DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

FY 2000 Congressional Justification

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Justification

National Institute on Aging

Authorizing Legislation: Section 301 and Title V of the Public Health Service Act, as amended. Reauthorizing legislation will be proposed.

Budget Authority:

FY 1998 Actual		FY 1999 Estimate		FY 2000 Estimate		Increase or Decrease	
FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
392	$518,344,000	427	$598,258,000	427	$612,599,000	--	+$14,341,000

INTRODUCTION

This document provides justification for the FY 2000 non-AIDS activities of the National Institute on Aging (NIA). Justification of NIH-wide FY 2000 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

For nearly 25 years, NIA has led a national scientific effort to understand the mechanisms of aging and to extend the healthy, active years of life for all Americans. This enterprise has rapidly expanded knowledge about the biological, behavioral, and social changes that occur with advancing age and has challenged stereotypes about the inevitability of decline as people age. These advances have generated effective strategies that can maintain or even enhance physical function and cognitive abilities--which include memory, reasoning, judgment, and speed of processing information--in old age. They have also contributed to progress in public health and health care and to preventing disease. These successes benefit all generations.

To help ensure that the public benefits from these advances, the NIA provides accurate and timely information on the results of aging research and on related health data to older consumers, patients and family members, health care professionals, the media, and others. In 1998, NIA's public information program received the first Emmy Award given to a Federal agency for a nationally televised public service announcement, "Mme. Eterno, Looking for the Fountain of Youth." This announcement encouraged viewers to seek more information about increasingly popular "anti-aging" therapies, which are often not fully characterized for efficacy or potential danger. Also in 1998, the NIA, with astronaut and Senator John Glenn, the National Aeronautics and Space Administration (NASA), and other Federal agency partners, launched a national

education campaign for keeping fit after 50. The project is tied to release of a new book, free to the public, "Exercise: A Guide from the National Institute on Aging," that shows older Americans how to step up their physical activity to improve health and well-being with age.

There is no time to lose in discovering how to age well. Only 12 years from now, the 75 million babyboomers, people born between 1946 and 1965, will begin to turn 65. By the middle of the next century, the number of Americans over age 65 will more than double, and the number of Americans over age 85 will increase five-fold or more--placing a significantly greater number of people at risk for disease and disability. Today, elders account for about a third[1] of the estimated $1 trillion in U.S. health expenditures.[2] It is urgent to develop more effective treatment for age-related diseases and to prevent or delay the onset of disease and disability among older persons.

There is evidence that health research is making progress toward both these goals. In the fight against disease, for example, collaborative clinical trials funded by the NIA and the National Heart, Lung, and Blood Institute (NHLBI) confirmed the efficacy of lowering systolic blood pressure in significantly reducing the risk of major cardiovascular illness and stroke in older people. As another example, a trial of daily supplementation with calcium and vitamin D was shown to halve the risk of debilitating bone fractures in people over age 65. Drugs such as Tacrine, Aricept, and vitamin E have been shown to delay the progression of Alzheimer's disease.

In addition, progress has been made to begin to allay fears of an exponential growth in disability as our population ages. Longitudinal studies carried out over the past 16 years have documented a significant decrease in the rate of disability among Americans over the age of 65. Today there are at least 1.4 million fewer disabled older persons in the U.S. than there would have been if the disability rates of the elderly had not improved since 1982.[3] Moreover, the decline in disability rates has accelerated over the past decade. It is clear that much old age disability can be prevented. The NIA will continue to support research to improve approaches for maintaining fitness and preventing disease in order to ensure that successful aging is within everyone's reach.

Since the beginning of the 20th century, life expectancy at birth in the U.S. has increased from less than 50 years to more than 76 years. This represents a major victory for public health and medical care. The challenge for the 21st century will be to make these added years as healthy and productive as possible. Aging research is key to achieving this goal. When the NIA was first established, gerontology was a young science. Since then, there has been a revolution in aging research fueled by advances in basic and clinical research. Some of the most exciting recent findings will be described throughout this document. In this narrative, the NIA's stories of discovery, scientific advances, and future research directions are discussed under each of four

[1]Putting Aging on Hold: Delaying the Disease of Old Age: Official Report to the White House Conference on Aging, American Federation of Aging Research and the Alliance for Aging Research, 1995.

[2]National Center for Health Statistics: Health, United States, 1996-97, and Injury Chartbook, Hyattsville, Maryland, 1997.

[3]Manton KG, et al.: Chronic disability trends in elderly U.S. populations: 1982-1994. Proc. Natl. Acad. Sci.: 2593-2598, 1997.

main topic headings: Alzheimer's Disease and the Neuroscience of Aging, Biology of Aging, Reducing Disease and Disability, and Behavioral and Social Research.

ALZHEIMER'S DISEASE AND THE NEUROSCIENCE OF AGING

Alzheimer's disease, the most common cause of dementia, is the result of abnormal changes in the brain that lead to an irreversible decline in intellectual abilities and changes in behavior and personality. As the primary Federal agency responsible for research on Alzheimer's disease, the NIA leads national efforts to gain greater understanding of the biological mechanisms underlying Alzheimer's disease and to develop preventive measures and treatments based on research findings. Tragically, as many as four million Americans now suffer from Alzheimer's disease,[4] and the predicted explosive growth in the number of people living to 85 years and older, persons most at risk for dementia, lends an urgency to this research. Although the early signs of Alzheimer's disease involve mild forgetfulness, the progressive dementia ultimately leaves patients incapable of caring for themselves. Behavior changes may cause patients to become agitated, sometimes to the point of causing harm to themselves or others. Alzheimer's disease devastates its victims and profoundly affects the millions of family members and other loved ones who provide most of the care for people with this disease. Alzheimer's disease also necessitates formal services at substantial cost to individuals and public programs. While much remains to be done, research progress has been accelerating rapidly, bringing the field to the threshold of prevention trials.

***Story of Discovery*–Progress on Alzheimer's Disease Risks and Causes**

For several decades after Dr. Alois Alzheimer's 1906 discovery of the amyloid plaques and neurofibrillary tangles that would become the hallmarks of Alzheimer's disease, dementia was generally thought to be an inevitable part of growing older. In the past two decades, after the NIA and other NIH institutes developed research programs to study dementia, scientists have produced an outpouring of findings about the sequence of events that lead to formation of plaques and tangles and their contribution to the symptoms of Alzheimer's disease. In patients with Alzheimer's disease, amyloid plaques occupy tissues surrounding brain cells (neurons) in regions of the brain involved in memory and cognition. The plaques consist of insoluble filamentous deposits, chiefly comprised of a protein fragment known as beta-amyloid, associated with non-nerve cells activated to clear away damaged cells or foreign substances. Beta-amyloid is formed during the breakdown of a larger protein, called amyloid precursor protein (APP), which was discovered and sequenced only as recently as 1987. Certain enzymes can cleave APP to form one of two variants of beta-amyloid, both of which can aggregate to form insoluble amyloid plaques. Mounting evidence defines the importance of beta-amyloid in the disease process. The four known genetic alterations associated with Alzheimer's disease, discovered between 1991 and 1995, have been found to increase the production or deposition (or both) of beta-amyloid in the brain. Accumulation of beta-amyloid in the cerebral cortex is an early and consistent feature of Alzheimer's disease. Amyloid plaques are associated with inflammatory cells and processes that could contribute to neuronal damage. This and other evidence define amyloid beta as a prime target for intervention in the cascade of events that initiate neuronal degeneration.

[4]Evans DA, et al.: Prevalence of Alzheimer's disease in a community population of older persons. JAMA: 2551-2556, 1989.

