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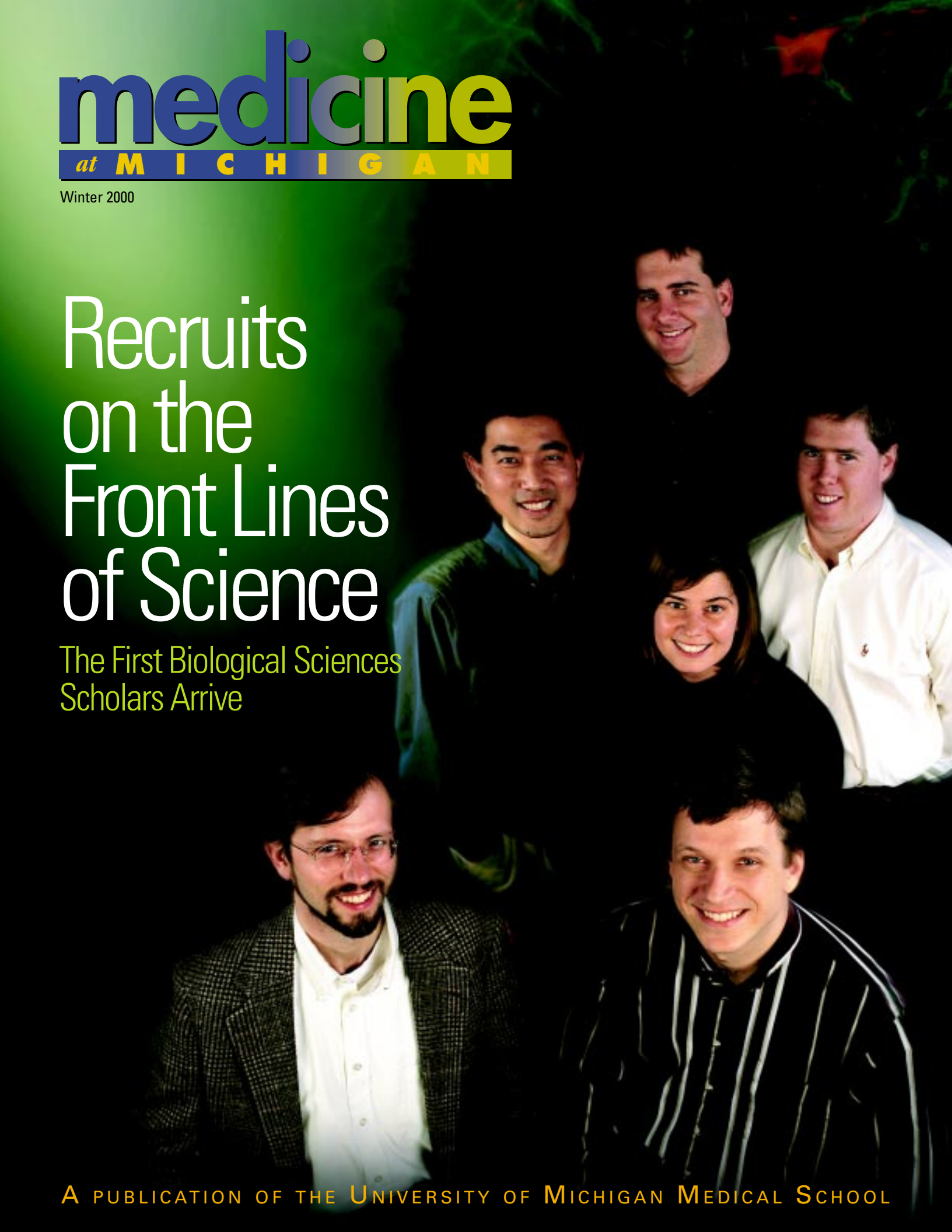
Recruits on the Front Lines of Science

The First Biological Sciences Scholars Arrive



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Will You Still Need Me, Will You Still Feed Me, When I'm *a Hundred and Twenty-Four?*

By Eric Lerner

The old Beatles classic, "When I'm Sixty-Four," imagined old age to be about half of what today's scientists are imagining old age to be. But despite the optimism of researchers like Richard Miller at the University of Michigan, the song lyrics don't have to be rewritten yet.

