

Pitt Researchers

Investigate Aging



Clinicians, educators, and researchers link forces to break new ground.

A 45-year-old woman, the mother of three, is incontinent when she coughs. After a series of tests, doctors decide the strain of bearing children has weakened her pelvic floor; she is in otherwise good health. Surgery is the most effective remedy, doctors decide. Her prognosis for a normal life is excellent.

The woman's 85-year-old grandmother has a similar problem with incontinence. The remedy for her recovery, however, is not so simple.

Doctors have determined that she, too, has a weak pelvic floor because of her childbirth experiences, but she also has weakness in the bladder muscles and

in the nerves that control the bladder. She's had a stroke, and her memory wanes now and then. She sometimes forgets her incontinence and fails to make regular trips to the bathroom to prevent leakage. So, her full bladder leaks when she coughs. And that is on a good day. On her worst days, chronic back and hip pain make it hard to walk,



from the same disease. Conventional wisdom also had it that if the older woman's treatment was unsuccessful, it was because she was old.

But medicine has come a long way in treating incontinence (and, in so doing, overturning aging stereotypes), a disease similar to so many geriatric syndromes facing today's aging population in that it requires research by many scientists with different expertise for the delivery of proper treatments.

In large measure, Neil Resnick, chief of the Division of Geriatrics in the Department of Medicine at the University of Pittsburgh School of Medicine, and his colleagues have conducted the research that covered much of that ground in treating incontinence since the 1980s, beginning at Harvard University and continuing when Resnick came to Pitt in 2000.

Among numerous discoveries, Resnick's research has shown that incontinence is not normal at any age—even for people 90 and older, that incontinence is not the same disease in older women as it is in younger women, that aging affects the bladder's microstructure in predictable ways, and that there might be gene therapy methods of curing incontinence.

“For millennia, old people were consigned to suffer from the misconception that ‘sick-old’ was a single term,” says Resnick. “One of the major breakthroughs was the realization that it was in fact two terms that were generally unrelated. That permitted one to ask, ‘Then what is the underlying cause of this older person's symptom?’ That's where geriatrics has really made its mark.”

Resnick made his mark through a series of collaborative investigations that have relied on the skills of scientists from a wide range of disciplines, among them epidemiology, physiology, pathology, psychology, molecular biology, and

and the trip upstairs to relieve herself, when she does remember her incontinence, takes Herculean effort.

This does not even begin to take into account her as-yet undetected heart problem, which causes an extra quart of fluid to back up throughout the day into her legs. So in bed at night, her bladder seeps the extra fluid, which causes her to lose sleep as she shuffles off to the bathroom every hour, which

has necessitated her new prescription for sleeping pills, which have begun to knock her out until morning—when she wakes soaked in urine because she did not use the bathroom to relieve her swollen bladder.

Twenty years ago, most doctors would have taken the same approach to treat the grandmother's problem as they did the younger woman's, since conventional wisdom said they both suffered

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molecular genetics. Such collaboration is a sign of things that are and will continue to be in aging research at Pitt. With its Institute on Aging, directed by Resnick and Richard Schulz, director of Pitt's University Center for Social and Urban Research (UCSUR), Pitt is making a concerted effort to link people working on the problems of aging in ways that ensure interaction among clinicians, educators, and researchers to the benefit of all.

“Linking all three is how we're really pioneering new ground,” Resnick said.

And it's paying dividends for what is already a well-positioned aging research platform at Pitt.

Aging America

Despite its relative youth as a nation, America is aging at a breakneck pace. About 80 million people today, some 27 percent of the population, are age 50 or older. In 20 years, thanks to a massive group of 76 million baby-boomers who begin turning 65 in 2011, that total chunk of the nation's population will boom to 35 percent.

