DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

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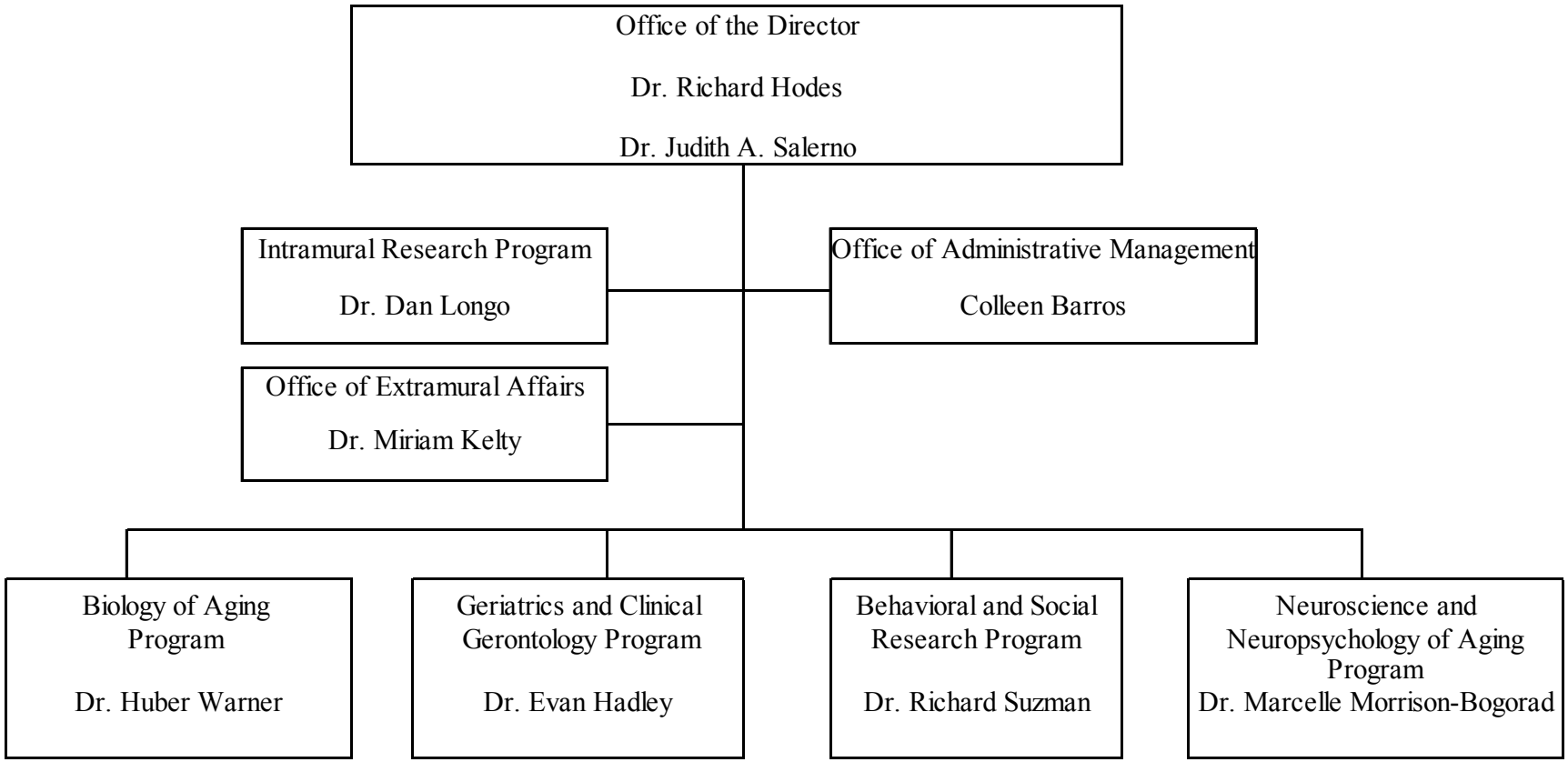
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

For carrying out Section 301 and title IV of the Public Health Service Act with respect to aging, $994,411,000.

Justification

National Institute on Aging

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
412	$890,816,000	414	$957,626,000	407	$994,411,000	(7)	$36,785,000

This document provides justification for the Fiscal Year 2004 activities of the National Institute on Aging (NIA), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2004 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

Since the Institute's founding in 1974, research has shed considerable light on aging and health. It is now known that aging itself is not the cause of disease, disability, and frailty. Rather, it is disease and disabling processes, influenced by age-related changes in the body and by unhealthy choices and sedentary lifestyles, that are the most important factors in compromising the quality of life for older people. This fundamental shift in thinking was reinforced most recently with insights from the National Long Term Care Survey (NLTCS). According to this study, the rate of disability among older Americans dramatically declined from the 1980s through the mid 1990s, even among people age 85 and older. These findings, along with evidence from a number of clinical trials and studies, suggest more strongly than ever that disease and disability can be delayed or even prevented through specific interventions.. The challenge now is to maintain and even accelerate the trend in declining disability and to reduce rates of disease amid a steep rise in the number and proportion of older people. The task is urgent. Demographic projections show that the U.S. population is beginning to age at a rapid pace, with the first baby boomers turning 65 in 2011. Between now and the year 2030, the number of individuals age 65 and older likely will double, reaching 70.3 million and comprising a larger proportion of the entire population, up from 13 percent today to 20 percent in 2030.[1] Of great interest is the explosive growth anticipated among those most at risk of disease and disability, people age 85 and older. Their ranks are expected to grow from 4.3 million in 2000 to at least 19.4 million in

[1] Federal Interagency Forum on Aging Related Statistics. *Older Americans 2000: Key Indicators of Well-Being.* 2000.

2050. The racial and ethnic makeup of the older population will change dramatically as well, creating a more diverse population of older Americans. These demographic factors combined threaten to increase the burden of age-related diseases and conditions on individuals, families, and society. Unless new understandings and interventions are developed and implemented to reduce disease and disability, the costs, in both human and financial terms, could be extraordinary.

In the 20th century, health research and public health practices did much to extend life and improve health. At the start of this new millennium, the NIA's research portfolio is aimed primarily at increasing "healthspan," or years of healthy active life expectancy. Aging research is well poised to build upon the work of recent years to improve the lives of older Americans and their families. Toward that end, NIA's overall program is wide-ranging and includes research on: the biochemical, genetic, and physiological mechanisms of aging in humans and animal models; the structure and function of the aging nervous system; social and behavioral aspects of aging processes and the place of older people in society; and the pathophysiology, diagnosis, treatment, and prevention of age-related diseases, degenerative conditions, and disabilities. In close collaboration with the National Advisory Council on Aging and other public and private organizations, the NIA has developed a strategic plan for aging research, to identify goals for the years 2001–2005. These goals address scientific areas with the greatest promise for advancing knowledge, many outlined in this narrative. The NIA also recently completed a strategic plan on disparities in health status of older Americans of different racial and ethnic backgrounds.

In this narrative, the Institute focuses on recent progress and future directions for research in four key areas: Section I) Alzheimer's disease and the neuroscience of aging; Section II) reducing disease and disability; Section III) the biology of aging; and Section IV) the behavioral and social aspects of growing older. In all of its efforts, the Institute is paying special attention to reducing health disparities among different groups of Americans (Section V).

ALZHEIMER'S DISEASE AND THE NEUROSCIENCE OF AGING

Alzheimer's disease (AD) is a progressive, currently irreversible brain disorder. People with AD gradually suffer memory loss and a decline in thinking abilities, as well as major personality changes. These losses in cognitive function are accompanied by pathologic changes in the brain, including the buildup of insoluble protein deposits called *amyloid plaques* and the development of *neurofibrillary tangles*, which are abnormal collections of twisted protein threads found inside nerve cells. Such changes result in death of brain cells and breakdown of the connections between them. AD advances gradually but inexorably, from early, mild forgetfulness to a severe loss of mental function called dementia. Eventually, people with AD become dependent on others for every aspect of their care. The risk of developing AD increases exponentially with age, but it is not a part of normal aging.

AD is the most common cause of dementia among people age 65 and older and is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. Scientists estimate that as many as 4 million people currently suffer with the disease, and annual costs associated with AD are estimated to exceed

$100 billion.[2], [3] As the population ages, the numbers of people with AD and costs associated with increased prevalence could rise significantly.

The following section on AD and related neuroscience describes recent advances in seven areas of AD research: early diagnosis, normal age-related cognitive change, the role of environmental factors in the development of AD, new animal models that may provide insights into the etiology of AD, preclinical studies of new preventive and therapeutic agents, clinical trials to test new therapies that may delay or prevent development of the disease, and studies related to easing caregivers' burdens.

Early Diagnosis of AD

Early diagnosis of AD benefits affected individuals and their families, clinicians, and researchers. For patients and their families, a definitive early diagnosis provides an opportunity to plan and to pursue options for treatment and care while the patient can still take an active role in decision-making. For clinicians, accurate early diagnosis facilitates the selection of appropriate treatments, particularly as new interventions are developed to stop or slow progression of symptoms. And for researchers, earlier and more accurate diagnosis may facilitate clinical studies of new therapies and preventive measures by allowing early intervention, before cognitive loss becomes significant.

Research suggests that the earliest AD pathology may begin to develop in the brain 10 to 20 years before clinical symptoms yield a diagnosis. Scientists have made tremendous progress looking for ways to diagnose AD in its pre-symptomatic or pre-clinical stages. They are searching for reliable, valid, and easily attainable biological markers that can identify cases very early in the course of disease. Eventually, combinations of specific strategies to image the brain, along with genetic, clinical, and neuropsychological assessments may become the key to identifying people at very high risk of developing AD.