What causes aging? What, if anything, can cure aging or slow it down? Although aging affects all who live long enough, and although it has a huge impact on nearly all disease, especially common killers like cancer and heart disease, its cause and cure—if any is indeed possible—remain a mystery.

> ***"It's certainly possible that aging research could lead to a 50 percent extension in the human life span."***
>
> ***—Richard Miller***

But Richard Miller, M.D., Ph.D., senior research scientist in the Institute of Gerontology and professor of pathology, thinks that finding the cause, and perhaps even the cure, for aging is feasible and that the results may very well be spectacular at some time in the future. "It's certainly possible that aging research could lead to a 50 percent extension in the human life span," he says, "but we are definitely not yet close to knowing how."

His research has focused on finding some of the clues that may bring us closer to solving the mystery of aging. Miller has been a leading researcher in this area for the past two decades, specializing in the genetics of aging and aging's effects on the immune system, as well as in the effort to understand what controls the rate of aging.

A single aging clock

Although it's not the most popular view in the field, Miller believes strongly that aging is a unified process, that there is a single "aging clock" that times the aging process, at least in mammals. "Aging is a process that involves the whole organism, not just a single organ system, just as development is," Miller emphasizes, "although of course aging is as different from development as the process of manufacturing a car is from the process of turning new cars into rust buckets."

Miller argues that there are a number of strong lines of evidence for the existence of a single aging process or clock, even though we don't have any real idea what that clock is. One type of evidence comes from evolution, both between species and within species. "We know that there are differences in rates of aging between different species. But if there were many different aging processes, controlled by many different genes, it would be hard to see how these could evolve," Miller contends.

Is there a "single clock" that controls the aging process in humans? Evolutionary clues suggest that perhaps there is. But as with many of the current theories related to aging, the evidence to support the idea is limited and often contradictory.

"For example, if a gene just postponed one form of cancer, it would have hardly any effect on an animal's life expectancy and its ability to survive. There must be a relatively small number of genes that control some central rate process to enable species to live significantly longer than their ancestors."

To give one example of how dramatic rate differences can exist between species, Miller points to the difference in tumor genesis rates between mice and humans. A given group of cells in a mouse is 100,000 times more likely to develop into a tumor than the same-sized group in a human in a given length of time. Similarly dramatic rate changes have to occur in many other aging processes to allow the much larger human to live 50 times longer than a mouse.

Considerable changes in rate of aging can happen in relatively short spans of time, again indicating that a few genes regulating a central rate process are at work. For example, Miller points out, an isolated group of opossums in Virginia decreased their aging rate by a factor of two in only a few thousand generations. Within species, too, differences in aging rates can be ➤

THE STEPS TO AGILITY IN OLD AGE: "GAIT GUY" NEIL ALEXANDER IS WORKING TO FIND THEM

By Jane Myers

Living forever (or even just into your 120s or 130s) is one thing. Being able to walk and run and sit and stand and climb stairs in your 60s, 70s, 80s and 90s, is another.

Neil Alexander

For Neil Alexander, M.D., associate professor of internal medicine and a senior associate research scientist in the Institute of Gerontology, the fountain of youth once associated with dreamy explorers of the past like Ponce De Leon and now associated with dreamy explorers of the future, is still just that—dreamy. Perhaps it's the giddiness of millennium fever, but when "The Exploding Science of Superlongevity—Our Life Span Revealed" is part of the fluorescent orange cover of the January, 2000, issue of *Wired* magazine, it's clear that living forever is "in."

Never mind forever. Neil Alexander has more modest hopes. "We're just trying to slow the decline in functional ability," he says of his research on mobility in older adults. In other words, making it possible for people to keep moving, to perhaps lift themselves off their chairs and stand up to blow out those 78 or 84 or 96 candles on the cake, maybe even do a little dance around the table.

Neil Alexander began his academic career at the University of Minnesota thinking he'd study child psychology. But when, for his senior honor's thesis, he tried to train a group of junior high school students to do volunteer work in a nursing home, a whole new field of inquiry, one involving subjects at least a half-century older than his teen-aged volunteers, opened up before him. "I didn't know what to tell the kids," he recalls. "There wasn't a lot of good information out there that was scientifically-based about working with older people."

At first he was simply interested in the whole subject of geriatric rehabilitation, but when he looked closer and realized how little true science had been applied to the subject, he headed for the lab.