In Allegheny County alone, the county with the second-oldest population in America, the U.S. Census Bureau's 2001 Supplementary Survey revealed

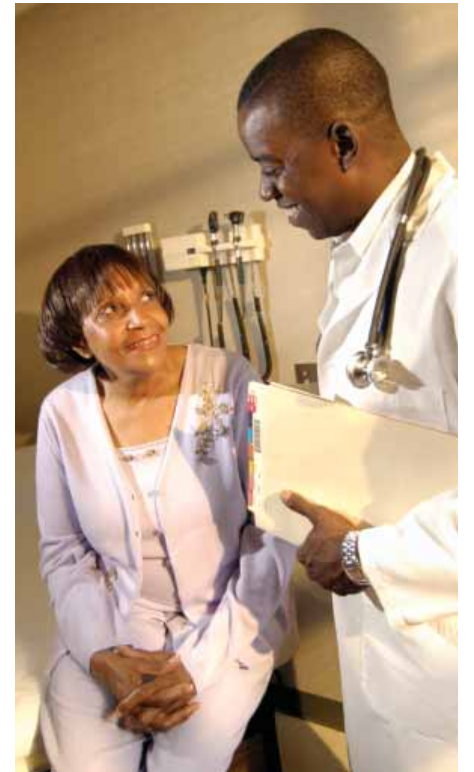
the county is home to 330,000 people above the age of 55 and 190,000 people who will reach 55 within the next decade—this among a total population of just over 1.2 million.

And even though those people are living longer, healthier lives, many have multiple chronic diseases. As such, an increasingly older nation presents a series of challenges to the healthcare system, the Medicare system, and long-term care for the elderly.

By its nature, aging presents multidimensional challenges, requiring the expertise of many different people to adequately address its problems. Pitt administrators recognized this inevitability as the millennium approached. Because of the growing elderly population in Allegheny County and nationwide, Arthur S. Levine, senior vice chancellor for the health sciences and dean of the School of Medicine, and Provost James V. Maher convened a Council on Aging at the University in 1999, calling together aging experts from each of Pitt's 16 schools. The council became a working group of researchers under the direction of UCSUR's Schulz. Now, with the Institute on Aging in full swing, the level of funding for aging research and training at Pitt approximates \$140 million for 85 individual research grants, six center grants, and six training grants.

“The process of bringing together interdisciplinary teams of experts is relatively easy,” says Schulz. “Wonderful working relationships across schools and departments really facilitate the ability to put complicated projects together—inter- and multidisciplinary projects that the National Institutes of Health increasingly look to fund,” Schulz adds.

Schulz often receives a call from School of Nursing Dean Jacqueline Dunbar-Jacob when a new faculty



candidate interested in aging research visits the Pittsburgh campus. Schulz will get scheduled on the candidate's agenda to give an overview presentation of just who is doing what in aging research on campus.

“So our candidate immediately gets a picture of what's happening, and if possible we get together again, and those connections are formalized, and that person is quickly integrated into the network,” Schulz says.

Dunbar-Jacob, as the director of Pitt's Center for Research in Chronic Disorders, since its inception in 1994, has focused on aging in such areas as patient adherence to treatment. In one interesting study, she has worked since 1999 with Sebastian Thrun, codirector of the Robot Learning Lab at Carnegie Mellon University, currently at Stanford University, on a project that has developed several iterations of a personal-assistant robot for the elderly. This project was a collaboration among

Pitt, Carnegie Mellon, and the University of Michigan. The “nursebot” robot, Dunbar-Jacob has said, could become “an advanced communication device that could provide some safety, some companionship, for the individual.” Among the Pitt researchers in the network of that project are School of Nursing assistant professors Sandra Engberg and Judith Matthews; Don Chiarulli, a professor in Pitt’s Department of Computer Science; Resnick, of the School of Medicine; and Joan Rogers, professor and chair of the Department of Occupational Therapy in the School of Health and Rehabilitation Sciences.

And soon, the network of aging investigators across the Pitt campus will become even better. The Institute on Aging is building a Web site for the



The “nursebot” is being developed as a personal-assistant robot for the elderly.

University’s researchers to locate Pitt colleagues working on gerontology research, in an attempt to strengthen the bond of collaboration and encourage investigators to work together to design new research ideas and projects.