Neurofibrillary tangles, the twisted wreckage of the cell's internal nutrient transportation and skeleton-like support systems, are found in the same areas of the diseased brain but within neurons. The major component of tangles is an altered form of the protein *tau*. In healthy neurons, microtubules form structures like train tracks--long, parallel rails stabilized by "railroad ties" consisting of *tau*. In Alzheimer's disease and in some other dementias, however, the altered *tau* can no longer hold the microtubule "tracks" together, causing the transport system to collapse. The *tau* itself twists into paired helical filaments, like two threads wound around each other. Disruption of the microtubule assembly can lead to cell death. *Tau* also has long been associated with nerve cell destruction. Evidence correlates the formation of tangles and the loss of neurons in the part of the brain most affected by Alzheimer's disease with increased severity of dementia. Nevertheless, until this year there was no evidence that changes in *tau* protein could directly initiate neuronal degeneration. Now, after years of multi-national research on families affected by rare dementias, there is hard evidence that *tau* can play a primary role in causing at least some cases of neurodegenerative disease. Since mid-1998, teams of researchers have linked several *tau* mutations on chromosome 17 to other inherited dementias characterized by brain tangles and nerve cell destruction. This class of dementias, collectively called "fronto-temporal dementia and Parkinsonism linked to chromosome 17," exhibits a wide range of symptoms, including schizophrenia-like dementias, Parkinson's-like tremors, difficulty in speaking, loss of inhibitions, and personality changes, in addition to loss of cognitive abilities. These exciting findings confirm that mutations in *tau* alone can lead to disease. The advances offer new directions for exploring treatments for these dementias, perhaps using drugs that mimic the properties of normal *tau* or drugs that halt aggregation of tau into brain tangles. Additional research is also needed to reassess the relationship between *tau* and beta-amyloid in dementing disease and to understand how abnormal protein filaments cause cell death in Alzheimer's disease and other neurodegenerative diseases, including Parkinson's disease, Huntington's disease, and prion diseases.

Science Advances—Alzheimer's Disease and the Neuroscience of Aging

Neurons in the human brain shown to replicate in adulthood. It has been a fundamental tenet of brain research that neurons of the adult brain do not replicate, making the possibility of replacing neurons lost through age, trauma, or disease extremely unlikely. Findings reported by Fred Gage and colleagues of the Salk Institute in La Jolla, California, however, have upset this notion. They first showed in rodents that neuron precursors in the hippocampus can replicate and become new, mature neurons even in adults. In old mice, new neurons were also born, but at a slower rate. Intriguingly, these researchers also showed that in mice exposed to enriched environments, even as adults, more new neurons survived, suggesting that the number of new neurons could be naturally enhanced. Subsequent research has shown that precursor cells also proliferate in the hippocampus (a part of the brain involved in memory) of non-human primates. And most recently, Gage and his Swedish collaborators showed that neurons can replicate in adult human brains. They examined at autopsy the brains of cancer patients who had been given a radioactive compound, BrdU, as part of their therapy. BrdU is taken up into DNA when cells reproduce, thus serving as a marker for dividing cells in the tumors and elsewhere, including the brain. Even in older adults, the researchers found that new neurons were generated in the part of the hippocampus called the dentate gyrus. This is a major step forward. Although neurogenesis in the adult human brain may be limited, showing that it can occur opens the way to finding out how it can be enhanced, as is already being done in rodents. The discovery of better methods for

stimulating neurogenesis might lead to therapies for neuron loss and cognitive decline in humans suffering from neurodegenerative diseases or traumatic injury.

NIA-supported studies play key role in National Academy of Sciences Report on Dietary Reference Intakes for Vitamins and Choline. In 1998, choline, a precursor for the neurotransmitter acetylcholine, was for the first time classified as an essential nutrient for humans and assigned recommended intake levels. Citations to justify these decisions, made by the Food and Nutrition Board of the National Academy of Sciences' Institute of Medicine, included findings from NIA grantee Dr. Jan K. Blusztajn of the Boston University School of Medicine and other NIA grantees. Blusztajn and colleagues had examined the long-term consequences of prenatal choline supplementation on the structure and function of rat brain neuronal systems. Pregnant rats during embryonic days 11-17 were fed a diet containing either no choline (choline-deficient), normal amounts of choline (control), or about four times control amounts of choline (choline-supplemented). After that gestational period, both mothers and offspring consumed the control diet throughout their life. Offspring from choline-supplemented mothers were more adept as adults at tasks that measured attention and spatial and temporal memory compared to controls, while rats from choline-deficient mothers were impaired in these behavioral tasks. Other NIA-funded studies linked choline supplementation in rats to improved neurotransmitter activity and to other enhanced nerve cell function. In contrast, prenatal choline deficiency was associated with an increased rate of cell death in embryonic brain regions related to memory and cognition. The NIA-supported studies suggest that optimal dietary choline early in development may improve human cognitive processes and delay age-related mild cognitive impairment.

Prion studies highlight importance for neurodegenerative disease of aberrant conformational changes in proteins. Dr. Stanley Prusiner was awarded the 1997 Nobel Prize in Physiology or Medicine for his discovery of the prion, a novel type of protein that through a change in molecular shape (conformation) converts from innocuous to infectious using itself as a template. Abnormal protein conformation may underlie several neurodegenerative diseases as well as age-related changes in function. These investigations have uncovered a previously unknown mechanism of neurodegenerative diseases of humans and animals. Prion diseases, including kuru, Creutzfeldt-Jakob disease, and bovine spongiform encephalopathy (known as "mad cow disease"), cause dementia and death. As in Alzheimer's disease, prion diseases are associated with insoluble protein deposits in the brains of patients consisting chiefly of amyloid. In the prion diseases, the infectious form of the prion protein, truncated by enzymes, is transformed into fibrils and can contribute to these amyloid deposits. Research is ongoing to find ways of stopping the transmission of prion diseases and to improve understanding of these fatal disorders of protein malformations and their contributions to dementia-related diseases, including Alzheimer's disease. This work has not only revolutionized our concepts of what constitutes an infectious disease, but it also emphasizes the important role of changes in protein conformations in the neurodegenerative changes in the aging nervous system.

Future Research Directions—Alzheimer's Disease and the Neuroscience of Aging

Preventing Alzheimer's Disease--The Alzheimer's Disease Prevention Initiative. This new effort is building upon current studies to launch a redoubled effort to arrest Alzheimer's disease and prevent future cases. Research has indicated that the neuropathologic changes of Alzheimer's disease begin as much as several decades before the clinical symptoms are recognized. The ultimate goal of this initiative is to intervene early in Alzheimer's disease pathology to prevent the disease from ever manifesting itself clinically. For example, one strategy will involve developing greater understanding of the initial stages of the underlying degenerative processes in Alzheimer's disease, with the help of laboratory models, and targeting the early pathologic changes before they lead to irreversible structural damage. Drug discovery studies and clinical trials will be designed to interfere with one or another neuropathologic process, such as formation of plaques and tangles, inflammation, and oxidative stress, as well as maintaining the health of neurons at risk. Efforts will also be made to identify additional risk factors and better predictive markers, as well as to develop tests of sufficient sensitivity and specificity to distinguish persons along the spectrum from normal aging through mild cognitive impairment to Alzheimer's disease. Some additional components of this initiative, which include clinical trial development and improving methods of care and treatment, are described below.