Ten years later, he's pleased that he's established a national reputation as a "gait guy" (also a "fall guy") and that he and his biomechanician collaborators, as he calls them, were able to contribute a chapter to a major geriatrics textbook, *Principles of Geriatric Medicine and Gerontology* (McGraw Hill, 1994), establishing themselves as major movers in the area of geriatric mobility.

The subject of mobility and aging, and the consequences of time, life habits and disease, is not as simple as it might at first seem. "There is an accumulation of things over which you may or may not have control," Alexander says. And then there's the whole psychological component of aging, one not to be taken lightly in a youth-obsessed culture. "We want to start looking at people in their peri-menopausal years—their 40s, 50s, 60s," he says. "Our theory, based on some anecdotal observations, is that they start giving up stuff. They express expectations of frailty and decline." And, of course, there are the catastrophic events that people fear as they grow older, the strokes and hip fractures that cause, at least temporarily, sharp declines in mobility, that, at best, level out to the earlier rates of slower decline.

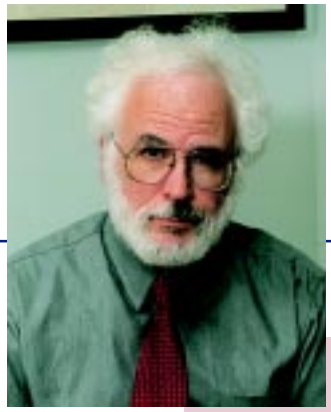
The focus of Alexander's research, really, is to understand the mechanisms that determine whether or not a person can maintain good mobility as they age, and, at least, as he puts it, help to "make a dent in the slow slide." When he looks at an act as clear-cut as getting in and out of a chair, Alexander now sees a sea of complexity involving not only the biomechanics of such an act, but the cognitive piece as well, which speaks to such factors as memory, affect, mental flexibility and visual/spatial acuity. And then there's the chair itself, which falls into the large category of "environment."

His work, and the work of his team in the Mobility Research Laboratory on the second floor of the Geriatrics Center, focuses on the key components of such a task, and the interventions that might help a person more easily get into and out of the chair. Understanding the mechanisms that underlie common motions should make it possible, eventually, to give people strategies that will, for instance, help reduce the number of falls in older people.

Alexander is keeping an open mind about what might work. He and his team are now proposing to add to their catalogue of potential "saves" such regimens as aerobic training, balance training and tai chi to see if they might help. Tap dancing perhaps? He doesn't have that on the list, but he is presently developing ways to assess and train rapid foot movement to determine whether rapid stepping is important in maintaining mobility.

Exercise physiologist Wendy Champoux and Neil Alexander prepare research participant Gertraud Reynolds for assessment in the Mobility Research Laboratory

At the moment he and his team have plenty of analysis ahead of them. "We're drowning in data right now," he says. "But we hope before long we'll have some good solid answers that will make a difference in the way people move and keep moving as they age." If Alexander succeeds in his work, those 120-year-olds of the future may not be playing tennis — but they won't be falling down either.



> ***"Clearly caloric restriction is somehow affecting a central aging process."***
>
> ***—Richard Miller***

dramatic: some breeds of dogs can live, on average, 50 percent longer than others, although they are all the same species so must share all but a relatively few genes.

How could such genes that regulate the rate of aging evolve? Citing ideas and work by Peter Medawar (the late Nobel Prize-winning English zoologist noted for his work in immunology) and others, Miller contends that environments that pose a high risk of mortality to animals naturally favor genes that allow for quick development and high rates of reproduction, even if this, as a byproduct, causes increased rates of aging in older animals. "Think about a population of mice living in a tough neighborhood filled with owls, cats and mouse viruses, where mice generally don't live to a ripe old age," he says. "A gene that postpones aging in 18-month-old mice, but at the same time slightly impairs fertility or retards the age of the first litter, will be strongly selected against, while genes that do the opposite will be strongly selected for. There just are not many 18-month-old mice around to benefit from retarded aging. The result is mice who, when preserved from predation and infection, age rapidly after 18 months."