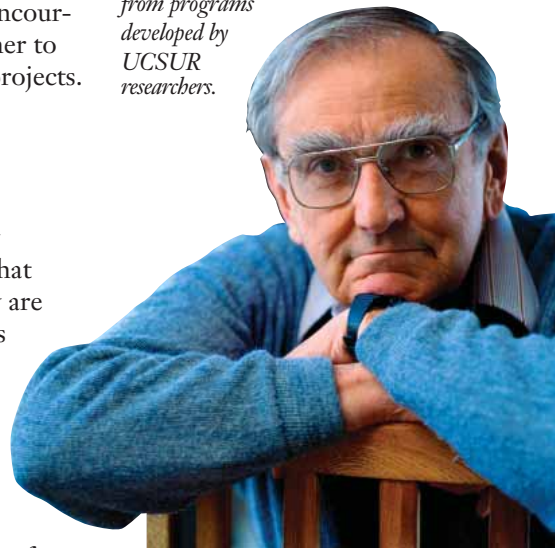
Multidisciplinary Research

While Resnick is one of the key researchers to quash the myth that old people are sick because they are old, Schulz is one of the nation’s top social behavioral experts on aging. For starters, he heads a group of gerontology researchers in UCSUR that is arguably one of the best in the nation, as reflected by the fact that its faculty generate millions of dollars in NIH grants annually, publish in the most prestigious medical, psychology, and gerontology journals in the nation, and receive the most prestigious awards given to social gerontologists. UCSUR faculty also serve on National Academy of Science research policy committees on aging.

In his own studies, Schulz has focused specifically on issues related to the impact of illness and disability in late life on both older people and their families. Led by Schulz, UCSUR’s gerontology program has documented the public health impact of caring for people with Alzheimer’s disease, depression, and stroke, showing how caregiving affects people in physical and psychological terms and how it impacts their finances. His team also has devised prevention programs designed to help caregivers. (It should be noted that few aging researchers at Pitt take on a project without inviting Schulz to join it in some capacity.)

One study led by Schulz, published in the *Archives of Internal Medicine* in 2000, concluded that high levels

People who serve as caregivers for individuals with Alzheimer’s disease, depression, or stroke have benefited from programs developed by UCSUR researchers.



of depressive symptoms are an independent risk factor for mortality in the elderly. Older males who were divorced, widowed, or separated were more likely to die, the study showed. While depression was a link to mortality from all causes, the evidence suggested depression was a contributing factor in cardiovascular disease as well.

In the study, Schulz collaborated with people from across the Pitt research community, including Lynn Martire, an assistant professor of psychiatry; Scott R. Beach, director of the survey research program for UCSUR; and Diane G. Ives, a senior research associate at the Graduate School of Public Health (GSPH).

In 2001, Schulz took a different direction with his research, publishing in the June 26 edition of the *Journal of the American Medical Association (JAMA)* that while a caregiver can become depressed after the death of a spouse, in many ways the death can bring relief from some of the more demanding tasks of caregiving and, as such, help

the surviving spouse to cope once the loved one is gone. This study was the first to show such results.

(Interestingly, other research by Schulz’ group, published in *JAMA* in 1999, revealed that spouses who provide support to their dying spouse and who are under stress are more than twice as likely to die within four years as spouses who do not serve as caregivers. This study, though confirming what many generally believed, was the first to show that caregiving might contribute to premature death.)

Now, Schulz is heading a new study on caregiving for people with spinal cord injuries that involves faculty from the School of Rehabilitation Sciences and the School of Nursing.

“I think you’d find that any aging-related study on this campus, unless it’s very focused, is going to involve multiple schools and multiple departments across schools,” Schulz says.

Novel Therapies

Beyond the social and behavioral aspects of aging research ongoing at Pitt, Schulz and Resnick point out numerous researchers who are investigating novel therapies at the University in a variety of areas of aging.

Researchers at the Geriatric Research, Education and Clinical Center at the VA Pittsburgh Healthcare System have developed herpes simplex virus-based vectors for gene transfer to the nervous system. Researchers are engaged in preclinical studies using the vectors in the treatment of Parkinson’s disease, diabetic neuropathy, and intractable pain.