Launching new Alzheimer's disease clinical trials. Over the last five years, major advances in our understanding of Alzheimer's disease have suggested promising targets for future therapies to slow, reduce, or reverse cognitive and behavioral declines. There are now an estimated 50-60 drugs in or about to enter human trials in the public and private sectors. For example, building upon an earlier study that showed that vitamin E could slow the progress of symptoms in persons with diagnosed Alzheimer's disease, a novel secondary prevention trial will test whether high dose vitamin E slows the conversion to Alzheimer's disease of people with mild cognitive impairment (indicated by having a memory deficit but no dementia). This trial is the first funded by the NIA to delay the onset of Alzheimer's disease. Upcoming trials will also examine the effectiveness of ibuprofen (an anti-inflammatory drug) versus placebo in reducing the risk of Alzheimer's disease, whether estrogen replacement therapy can prevent Alzheimer's disease in women with a family history of the disease, and whether treatment with a variety of agents (aspirin, vitamin E, antioxidant, or folate/B6/B12 supplementation) can prevent older women from developing Alzheimer's disease. The NIA and the National Institute of Neurological Disorders and Stroke will also collaborate in initiating awards for pilot clinical trials and clinical trial planning in order to allow potential grantees to test their protocols and other strategies in advance of applying for large clinical trials.

Vascular disease and age-related cognitive impairment. Age is a major risk factor for cardiovascular disease, stroke, and Alzheimer's disease, which often occur together. These disorders may interact to exacerbate symptoms, as suggested by recent findings that associated the presence of small strokes in patients with Alzheimer's disease with greater overall severity of clinical dementia as well as poorer performance in tests of language and cognitive function. The diseases may also benefit from potential prevention strategies, such as estrogen replacement therapy. The NIA will explore the scientific basis of these interactions to develop better methods for early identification of people at risk for dementia and to provide new approaches to treatment

and prevention targeted to coexisting diseases. This initiative will exploit new technological developments in cardiac, vascular, and neural imaging and monitoring.

Helping caregivers of patients with Alzheimer's disease. Alzheimer's disease caregivers can themselves be "hidden patients," often facing "triple jeopardy" from emotional stress, physical strain, and financial burdens. A focused NIA initiative will develop and test new ways for families and friends to manage the daily activities and stresses of caring for people with Alzheimer's disease. The five-year effort will provide caregivers with support, skills, and information and will include a focus on African American and Hispanic families. In addition, efforts will be made to develop approaches to avoid triggering troubling behaviors and to help in retaining basic skills, for example, providing guidance to enable Alzheimer's patients to dress themselves.

Improving Sensory Function. Age-associated changes in sensory function, including vision, hearing, taste, smell, proprioception, and vestibular function, can lead to significant morbidity, as well as decrease the quality of life for many older persons. Progress is being made in discovering risk factors for age-related hearing loss and vision decline. Increased emphasis is being given to research on multiple sensory deficits in older people, which increases their risk for mortality and loss of independence. Understanding the mechanisms involved in decreased sensory function is expected to lead to interventions to maintain optimal function into the later years.

Preventing and Treating Sleep Disorders. Studies suggest that sleep disturbances afflict a majority of the older population in the U.S., contributing to personal discomfort and illness, caregiver burden, and health care costs. Contrary to commonly held belief, however, NIA researchers have found that chronic insomnia, which occurs in about a third of our elderly population, is not a normal consequence of aging. Chronic insomnia is almost always associated with a co-existing physical or mental condition, and improvement of those conditions is associated with remission of insomnia. The NIA also is collaborating with the NASA space agency on studies aimed at understanding how space flight results in some of the same conditions that occur in our elderly, such as disturbed sleep. This collaboration has led to jointly sponsored research on the use of melatonin to alleviate this problem on the Neurolab mission (STS-90) in April 1998, as well as in the opportunity to study the sleep of astronaut-Senator John Glenn on STS-95 in October 1998. NIA's sleep research encompasses the mechanisms underlying sleep-wakefulness cycles, normal and abnormal biorhythmicity of the aging nervous system, and the effects of concurrent disease states on sleep. Results of this research program should contribute to developing new and more effective therapeutic methods targeted at replacing symptomatic treatment with correction of the underlying pathology of sleep disorders.

BIOLOGY OF AGING

Research on the biology of aging has led to a revolution in aging research. This new gerontology investigates the progressive, nonpathological biological and physiological changes that occur with advancing age and the abnormal changes that are risk factors for or accompany age-related disease states. Progress is being made in understanding the gradual changes in structure and

function that occur in the brain and nerves, bone and muscle, heart and blood vessels, hormones, nutritional processes, immune responses, and other aspects of the body. Research has begun to reveal the biologic factors associated with extended longevity in humans and animal models. The ultimate goal of this effort is to develop interventions to reduce or delay age-related degenerative processes in humans.

***Story of Discovery*–Oxidative Damage and Cell Death in Aging**

Oxygen free radicals, produced normally as cells turn food and oxygen into energy, each have an unpaired, highly reactive electron. To pair its electron and stabilize itself, the free radical can capture an electron from another molecule, which in turn becomes unstable, perhaps causing a chain reaction that produces compounds harmful to the cell. For this reason, oxygen radicals may be regarded as villains in the life of cells. The free radical theory of aging, first proposed in 1955 by Denham Harman at the University of Nebraska, holds that damage caused by oxygen radicals is responsible for many of the bodily changes that come with aging. It is now widely accepted that oxidative stress leads to damage which may accumulate with age, and that this damage can contribute to age-related pathology, including cancer, atherosclerosis, cataracts, and Alzheimer's disease.

While it is far less clear whether there are specific targets which initiate critical events leading to age-related pathology, recent results obtained by several NIA grantees are beginning to pinpoint possible critical targets. Most oxidative stress produced in living organisms is an unavoidable byproduct of energy production in cell organelles called mitochondria. Several investigators have found that two mitochondrial enzymes involved in energy production, aconitase and adenine nucleotide translocase, are themselves prominent targets for oxidative stress. With age, cumulative oxidation-induced loss of activity in these enzymes can lead to cellular dysfunction.

Free radicals have their own cellular opponents: *antioxidants.* Superoxide dismutase (SOD) is an example of an enzyme with antioxidant activity. An NIA-supported investigator recently generated mice lacking this enzyme. These mice died prematurely, usually in less than one month, with severe disease of heart muscle. Mice with one good SOD gene paired with one mutant gene showed signs of elevated oxidative stress and decreased mitochondrial function, in some cases leading to death of cells. These results suggest a definite link between oxidative stress and loss of function and an enhanced risk of cell death. Research is needed to better understand the link between these processes and to identify possible interventions to reduce oxidative stress, particularly in tissues such as heart, muscle, and brain.

Science Advances—Biology of Aging

Gene therapy in mice maintained muscle strength in old age. A team of investigators including Lee Sweeney of the University of Pennsylvania and Nadia Rosenthal of Massachusetts General Hospital have collaboratively shown in a mouse model system that a gene therapy approach may be able to prevent age-related muscle atrophy and preserve muscle size and strength in old age. The new treatment increased muscle strength 15 percent in young adult mice and 27 percent in older mice, as compared with untreated muscle. For older mice, muscle strength was restored to what it was in young adulthood. To produce these results, the researchers engineered a virus to help deliver into mouse muscle a normally-occurring gene called insulin-like growth factor I (IGF-I), which plays a critical role in muscle repair and is believed to become less effective with age. Damaged muscles produce IGF-I to activate muscle stem cells--progenitor cells--to become muscle cells and effect the repair. While technical and ethical issues

must be overcome if the procedure is to be tested in humans, this therapeutic approach has promise not only for reducing age-related muscle loss, but for treating diseases of the muscle and for other applications involving muscle enhancement.