Human beings, too, have been subjected to much the same pressures during nearly all of our history. For most of that time, people were struck down, mainly by infectious disease, at a steady rate of two or three percent a year, almost regardless of age once they survived infancy, leading to a life expectancy of 25-35 years. Only a quarter or less of the population that survived could expect to reach 50 (as compared with more than 90 percent in the U.S. today) and only 10 percent would reach age 70. Genes that promoted slower aging after 50 and especially after 70 would tend to be swamped if they adversely affected the reproductive capacity of the much larger numbers of 20-30-year-olds, so it should not be surprising that aging makes it difficult for people to survive more than about twice as long as our ancestors did.

Another strong argument for a single aging clock comes from the well known fact that reduction of caloric intake in rodents can slow aging, extending life spans by as much as 50 percent. As was discovered 50 years ago, rats and mice fed well balanced diets with 50 percent less calories than they would eat if given free access to food, live half again as long, remaining healthy and very active long after their well-fed cousins have passed on. "Consuming fewer calories retards equally nearly every sign and symptom of aging," Miller points out, "with effects on cells that divide, cells that never divide, protein changes, disease rates, as well as mortality. To assume that each of these is the result of an effect on a separate aging process seems to me to flout Ockham's Razor. Clearly caloric restriction is somehow affecting a central aging process." (Ockham's Razor is the principle credited to medieval philosopher William of Ockham, which suggests that the simplest explanation consistent with all observations is the best.)

A "cure" for aging?

The idea that aging is controlled by a single clock has one very important implication—that potentially the clock's rate can be changed and aging slowed down, perhaps significantly. "We know that evolution can change life spans radically and swiftly," says Miller. "Take some mice to a tropical island paradise, free from predators and pathogens and a gene that slows the aging process even at the expense of say, smaller litters, rapidly takes hold. Evolution has done the trick many times." In addition, we know that caloric reduction and other ➤

If there is an aging clock, where is it located and what is its nature?

somewhat less drastic environmental modifications can also reset the aging clock. So the prospect of the extension of human life and the slowing of the aging process by even 50 percent is not out of the question, Miller believes.

A "cure" for aging or a way to slow it down would also radically reduce all forms of disease, Miller points out. Indeed, without retardation of the aging process, it will be very difficult for medical science to continue to improve human life expectancies as it has done in the past. To give some perspective on this, look at the history of human longevity. From the Middle Ages all the way up to 1930 in the United States, improvements in nutrition, public health, housing and working conditions slashed the mortality rate for those under 50 by more than four-fold and for those 50-70 years old by half, leading to an increase in life expectancy at birth from 35 years to 60 years. From 1930 to 1950, antibiotics attacked the ancient scourge of infectious disease and further improvements in living standards knocked under-70 mortality rates down by another factor of 1.6, adding almost a decade (8.4 years) to U.S. life expectancies.

But since 1950, gains have come much more slowly. Despite all the medical advances of the past half century, only 7.4 years have been added to U.S. life expectancy, even with under-70 mortality rates still dropping by about one percent per year for most of that time. Part of this slowdown may well have to do with societal factors. Life expectancies for African Americans, for example, have nearly stagnated since the mid-1980s at levels reached 40 years earlier for Americans of European descent, presumably for reasons unrelated to medical research advances.

But another major factor in the slowing of increase in human life span is the difficulty of reducing mortality rates among those over 70. While a person under 50 has only five percent the mortality rate of a same-aged ancestor in the Middle Ages, a modern 70-80-year-old has 60 percent the mortality rate of his similarly aged medieval ancestor—or, for that matter, of similarly aged well-to-do Romans. Without discoveries that retard the aging process itself, mortality rates in the elderly will continue to be difficult to change, thus preventing future increase in life expectancy.

Telomeres are not the answer

If there is an aging clock, where is it located and what is its nature? One place that Miller strongly believes the clock will not be found is in the telomeres at the end of human chromosomes, despite the large amount of publicity such repetitive sequences have had in mass media reports recently. Interest in telomeres originated ultimately in studies done more than 50 years ago that indicated that human fibroblasts would undergo no more than about 50 doublings in cell cultures. Such a "Hayflick limit" was observed to grow shorter with cells from older individuals, inspiring the hypothesis that aging was the result of an inherent limit in the number of times that human cells can undergo division. (Leonard Hayflick is a cell biologist at the University of California-San Francisco who first noted that human cells grown in tissue culture will only divide a certain number of times.) Later it was discovered that the length of telomeres tended to be less in older animals and humans and that telomere length remained constant in cancer cells, which can replicate indefinitely. The conclusion was that telomeres were the aging clock, slowly counting down the number of divisions cells had left.

