospital/Drexel partnership, The Portsville Hospital and Warne Clinic and Penn State Milton S. Hershey Medical Center will be Schuylkill County participants; the University of Delaware’s Center for Disabilities Studies and School of Nursing, Christiana Care Health System, and Nemours/Alfred I. duPont Hospital for Children will participate from New Castle County, Del. The University of Pennsylvania School of Nursing and the National Opinion Research Corporation will also be partners in this local part of the national study.

The Vanguard award from 2005 and the most recent contract equals $57 million in funding over five years to Children’s Hospital.

In total, the study will be conducted in 105 previously designated study locations across the U.S. that together are representative of the nation’s population.

A national probability sample was used to select the counties in the study, which took into account factors including race and ethnicity, income, education level, number of births and babies born with low birth weights.

OCTR Associate Director Named

Louis M. Bell, M.D., has been named an associate director for the Office of Clinical and Translational Research. As the newest member of the OCTR, Dr. Bell will work with the Stokes leadership to improve its ability to perform clinical epidemiology and health services research at Children’s Hospital.

Over the last decade, an increasing number of Hospital investigators have focused their research on discovering ways to improve health care delivery, accessibility and equity in our communities; improve clinical effectiveness for the individual patient; and provide data to help formulate governmental health policies. These projects are often complex and require a multidisciplinary approach, combining research methods from epidemiology, statistics, economics, sociology, psychology and medicine.

In this new role, Dr. Bell aims to strengthen and enhance the Stokes Institute’s clinical epidemiology and health services research by focusing on improving communication and collaboration among investigators, and growing the clinical research infrastructure required for this research.

Dr. Bell is currently a professor of Pediatrics and the chief of the Division of General Pediatrics and holds the Patrick S. Pasquariello, Jr., Endowed Chair in Pediatric Medicine. Over the last seven years, Dr. Bell has created the Pediatric Generalist Research Group, which includes faculty from the divisions of General Pediatrics, Emergency Medicine and Infectious Diseases. He is the medical director of the Pediatric Research Consortium, the Hospital’s practice-based research network.
Brain Imaging Expert Joins Children’s Hospital to Study Autism

An internationally prominent expert in brain function in children and young adults with autism, Robert T. Schultz, Ph.D., joined the autism research program at Children’s Hospital on Oct. 1. Most recently the director of the Yale Developmental Neuroimaging Program at the Yale Child Study Center in New Haven, Conn., Dr. Schultz now holds The Children’s Hospital of Philadelphia Regional Autism Center Endowed Chair. A neuropsychologist, Dr. Schultz investigates the “social brain” in children with autism.

“Dr. Schultz has performed groundbreaking research into brain regions involved in social interactions, a central issue for people with autism,” says Susan E. Levy, M.D., director of the Regional Autism Center at Children’s Hospital. “We are excited that he will be adding his expertise to our autism program.”

Since joining the Child Study Center at Yale University in 1991, Dr. Schultz has used neuroimaging techniques to investigate autism and other childhood psychological disorders under an extensive series of grants from the National Institutes of Health and private organizations. His research uses neuroimaging to measure brain structure and brain function in order to reveal the underlying neural systems causing autism spectrum disorders (ASDs).

Much of Dr. Schultz’s work has employed functional MRI, which measures activity in various brain regions during specific tasks. He has demonstrated that people with ASD have different patterns of brain activity when seeing faces, compared with people without those disorders.

In one notable imaging study, Dr. Schultz showed that the area of the brain that normally shows strong activity when a person recognizes faces was underactive in a child with autism, but lit up when he saw a “Digimon” cartoon character — the child’s preferred interest.

Based on such findings, Dr. Schultz has worked with colleagues to train children with autism to become better at recognizing faces and facial expressions, using customized computer games.

Dr. Schultz is beginning a new brain imaging study here, funded by the Autism Centers of Excellence grant program of the National Institute of Mental Health. The new study will recruit and study infants and toddlers at risk of developing autism as a way of learning the precursors to this devastating disorder. That study will produce brain images of young children with an older sibling already diagnosed with ASD. Another large-scale imaging study will involve school-age children and young adults with ASD.