Telomerase expression can induce cell replicative immortality. Major advances have recently been made in understanding the role of telomeres and telomerase in aging and cancer. Telomeres, repetitive DNA segments found on the ends of chromosomes, help maintain the integrity and function of chromosomes. When cells divide, telomeres normally lose segments and shorten until, at a critical length, cell division ceases and cells become senescent. Telomeres have therefore been regarded as the cell's "molecular clock." The enzyme telomerase compensates for telomere loss by adding DNA segments to the ends of chromosomes. This process generally does not take place in normal human cells, where telomerase response is most often absent or insufficient. In contrast, 80-90 percent of human tumor cells have robust telomerase activity, and cells divide endlessly. How and why telomerase reactivates to contribute to cell immortalization is not known, but the correlation between telomerase activation and cancerous growth has stimulated many scientists to view telomerase inhibition as a potential new approach to cancer therapy. As reported last year, Thomas Cech in collaboration with the Geron Corporation discovered and cloned the gene for the active subunit of human telomerase in late 1997, making possible the critical study of how telomerase activity is regulated. In early 1998, Andrea Bodnar and colleagues at Geron Corporation and collaborating investigators at the University of Texas in Dallas inserted copies of the newly-cloned gene into normal, telomerase-negative cells in the laboratory, causing these cells to produce telomerase. Compared to normal cells, which exhibit telomere shortening and cessation of cell division, the telomerase-expressing cells had elongated telomeres and have continued to replicate far beyond the limits observed for normal cells. The cells have retained the appearance and function of young cells and have not become cancerous. These results confirm that telomere shortening causes cellular senescence under laboratory conditions. The ability to avoid senescence in normal human cells is expected to have important applications in research and medicine.

Exponential accumulation of extrachromosomal rDNA circles (ERCs) can cause aging in yeast; mutations in the yeast gene equivalent to the Werner's syndrome gene accumulate ERCs more rapidly and have shorter life span. The means by which the life span of an organism is determined remains an unsolved problem in biology. In the budding yeast, *S. cerevisiae,* cell division is asymmetric: a mother cell gives rise to a small daughter cell with each division. Life span is determined by following a mother cell through a number of rounds of division. Leonard Guarente and David Sinclair of the Massachusetts Institute of Technology in Cambridge observed that mother cells divide a relatively fixed number of times and undergo morphological changes of aging, including a slowing of the cell cycle until finally division ceases and senescence (cessation of cell division) occurs. A number of theories about control of the yeast life span have been proposed. The most recent observation builds on the finding that, with age, yeast mother cells showed a progressive enlargement and fragmentation of the nucleolus. It is believed that the accumulation of extrachromosomal rDNA circles (ERCs) in old cells give rise to these changes in the nucleolus, a structure within the cell's nucleus. Mutants for *sgs1*, the

yeast homologue of the gene for Werner's syndrome (a rare human disease that shares some aspects of accelerated aging), accumulate ERCs more rapidly than normal yeast cells, leading to premature aging and a shorter life span. It is proposed that the ERCs may be the "aging clock" in yeast.

Complex intercellular signaling regulates aging process in *C. elegans.* NIA researchers have identified several "longevity genes" that can double or triple the life span of experimental animals. Three genes, *daf-2*, *age-1*, and *daf-16*, are involved in determination of life span in the worm *C. elegans*. These genes appear to be involved in the worm's nutrient-sensing pathway. Moreover, these *C. elegans* genes have striking homologies to genes found in mammals, including humans. For example, *age-1*, discovered by Gary Ruvkun at Massachusetts General Hospital and Harvard Medical School, is homologous to an enzyme, PI3 kinase, that mediates signaling through the human insulin receptor; and *daf-16* resembles a class of molecules that control gene expression in mammalian cells. *Daf-2* codes for a protein in *C. elegans* that is homologous to and functions much like the insulin receptor in mammals. In 1998, Cynthia Kenyon, at the University of California, San Francisco, explored which cells require *daf-2* gene activity in order for the animal to develop to adulthood and to age normally. She found that the gene regulates both development and aging indirectly by initiating a signal that controls the production or activation of a second signal, which in turn affects the longevity of individual cells and tissues. These findings indicate that a complex, multi-step signaling pathway is used to regulate the aging process in *C. elegans*, and that the nature of the pathway may coordinate the aging process in the various tissues of the organism. The similarities between the protein produced by *daf-2* and the human insulin receptor may advance understanding of how human insulin regulates metabolism and why this regulation fails in diabetes.

Future Research Directions—Biology of Aging

Understanding the Genetics of Aging. Genetics and gene-environment interactions are major determinants of aging and longevity. Within the last 10 years, numerous genes have been implicated in normal aging processes, in age-related pathologies and diseases, and in determination of longevity in several species, including humans. The NIA plans to accelerate its efforts, using the most advanced technology, to discover age and longevity-related genes and to characterize their biological function. One strategy will include study of animal models, such as yeast and fruit flies, to find genes related to organismal changes that affect aging. Genetic findings in lower organisms can facilitate identification of genes with similar functions in humans. Another approach will try to identify genetic influences by studying large populations of older people who have previously been studied longitudinally, including large sets of twins or sibling pairs. These population studies will relate the individuals' traits, including longevity and vulnerability to age-related disease, to genetic makeup. Understanding the steps that enable these genes to promote human longevity or prevent age-related diseases is extremely valuable for extending human health span.

Defining How Alterations of Proteins Affect Aging and Disease. Proteins are key entities in the life of living tissue. They consist of sequences of amino acids, but their shape may determine whether their function is benign or toxic. Abnormal protein conformation may underlie age-related changes in function as well as age-related diseases. For example, refolding of normal cellular proteins into abnormal forms is common to disease processes in both Alzheimer's disease and prion diseases. The NIA, with other NIH institutes and the Institute of Medicine, are planning an initiative to develop strategies that will lead to identification of events responsible for converting functional proteins into toxic ones. This knowledge may provide targets for intervention in a wide range of diseases.

REDUCING CHRONIC DISEASE AND DISABILITY

As life expectancy increases, there is an ever greater need to keep these additional years disease and disability-free. Research has shown that life-style and other environmental influences can profoundly impact outcomes of aging, and that remaining healthy and emotionally vital until advanced ages is a realistic expectation. NIA's research is helping to define optimal needs regarding diet, diet supplements, exercise, safety, and other factors to ensure that endurance, strength, and balance are kept at the highest possible level and that the risks of disease and disability are kept to a minimum.

Science Advances—Reducing Chronic Disease and Disability

Lifestyle changes can reduce the need for blood pressure medication in the elderly. More than two out of every three Americans over the age of 60 have hypertension. Many of these people take medications to treat both hypertension and other conditions, increasing the risk of adverse drug interactions. Also, blood pressure medications can produce unpleasant or adverse side effects. Nonpharmacologic interventions were often recommended for treating hypertension in the elderly, but there was little evidence on their efficacy in this population. Results from trials in younger patients could not confidently be extrapolated to older persons because of potential differences in causes of hypertension in the two groups. This year, Paul Whelton of Tulane University and investigators at several other sites completed the Trial of Nonpharmacologic Interventions in the Elderly (TONE), co-funded by the NIA and the NHLBI. The 975 men and women ages 60 to 80 who were admitted to the trial had been successful in controlling their blood pressure with a single antihypertensive medication. The trial tested the efficacy and safety of withdrawing antihypertensive medication and substituting weight loss, dietary sodium reduction, or both to control blood pressure. Compared to the control group, the risk of recurrence of hypertension and/or cardiovascular complications was lowered by 31 percent in those assigned to sodium reduction alone, by 30 percent in those assigned to weight loss alone, and by 53 percent in those assigned to both weight loss and sodium reduction. TONE thus concluded that reducing sodium intake and weight loss could provide effective and safe nonpharmacologic therapy of

hypertension in older persons. TONE also demonstrated that older patients with hypertension were able to make and sustain the lifestyle changes necessary for these results.