Recently, researchers have made progress in several areas related to early diagnosis of AD:

- **Tracking changes in brain metabolism.** Investigators in several recent studies have identified specific metabolic changes in the brain that are characteristic of AD, and in one study have demonstrated that measuring patterns of brain metabolic changes can be used to diagnose AD with a high degree of accuracy.
- **Tracking changes in brain structures.** AD is associated with changes in many brain structures. Investigators have found that atrophy of the hippocampus, a part of the brain affected by AD, is a sensitive marker of AD-related pathologic damage and changes in cognitive function. MRI measurement of hippocampal volume may be useful for identifying

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[2] Small, G et al. Diagnosis and treatment of Alzheimer disease and related disorders. JAMA 16: 1363-1371, 1997.

[3] Ernst, RL, et al. Cognitive function and the costs of Alzheimer's disease, Arch Neurol 54:687-693, 1997.

early AD or for assessment of cognitive decline.

- **Imaging and evaluating AD's unique pathologic features.** Researchers are developing new ways to view and track AD's characteristic amyloid plaques in the brain. In one study in mice, investigators developed a radioactive tracer that is attached to an antibody that binds to the plaques, enhancing the ability to image them. In another mouse study, researchers developed a dye-based compound that also binds to plaques, again facilitating imaging. Preliminary human studies using amyloid tracers have been described.

These and other techniques may also provide effective methods of tracking early AD changes in brain as well as treatment effectiveness, particularly through imaging amyloid burden in the brain.

Normal Age-Related Cognitive Change

While most people remain alert and mentally able as they age, some age-related changes in memory, learning, and attention are normal. Improved characterization of normal cognitive function and underlying brain changes throughout life will help us distinguish normal from abnormal age-related cognitive changes. A better understanding of what is "normal" and what is not may aid the early diagnosis of AD; it could also alleviate the anxiety of people who observe modest but perceptible changes in cognitive function in themselves or a loved one and fear that such changes are the harbingers of a decline into dementia.

Prevalence of cognitive impairment is high among a group of older community-dwelling individuals. Scientists are trying to determine the prevalence of cognitive impairment that is not dementia. Individuals with dementia are forgetfulness and have impairments in thinking, judgment, and the ability to perform daily activities. The condition called Mild Cognitive Impairment, or MCI, is not dementia, but it may be related to the eventual development of dementia and AD. Results from the first population-based study of cognitive impairment in the United States, composed of 2212 African-American residents of Indianapolis, Indiana, ages 65 and older, indicate that 23.4 percent of the community-dwelling participants and 19.2 percent of the nursing home residents had MCI. The prevalence of cognitive impairment grew significantly with age, with rates increasing by about 10 percent for every 10 years of age after age 65. MCI was almost five times more common in the community than dementia. In addition, the scientists found that 26 percent of those characterized with MCI at the start of the study went on to become demented only 18 months later, although 24 percent of participants who were first diagnosed with MCI appeared normal after 18 months.

These results suggest that the condition may affect a significant proportion of older people. The factors that influence whether or not MCI will progress to dementia have not yet been defined. Whether the prevalence of cognitive impairment short of dementia in the Indianapolis group is any higher or lower than other population groups is unclear, although the results appear to be consistent with the few studies done so far in other countries.

Neurons Know Where We're Going. Researchers are finding out the ways in which we spatially orient and maneuver ourselves in the environment. In a study of monkeys, they found that neurons in the brain's medial superior temporal area (MST) appear to encode information about direction of heading, path and place. These functions allow an individual to orient

spatially in the environment. Since anatomical pathways from MST are associated with other brain areas that connect to the hippocampus (which is involved in AD pathogenesis), MST could play an important role in the spatial disorientation that is seen in AD and other neurodegenerative disorders.

Environmental Factors and AD

There is a great deal of interest in finding risk and preventative factors for age-related cognitive decline and AD. Of particular interest are those factors that are modifiable, because interventions that decrease the effect of a risk factor or facilitate a preventative factor could potentially delay the onset of the disease or prevent it altogether.

Can Diet Affect Risk of AD and Dementia? Scientists increasingly believe that the answer to this question may be "yes." For example, researchers recently found that elevated blood levels of the amino acid homocysteine were associated with a significantly increased risk of AD. The association between homocysteine and AD was found to be strong and independent of other factors. Blood levels of homocysteine can be reduced by increasing intake of folic acid and vitamins B6 and B12; the use of these compounds is being explored in ongoing and planned clinical trials for the treatment and prevention of cognitive decline and AD.

In fact, NIH investigators are elucidating the mechanisms by which folate deficiency and elevated homocysteine can influence risk of neurodegenerative disease. In a recent study, they found that folate deficiency renders neurons in the hippocampus, an area of the brain critical to learning and memory, vulnerable to degeneration in a mouse model of AD. Additional studies showed that homocysteine increases the vulnerability of neurons to being killed by amyloid beta-peptide, a toxic protein whose organization into plaques is a hallmark of the condition. In a mouse model of Parkinson's disease (PD), folate deficiency resulted in increased damage to specialized neurons in an area of the brain called the substantia nigra, worsening motor dysfunction as a result. When infused directly into either the substantia nigra or striatum, homocysteine promoted neuronal degeneration and motor dysfunction. The researchers also determined the mechanism through which homocysteine endangers neurons: It promotes oxidative stress (cellular damage caused by molecules generated during normal energy metabolism) and impairs the repair of damaged DNA, thereby triggering a form of programmed cell death called apoptosis.

Active Lifestyle Generates New Neurons in Aged Brains. Human studies suggest that a mentally and physically active lifestyle gives some protection against developing dementia and neurodegenerative disorders, and a recent NIA-supported study suggests that this may be due to increased neurogenesis, or development of new neurons, in active individuals' brains. Investigators found that mice housed in an "enriched" environment (including exercise and play equipment) for up to 10 months showed a fivefold higher level of neurogenesis in the hippocampus (a brain area central to learning and memory) than mice housed in standard bare cages. "Enriched" mice also demonstrated improvements in learning, exploratory behavior, and motor activity, and showed fewer lipofuscin deposits, an age-related indicator of neural degeneration, in hippocampal neurons.

Diabetes, ApoEε4 and the Risk for Alzheimer's Disease. Researchers evaluated the connection between type 2 diabetes, dementia, and APOEε4 (the major AD susceptibility gene) in a large group of Japanese-American men. They found that participants with both type 2 diabetes and the APOE ε4 allele had a risk for AD 5.5 times higher than those with neither risk factor. At autopsy, participants with type 2 diabetes and the ε4 allele had a higher number of AD's characteristic amyloid plaques and neurofibrillary tangles in the hippocampus, the region of the brain where AD is thought to start. They also had a higher incidence of amyloid deposition in the blood vessels in the brain. Further investigation is needed into the underlying pathology and effects of treatment of diabetes on the incidence of AD.

Animal Models of Neurodegenerative Disease

Animal models that mimic human disease are central to research for many reasons. Animals and humans share many genetic and physiologic features, so experimental results obtained in animals can frequently (although not always) be extrapolated to humans. It is much easier to create specific genetic mutations and observe their effects in animals than to search for them in humans, and because the lifespan of most animals is relatively short, it is easier to observe the effects of those mutations over several generations.

A Tale of Two Proteins. Investigators engineered a fruit fly model that carried genes for human Hsp70 and alpha-synuclein, two proteins that when altered are implicated in the development of PD and other neurodegenerative diseases. Hsp70 is a chaperone protein, meaning that it aids in the proper folding of other proteins, and scientists are using this model to elucidate the roles of chaperone proteins in neurodegenerative diseases. Results to date suggest that finding ways to enhance and appropriately target chaperone proteins' activity may be an effective approach to treating neurodegenerative diseases such as AD and PD that are accompanied by altered protein conformation and aggregation.

Prions, Misshapen Proteins, and Out-Of-Shape Brains. Prions are infectious proteins that transform a normal cellular protein (PrP^{C}) into an abnormal virulent form (PrP^{Sc}) that accumulates in the central nervous system, producing fatal neurological disease characterized by sponge-like holes in the brain that result in movement, emotional, sleep, and cognitive disturbances. These and other neurodegenerative diseases, including AD, PD, and Huntington disease (HD), now are thought to be diseases of protein conformation in which a misfolded version of a normal cellular protein aggregates and causes neurodegeneration.

Investigators have made a number of advances in our understanding of prion diseases. In the first study, researchers noted that, although chemically the same, PrP^{C} and PrP^{Sc} differ in structure. A fragment of the mouse prion protein with a single alteration that causes Gertsmann-Sträussler-Scheinker disease (a prion disease) can induce this disease in transgenic mice only if it is in the pathological form, indicating that prion proteins must exist in a particular structure to become infectious and produce neurodegeneration. The specificity of the prion structure may also limit transmission of prion diseases between different species: Researchers have demonstrated that breaching of the species barrier involves the generation of prions with different structural templates that slowly accumulate over multiple transmissions in recipients. In another study, investigators identified a neurodegenerative disorder that mimics the symptoms of HD, but lacks HD's characteristic

genetic mutation. Instead, the disorder is associated with mutations in the prion protein gene. Finally, researchers have found that, in mice, specially engineered antibodies can inhibit interaction between PrP^{C} and $PrP^{Sc,}$ which is necessary to PrP^{Sc} replication. In cells treated with the most potent antibody, prion replication was halted and existing prions were rapidly cleared, suggesting that the antibody may cure established infection.