At the Regional Autism Center at Children’s Hospital, Dr. Schultz is joining a robust existing program that investigates the early identification and prevalence of autism. He also is adding his research efforts to those of scientists at the center using other imaging techniques to identify brain regions involved in language and communication impairments. “Dr. Schultz’s studies of the social brain will greatly complement our current brain research and will strengthen our ability to develop treatments for children with autistic spectrum disorders,” says Dr. Levy.

The current president of the International Society for Autism Research (INSAR), Dr. Schultz is a member of the INSAR executive board and an associate editor of the society’s journal, Autism Research. In addition, he serves on the scientific advisory board of Autism Speaks and the Scientific Advisory Board of the United Kingdom’s MRC Neuroimaging Consortium on Autism.

FYI

Did you know... you can peek behind the scenes at a NIH study section at work?

For an inside look at how NIH grant applications are reviewed for scientific and technical merit, visit http://www.csr.nih.gov/Video/Video.asp, where you will find a video showing a mock study section meeting. Reviewers who served on actual study sections and NIH staff members enact the roles of study section members. The R01, K08 and R03 applications they discuss are real submissions that have been altered and disguised. You can read the applications along with the reviewers by downloading them from the Web site where you will also find summary statements.

This item originates from the Office of Faculty Development. Visit the office’s Web site at http://stokes.chop.edu/programs/facultydevelopment/ for more information.
Grant Award Funds Epilepsy Research

Temporal lobe epilepsy (TLE) is among the most prevalent and least medically responsive forms of epilepsy. It is frequently associated with a head trauma, CNS infection, or other brain injury that eventually leads to recurring, spontaneous seizures. A better understanding of seizure-initiating mechanisms may facilitate development of enhanced therapeutic strategies to improve treatment, and might eventually contribute to the development of a cure for epilepsy.

Current therapies for acquired seizure disorders such as TLE are either drastic (removing part of the brain) or purely symptomatic (using drugs to control seizures). No current therapy targets the disease process. To address this therapeutic need, the National Institute of Neurological Disorders and Stroke awarded Children’s Hospital a $6.6 million, five-year program project grant to study the mechanisms underlying the process in which a normal brain becomes epileptic, a process known as epileptogenesis. Douglas A. Coulter, Ph.D., Division of Neurology, leads the study and hopes to identify these mechanisms, target them in patients at risk to develop epilepsy, and develop a way to cure the disorder before the onset of spontaneous seizures.

Investigators led by Dr. Coulter are focusing on GABA, a neurotransmitter that acts at inhibitory synapses in the brain. GABA recycling is required to reload synaptic vesicles following release and is critical to regulating circuit excitability in active areas of the brain. Dr. Coulter’s previous investigations have found evidence that GABA recycling mechanisms are compromised in inhibitory synapses in the brains of animals with TLE, and that this alteration develops very soon after the injury that later leads to TLE.

“Compromise in GABA recycling mechanisms appears to be a pivotal, early event in epileptogenesis,” says Dr. Coulter. “Restoration of normal GABA production soon after an epileptogenic injury may be a viable therapeutic intervention, capable of blunting the severity of, or completely blocking, the subsequent development of epilepsy.”

Using a combination of electrophysiological, molecular and disease model approaches, Dr. Coulter’s research will examine the mechanisms mediating GABA production and recycling, and determine the timing of altered GABA recycling during epileptogenesis. In addition, it will determine the consequences of alternate GABA-recycling mechanisms to restore normal function and determine strategies to restore normal recycling or alternate GABA production.

Understanding how changes in metabolic processes within inhibitory synapses influence seizure generation in TLE may lead to early interventions in these processes and alter disease progression, ultimately resulting in new therapeutic strategies to better treat and perhaps cure this devastating disorder.