This vector work, in collaboration with that of Joseph Glorioso, chair of the Department of Molecular Genetics and Biochemistry and director of the Molecular Medicine Institute in Pitt’s School of Medicine, has shown promise in blocking a protein at the cellular level

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to significantly reduce cancer-related pain in mice with tumors, as reported in the November 2002 issue of the journal *Annals of Neurology*.

Another of Pitt’s key aging researchers that Schulz and Resnick single out is Steven DeKosky, chair of the Department of Neurology in Pitt’s School of Medicine, director of Pitt’s Alzheimer’s Disease Research Center, and director of the Pittsburgh Institute for Neurodegenerative Diseases. DeKosky is widely regarded for his clinical expertise and research achievements in the areas of Alzheimer’s disease and dementia (an affliction

projected to affect 14 million Americans by 2040, with 75 percent of them also projected to have Alzheimer’s disease).

DeKosky’s research has shown that the brains of 30 percent of the people who die of Alzheimer’s disease also will have the widespread presence of distinctive, Parkinson’s disease-related cellular bodies called “Lewy bodies”—a powerful potential link between two devastating diseases that affect typically older people. Just last year, a DeKosky-led study uncovered the possible mechanism that might cause mild cognitive impairment, an increasingly common memory problem thought to be a precursor to Alzheimer’s disease. The results might explain why current medications don’t improve memory function effectively and could even redirect research into many of the newer treatments designed to prevent memory problems.

With more than \$15 million in grants from the National Center for Complementary and Alternative Medicine and the National Institute on Aging, DeKosky is in the middle of a six-year



A six-year study led by Pitt’s Steven DeKosky and funded by more than \$15 million in grants from the National Center for Complementary and Alternative Medicine and the National Institute on Aging is examining the efficacy and safety of the use of the tree extract ginkgo biloba in the improvement of memory function.

study of the effects and safety of the tree extract ginkgo biloba in some 3,000 study participants, along with GSPH's Lewis Kuller and Ives and collaborators at the medical schools of Johns Hopkins University, the University of Vermont, and Wake Forest University. Oscar Lopez, associate core director at Pitt's Alzheimer's Center, has called the clinical trial "the first scientific study that will examine whether ginkgo biloba works or not."

DeKosky's research could be particularly poignant. In the fall of 2002, a review by a team from the Alzheimer's Society and the Cochrane Collaboration of 33 clinical studies of the extract dating back to 1976 found "promising evidence" that the herbal remedy could help improve brain function in people with dementia.

Like Resnick, the physician most responsible for changing how researchers approached incontinence in older women, Charles F. "Chip" Reynolds III has validated in his research that

depression is not a "normal" part of aging. In a 10-year, NIH-funded study, Reynolds, director of the Intervention Research Center for Late-Life Mood Disorders at Pitt's Western Psychiatric Institute, showed that depression, if left untreated, amplifies other health problems. The study—conducted with Ellen Frank, a Pitt professor of psychiatry and physiology; David Kupfer, the Thomas Detre Professor and chair of psychiatry at Pitt; and James M. Perel, a professor of psychiatry and pharmacology at Pitt—proved that depression in the elderly is a recurring illness that can be treated with drugs and long-term, monthly psychotherapy.

Moreover, Reynolds showed in another study published in 1999 in *JAMA* that depressed seniors who were treated with both drugs and counseling had only a 20 percent rate of relapse compared with a 90 percent rate of relapse in seniors treated with placebo alone.

Healthy Aging

About a third of the \$140 million in the ongoing aging research at Pitt is in one way or another related to GSPH. Bernard Goldstein, GSPH dean, will argue gently that in many ways all of the \$70 million in research done by the school contributes to aging research—primarily because the school's mission is to focus on disease prevention.

"There's a tremendous coming surge in the elderly population in the United States," Goldstein says. "The issue of healthy aging is: What do we do now so that people are healthy and aging successfully in the future, not so much 'how do we treat people who are already ill?'"