In 1998 this hypothesis led to a flurry of public attention when researchers engineered cells that maintained their telomere length, could replicate indefinitely in vitro and were not cancerous. As articles in the mass media multiplied like dividing cells, other researchers speculated that "immortalized" cells could be reintroduced into the human body to rejuvenate organs and perhaps slow the whole aging process. ➤

FUNDING FOR AGING RESEARCH AT THE UNIVERSITY OF MICHIGAN

Last fall was the tenth anniversary of the establishment, at the University of Michigan, of the nation's first Claude D. Pepper Older Americans Independence Center. The Center was initially funded with a $6.1 million grant from the National Institute of Aging to advance research on health care problems of the elderly and to train future academic leaders in geriatrics. A recent, successfully competitive renewal grant will continue funding for the Center through 2004. (Claude Pepper [1900-1989] was a U.S. senator and congressman from the state of Florida. A confidant of President Franklin Roosevelt, he led the fight to bring the U.S. into the Allied effort in World War II. The ranking Democrat on the House Select Committee on Aging when it was created in 1975, he became a powerful advocate for older Americans, crusading for the strengthening of the Social Security system and Medicare, and against involuntary retirement, age discrimination and abuse of the elderly.)

The Pepper grant supports research within the U-M Geriatrics Center in basic science, clinical science and health services research dedicated to improving the health of older adults. Jeffrey B. Halter, M.D., is program director of the Pepper Center and director of the U-M Geriatrics Center.

Research programs funded by the Pepper grant at Michigan are in four areas:

- **Homeostasis.** Coordinator is Jeffrey B. Halter, M.D. Homeostasis refers to the internal control mechanisms that regulate important body functions such as blood pressure, metabolism and temperature. Of particular interest at Michigan are diabetes mellitus and its complications, altered blood pressure regulation, and immune system defense and response to injury.
- **Cognitive Function.** Coordinator is Roger Albin, M.D. Cognitive function focuses on the study of the aging nervous system. Scientists engaged in this area of research interact with scientists in the Michigan Alzheimer's Disease Research Center, one of 15 centers established by the National Institute of Aging, and the Center for Applied Cognitive Research on Aging, which focuses on neuropsychological effects of aging.
- **Physical Function.** Coordinator is James Ashton-Miller, Ph.D. This research addresses problems of impaired mobility, including underlying molecular biological mechanisms, the role of coordination, skeletal muscles, bones and joints, and the biomechanics of movement.
- **Health and Well Being.** Coordinator is William Weissert, Ph.D. Research in this area focuses on such issues as comparative health, successful aging, health policy and health systems, and health behavior and education.

The Pepper Center also includes four "research resources cores" to support U-M geriatrics research, and a "research development core" specifically designed to help train junior faculty in geriatrics research.

The National Institute of Aging also supports many other centers at the U-M for research on aging, including the Alzheimer's Disease Research Center, the Nathan Shock Center for the Biology of Aging (molecular and cellular mechanisms of the basic biology of aging), the Michigan Center on the Demography of Aging, the Center for Applied Cognitive Research on Aging, and the Michigan Center for Urban African American Aging Research. In addition, funding from the National Institutes of Health supports the Alcohol Research Center and studies of alcoholism in the elderly.

The Department of Veterans Affairs also supports aging research and established a Geriatric Research Education and Clinical Center at the VA hospital in Ann Arbor in 1988, one of 17 in the nation. The Center, directed by Mark Supiano, M.D., is funded with more than $1 million annually.

The State of Michigan has supported aging research at the University of Michigan since 1965, when it established the Institute of Gerontology at the U-M. One of the oldest and most highly regarded academic programs of its kind, the Institute's public mandate to pursue research, education, and public service related to aging has resulted in a large number of graduate courses and faculty-initiated research projects. The Institute is a major research resource, encompassing biomedical and social sciences and their interdisciplinary interaction in studying the aging process. The Institute provides research training in gerontology for pre- and post-doctoral students, including all fellows in geriatric medicine. Ari Gafni, Ph.D., is director of the Institute and Jeffrey Halter is medical director.