Hospital Launches Center for Pediatric Clinical Effectiveness

Children’s Hospital, through the Joseph Stokes Jr. Research Institute, has launched the Center for Pediatric Clinical Effectiveness (CPCE), whose mission is to discover and disseminate knowledge about best practices in the management of pediatric disease.

The CPCE is a new Center of Emphasis at the Stokes Institute that will provide infrastructure for training in and performance of clinical effectiveness research — research aimed at understanding the best ways to prevent, diagnose and treat diseases in children.

The Center will build on existing research expertise and infrastructure at the Hospital to create an environment and opportunities for the exchange of ideas among clinical effectiveness researchers, facilitate the performance of clinical effectiveness research through a pilot grant program and assistance with projects that use existing national and local databases, and educate the next generation of clinical-effectiveness researchers in the methods of clinical epidemiology. In addition, the Center aims to partner with other hospital organizations to improve the care of our patients and disseminate research findings that define the most effective healthcare for children.

Ron Keren, M.D., M.P.H., will serve as the inaugural director of the Center. Along with the associate directors, Theoklis Zouaitis, M.D., M.S.C.E., and Susan Coffin, M.D., M.P.H., Dr. Keren will work closely with the division chiefs and the critical mass of highly trained and experienced investigators at the Hospital to realize the Center’s vision. The Center’s accomplishments will distinguish Children’s Hospital as a leader among healthcare centers seeking to improve the health of their patients through clinical effectiveness research.

Stokes Investigator Elected to Institute of Medicine

Katherine A. High, M.D., has been elected to the Institute of Medicine (IOM) in honor of her leading research in hematology and gene therapy. Dr. High is one of 65 new members elected to the IOM from throughout the United States in recognition of their major contributions to the advancement of medical sciences, healthcare and public health.

Current members of the Institute elect new members from a slate of candidates nominated for their professional achievement and commitment to service.

An internationally prominent hematologist and researcher, Dr. High is the director of the Center for Cellular and Molecular Therapeutics at Children’s Hospital. She is the William H. Bennett Professor of Pediatrics at the University of Pennsylvania School of Medicine, and a Howard Hughes Medical Institute investigator. She also is a past president of the American Society of Gene Therapy.

Dr. High’s studies of the molecular biology of the bleeding disorder hemophilia led to clinical trials of gene therapy for hemophilia at Children’s Hospital. She leads a National Institutes of Health-funded laboratory and has contributed scores of papers to the scientific literature. Established in 1970 by the National Academy of Sciences, the IOM honors professional achievement in the health sciences and serves as a national resource for independent analysis and recommendations on issues related to medicine, biomedical sciences and health.
Grant Funds Acute Lymphoblastic Leukemia Research

Relapsed acute lymphoblastic leukemia (ALL) is a common pediatric cancer with a poor prognosis. The primary treatment for relapsed ALL is hematopoietic (blood-forming) stem cell transplant (HSCT), but stem cell transplant is successful in half or fewer cases, usually because the leukemia returns after the transplant.

HSCT treatment can fail if the chemotherapy or radiation therapy does not eradicate the leukemia, leaving minimal residual disease, or if the transplanted immune system does not successfully attack the disease.

Stephan Grupp, M.D., Ph.D., and coworkers in the Division of Oncology have performed laboratory and translational studies supporting a new concept in ALL therapy — the use of a signal transduction inhibitor to decrease risk of ALL relapse following HSCT. This work has led to pilot clinical trials performed by Nancy Bunin, M.D., and Susan Rheingold, M.D., both in the Division of Oncology, and now a nationwide Phase III trial for patients with relapsed ALL. Dr. Grupp was recently awarded a grant from the National Cancer Institute to study ALL biology in patient specimens collected on this clinical trial. The five-year, $2 million study provides a unique opportunity to study mechanisms of this new therapy in the context of the trial, bringing the initial concept full circle from the lab, to phase III trial, and back to the lab.