Identification of Learning-Associated Genes in the Rat. The specific genes and proteins involved in the maintenance of long-term memory and learning remain largely unknown. NIH researchers recently trained rats in a maze, then used cDNA miroarrays – chips containing information from thousands of genes, which are electronically assessed and compared – to analyze the activity of genes known to be active in the hippocampus, a brain area central to learning and memory. They identified 18 known genes and 10 previously uncharacterized genes whose activity increased after the maze learning. These findings provide the groundwork for future, more focused research to elucidate the contribution of these genes in learning and memory processes.

Pre-clinical Research

There are currently no effective, generally useful treatments for AD -- i.e., a treatment that works on large numbers of patients, that maintains its effectiveness for a long period, that works in both early and late stages of the disease, that improves functioning of patients in activities of daily living as well as on sensitive neuropsychological measurements, and that has no serious side effects. In addition, none of the treatments presently approved for AD alter the progressive underlying pathology of the disease. One way to treat the disease successfully may be to interfere with early pathological changes in the brain, including the development of amyloid deposits and the formation of neurofibrillary tangles. A number of promising approaches, many of them targeted at the reduction of amyloid plaques, are currently being developed and tested in various model systems. If these approaches prove safe and effective in animals, studies in humans could follow.

Common Compounds May Be Effective Against Alzheimer's Disease. Recent research has suggested that use of several common, over-the-counter compounds may be associated with reduced risk of AD and dementia. For example, epidemiologic research indicates that there is a correlation between long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), such ibuprofen and a reduced risk of developing AD. Several recent studies are consistent with the hypothesis that NSAIDs are effective against AD, in part through inhibition of inflammation-promoting cells within the central nervous system Clinical trials are necessary to test directly whether NSAIDs can prevent AD and dementia, and such trials are currently ongoing.

Likewise, researchers are developing new "antioxidant" drugs that ameliorate or prevent cell damage or death caused by oxidative stress, a form of cell damage caused by molecules generated during normal energy metabolism. Oxidative stress is implicated in a number of diseases, including AD and PD, as well as in normal aging. Recently, investigators tested the activity of three new compounds in mice lacking one form of a key antioxidant enzyme; the researchers found that the drugs increased the lifespan of the diseased mice by up to 3-fold and prevented harmful pathological and behavioral changes. Continued research on such antioxidant

compounds may lead to new approaches to the treatment of AD, and perhaps other degenerative processes of aging.

Beneficial Effects of an Anti-Diabetes Hormone on Metabolism and Brain Function. Investigators have found that GLP-1, a gut peptide hormone that is present in the blood and that has generated interest as a potential treatment for type 2 diabetes, may have beneficial effects on brain functions. In a recent study, GLP-1 and its long-acting analog, exendin-4, stimulated the growth of nerve cells in culture. Moreover, GLP-1 and exendin-4 protected neurons in culture and in the brains of adult rats against injury and death in experimental models relevant to the pathogenesis of stroke and AD. Both prevented the loss of acetylcholine, a neurotransmitter that plays a critical role in learning and memory, and which is depleted in AD. These studies suggest that GLP-1 and related peptides may be useful in reversing or halting the neurodegenerative processes that occur in disorders such as stroke and AD.

Clinical Trials

Today, the few FDA-approved drug treatments for AD maintain cognitive function in AD patients in only a subset of patients and for only a limited time. However, an estimated 30 compounds are presently or will soon be tested in human AD clinical trials. These studies are sponsored by a number of sources, including the NIA, other NIH institutes, and the private sector, primarily pharmaceutical companies. Compounds now under scrutiny focus on three major areas of treatment: short-term maintenance of cognitive function; slowing the progress of the disease, delaying AD's onset, or preventing the disease altogether; and managing behavioral problems associated with AD.

Interest is currently focusing on compounds that directly target disease-related pathologies. A rapidly evolving research focus lies in prevention trials, and a number are underway to test the effectiveness of therapies in people without symptoms or who have only slight memory problems. Recruitment is now complete for the first NIH AD prevention trial, taking place at more than 70 sites across the U.S. This trial compares the effects of vitamin E and donepezil (brand name Aricept) in preventing the development of AD in people diagnosed with mild cognitive impairment, a population at high risk for developing AD. Further examination of estrogen and studies of various classes of anti-inflammatory drugs and antioxidants are also ongoing, and as scientists test these currently available medications, the next generation of drugs is being developed, targeting specific abnormal cellular pathways uncovered by recent discoveries, including plaque and tangle formation and death of brain cells. Prevention trials are among the most costly of research projects, but, if successful, the payoff in terms of reduced disease and disability will be significant.

Caregiving of AD Patients

Most of the approximately 4 million Americans with AD today are cared for outside the institutional setting by an adult child or in-law, a spouse, another relative, or a friend. Caregivers frequently experience significant emotional stress, physical strain, and financial burdens, yet they often do not receive adequate support. Several recent studies have explored the problems faced by caregivers of AD patients, as well as possible interventions to reduce their burdens.

Supporting Caregivers of Persons with Dementia. The National Institute on Aging's REACH Project (Resources for Enhancing Alzheimer's Caregiver Health), a large, multi-site intervention study aimed at family caregivers of AD patients, was designed to characterize and test promising interventions for enhancing family caregiving. Nine different social and behavioral interventions and two types of control conditions (usual care or minimal support) were tested at six different sites, and 1,222 culturally and ethnically diverse caregiver/patient pairs participated in the study. The investigators found that the combined effect of interventions alleviated caregiver burden, and that active treatments that enhanced caregiver behavioral skills reduced depression. The results also show that subgroups of caregivers benefit in different ways from the same interventions. Women caregivers, Hispanic caregivers, non-spouse caregivers, and those with high school or lower education benefited significantly more from active intervention when compared to similar individuals in control conditions. These results indicate that individualized, but tested, caregiver interventions and the means to deliver them are critically needed. The second phase of the study, REACH II, has combined elements of the diverse interventions tested in REACH into a single multi-component psychosocial behavioral intervention and is ongoing.

Selected Future Research Directions in AD and the Neuroscience of Aging

The NIA will continue to focus major efforts on two major areas of neuroscience research. The first is to characterize normal age-related changes in the nervous system, with its associated changes in function, and the other is to understand and treat the most common neurodegenerative disease of later life, AD, and related dementias. Trans-NIH initiatives are addressing these two areas. The Healthy Brain Initiative is a collaboration across Institutes to identify and understand factors impacting healthy brain aging. The AD Prevention Initiative is a similar trans-Institute collaboration with the ultimate intent of developing treatments to prevent the development of AD in susceptible individuals.

Specific initiatives will be pursued to identify imaging and biological markers for prediction, diagnosis, and charting the progression of AD; to test new approaches for drug develoment for AD; and to understand how genetics, environment, and age-related changes in the brain affect the development of AD.

Another important focus is the identification of risk factors for mild cognitive impairment (MCI) and AD. Since individuals with MCI are at a high risk of developing AD, it is critical for researchers to be able to define MCI and to differentiate it from normal cognitive aging and from AD. This is important not only in elucidating etiology and in targeting possible interventions, but also in understanding what the conversion rates from MCI to AD are in the general population and how this will impact the numbers of people with cognitive impairment and AD in the future.

REDUCING DISEASE AND DISABILITY

Chronic disease and disability can compromise the quality of life for older people. Some 79 percent of people age 70 and older have at least one of seven potentially disabling chronic conditions (arthritis, hypertension, heart disease, diabetes, respiratory diseases, stroke, and

cancer).[4] The burden of such chronic conditions poses a challenge to individuals as well as families, employers, and the health care system. Research to improve understanding of the risk and protective factors for chronic disease and disability can lead to the development of effective prevention strategies. This section describes some of the latest findings on the treatment and prevention of various age-related diseases, as well as the molecular underpinnings of disease.

Treatment and Prevention of Disease

Treatment of any specific disease in older people can be complicated by the presence of other diseases and disorders and by the concomitant use of multiple medications to treat various conditions. Potential interactions of medications, including those of prescribed drugs with over-the-counter drugs and dietary supplements, represent additional concerns. Moreover, adherence to treatment regimens can be difficult, as older patients often must maintain a complex schedule for taking several different medications. Research is ongoing to determine the best treatment approaches for older patients, particularly those with concurrent medical conditions, and to identify strategies for improving adherence and minimizing potentially adverse effects of medications.

Beneficial Effects of an Anti-diabetes Hormone on Metabolism. New studies show that GLP-1, a gut peptide hormone that is present in the blood and that induces secretion of insulin from the pancreas, has beneficial effects on cellular absorption of glucose among people with insulin resistance, a prediabetic condition. In one study, GLP-1 increased glucose uptake among insulin-resistant people over age 70 in whom insulin secretion had been artificially suppressed. The investigators also found that, in young people who were severely insulin resistant due to obesity, administration of GLP-1 brought their glucose uptake capability into line with that of their lean counterparts.

Bisphosphonates May Combat Glucocorticoid-Induced Bone Loss. Glucocorticoids, often used to treat a variety of conditions that arise in the elderly, also cause a rapid and marked decrease in bone mineral density, making a population that is already susceptible to osteoporosis even more subject to bone loss. Common treatments for osteoporosis, such as calcium, vitamin D, or fluoride, are not very effective against glucocorticoid-induced bone loss. However, a class of drugs known as bisphosphonates shows promise. Now, NIH-supported researchers have dissected the individual actions and the interactions of glucocorticoids and bisphosphonates on bone. This work demonstrates that each of these drugs tips the balance between bone formation and bone resorption in mice in both an early and later phase. The early phase of bone resorption caused by glucocorticoids cannot be counteracted by bisphosphonates, but in the longer term this balance shifts as bone-resorbing cells die and the lifespan of bone-building cells is extended due to bisphosphonate treatment. Understanding how bisphosphonates work has direct implications on the treatment of osteoporosis, a common condition among older Americans, and other diseases and conditions involving bone loss.