A main thrust of that research comes from GSPH's Department of Epidemiology and its Center for Healthy Aging. Headed by Lewis Kuller, former longtime chair of the epidemiology department, the Center for Healthy Aging was formed in early 2002 as one of the first of its kind to be funded by the Centers for Disease Control and Prevention. The center aims to help senior citizens avoid diseases and disabilities through prevention efforts.

The center is working with Chinese investigators at the University of Hong Kong, who are looking at bone loss leading to fractures in the elderly. Center researchers also are working with colleagues in Japan to find out why there is a low incidence of arteriosclerosis in that country.

For his part, Kuller has spent the past 30 years studying risk factors for people with heart disease and diabetes and women going through menopause, as well as investigating the prevention of cancer and its risk factors. He was among the first to use bone density measures in osteoporosis studies, carotid artery ultrasound to measure vascular disease risk, and brain imaging in dementia epidemiology.



Helping senior citizens to avoid diseases and disabilities through prevention efforts is the focus of the Center for Healthy Aging. Center researchers are working with investigators at the University of Hong Kong to study bone loss and fractures in the elderly and with colleagues in Japan to understand that country's low incidence of arteriosclerosis.

A large part of Kuller's work is the Pittsburgh arm of a long-running multicenter study called the Cardiovascular Health Study (CHS), ongoing at Pitt since 1988 and following some 6,000 people 65 and older until their deaths. The study, of which UCSUR's Schulz is a coinvestigator, is determining the factors associated with developing illnesses and the factors associated with mortality. One of the key questions is: What factors predict who in this group is going to die sooner rather than later?

"The most important thing that this study has done is demonstrate the huge amount of vascular disease and what we call 'subclinical vascular disease' among the elderly," Kuller says. From the CHS trial and other related clinical trials it has spawned, Kuller's group of researchers has determined that treating hypertension aggressively, knocking back the level of lipids in a person with vascular disease, controlling diabetes, and prescribing such drugs as aspirin and ace inhibitors substantially reduce the risk of disease.

The investigation is one of many at Pitt, says Schulz, that benefits study participants because so often researchers discover in them health problems that might not have been identified otherwise.

Another major population study, the Health ABC Study of 1,500 people led by Anne Newman, associate professor of epidemiology in GSPH and of medicine in the School of Medicine, has assessed for the past six years the extent of sarcopenia, the progressive loss of muscle mass, in older men and women. Pitt faculty participating in the research, funded by the National Institute on Aging, are Kuller; Jane Cauley, professor of epidemiology in GSPH; Joseph Zmuda, assistant professor of epidemiology in GSPH; and Bret Goodpaster, assistant professor of medicine.

Kuller says the study looks at such questions as: What makes people



The findings of University of Pittsburgh studies on osteoporosis, cardiovascular disease, loss of muscle mass, and many other conditions that can affect the elderly are helping individuals to stay healthier, longer.

disabled? How does this relate to muscle function? How does it relate to strength? How does it relate to physical activity and nutrition and genetic factors?

Yet another large population study of aging, this one led by Cauley, looks at osteoporotic fractures in a cohort of 9,704 older women. The study has led to estimating the cost-effectiveness of screening for osteoporosis and planning trials of osteoporosis therapies.

Meanwhile, Cauley and colleagues have called into question the effectiveness of hormone replacement therapy in preventing bone fractures and osteoporosis, showing in another study the failure of estrogen supplements to protect older women from heart disease. Now, Cauley is engaged in a seven-year study of osteoporosis in older men.

"These are the areas that we've sort of developed the wheel for in aging research," Kuller says of the epidemiological data he and his colleagues have compiled. But in reality, he could be talking about much of the aging research at Pitt, investigations occurring in any of the University's 16 schools. From research into Alzheimer's disease to cardiovascular disease to osteoporosis—only a fraction of it detailed here—some of the most fundamental findings and treatment ideas are coming out of Pitt, with investigators working very much in collaboration with their colleagues across the University and beyond.

Says Schulz, "This is one of—if not the—leading aging research universities in the country"—an important place for Pitt to be as the population of America and the region around Pittsburgh becomes older and older. ■