Dr. Grupp will study the anti-leukemic effect of sirolimus, a signal transduction inhibitor widely used as an immunosuppressive agent, and evaluate its impact on residual ALL after HSCT. The use of sirolimus to limit the risk of ALL relapse after HSCT is a novel approach, and a method to improve HSCT outcome using sirolimus would be a major advance in antileukemia therapy and transplantation.

Investigators will compare standard post-HSCT treatment with the same treatment plus sirolimus, determining the impact of the new treatment on clinical success. Using samples collected from children on the trial who have relapsed ALL, Dr. Grupp and his colleagues will demonstrate the impact of sirolimus treatment on patient ALL cells, study the immune reactions of the donor immune system against the ALL cells, and study measurements of minimal residual disease in each patient.

The clinical trial is a major area of emphasis for the Children’s Oncology Group, a National Institutes of Health-funded multicenter clinical research organization that supports clinical trials for pediatric cancer patients. The trial is now open nationwide.

NIH Loan Repayment Program Announced

NIH is inviting health professionals engaged in biomedical and behavioral research to apply online for a loan repayment award. The loan repayment programs (LRPs) are a vital component of our nation’s efforts to recruit and retain highly qualified professionals to careers in research.

NIH annually awards loan repayment contracts to approximately 1,600 health professionals with an average award of $52,000. More than 50 percent of the awards are made to individuals fewer than five years out of school. Approximately 40 percent of all new applicants are funded and 70 percent of renewals are funded.

The LRP application cycle is open through Dec. 1. NIH will repay as much as $35,000 annually of qualified educational debt for health professionals pursuing careers in one of the five LRP’s. The programs also provide coverage for federal and state tax liabilities.

To qualify, applicants must possess a doctoral-level degree and devote an average of 20 hours per week or more to research funded by a nonprofit organization, university or government entity (NIH grant support is not required). Applicants must also have outstanding educational loan debt equal to at least 20 percent of their institutional base salary and be U.S. citizen or permanent resident.

The program announcement, which includes eligibility criteria, is available at http://grants.nih.gov/grants/guide/pa-files/PA-07-440.html.

Visit the LRP Web site at http://www.lrp.nih.gov/ for more information on the program. You may also send an e-mail to lrp@nih.gov, or call the LRP helpline at (866) 849-4047. Remaining questions regarding research projects should be directed to the relevant NIH scientific program contact listed on the LRP Web site.

The application deadline is Dec. 1. Deborah Grupp-Patruitz, assistant director of Sponsored Projects, is the institutional coordinator for the program and can be reached at gruppatruitz@email.chop.edu.
Researchers Find Steroids Ineffective for Bronchiolitis

The use of steroid medication to treat bronchiolitis — a common viral lower respiratory infection in infants — does not prevent hospitalization or improve their respiratory symptoms, according to a recent multicenter clinical trial published in the *New England Journal of Medicine*.

The findings by the Pediatric Emergency Care Applied Research Network (PECARN) resolve controversy from prior research and are expected to help guide treatment for the most common cause of infant hospitalization.

The PECARN network includes 21 affiliated hospitals and their emergency departments and conducts multi-institutional research in the prevention and management of acute illnesses and injuries in children.

Children’s Hospital investigators served as co-leaders of the PECARN study, which compared hospitalization rates for 600 children between the ages of 2 months and 12 months who visited emergency rooms with bronchiolitis between November and April during a three-year period. Bronchiolitis is most common during the winter months.

Patients taking part in the study were treated with either a dose of dexamethasone (a glucocorticoid form of steroid medication) or a placebo, and evaluated after one hour and again at four hours. The hospital admission rate for both groups was identical at nearly 40 percent. Both groups improved during treatment, but the investigators found the placebo group did as well as those treated with active medication.

“This study provides solid evidence to guide treatment of this common illness,” said Joseph Zorc, M.D., an emergency physician at Children’s Hospital and a lead co-investigator on the PECARN study. “Current recommendations suggest that simple supportive care is the best available treatment for bronchiolitis. This study will help resolve some of the uncertainty for physicians and families and prevent unnecessary side effects.”