Careful monitoring of acetaminophen use during warfarin therapy can reduce the risk of excessive anticoagulation. Warfarin (Coumadin) can lower the risk of stroke by about two-thirds in high-risk patients with atrial fibrillation, a condition in which the normal rhythmical contractions of the upper chambers of the heart are replaced by rapid irregular twitching of the muscular wall. Although shown to be effective in controlled clinical trials, warfarin use is more difficult in clinical practice. Proper dosage of warfarin is key: if the dosage is too low, the risk of forming clots, which can cause strokes, rises significantly. If the dosage is too high, there is an elevated risk of significant bleeding, especially intracranial hemorrhage, due to excessive anticoagulation. This careful equilibration of a prescription by the physician may be complicated by a patient's taking over-the-counter medications, such as acetaminophen (e.g., Tylenol), which can increase the risk of hemorrhage through a drug-drug interaction with warfarin. Daniel Singer and colleagues at Harvard University recently assessed the problem of excessive anticoagulation caused by acetaminophen-warfarin interaction. They found that as little as four regular-strength (325 mg) acetaminophen tablets per day for one week can cause this underrecognized problem, and that physicians are often unaware of patient use of acetaminophen or other medications that can cause excessive blood-thinning. The researchers concluded that clinicians need to inform patients of the risks of taking certain medications with warfarin, and that patients need to advise their physicians of all medications they are taking. These practices should translate into better management of anticoagulation therapy that, in turn, should reduce hemorrhagic complications. With these changes, warfarin use may increase, to the benefit of older people with atrial fibrillation.

Modest estrogen levels may protect older women and men from fractures. The NIA and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have shared a long collaborative effort in preventing osteoporosis and in the use of hormone replacement toward this end. This year, four studies reported findings on the contribution of sex hormone levels and other factors in minimizing bone loss and osteoporosis in men and women. A study led by Lawrence Riggs at the Mayo Clinic in Rochester, Minnesota, identified estrogen deficiency as the cause of both the early accelerated and continued slower phases of bone loss in women and as a contributor to bone loss in aging men. Another research team, led by Steven Cummings at the University of California, San Francisco, studied the internal levels of estrogen in nearly 900 women over age 65. These investigators found that women who had measurable blood levels of estrogen--much lower than women currently achieve by taking hormone supplements--had less than half the risk of experiencing a subsequent hip or vertebral fracture than women with undetectable levels of estrogen in the blood. This research team also found that the risk of hip fracture increased with higher blood levels of a protein that reduces the body's access to estrogen in the blood. Women with both high levels of this protein and undetectable levels of estrogen were found to be at a 7-fold higher risk for hip fracture and an 8-fold higher risk for vertebral fracture. These studies suggest that lowering the risk of postmenopausal fractures by taking very low-dose estrogen supplements or by using new estrogen-like therapeutic agents may prevent

bone fractures in men and women without causing adverse effects sometimes associated with estrogen therapies.

Future Research Directions—Reducing Chronic Disease and Disability

Preventing and Treating Cardiovascular Disease. Cardiovascular diseases are the leading cause of hospitalization and death in older Americans. The NIA is pursuing a broad program of basic and clinical cardiovascular research, in close collaboration with the NHLBI. The two institutes are working together to expedite progress in understanding the biological processes underlying heart failure and atrial fibrillation, with the goal of improving recognition and treatment of these conditions. Other research priorities include preventing vascular stiffening, a potential risk factor for cardiovascular disease, and reducing the progression of early atherosclerotic disease. The potential public health benefits of this research program are considerable.

Enhancing Musculoskeletal Function. Osteoporosis, osteoarthritis, and age-related loss of muscle mass contribute to frailty and injury in millions of older people. The NIA supports several initiatives to unravel the underlying mechanisms of aging in bone, muscle, and joints, and to design and evaluate effective prevention and intervention strategies for age-related musculoskeletal decline. In collaboration with the NIAMS, the NIA is encouraging new studies on sarcopenia--age-related loss of skeletal muscle mass, quality, and strength--that can lead to frailty and injury in the elderly. These studies will contribute to development of new approaches for clinical diagnosis and effective interventions for sarcopenia.

Reducing the Risk of Cancer. Cancer is the second leading cause of death among the elderly, with individuals age 65 and over accounting for 70 percent of cancer mortality in the U.S. Yet cancer clinical trials have not addressed many crucial treatment issues in older patients. In collaboration with the National Cancer Institute, the NIA is launching a new initiative to expand participation of older patients in clinical trials, as well as enhance non-clinical research on issues relevant to older-aged cancer patients. Research topics will include dose adjustment for anti-tumor agents and radiation therapy, how coexisting diseases affect cancer treatment and survival outcome, and survival advantages or disadvantages of minority or ethnic populations. Collaboration is in progress on age-related factors in development of tumors in older persons and on anticancer drugs in older-aged patients. The NIA is also continuing to expand its support of research on breast and prostate cancer research. These initiatives aim to apply scientific and technologic advances on malignancies to the special needs of older people.

Expanding Participation in Clinical Trials by Older Individuals. The NIA is collaborating with the Veterans Administration (VA) to stimulate clinical research on the medical problems of older men and women. Twelve research priorities have been identified as target areas for the conduct of multi-site clinical trials, including management and prevention of osteoporosis in men, androgen replacement therapy in older men, cardiovascular surgery in older patients, preventing lower respiratory and urinary tract infections in older nursing home residents, management of

behavioral disturbances among institutionalized patients with Alzheimer's disease, and adverse effects of medication prescribing in geriatric patients. This cooperative effort with the VA constitutes a special opportunity to support clinical geriatric research in excellent facilities through a cost-efficient mechanism.

Assessing Hormonal Supplements. Supplements of hormones and hormone-like molecules, such as melatonin, DHEA, testosterone, and growth hormones, are of growing popular interest. Claims have appeared in the news that taking such supplements can make people feel young again or that they can prevent aging. Unfortunately, these claims have not been proven, and the wrong balance of hormones can be dangerous. The NIA is conducting research to define the biologic action of these hormones and to assess the clinical utility of replacement therapy of hormones that tend to decline, on average, with age. For example, research is being stimulated to understand the steady age-related declines in testosterone observed in older males, which could contribute to the decreased muscle and bone capacity observed in frail older men. Studies are also under way on the biology of the menopausal process and on its associated pathophysiology, especially decreases in bone density and increases in cardiovascular disease. Related work will develop synthetic compounds that can provide estrogen-like effects to protect tissues and organs from the consequences of aging while minimizing risks. This initiative has great potential for developing effective strategies to promote strength and prevent disability in old age.

BEHAVIORAL AND SOCIAL RESEARCH

A goal of NIA behavioral and social research is to maintain or enhance the health and well-being, including physical and cognitive function, of older individuals throughout the life span. For example, new interventions are being developed to encourage long-term changes in health behaviors that will lead to reduced risk of disease and disability. Cognitive interventions are being tested to maintain cognitive function and retain independence. Components of the physical environment are being redesigned to match the skills and abilities of older persons, thus helping to prevent injuries and to improve performance of daily activities. Such human factors research has produced new and improved medical devices and treatment regimens, instructional designs, and product labeling. As more older people are able and willing to work well into late adulthood, researchers are studying the physical and social barriers to their sustained participation in the workforce and the factors needed to enhance their skills and productivity. A related body of demographic research documents trends in health, retirement, long-term care, and the economic aspects of aging, and uncovers their causes and inter-relationships.