The late U.S. Senator Claude Pepper (D-Fla.) circa 1937

"We're seeing how the life span, immune response, stress response and other markers for aging vary."

—David Burke

Miller (as well as many other aging researchers) is extremely skeptical that the new data tell us much about aging. "This is interesting research but I don't think it has anything to do with the real aging process," he says. First of all, Hayflick's observation which drew a correlation between age and cell division was based on cells growing in the alien environment of a test tube, and while there were many cell types in the body for which cell division is limited—nerve cells, of course, and probably fibroblasts as well—there's no reason to think that these growth limitations contribute to aging in the whole organism. The Hayflick limit is 50 or so cell divisions, bat intestinal epithelium cells undergo thousands of divisions in a human or mouse lifetime. Conversely, human neuron cells, which do not divide at all in adulthood, show clear signs of senescent changes in older individuals.

Perhaps the most damaging evidence against the telomere clock theory comes from recent experiments in which genetically altered mice lost the telomerase enzyme that maintains telomere length. Six generations of mice with successively shorter telomeres still seemed to age at about the same rate as their normal ancestors.

Clues from effects of caloric restriction

While Miller doesn't think that researchers have in any way found the aging clock, he feels that there are a number of very useful research paths that can give clues to how the clock operates. One path is to study the effects of caloric restriction and other dietary changes to try to find out the underlying biochemical changes that lead to life extension. "If we can find how caloric restriction works, what biochemical pathways are involved, we could eventually perhaps devise pharmacological methods of achieving the same results," Miller comments.

There are hints of these mechanisms already. Caloric reduction produces low glucose levels in the blood, and aging researchers know that high glucose levels in the blood seem to accelerate several symptoms of aging. Another U-M researcher, Jeffrey B. Halter, M.D., director of the Geriatrics Center in the Medical School and medical director of the Institute of Gerontology, had studied the effects of obesity and lack of exercise, both of which raise blood glucose levels. "High blood sugar levels accelerate the damage to certain types of important molecules, somewhat akin to the browning of apples exposed to air," he explains.

Other clues may come from studies that show that different kinds of nutritional reduction can also lengthen laboratory animal life spans. For example, Miller points out, recent research has shown that

"High blood sugar levels accelerate the damage to certain types of important molecules, somewhat akin to the browning of apples exposed to air."

—Jeffrey Halter

just reducing the methionine (an essential amino acid) in rats' diets extends their life span by 30 percent. Looking at common biochemical pathways that could be affected both by methionine reduction and caloric reduction, could lead researchers closer to the systems that determine the rate of aging. Additional experiments now underway on the effect of caloric reduction on rhesus monkeys could help to show how relevant this is to humans.

Hunting the aging genes

Another main research pathway is to try to find the genes that influence aging rates. Miller and his colleague David Burke, Ph.D., associate professor of human genetics and a senior associate research scientist in the Institute of Gerontology, have been exploring some of these areas. In one line of work, they are looking at mutations known to affect life spans in mice. For example, two dwarf mutations that produce mice about one-third the weight of normal mice also extend life span by 50-75 percent. Studying these mice may show how thyroid and pituitary hormones, deficient in the mutants, affect aging rates. Such a link between growth and aging is also indicated by experiments in dietary restriction which result in impaired growth but longer life, although some lengthening of life span occurs even if these diets are started in full-grown animals.

"We've found that proteins start to fold incorrectly in older cells and this can lead to diseases like Alzheimer's," Gafni explains. This seems to involve signals the cells get from the rest of the body."

—Ari Gafni

"We're also looking at wild mouse populations that we think are likely to be long-lived because of their more benign environments—those that have smaller, later litters," Miller comments. Mapping genetic differences between naturally long-lived and normal strains can help map where aging genes lie. In another project, Burke and Miller are looking at what Burke calls "the world's largest living family": a group of 600 mice that are genetically equivalent to siblings. "We're seeing how the life span, immune response, stress response and other markers for aging vary," says Burke. "We think we will be able to narrow down genes that control some of these phenomena to perhaps a thousand genes or less than a tenth of a chromosome.