With the knowledge that glucocorticoids aren’t effective in treating bronchiolitis, future research should focus on finding other treatments and preventive strategies. One such strategy may involve a vaccine for the respiratory syncytial virus (RSV), which accounts for 50 to 80 percent of all bronchiolitis cases.

Kathy Shaw, M.D., chief of emergency medicine at Children’s Hospital, and Kyle Nelson were other Hospital co-investigators on the study.

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Vaccine Expert Poses Questions for Surgeon General Confirmation Hearing

Paul Offit, M.D., chief of the Division of Infectious Diseases, was asked by *The New York Times* to submit questions he might ask the new nominee for surgeon general, James W. Holsinger Jr., M.D., Ph.D., at his confirmation hearing on July 12.

Dr. Holsinger, a Kentucky cardiologist who was nominated for the office of surgeon general by President Bush, went before the Senate Committee on Health, Education, Labor and Pensions to be questioned as part of the confirmation process to become the top doctor on U.S. health policy. Committee members as well as Senate Democrats examined him to get a feel for the direction he would take in office, after Dr. Richard Carmona, the previous surgeon general, claimed that the Bush administration pressured him into putting politics before science and prohibited him from publicizing important public health issues.

Dr. Offit is one of five individuals whom *The New York Times* asked to submit questions representative of the pressing issues the office of surgeon general faces today, and that they would want to ask Dr. Holsinger during the nomination hearing. Dr. Offit is the author of *Vaccinated: One Man’s Quest to Defeat the World’s Deadliest Diseases*, and is one of the developers of the rotavirus vaccine. He has a research focus on vaccine development and the genetics of rotavirus virulence, and has testified before both Senate and House committees about vaccines.

Dr. Offit submitted two questions. The first concentrated on how the surgeon general would address the cutbacks in state health programs that may limit the availability of vaccines for meningitis, bacterial pneumonia and papillomavirus for children. The second asked Dr. Holsinger what role he felt advertising should play in educating the public about diseases and medical treatments.

Other committee members submitted questions about Dr. Holsinger’s plans on a variety of topics ranging from healthcare and organ donation to religion’s role in medicine, and medical service inequities due to race and sexual orientation.

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CHOP Research Poster Day 2008 Announced

The 2008 Fellows’ Poster Day, scheduled for Feb. 27, will feature a revamped and expanded format. All researchers in training (i.e. M.D. fellows, pre- and postdoctoral researchers, residents) and all ancillary groups (i.e. nursing, respiratory therapy) who are conducting research at Children’s Hospital are welcome to participate.

The event has been renamed CHOP Research Poster Day and it will take place on from 9 a.m. to 5 p.m. in the atrium of the Abramson Research Center. Presenters should set up their posters at 9 a.m. and be prepared to attend their posters from 1 p.m. to 2 p.m. for the judging portion of the event. A reception and awards ceremony will take place from 3 to 5 p.m. in the Abramson cafeteria.

This poster session is sponsored by the Joseph Stokes, Jr. Research Institute, the Department of Pediatrics, and supported by a generous endowment from the wife of Dr. Klaus Hummeler, the first director of Stokes. Research Education is coordinating the event.

Last year marked the 17th year of this event and we had nearly 148 presentations from numerous hospital departments. This year closer to 200 poster presentations are anticipated. Everyone is welcome to join in and all participants will be eligible for substantial cash prizes.

The 2008 event will introduce a two-track judging system. Participants will be prompted at abstract submission to choose from a patient-oriented or laboratory-based track. A selection team led by William Fox, M.D., will judge clinical posters. Tom Curran, Ph.D., will chair the basic research poster selection committee. Multiple prizes will be awarded within each track.

Contact Wendy Williams, director of Research Education, at williamsw@email.chop.edu for additional details or go to http://stokes.chop.edu/forms/FellowsPosterDayMemo2008.pdf for the full announcement.
Low Vitamin D Levels Found in Otherwise Healthy Children

Many children who are otherwise healthy have low levels of vitamin D, according to a study by Children's Hospital investigators.