***Story of Discovery*--Disability Rates Continue to Decline among Older Americans**

Not long ago, a Milbank Memorial Fund Quarterly article, "The Failures of Success" (Gruenberg, 1977), predicted that technology would save people from dying without curing them, producing a pandemic of old age disability and an exponentially increasing burden of health care services and costs. The specter of these dire predictions persisted until Kenneth Manton and colleagues at Duke University in Durham, North Carolina published his 1997 findings, based on waves of data from the National Long-Term Care Study, that demonstrated a dramatic and unexpected reduction in rates of disability among older persons. Manton calculated that at least 1.4 million fewer older Americans were disabled in 1994 than there would have been if disability rates had not improved since 1982, and that these reductions accelerated over the 12 years. Manton's conclusions were met with considerable skepticism, and efforts were launched to either disprove or support these findings. In early 1998, Vicki Freedman and Linda Martin of RAND, using a different dataset and different measures of functional ability, found equally large declines from 1984 to 1993 in the prevalence of chronic disability, after controlling for changes in the composition of the population during the study period. They also found that improvements in functioning in absolute terms were greatest among those 80 and older. Their findings and those beginning to be reported by other scientists lend support to the position that physiological changes in capability underlie the trend toward declining disability. A broad research effort is now under way on the economic consequences of the disability decline and the adoption of new medical technologies. Maintaining the current level of decline over the next 50 years could keep level the number of disables Americans in the face of the demographic challenge posed by the baby boom. Since there has been a deceleration of mortality at the oldest ages, as reported by James Vaupel of the Max Planck Institute for Demographic Research in Germany and Duke University, the goal of keeping the disability burden level has an increased importance. The changing family demography of the Baby Boom generation--fewer biological children and more step children--may erode the informal caregiving infrastructure within the family. Understanding the causes of the observed reductions in disability will enable us to develop interventions to maintain and accelerate continued functional improvements. There is also new evidence, developed by Anthony Vita and colleagues at Stanford University in California, that persons with better health habits not only survive longer but their disability is postponed and compressed into fewer years at the end of life. These findings are stimulating research on the specific interventions, behavioral changes, and survival attributes that can accelerate the trend toward decreased cumulative disability, postponed onset of disability, and improved quality of life.

Science Advances—Behavioral and Social Research

Biodemographic trajectories of longevity. A number of factors are contributing to the growth of the older population. Two are well recognized: the baby boom generation is growing older and the chance of surviving to old age is increasing. A third factor is a remarkable and largely unexplained reduction in mortality among those who have already survived to older ages. The percentage of 80-, 90-, or 100-year-olds that die in a year is getting smaller. This phenomenon raises questions about how long this reduction can continue and why we live long past normal reproductive ages. James Vaupel and colleagues in the U.S., Germany, Denmark, and China have been investigating these trends. A surprising finding of recent research is that the pace of the decline in old age mortality is actually increasing, and seems to be at least as fast in the countries that already have the lowest old-age mortality as it is in countries with slightly higher old-age mortality. The research also showed that rates of increase in death rates seem to level off at older ages, and may even decline. These provocative findings have inspired parallel studies of other species and analyses of the genetic determinants of longevity. They have also led to studies of the "survival attributes" that determine how long people will live and the extent to which these attributes are obtained from genetic factors, from factors occurring early in life, and from factors occurring later in life. It is suggested that about a quarter of the variation in human life spans after age 30 may be attributed to genetic variation among people, that another quarter may be due to variation in survival attributes that are fixed by age 30 (such as health and nutrition in early life, educational achievement, etc.), and that subsequent events and current conditions account for the remaining half.

Visual Processing impairment among older drivers. Although individual older drivers differ widely in driving ability, most older drivers have never caused a crash. Nevertheless, older drivers have a higher rate of crashes per mile driven compared to other adult age groups and are more likely to suffer disabling conditions or die as a result of collisions than are younger adults. Researchers are therefore trying to determine factors, such as impairments and medical conditions, that place certain older drivers at increased risk for crashes. Previous retrospective research by Cynthia Owsley at the University of Alabama at Birmingham and colleagues indicated that visual processing deficits--involving visual processing speed and visual attention skills--are strongly associated with a history of driving problems. These investigators developed a measurement of these visual processing skills, which they called Useful Field of View (UFOV). The researchers tested the UFOV of a group of older people and later followed up on their history of vehicular crashes. In 1998 these researchers reported that older drivers with a 40 percent or greater impairment in the UFOV were more than twice as likely to incur a crash during the three-year follow-up period than older drivers with a lesser impairment. The inability to divide attention at brief durations was determined to be the main risk factor for future vehicle crashes for older adults. In a separate study, Mary Tinetti and colleagues at the Claude D. Pepper Older Americans Independence Center at Yale University have developed a test battery that could be performed in a clinician's office of visual, cognitive, and physical abilities potentially relevant to driving. The study tracked the occurrence of a crash, moving violation, or being stopped by police over a period averaging six years. Among the 125 community-living drivers who participated, 50

reported one of these adverse events. Elements of the test that were significantly related to these events included near visual acuity worse than 10/40, limited neck rotation, and poor performance on a test of visual attention. The battery effectively detected disabilities in drivers at risk for adverse driving events, but abnormalities were also found in many who had no adverse events. These findings suggest it may be possible to identify individuals potentially at risk for self-reported driving events using simple tests of functional ability. Further research may help determine interventions to correct or compensate for the impairments.

Elders who experience mistreatment or self-neglect are at substantially greater risk of dying over time. Mark Lachs and colleagues at Cornell University in New York City traced the survival of a group of older adults, some of whom suffered from mistreatment and self-neglect. These older people sustained disproportionate death rates, even though none of them died as a result of injury directly attributable to abuse. The investigators found that only nine percent of those with a reported incident of mistreatment and only 17 percent of those suffering from self-neglect survived during a 13-year follow-up period. In contrast, 40 percent of persons studied who had no known history of mistreatment or self-neglect survived during the same period. This study, the first to compare the mortality experience of people who have been mistreated to that of their non-victimized counterparts, provides initial confirmation of what has long been suspected: elder abuse and mistreatment may be an insidious threat to life. Even when adjustments were made to account for other factors associated with increased death rates among the elderly, mistreated older people were three times more likely to die than older people who were not identified as mistreated and almost twice as likely to die if they were identified to be suffering from self-neglect. Efforts are underway to improve understanding of the risk factors and prevalence of elder abuse.

Future Research Directions—Behavioral and Social Research

Preventing Disease through Behavior Change. Although close links have been established between lifestyles and health outcomes, more needs to be learned to ensure that people will both initiate beneficial behavior changes as well as sustain them over the long term. Special attention needs to be given to changing adverse behaviors and to improving understanding of mind/body interactions with health. Efforts will also be made to target vulnerable populations in diverse ethnic/minority groups, age groups, and geographic regions. The results of this multifaceted initiative could be especially important for older individuals, who are at risk for multiple pathologies, disability, and functional limitations.

Maintaining Productivity. NIA's Edward R. Roybal Centers of Research on Applied Gerontology conduct research with the goal of keeping people independent, active, and productive in later life. Investigators at these centers focus on translating promising social and behavioral research findings into strategies to help improve the lives of older people and their families in such areas as computer skills, driving, exercise, caregiving, and nursing home care.