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[4] National Center for Health Statistics. *Health, United States, 1999 With Health and Aging Chartbook.* Figure 11, pg. 41. Hyattsville, MD: 1999.

Structured Restorative Home Care Produces Better Health and Function After Acute Illness and/or Hospitalization in Older Persons. Illness and hospitalization often initiate functional decline in older persons, and this decline can often persist long after the acute episode is over. An increasing number of older persons receive home care services after such episodes. In a recent NIA-supported study, patients on a "restorative care program" were significantly less likely to need rehospitalization, nursing home placement, or emergency room care after hospitalization as compared to people receiving "usual" home care. The restorative home care program consisted of the establishment of integrated teams of nurses and other health professionals and the application of structured interventions for disabilities, including exercises, behavioral changes, environmental adjustments and adaptive equipment, medication adjustments, and patient and family education. Functional abilities for living at home such as preparing meals, using transportation, shopping, doing laundry, and taking medicines appropriately were also significantly better in the restorative care group, as was mobility.

Benefits and Costs of Cervical Cancer Screening into Old Age. Although mortality rates for cervical cancer have declined substantially because of widespread use of Papanicolaou (Pap) screening, the test may fail to detect cancer. An increased understanding of the role of human papillomavirus (HPV) infection in the development of cervical cancer and advances in technologies for HPV detection have prompted exploration of HPV testing as an adjunct or primary screening tool. As with many common conditions, a critical public health issue regarding HPV screening is the cost-effectiveness of screening persons of all ages versus setting an upper age limit for screening.

Researchers constructed a model based on U.S. cervical cancer incidence, current screening rates, accuracy of diagnostic tests, and effectiveness of treatment, to examine the cost-benefit ratios of different population screening strategies every two years or every three years -- joint Pap and HPV testing, Pap testing alone, and HPV testing alone. The benefits of screening were measured by the gains in years of survival adjusted for the absence or presence, and severity, of cervical cancer. This model was used to estimate cost-benefits of the different strategies for women beginning at age 20 and continuing to either age 65, to age 75 years, or death. They found that the greatest benefits of screening came from combined Pap and HPV testing every two years through death, with only a modest increase in cost above Pap screening alone. 98 percent of the benefits were retained if an upper age limit of 75 was set for screening. However, the proportion of the benefits retained was substantially lower (87 percent) if the upper age limit was set at 65.

Age Does Not Influence the Response to Resistive Strength Training. Loss of muscular strength and muscle mass with age (termed sarcopenia) is associated with the development of disability and frailty in the elderly. Men and women in two age groups – 20-30 and 65-75 – participated in a resistive strength training program. Both age groups increased strength, and showed similar increases in muscle mass. In addition, both age groups showed similar increases in resting metabolic rates, which generally decrease with age.

A Drug to Improve Bone Marrow Transplant Success. In an allogeneic bone marrow transplant (BMT), in which the recipient receives bone marrow from a donor, the recipient must be given drugs that suppress the immune system in order to prevent the body from rejecting the transplant. Immunosuppressive drugs commonly used with BMT patients include Cyclosporin A

(CsA) and FK506, which are also used to treat a number of autoimmune diseases. However, these drugs have a limited success rate; the body resists their activity through a specific molecular pathway. NIH researchers have demonstrated recently that the immunosuppressive drug rapamycin, an antibiotic, blocks this pathway, suggesting that the success of immunosuppressive therapy in allogeneic bone marrow transplantation and autoimmune disorders could be improved by combination treatment with CsA/FK506 and rapamycin.

Lifestyle Change and Medication Can Prevent Type 2 Diabetes, but Efficacy of These Interventions May Vary by Age. NIA-supported researchers participated in the Diabetes Prevention Program, a major, multi-institutional study that was initiated by the National Institute on Diabetes and Digestive and Kidney Diseases and was designed to identify interventions that could prevent or delay the development of type 2 diabetes. The researchers found that people who are at high risk for diabetes can sharply reduce their risk by adopting a low-fat diet and moderate exercise regimen. This effect was most pronounced among study participants age 60 and over. Treatment with the drug metformin (Glucophage®) also reduced diabetes risk among study participants, but for unknown reasons was less effective among older participants. Nearly half of the study participants were members of racial and ethnic groups that suffer disproportionately from type 2 diabetes, including African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and American Indians.

Molecular Understanding of Disease Processes

Old Immune Systems are Less Responsive to New Infections. The immune system becomes less effective as we age, and this loss of function contributes to illness and death in the elderly. B cells, or specialized white blood cells that produce antibodies against invading pathogens, are critical to the immune response, but their role in the aging immune system is not yet well understood. Researchers have observed that subsets of B cells respond to each new infection by producing antibodies that react specifically to the infectious agent. These "experienced" B cells are then highly effective at responding to re-encounter with the original infectious agent, but are less able to respond to new infections. The body also produces "naïve" B cells that are capable of tailoring their response to new infections, but as people age, fewer new B cells are produced. In a recent study, NIH-supported investigators closely examined B cells in young and elderly mice and found that the aged mice have much higher levels of experienced, as opposed to naïve, B cells when compared to younger mice. They suggest that the experienced B cells are retained in the body as a result of chronic stimulation from the environment. This is correlated with a decline in generation of new B cells in the bone marrow, with the consequence that the overall immune response is less effective for new infections.

Lipid Abnormalities Linked to Lou Gehrig's Disease. NIH investigators have identified severe abnormalities in the metabolism of cholesterol and of sphingolipids, a type of fat, in the spinal cords of amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) patients and in mice that have been genetically engineered to manifest symptoms of ALS. These abnormalities result in the production of increased levels of sphingolipid byproducts and accumulation of cholesterol which prove toxic to motor neurons at high levels. In mice, the appearance of metabolic abnormalities precedes the development of symptoms, suggesting that the abnormalities have a role in killing the neurons. The researchers also found that drugs that rein in sphingolipid synthesis can prevent the accumulation of toxic byproducts and thereby protect motor neurons

from damage. The ability of a drug that prevents accumulation of sphingolipids and their byproducts to protect motor neurons suggests that this and related drugs, as well as modifications of dietary intake of fats, may reduce the risk of ALS.

BIOLOGY OF AGING

Aging is accompanied by gradual changes in most body systems. Research on the biology of aging focuses on understanding the cellular and molecular processes underlying these changes as well as those accompanying the onset of age-related diseases. As scientists learn more about these processes, experiments can be designed to understand when and how pathological changes begin, providing important clues toward developing interventions to prevent or treat disease. A great deal has been learned about structural and functional changes that occur in different body systems. Research has expanded our knowledge, too, of the biologic factors associated with extended longevity in humans and animal models.

Public Release of Novel Full-length Mouse cDNA Clone Collections. Arrays of DNA for specific genes permit the comparison of tens of thousands of genes at one time to determine which are turned on or off in a particular cell or condition. The NIA has assembled a collection of 7409 unique genes called the NIA mouse 7.4K cDNA clone set, which includes genes from various mouse stem cell lines, mouse early embryos, and mouse newborn organs. This set complements the existing NIA mouse 15K cDNA clone set, which has achieved international recognition as a unique and widely used resource. Like the 15K set, the 7.4K has been shipped to academic distribution centers for further replication and distribution throughout the research community. NIA scientists hope the immediate release of this additional high-quality DNA clone set to the scientific community will foster institutional collaboration and sharing of resources and speed the analysis of changes in the expression of many genes during aging processes.

A New Mouse Model of Accelerated Aging Provides Insights Into the Aging Process. NIA-supported investigators recently created a transgenic mouse carrying a mutation in the *Xpd* gene, which codes for an enzyme involved in both repair of DNA damage and transcription of DNA into RNA (an important first step in gene activation). This new model appears normal at birth but ages rapidly and lives only about half as long as normal mice. While not an exact model of premature aging, the new mouse model will be useful for studying a number of aspects of aging, including the roles of DNA damage and cell death, as well as the mechanisms through which the genome maintains itself and how such maintenance contributes to longevity.

Role of Telomeres in Cellular Senescence. Human cells have an inborn "counting mechanism" that tells them when to senesce, or stop dividing: Each time a cell replicates, the ends of each chromosome, called telomeres, get shorter, and once the telomeres get too short, they trigger a "senescence program" that arrests the cell's growth. Loss of telomere function can lead to genetic instability. Recent findings suggest that the senescence program is triggered by changes in the "protection state" of critically shortened telomeres, rather than their length -- in other words, the cell detects the likelihood that a shortened telomere will lead to genomic instability, regardless of the length of the telomere itself, and stops dividing as a result. Other findings suggest that the shortest telomeres in a cell become unstable and unleash the senescence program in order to avoid the propagation of genetically unstable cells.

Genetic Influences in Human Longevity. Researchers are beginning to identify biological and genetic mechanisms that might explain exceptional longevity. Using data from a study of families in which at least one member lived to be 100 or older, researchers recently found that siblings of centenarians had about half the risk of dying at every age throughout their lives compared with people who did not have a centenarian sibling, and that brothers of centenarians were at least 17 times more likely to reach the age of 100 themselves and sisters were at least 8 times more likely to live at least a century. These findings are supported by research indicating that excess longevity (the difference between observed and expected length of life) is 15 percent heritable, and that the longevity of both siblings and more distant relatives may be predictive of one's own lifespan. Together, these findings point to strong underlying genetic components of longevity and provide an approach to mapping and identifying specific genes that may play a role in determining human longevity.