Vitamin D is vital for musculoskeletal health as well as immune function, and deficiency in the vitamin is an underacknowledged problem. The main dietary source of vitamin D is fortified milk, but exposure to sunshine also increases blood levels of vitamin D. Severe shortages of vitamin D can cause muscle weakness, defective bone mineralization and rickets. Low blood levels of the vitamin may be a factor of hypertension, cancer, multiple sclerosis, and type 1 diabetes. A study in the American Journal of Clinical Nutrition measured blood levels of vitamin D, dietary and supplemental vitamin D intake and body mass index of 382 healthy children between 6- and 21 years of age in the northeastern U.S.

Findings revealed that more than half the children had low blood levels of vitamin D, 55 percent had inadequate blood levels and 68 percent had low blood levels in winter. Children's Hospital researchers found that African-American children, children over the age of 9 and children with low amounts of vitamin D in their diets were most likely to have low blood levels of vitamin D. Though low levels of the vitamin can be detrimental to health, further study will determine what can be considered appropriate levels of vitamin D in children.

“The best indicator of a person’s vitamin D status is the blood level of a vitamin D compound called 25-hydroxyvitamin D,” says Babette Zemel, Ph.D., a nutritional anthropologist at Children’s Hospital and the primary investigator of this study. She adds that further studies are needed to determine the appropriate blood levels of vitamin D in children and the optimal dietary intake of the vitamin.

Grants from the Joseph Stokes Jr. Research Institute, National Institutes of Health and several private sources supported this study. Dr. Zemel’s Hospital co-authors include Mary Leonard, M.D., Division of Nephrology, and Virginia Stallings, M.D., Division of Gastroenterology, Hepatology and Nutrition.

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FY07 Journal Impact Factor Project Completed

The Stokes Institute recently completed its second annual impact factor report, which ranks the journal publications from Hospital investigators.

Similar to last year, the analysis centered on the ISI Impact Factor, which ranks more than 6,000 journals based on the frequency with which the average article in a journal has been cited during a particular year.

In contrast, last year's report focused only on articles listing Children’s Hospital as the affiliated institution. This year’s report also catalogues citations from other institutions that included Stokes investigators as collaborators. This approach, which involved investigators self-reporting their citations, allowed Stokes to present a broader and more thorough picture of the importance and influence of investigators’ work and the potential impact on the health of children worldwide.

Stokes investigators published more than 450 journal articles during fiscal year 2007, with the number published in the highest-ranking journals increasing significantly over last year. Specifically, 269 Hospital publications were featured in the top 1,000 journals, compared with 205 last year.

Our investigators had 13 publications in the top 25 biomedical journals — including the New England Journal of Medicine, Science, Nature Medicine, Nature, Lancet, Nature Genetics and JAMA — compared with nine articles in the highest journals last year.

In addition, Stokes investigators published 26 articles in the top 50 journals last year (compared with 20 in fiscal year 2006) and 50 in the top 100 (compared with 26 last year). Pediatrics, the highest-ranking pediatric journal on the ISI list, featured 21 articles from Hospital investigators last year, compared with 17 published the year before.

The increase in the number of articles in the highest-ranking journals is a testament to the influence of our investigators’ research and helps solidify the Stokes Institute’s reputation as the preeminent pediatric research institution in the world.

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Nursing Research Highlighted in New Intranet Site

A new intranet site highlights the importance, and the scope, of nursing research and evidence-based practice at Children’s Hospital.

The site introduces the Center for Pediatric Nursing Research and Evidence Based Practice, which was established in 2006 to foster a culture of scientific inquiry about nursing practice.

The site includes a list of recent and current nursing research projects, information on a nursing research grant program and links to a wide variety of external resources.

Go to http://intranet.chop.edu/employee/jsp/dept/department.jsp?id=33696 to visit the site.

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HAVE NEWS? Contact Jennifer Long at ext. 4-2105 or by e-mail at longj@email.chop.edu. Read this and previous versions of Bench to Bedside online at http://stokes.chop.edu/publications/

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