Promoting Health in Older Minority Populations. This initiative will address health disparities among racial and ethnic groups through research on enhancing management of medications, on improving older people's styles of self-management of chronic diseases, on developing strategies to reduce health disparities associated with poor interactions between patients and their physicians and other health care providers, and on social factors leading to access problems in health care delivery systems. Studies will also be designed to reduce disproportionately high rates of stress-related diseases and their effects on decline in cognitive functioning.

Understanding the Genetics of Complex Behaviors. Little is known about the relative contributions of genetic and environmental factors to behavioral traits in middle-aged and older adults. Revolutionary advances made in recent years hold great promise for the search for genetic determinants of complex behaviors. Traditional approaches have yielded important and provocative findings regarding complex behaviors with age. For example, contrary to previous assumptions, genetic influence on general cognitive ability remains substantial throughout the life span. Modern technologic approaches should enable rapid progress in identifying genes that affect behavior and in modeling the effects of age on complex behaviors.

Improving Health and Long-Term Care. Research advances present new opportunities for improving acute and long-term health care for older people. Research on acute care includes strengthening the doctor-patient relationship and improving compliance with medical regimens. Research on long-term care focuses on improved detection and treatment for the most vulnerable persons (that is, those at risk for abuse and neglect), on developing strategies to ease the burdens of caregivers, on enhancing quality of care, and on different long-term care settings, such as nursing homes and continuum-of-care communities. These initiatives should result in more effective strategies for prevention, treatment, and rehabilitation.

Following Trends in Health and Retirement. The unique Health and Retirement Survey (HRS) and its auxiliary study AHEAD (Survey of Asset and Health Dynamics Among the Oldest-Old), now being combined to create a seamless sample of persons over age 50, are following the life circumstances and transitions of about 20,000 people. This initiative will provide the first up-to-date picture of work and retirement and the relation of these factors to health and mid-life family roles in the 1990s. The primary purpose of the HRS is to study the transition between work and retirement, with particular emphasis on sources of retirement income and health care needs. Data from this survey will contribute to analyzing key policy issues, such as those involving the Social Security System and Medicare and Medicaid. This combined longitudinal study will provide the premier dataset for studying interactions between health and economic factors.

Monitoring Health through Demography. As the world's older population grows, demographic research enables us to monitor the impact of population aging on the global burden of chronic disease and disability. This knowledge enables us to identify health and economic trends and to recognize opportunities for research on their causes and impact. NIA will collaborate with other NIH institutes in studying the changes in health and functional status over time of disabled and chronically ill older people. Investigators will develop new methods to

generalize findings from clinical trials that had imposed exclusion criteria, so that the results could be applied to older people who could not participate. Research is being developed to improve data on burdens and costs of diseases. In response to advances suggesting that disability rates of older Americans are declining, researchers are developing studies to identify and quantify the specific underlying causes contributing to the decline, as well as to design interventions. Demographic research is also planned to track the dynamics underlying the increase in old-age life expectancy in the U.S. and to define the implications of changes in health, disability, and life expectancy for national policies on retirement and on programs for the elderly. A special focus is being developed to provide the necessary data for understanding the large variations in health across racial and ethnic populations.

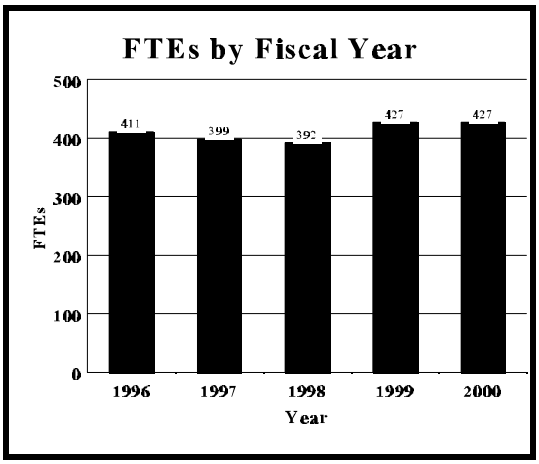
Conclusion - Meeting New Challenges through Aging Research

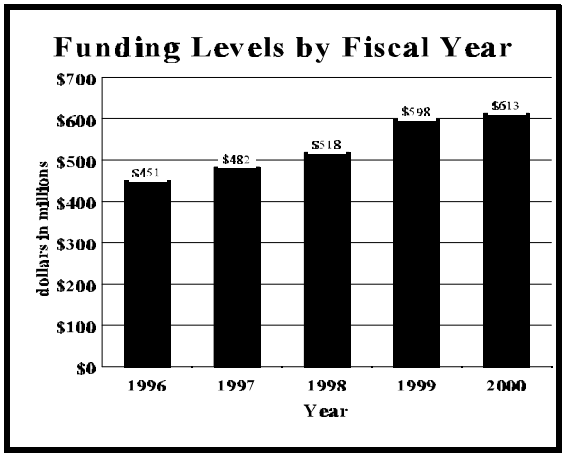
Throughout the world, populations are aging at an unprecedented rate. There is an urgent need to maintain the highest degree of function and quality of life for the longest period of time in older people. An understanding of aging and its relationship to disease and disability is one of the surest means to gain the knowledge needed to achieve these goals. Aging research has made significant strides in revealing the underlying processes that help determine longevity and the risk of disease. We are thus learning about factors important to maintain or improve high physical function and reduce premature death. We are developing tools to improve not only strength and balance but cognitive function, including memory, in old age. These advances are fueling health promotion and an optimism in attaining a successful old age. Efforts are intensifying to conquer Alzheimer's disease and to prevent or delay other age-related diseases and disorders. The goal is not merely to add years to life, but to add life to years. All of us stand to gain from the prospect of a healthy, fully engaged older population: the rapidly growing numbers of the aged, those they care for and who care for them, and all who will join this group in the future.

Budget Policy

The Fiscal Year 2000 budget request for the NIA is $612,599,000, excluding AIDS, an increase of $14,341,000 and 2.4 percent over the FY 1999 level. Included in this total is $4,000,000 for the NIH Area of Special Emphasis, "Biology of Brain Disorders." Ground-breaking advances in Alzheimer's disease (AD) have stimulated an accelerated search for underlying causes and an assault on the effects of the disease. Now, for the first time, drugs are being tested in clinical trials for their ability to delay or prevent the onset of AD. The NIH AD Prevention Initiative, to be undertaken in collaboration with other Federal agencies and the private sector, will invigorate efforts to discover new treatments, risk factors, methods of early diagnosis, and strategies for improving patient care and alleviating caregiver burdens. The Initiative will also expedite movement of promising new treatments and prevention strategies into clinical trials. The success of this initiative will thwart the impossible demands that unchecked growth of the population afflicted with AD would place on individuals, families, and society.