New Insights Into Premature Aging Syndromes. Cockayne Syndrome-B and Werner Syndrome are devastating genetic disorders that cause accelerated and premature aging in affected individuals. The disorders are caused by mutations in the *CSB* and *WRN* genes, respectively. NIH researchers continue to elucidate the mechanisms through which the *CSB* and *WRN* genes operate, and have found that each gene is involved in DNA clean-up and repair. Recently, they found that the protein associated with the *CSB* gene has a role in repair of DNA damage caused by oxidative stress (cellular damage caused by molecules generated during normal energy metabolism). The protein associated with the *WRN* gene facilitates the activity of another protein, FEN-1, which is critical to DNA replication and repair. In fact, WRN stimulates FEN-1 more dramatically and efficiently than any other known protein. WRN also interacts with the tumor suppressor p53. The researchers conclude that mutations in the *WRN* gene may lead to premature aging and cancer susceptibility through dysfunction of the coordinated action of WRN protein, p53, and FEN-1 in a complex DNA repair process. These findings may suggest potential target molecules for the treatment of Werner Syndrome and Cockayne Syndrome-B, or even regulation of the aging process.

Nitric Oxide Controls the Strength of the Heart Beat. The heart is the body's most powerful muscle; its fibers stretch and contract to form the heartbeat. During periods of stress, including physical exercise, blood is pumped more rapidly throughout the body, and heart muscle stretch increases in response. Stretch also affects contraction strength; when heart muscle fibers stretch, calcium ions, which regulate contraction, are released from a part of the fiber called the sarcoplasmic reticuluum (SR). The efficiency of this process is critical to the quality of life during periods of good health, as well as during periods of disease. NIH researchers have found that heart muscle stretch activates a particular pathway that generates nitric oxide (NO). NO, in turn, enhances the fibers' capacity to release calcium ions from the SR. When the stretch is increased, as in periods of physical exertion, NO release is increased, strengthening the contraction. This mechanism could determine an important part of intrinsic cardiac reserve capacity. In addition, the researchers hypothesize that the loss of naturally occurring NO mechanisms in the body could contribute to the development of functional impairments of heart muscle when other compensatory mechanisms fail.

Extending the Lifespan

In order to understand the aging process, it is important to identify those factors that affect the overall life span of an organism. Understanding the responsible physiological mechanisms and, further, identifying ways to slow down age-related changes are important. Beyond any gains in life span, studies in this area are aimed more importantly at developing interventions to keep older people healthy and free of disease and/or disability as long as possible. Experiments in a number of animal models are providing valuable insights into the mechanisms of longevity.

A Pharmacological Intervention to Delay Aging in Fruit Flies. Using animal models, researchers are identifying possible pharmacological interventions that might be useful in delaying aging in humans. In a recent study, fruit flies fed the chemical 4-phenylbutyrate (PBA) throughout adulthood lived significantly longer than average, with no negative effects on physical activity, stress resistance, or fertility. The investigators found that two genes that became overactive in response to PBA treatment code for specific proteins that could have an impact on longevity; thus, these results also suggest a new approach in the search for genes that may play a role in longevity regulation. More research is needed to determine whether PBA treatment of other animals also affects their longevity.

The Promise of Stem Cell Research

Human pluripotent stem cells – that is, cells that are capable of dividing extensively and of giving rise to most tissues of an organism – hold enormous potential for cell replacement or tissue repair therapy in many degenerative diseases of aging. For disorders affecting the nervous system, such as AD and PD, amyotrophic lateral sclerosis, and spinal cord and brain injury, transplantation of neural cell types derived from human pluripotent stem cells offers the potential of replacing cells lost in these conditions and of recovery of function. Human pluripotent stem cells can also provide a model for studying fundamental molecular and cellular processes important in understanding aging and age-related diseases.

Another type of stem cell, multipotent or "adult" stem cells, are committed to producing cells that have a particular function. For example, stem cells circulating in the blood give rise to red blood cells, white blood cells, and platelets, but not bone cells or liver cells. Until recently, there was little evidence in mammals that multipotent cells could "change course" and produce cells of a different type. However, recent findings suggest that under certain conditions, some adult stem cells previously thought to be committed to the development of one line of specialized cells are able to develop into other types of specialized cells.

Neural stem cells are of particular interest to the study of AD and other neurodegenerative diseases of aging. Through several recent studies, we have found that environmental cues, which vary among brain subregions, may determine the fate of a stem cell, that neurogenesis may require the cooperation of multiple protein factors, and that neural stem-like cells taken from post-mortem brain tissue can form neurons. Together, these studies continue to show the potential of adult-derived neural stem cells to make different kinds of brain cells.

Adult Neural Stem Cells Make Functional Neurons. The generation of new functional neurons from neural stem cells (neurogenesis), either from those present in the brain or from

those transplanted into the brain, could be harnessed to regenerate damaged brain tissue, to replace dying neurons, or to enhance the ability of the brain to respond to age-related impairments. Adult neurogenesis occurs in the hippocampus, a brain region important for learning and memory, which shows degenerative changes in aging and AD. Although the new cells resemble mature neurons, until recently it was unclear whether the new neurons are functional or integrate into existing neural circuits.

Two studies now show that neural stem cells in the adult hippocampus develop essential properties of functional neurons. In the first study, investigators labeled stem cells in the hippocampus of adult mice by tagging them with a protein called GFP. When the hippocampus was examined 2 days after the injection, the GFP-labeled cells looked like immature neurons, whereas by one month the GFP-labeled cells looked and behaved like authentic hippocampal granule neurons. Close examination showed that the new neurons had properties similar to their mature neighbors, and that they received input from other cells. In the second study, researchers isolated stem cells from the hippocampus of adult rat brain and then tagged the cells with the GFP protein. When these tagged stem cells were cultured along with normal hippocampal neurons or astrocytes, support cells that foster neuron growth, they formed neurons with axons and dendrites, which are structures critical for communication with other cells. In fact, these stem cell-derived neurons made functional connections, called synapses, with normal hippocampal neurons and with each other, and released neurotransmitters, the chemical mediators of neuronal communication.

Isolation of Neuron-Restricted Precursor Cells from Human Embryonic Stem Cells. Cells in the brain and central nervous system differentiate through a multi-step process. As development progresses, stem cells – cells with a unique capacity to regenerate and give rise to many tissue types – generate a class of cells known as precursors or progenitors, which in turn generate the highly specialized cells of the brain and nervous system. Scientists now have the ability to isolate human embryonic stem (hES) cells, and have found that hES cells proliferate and maintain their pluripotency (ability to give rise to different tissue types) in cell culture[5]. NIH researchers have recently developed a method for inducing hES cells to differentiate into neural progenitor cells and neurons. The newly-derived cells exhibit the appearance and properties of cells ordinarily found in the brain and central nervous system. These data indicate that hES cells could provide a source for neural progenitor cells and mature neurons for therapeutic and toxicological uses.

Selected Future Research Directions in the Biology of Aging

The Aging Intervention Testing Program. In 2002, the NIA issued a Request for Applications (RFA) for the Aging Intervention Testing Program, a large-scale initiative to test potential intervention strategies that may slow the rate of aging in animal models. It is anticipated that positive results could be followed up with clinical trials to establish safety and efficacy in humans. A secondary goal is to identify interventions that are not safe or are not effective; such knowledge would be highly relevant in assessing appropriate candidates for clinical trials.

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[5] Carpenter, MK et al. Enrichment of Neurons and Neural Precursors from Human Embryonic Stem Cells. Exp. Neurol. 172: 383-397, 2001.

BEHAVIORAL AND SOCIAL RESEARCH

Behavioral and lifestyle factors have a profound impact on health throughout the life span. Older adults can help to prevent disease and disability and improve their quality of life through healthy behaviors such as proper nutrition, exercise, use of preventive health care, and avoiding smoking and alcohol abuse. Several particularly encouraging studies have shown that disability rates are declining, and NIA research is focusing on ways to sustain and even accelerate the decline in disability, including the use of behavioral interventions and the health care system by older people. In addition, important research efforts, such as the national Health and Retirement Study, continue to collect and analyze demographic data that inform public policy and planning for the health, economic, and social needs of a growing older population.

Potential Impact of Attitudes on Health and Behavior

Emotional state has been associated with health and functional status in old age. Both positive and negative attitudes or emotions can influence health and physical and cognitive function.

Personality and Risky Behaviors. A recent study examined relationships between a comprehensive measure of personality, the Revised NEO Personality Inventory, and condom use and other HIV risk behaviors. Participants consisted of 201 disadvantaged, primarily African-American participants of an HIV risk reduction program. Participants were divided into three risk groups (high, medium, and low risk) based on their self-reported sexual history, sexual behaviors, and intravenous drug use with shared needles. Results indicated that high-risk behavior was associated with emotional distress, poor self-control, and hostile and antagonistic attitudes and behaviors. The high-risk group demonstrated less ability to resist cravings and urges than the medium- and low-risk groups. The high-risk group also scored lower on measures of feelings of self-efficacy, motivation to carry tasks through to completion, and aspiration levels. All participants, regardless of risk classification, scored within the average range on measures of excitement-seeking. These results suggest that individuals who engage in high-risk sexual behaviors are motivated less from a desire for "thrills" than for temporary relief from psychological suffering. Successful intervention in these AIDS-related behaviors may require interventions tailored to at-risk individuals' basic tendencies.

Story of Discovery: Disability Rates Continue to Decline Among American Elders

When scientists assess disability in the population, they may look at a number of factors. One is the extent to which individuals can conduct basic activities of daily living such as eating, dressing, or bathing or participate in routine care activities such as everyday household chores or managing money. Scientists also track the extent to which cognitive disabilities such as memory loss are present in the population.