Aging at the molecular level

A third avenue of attack on the aging process is to determine what changes take place at the cellular and molecular levels. "We know that the DNA of cells doesn't really change as the animal or human ages. But somehow the way genes express themselves as proteins changes, just as it does during development and differentiation—which we also don't really understand," says Burke. "The changes must be in the links between DNA and RNA or between RNA and proteins, and we are looking at how these changes occur in mice to try to find out."

Ari Gafni, Ph.D., professor of biological chemistry and director and senior research scientist in the Institute of Gerontology, has been investigating one aspect of how proteins change with age. "We've found that proteins start to fold incorrectly in older cells and this can lead to diseases like Alzheimer's," Gafni explains. This seems to involve signals the cells get from the rest of the body. "We know that when liver cells regrow in an older mouse, initially the cells produce the good proteins, but within weeks they are producing the same wrongly folded proteins as other older cells." Finding what those signals are may lead to another clue to how the aging process works and what controls it. ➤

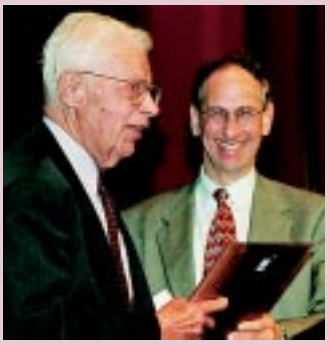
Charting the path ahead

Not all aging researchers by any means agree with Miller's view of the field. In fact, even among U-M researchers, neither Burke nor Halter agree that there is probably a single, central aging clock, although Gafni does. Nor are all researchers focused on the general goal of finding such a clock and slowing it down. "I'm more interested in preventing premature aging and getting everyone up to 80 or 85 years, rather than extending the maximum human lifetime," Burke states, and Halter concentrates on the prevention of the diseases of aging.

There is, however, a good deal of agreement that extending aging research could produce big benefits. "There are probably no more than 300 researchers worldwide working on the aging process," Burke says. "The research is uncertain, funding is not abundant and the problems lie in the whole organism, not in a single limited specialty." While billions are spent on specific diseases, research into the causes and control of aging receives no more than a few tens of millions, despite its huge potential for disease prevention. "If the publicity about telomeres spurs interest in the field, then it may be a boon," says Miller. Given even a faint chance of slowing aging, he and his colleagues believe that a large expansion of effort could well be justified. m

VETERAN JOURNALIST **DANIEL SCHORR** HONORED AT U-M GERIATRICS CENTER CELEBRATION

Over 800 patients, friends and supporters of Turner Geriatric Clinic attended the U-M Geriatrics Center's celebration in recognition of the 1999 United Nations International Year of Older Persons last October at Rackham Auditorium.



"What you like to do, do," advised NPR senior news analyst Daniel Schorr, a man who has taken his own advice for more than a half-century as reporter and commentator. He is shown here with Jeffrey Halter, director of the U-M Geriatrics Center.

The event featured a keynote address by Daniel Schorr, senior news analyst for National Public Radio, who began his career as a foreign correspondent in 1946, writing from postwar Europe for *The Christian Science Monitor* and later *The New York Times.* Schorr advised his audience, many of them, like him, in their 80s or older: "What you like to do, do. The people here could have chosen to retire. Instead they do things for other people. I'm being honored, but the honor is to me." Schorr received the U-M Geriatrics Center Outstanding Lifetime Achievement Award at a celebration that acknowledged the lifetime contributions of older adults and their vital role in community life.

Eight other community members received Turner Geriatric Clinic Community Lifetime Achievement Awards.

University of Michigan Music School faculty members William Bolcom and Joan Morris, the husband-and-wife performers noted nationally for their accomplished renditions of popular music from the 1920s and 1930s (he is a ragtime and jazz pianist and composer, she is a mezzo soprano cabaret singer) provided entertainment for the event. Their performance was in tribute to Katherine Morris, Joan's mother and a former patient of Turner Geriatric Clinic. The celebration also served to mark the end of the first year of a campaign to raise funds for Turner Geriatric Clinic programs that benefit senior citizens and their families throughout southeastern Michigan.

Also participating in the program were Gilbert S. Omenn, executive vice president for medical affairs; Jeffrey B. Halter, director of the University of Michigan Geriatrics Center; and Ruth Campbell, the Geriatrics Center's associate director of social work and community programs.