A five year history of FTEs and Funding Levels for NIA are shown in the graphs below:

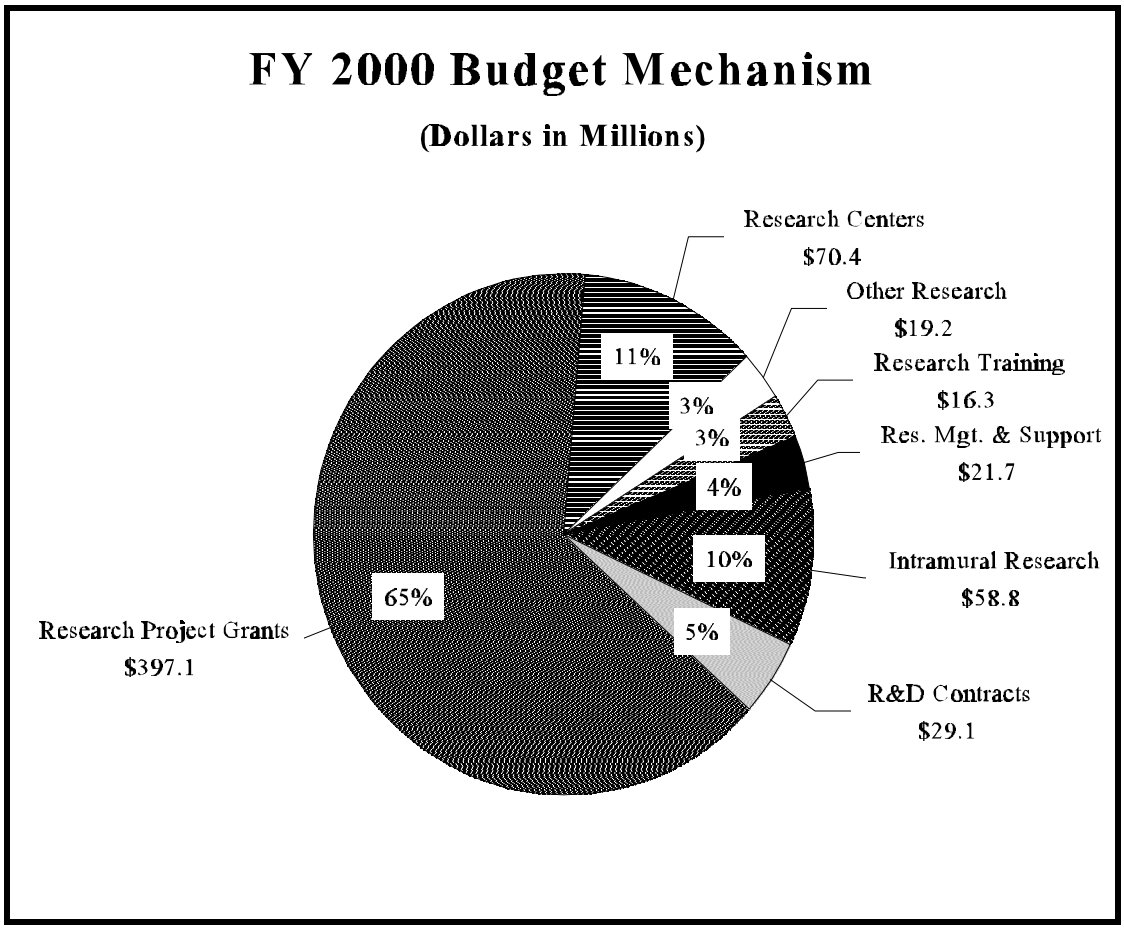


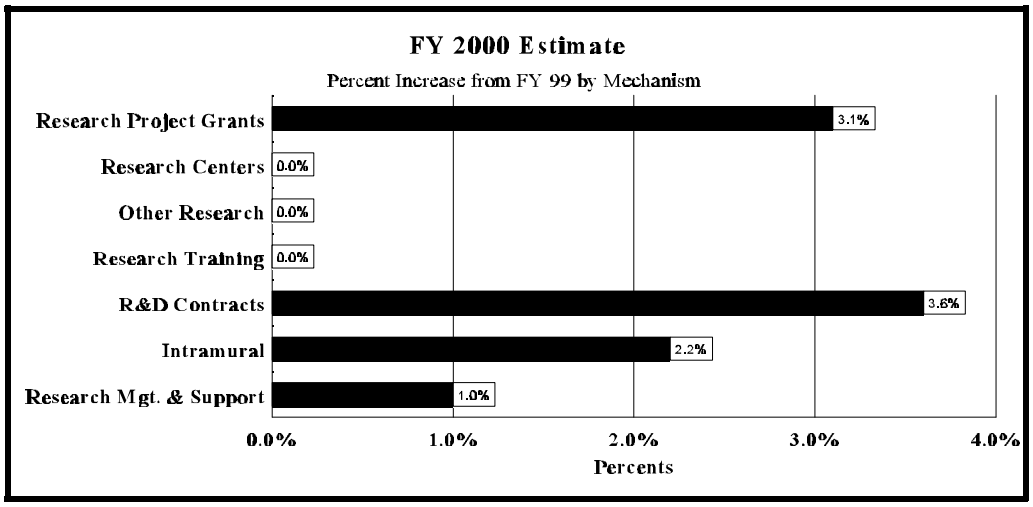


NIH's highest priority is the funding of basic biomedical research through research project grants (RPGs). The emphasis on RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. NIH is committed to ensuring that the number of new investigators does not erode. In order to fund a maximum number of competing research project grants, the Fiscal Year 2000 request provides funds for competing RPGs at the same average cost level as Fiscal Year 1999. Noncompeting RPGs will not receive inflationary increases.

Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the Fiscal Year 2000 request, NIA will support 539 pre- and postdoctoral trainees in full-time training positions. Stipends will remain at the Fiscal Year 1999 levels.

The Fiscal Year 2000 request includes funding for 61 research centers, 183 other research grants, and 53 R&D contracts. The Fiscal Year 2000 level will fund 155 research career awards. The NIA will continue to make support for clinical research training programs a high priority in Fiscal Year 2000. The mechanism distribution by dollars and percent change between FY 1999 and FY 2000 are displayed below:


FY 2000 Budget Mechanism
(Dollars in Millions)
Research Centers
$70.4
Other Research
$19.2
Research Training
$16.3
Res. Mgt. & Support
$21.7
Intramural Research
$58.8
R&D Contracts
$29.1
Research Project Grants
$397.1
11%
3%
3%
4%
10%
5%
65%


FY 2000 Estimate
Percent Increase from FY 99 by Mechanism
Research Project Grants
Research Centers
Other Research
Research Training
R&D Contracts
Intramural
Research Mgt. & Support
3.1%
0.0%
0.0%
0.0%
3.6%
2.2%
1.0%
0.0%
1.0%
2.0%
3.0%
4.0%
Percents

NATIONAL INSTITUTE ON AGING
Total by Mechanism
(Dollars in Thousands)

Mechanisms	FY 1998 Budget Authority Number	FY 1998 Budget Authority Amount	FY 1999 Estimate Number	FY 1999 Estimate Amount	FY 2000 Estimate Number	FY 2000 Estimate Amount	Percent Change From FY 1999
Research Project Grants							
Noncompeting	693	$236,397	761	$235,534	784	$273,643	16.2%
Admin Supplements	(113)	6,481	(110)	7,000	(110)	7,000	0.0%
Competing	373	81,562	486	130,796	387	104,184	-20.3%
Subtotal	1,066	324,440	1,247	373,330	1,171	384,827	3.1%
SBIR/STTR	52	11,731	58	13,110	59	13,485	2.9%
Subtotal, RPG	1,118	336,171	1,305	386,440	1,230	398,312	3.1%
Research Centers	59	63,916	61	70,400	61	70,400	0.0%
Other Research	152	15,042	184	19,345	184	19,345	0.0%
Training	549	14,191	539	16,319	539	16,319	0.0%
R&D Contracts	48	21,662	53	28,089	53	29,089	3.6%
(SBIR/STTR Contracts)	0	0	(1)	(375)	(1)	(375)	0.0%
Intramural Research		49,234		58,292		59,597	2.2%
Rsch Mgmt & Support		20,038		21,441		21,655	1.0%
TOTAL		**520,254**		**600,326**		**614,717**	2.4%

Total amounts include funding for AIDS: FY98-$1,910; FY99-$2,068; FY00-$2,118