The 1999 National Long Term Care Survey (NLTCS), the latest of a series of surveys of the elderly population (particularly those who are functionally impaired), continues to document a dramatic decline in the overall prevalence of physical disability among older Americans over the past two decades. While 26.2 percent of the elderly were assessed as disabled in 1982, this figure dropped to 19.7 percent in 1999. Of particularly note is the reduction in disability rates among African Americans during the 1990s, reversing trends from the 80s.

Results from the 1999 NLTCS also indicate the possibility that rates of severe cognitive impairments may also be declining, with 900,000 fewer cases in 1999 than expected based on the 1982 rates – a decline in prevalence from

5.2 to 2.7 percent. The finding that cognitive disability may be declining is supported by evidence from the Health and Retirement Study, a major national study of the lives of older Americans. In this study, declines were especially large among those with less than a high school education and those ages 80 and older.

These findings are potentially of great significance in identifying and addressing causes of disability, as well as informing national health care policy. Declining rates of chronic disability may also moderate the burden of caregiving, including the informal care provided within families, the care provided through home health services, and the care provided in long-term care institutions. Most importantly, they indicate that elderly Americans are more likely than ever to enjoy the robust health and independence that characterize a life free of chronic physical or cognitive disability.

HEALTH DISPARITIES

The health status of racial and ethnic minority groups in the U.S. has improved steadily over the last century. Despite such progress, disturbing disparities in health persist between majority and minority populations. For example, the average life expectancy for a white infant born in 1999 is 77.3 years, but is only 71.4 years for an African American infant.[6] Demographic projections predict a substantial change in the racial and ethnic makeup of the older population, heightening the need to examine and reduce differences in health and life expectancy. Research to date has shown that health disparities are associated with a broad, complex, and interrelated array of factors. Disease risk, diagnosis, progression, response to treatment, caregiving, access to care, and overall quality of life each may be affected by variables such as race, ethnicity, gender, socioeconomic status, age, education, occupation, country of origin, and possibly other lifetime and lifestyle differences.

The NIA is committed to addressing health disparities through its research programs. For example, Satellite Diagnostic and Treatment Centers, part of the national Alzheimer's Disease Centers (ADC) Program, have successfully recruited African Americans, Hispanics, Native Americans, and American Indian/Alaska Natives to AD prevention and treatment studies. Researchers on the NIA's Religious Orders Study have made a major effort to enroll African American members of the Catholic clergy; the nature of the study population enables the etiology and pathology of AD to be established among individuals with similar educations, occupations, socioeconomic status, and lifestyles. Five ADCs received funding in 2000 and 2001 specifically to encourage minority-related research, and in 2001 half of the NIA Director's Reserve funds, which encourage collaborative research projects, were allocated to minority-focused research. In addition, the NIA recently completed a year-long review of these issues and developed a comprehensive strategic plan to address health disparities in the older population.

Water, Race, and Health. During the early 1900s, the United States began to notice a dramatic decrease in mortality rates from infectious diseases. The tremendous decline in infectious disease prevalence was due primarily to increased sanitation and hygienic practices that were implemented at the community level. For instance, the advent of waste disposal services had a profound impact on declines among certain population groups, as did water purification measures. However, most sanitation services were reserved for affluent communities, which

[6] National Center for Health Statistics. *National Vital Statistics Report* 50 (March 21, 2002), pp. 33-34.

consequently resulted in health disparities between social classes. Given the demographic profile in the United States, these disparities were particularly apparent between different immigrant and racial groups.

An NIH-supported researcher investigated the claim that public water companies provided black communities with better service than private water companies. The research drew from three independent sources of econometric evidence: 1) an analysis of typhoid fever rates in cross-sections of American cities in 1911 and 1921; 2) an analysis of waterborne disease rates in a panel of fourteen North Carolina towns between 1889 and 1908; and 3) an analysis of investment patterns in cities with public and private water companies. A case study of New Orleans, which municipalized its water system in 1908, complements the statistical evidence. All of these sources indicate public ownership reduced white disease rates only slightly, but reduced black disease rates sharply. This research both underscores the importance of public health in reducing mortality and shows how public health innovations can be used as a mechanism to reduce health disparities.

Medical Care and Racial Disparities in Survival After a Heart Attack. In a study of Medicare beneficiaries ages 66 to 74 who were admitted to a U.S. hospital due to a heart attack, NIH-supported researchers found that the black patients did not live as long after discharge from the hospital as white patients. Much of this disparity could be explained by the lower rate among black patients in the use of cardiac procedures such as revascularization (one of several surgical procedures to reestablish blood flow to part of the heart) and implantable cardioverter defibrillators (devices that regulate heartbeat). This result suggests that expanded use of effective procedures in black patients would substantially reduce racial differences in long-term survival, and that racial disparities in lifespan following a heart attack could be reduced if systematic medical procedures were employed.

Selected Future Research Directions in Health Disparities

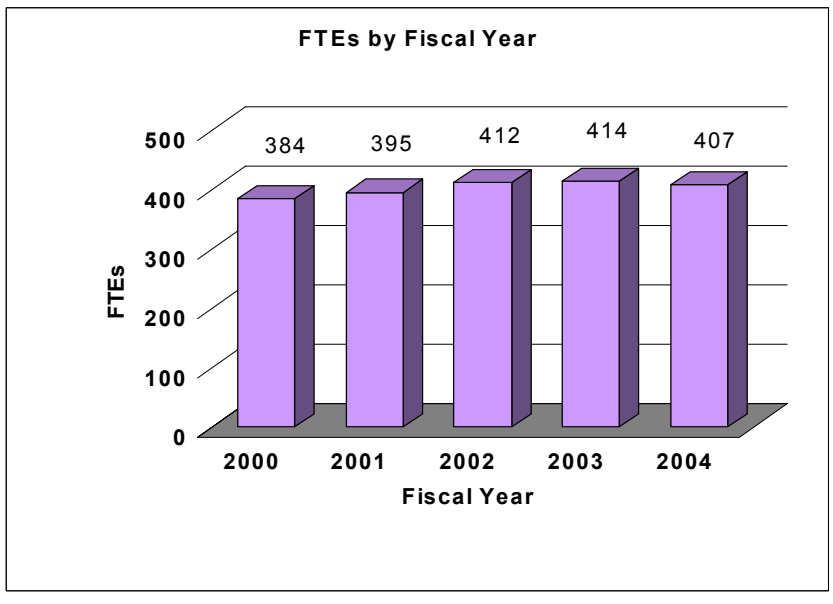
Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS). The need to understand the driving factors behind persistent black-white health disparities in overall longevity, cardiovascular disease, and cerebrovascular disease has led to the development of the HANDLS study, a community-based research effort designed to focus on evaluating health disparities in socioeconomically diverse African-Americans and Whites in Baltimore. This study is unique because it is a multidisciplinary project that will assess physical parameters as well as evaluating genetic, demographic, psychosocial, and psychophysiological parameters over a 20-year period. It will also employ novel research tools, mobile medical research vehicles to improve participation rates and retention among non-traditional research participants. HANDLS will investigate the longitudinal effects of socioeconomic status and race on the development of cerebrovascular disease and cardiovascular disease; changes in psychophysiology, cognitive performance, strength and physical functioning, health services utilization, and nutrition, and their influences on one another and on the development of cardiovascular, cerebrovascular, and cognitive decline. Selecting a cohort that spans ages 30-64 at baseline enhances the opportunities to gain insights into minority aging and the development of age-related disease over the planned 20 years of this study.

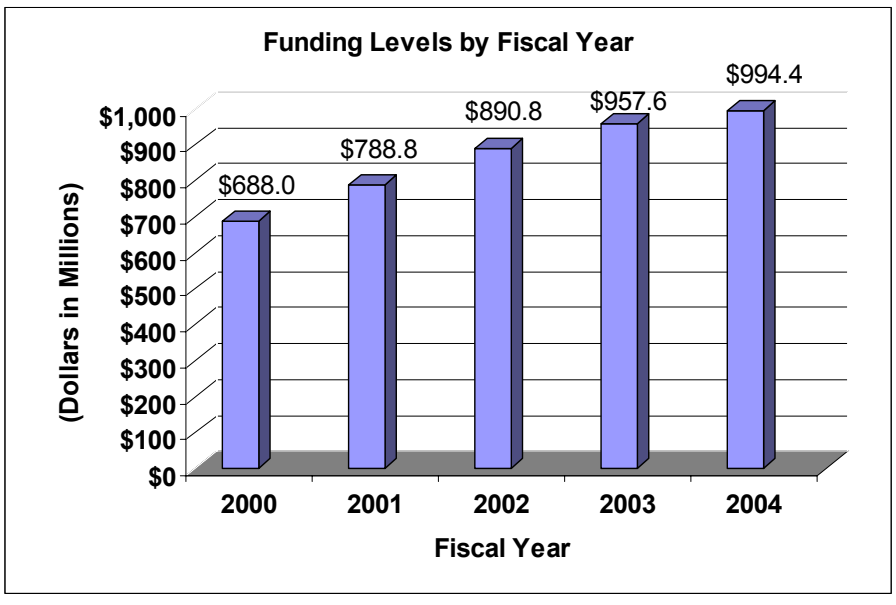
CONCLUSION: Meeting New Challenges through Aging Research

As our population rapidly grows older, it is ever more urgent that we find effective ways to address the often devastating diseases and conditions associated with advanced age. Since the NIA's founding in 1974, groundwork has been laid for today's important advances in understanding basic aging, preventing disease and disability, including AD, and defining special social and behavioral issues for older individuals, their families and caregivers, and clinicians. The latest studies provide additional basic understandings as well as improved interventions to treat and even prevent some of the more devastating and disabling aspects of aging. With such research continued and intensified, we can move forward in meeting the promise of extended life by improving the health and well being of older people in America.

Budget Policy

The Fiscal Year 2004 budget request for the NIA is $994,411,000 including AIDS, an increase of $36,785,000 and 3.8 percent over the FY 2003 amended President's Budget Request. A five year history of FTEs and Funding Levels for NIA are shown in the graphs below. Note that Fiscal Years 2001 and 2000 FTEs are not comparable for the NIH Human Resources functional consolidation.





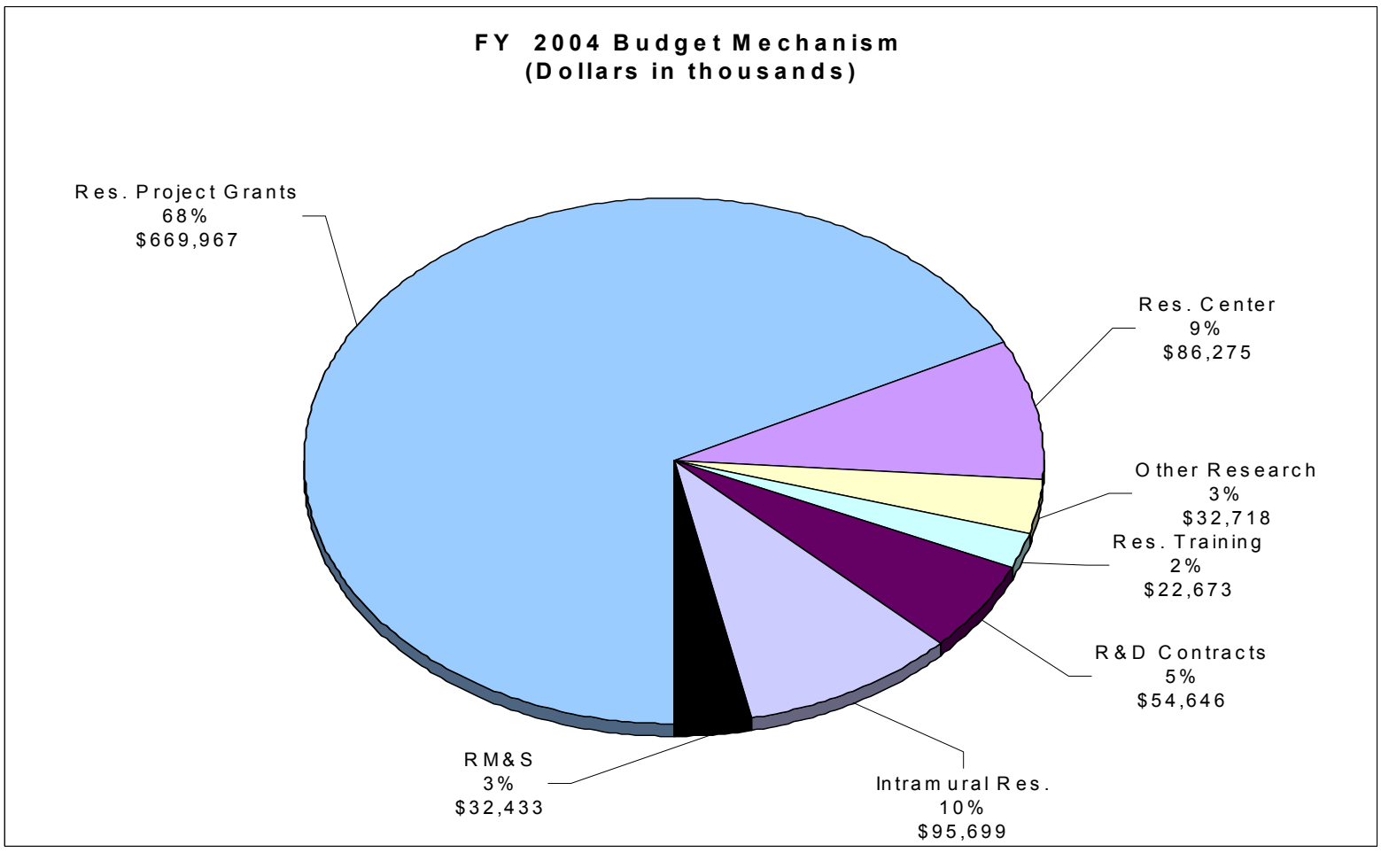
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. In FY 2004, NIA will provide an aggregate average cost increase of 2.6 percent for Research Project Grants.

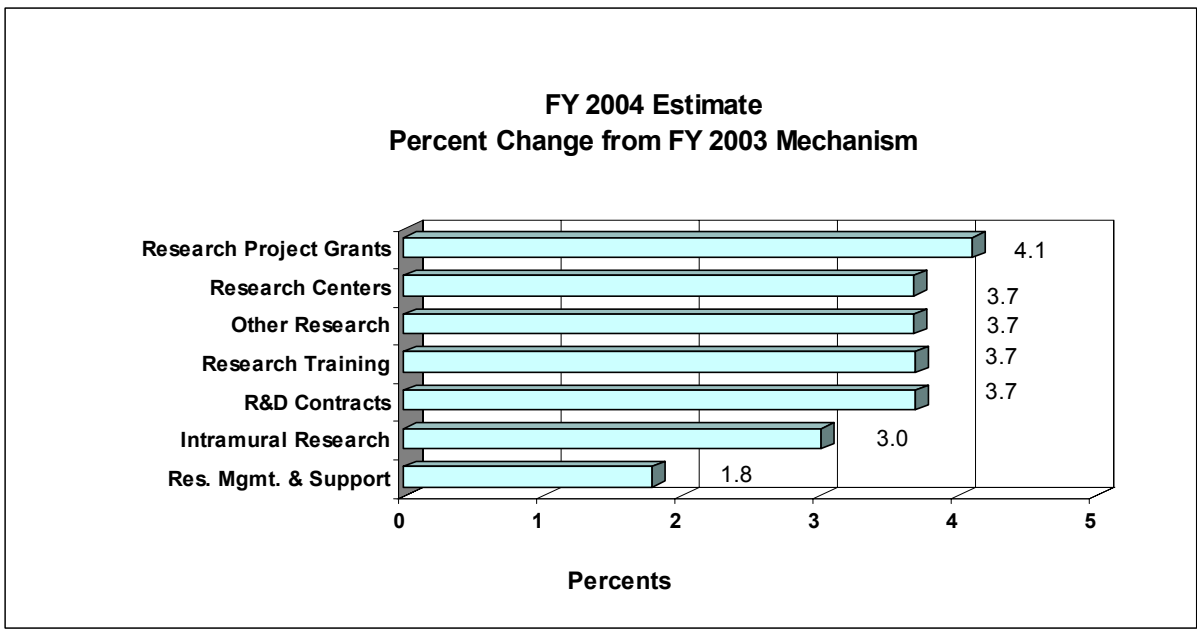
Also in FY 2004, NIA will fully fund 13 grants. NIA continues to support funding of AREA awards.

Promises for advancement in medical research are dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2004 request, NIA will support 571 pre- and postdoctoral trainees in full-time training positions, the same number as in FY 2003. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2003 levels for predoctoral fellows, and from 4-1 percent, based on years of experience, for postdoctoral fellows.

The Fiscal Year 2004 request includes funding for 67 research centers, 213 other research grants, including 181 clinical career awards, and 101 R&D contracts. Intramural Research receives a 3% increase and Research Management and Support receive a 1.8 percent increase over FY 2003.

The mechanism distribution by dollars and percent change are displayed below:




FY 2004 Estimate
Percent Change from FY 2003 Mechanism
Research Project Grants
Research Centers
Other Research
Research Training
R&D Contracts
Intramural Research
Res. Mgmt. & Support
4.1
3.7
3.7
3.7
3.7
3.0
1.8
0
1
2
3
4
5
Percents

National Institute on Aging

SIGNIFICANT ITEMS IN THE
SENATE APPROPRIATIONS COMMITTEE REPORT

The following section represents FY 2003 Congressional requirements for reports and significant items derived from Senate Report 107-216. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2003 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

Item

Alzheimer's disease research – The Committee urges the NIA to expand its investment in Alzheimer's disease research, focusing especially on its pathology, the identification of risk factors, more effective treatments, and large-scale clinical trials. In addition, advances in genetics and imaging now make it possible to study Alzheimer's in ways that were never before possible. The Committee encourages the NIA to apply this new knowledge to ongoing longitudinal studies. **(Page 126)**

Action taken or to be taken

In 1999, at the direction of Congress, the NIA, in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), and the National Institute of Nursing Research (NINR), embarked on the Alzheimer's Disease Prevention Initiative, which encompasses a number of interrelated efforts including basic, epidemiological, behavioral, and clinical research.

To identify targets for prevention efforts, basic research on Alzheimer's disease (AD) illuminates the mechanisms underlying disease pathology and determines the stages at which intervention might slow progression of dementia, delay onset of symptoms, or eventually prevent the disease. Expanded investment in basic research is identifying potential biomarkers (indicators of biological changes with age) that can aid in diagnosis and in understanding the progression of AD. New findings from basic research are also enabling analyses of disease progress and assessment of treatments in tissue culture and animal models. Epidemiological research on populations suggests genetic and environmental protective and risk factors for the disease and has led to new trials of anti-inflammatory drugs and other agents, such as statins, to treat or prevent AD. Recently funded epidemiological studies also include genetic analyses and neuroimaging components.

Expanding clinical trials, and in particular prevention trials, is another critical objective of the Alzheimer's Disease Prevention Initiative. Until recently, clinical trials have only studied persons who already have clinically detectable mild to moderate AD. While NIA is continuing to evaluate treatments for the cognitive and behavioral symptoms of AD, it is also going beyond treatment to initiate studies on prevention strategies. Under the auspices of the Alzheimer's Disease Prevention Initiative, substances are now being tested on individuals who are at high risk for developing AD in order to prevent or delay the onset of clinical disease.

Item

Early detection of Alzheimer's disease – The Committee also urges the NIA to focus on early detection of Alzheimer's disease so that clinical interventions to slow or stop the progression of the disease may be undertaken. The Committee notes that positron emission tomography (PET) may identify Alzheimer's disease at an early stage and encourages the NIA, in collaboration with the NINDS and the NIMH, to expand its research efforts into early diagnosis of Alzheimer's using PET and other brain imaging methods. **(Page 126)**

Action taken or to be taken

Neuroimaging studies are continuing to assess whether it is possible to measure aspects of brain function and/or structure that will identify those individuals who are at-risk for AD years before they develop the symptoms of the disease. As possible treatments for AD become more promising, diagnosing the disease at its earliest stages has become increasingly important, and a reliable biological marker of disease progression would also be useful for monitoring treatment response. A number of recently published brain imaging studies have reported results that hold promise for using regional changes on PET and magnetic resonance imaging (MRI) scans as early markers for disease. Progress is being made in understanding the earliest brain changes that occur in the transitions from normal cognition to mild cognitive impairment (MCI) and from MCI to AD, but more research is needed before we know whether and how imaging methods such as MRI and PET can be used most effectively and efficiently in the identification of early presymptomatic changes leading to AD. Therefore, NIA is expanding its focus on early, presymptomatic diagnosis.

The NIA, in conjunction with other NIH Institutes such as NIMH and NINDS, is also developing an Alzheimer's Disease Neuroimaging Initiative. This is being planned as a partnership among the NIA/NIH, academic investigators, the pharmaceutical industry, and the imaging equipment industry, with participation from the Alzheimer's Association and the Institute for the Study of Aging. This proposed longitudinal, multi-site study will include older cognitively normal individuals, people with MCI, and people with early AD. The overall study will be of 5 years duration, and will follow subjects over 3 years to collect serial MRI scans and serial PET scans, clinical and neuropsychological information, and biological fluids and cells for other potential biomarkers. An important aspect of this initiative is that the clinical, imaging, and biological data and samples will be made available to all qualified scientific investigators from both the public and private sectors; there will be no intellectual property claims attached to the data generated from this initiative. Results from this initiative will help to provide information that will allow early identification of those who may benefit from emerging preventative and treatment medications. The data gathered will also help to determine whether neuroimaging outcomes may serve as surrogate endpoints in AD clinical trials, information critically needed to facilitate the development and testing of new drugs for the treatment and prevention of AD.

Item

Cardiovascular aging research – Cardiovascular diseases remain America's leading causes of death of older men and women and a significant cause of disability. The Committee urges the NIA to make cardiovascular research a priority. **(Page 127)**

Action taken or to be taken

In FY 2002, NIA grantees further characterized a second and distinct type of heart failure (diastolic heart failure) - a progressively debilitating condition common among older people. The new information will help physicians better understand this form of heart failure, and suggests that additional research be undertaken to see if diastolic heart failure is as amenable to treatment as the more well-recognized form of the disease. NIA began support for two basic research projects on adult stem cells and heart disease in FY 2002. NIA is also continuing support for a clinical trial on B-vitamin supplementation and progression of atherosclerosis in healthy older persons. Important research continues on establishing links between high blood pressure, coronary heart disease, and coronary artery bypass surgery with brain changes, including changes in mental capacity. Using state-of-the-art technology, NIA's intramural research program continues to lead the NIH in determining the importance of age-related blood vessel stiffening on the development of cardiovascular disease in minority populations, including novel treatments for blood vessel stiffening. NIA also continues to facilitate the development of promising new investigators in aging research through its annual small grants program and also remains committed to fostering research training and career development of new investigators in the cardiovascular aging field.

Item

Claude D. Pepper Older American Independence Centers – The Committee continues to strongly support these successful centers, which focus on developing innovative and cost effective ways to enhance the independence of older Americans. The centers also play the critical role of developing top level experts in geriatrics. The Committee strongly urges the NIA to make all possible efforts to expand these centers to include a school of nursing. **(Page 127)**

Action taken or to be taken

NIA continues to value this important program and in FY 2002 has funded two applications that were judged to be of high quality; an additional high quality application will be funded in FY 2003. The most recently reviewed applications were in response to a RFA for Claude D. Pepper Older Americans Independence Centers (OAICs) that was open to applications from schools of nursing along with other institutions. Unfortunately, no applications were received from schools of nursing. At the current time, nursing faculty are actively involved in OAIC research, making important contributions to better our understanding of interventions to improve and maintain health and function among older persons. One of the currently funded OAICs is directed by a nurse with a faculty appointment in the school of nursing at her institution. NIA will continue to welcome applications from schools of nursing for inclusion in the Claude D. Pepper Older American Independence Centers Program.

Item

Demographic and economic research – The Committee commends the NIA for its demography and economic research. It is impressed by the importance of the findings from the Health and Retirement Study and the National Long Term Care Survey regarding the continuing decline in physical and cognitive disability. The Committee urges the NIA to expand funding for these studies and to explore the economic and social impact of the decline for families and society. The Committee also encourages the NIA to assess the role of health as a factor in premature retirement. **(Page 127)**

Action taken or to be taken

Development, collection, and analysis of longitudinal data on demographics, health, work, retirement, and savings are an NIA priority. NIA supports eleven "Demography and Economics of Aging" centers that are vital sources of information on: trends in population age structures; changes in levels of disease and disability; cost-effectiveness of interventions; decision-making about retirement, pensions and savings; relationship between health and wealth; and health disparities by gender and race. Research areas include: structural retirement analysis, pathways linking education and health, national health accounts, and the relationship between socioeconomic status and health. The Demography Centers will be recompeted this year. The competitive renewal for the National Long Term Care Survey (NLTCS) also is under review.

Item

Older Americans with mental illness – The Committee is concerned about the growing population of older Americans who suffer from mental illness. This is often an underserved population, particularly in rural areas. The Committee encourages the NIA to target funds to study and identify vulnerable older adults who are at risk for such mental illnesses as depression, anxiety, and psychoses. Because advanced practice psychiatric nurses work in a variety of settings, the Committee believes they may be in a unique position to be a critical component of research related to the assessment and treatment of older adults with these disorders. **(Page 127)**

Action taken or to be taken

NIA and NINR funded a large caregiver clinical intervention, Resources for Enhancing Alzheimer's Caregiver Health (REACH II), to assess a tailored behavioral/cognitive strategy in (a) reducing caregiver depression and burden and (b) increasing caregiver health. New data suggest that HIV+ adults may suffer from subtle cognitive and affective changes. NIA sponsored workshops on "*Mental Health Research Issues in HIV and Aging*" with NIMH and "*Neurobiology of Alcohol and Aging"* with the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to reveal gaps in our knowledge and develop research initiatives. Studies of physical exercise interventions suggest that such programs may be useful to abate depression, while loneliness and lack of social contact may respond to sociobehavioral interventions.

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Salaries and Expenses

OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$20,400,000	$20,800,000	$400,000
Other Than Full-Time Permanent (11.3)	8,800,000	9,000,000	200,000
Other Personnel Compensation (11.5)	1,040,000	1,060,000	20,000
Military Personnel (11.7)	800,000	820,000	20,000
Special Personnel Services Payments (11.8)	5,600,000	5,700,000	100,000
Total Personnel Compensation (11.9)	**36,640,000**	**37,380,000**	**740,000**
Civilian Personnel Benefits (12.1)	7,700,000	7,850,000	150,000
Military Personnel Benefits (12.2)	400,000	410,000	10,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**44,740,000**	**45,640,000**	**900,000**
Travel (21.0)	1,170,000	1,200,000	30,000
Transportation of Things (22.0)	177,000	181,000	4,000
Rental Payments to Others (23.2)	2,400,000	2,450,000	50,000
Communications, Utilities and Miscellaneous Charges (23.3)	2,600,000	2,670,000	70,000
Printing and Reproduction (24.0)	670,000	690,000	20,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	0	0	0
Other Services (25.2)	15,500,000	15,800,000	300,000
Purchases from Govt. Accounts (25.3)	11,898,000	12,523,000	625,000
Operation & Maintenance of Facilities (25.4)	12,850,000	13,290,000	440,000
Operation & Maintenance of Equipment (25.7)	1,900,000	1,960,000	60,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**42,148,000**	**43,573,000**	**1,425,000**
Supplies and Materials (26.0)	8,700,000	8,960,000	260,000
Subtotal, Non-Pay Costs	57,865,000	59,724,000	1,859,000
Total, Administrative Costs	**102,605,000**	**105,364,000**	**2,759,000**

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging
Detail of Positions

GRADE	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
ES-6	0	0	0
ES-5	0	0	0
ES-4	5	5	5
ES-3	1	1	1
ES-2	1	1	1
ES-1	0	0	0
Subtotal	7	7	7
Total - ES Salary	$960,782	$980,193	$994,896
GM/GS-15	26	26	26
GM/GS-14	25	25	25
GM/GS-13	35	34	33
GS-12	58	57	56
GS-11	57	55	53
GS-10	0	0	0
GS-9	30	29	28
GS-8	22	22	22
GS-7	30	29	28
GS-6	23	22	21
GS-5	10	10	10
GS-4	4	4	4
GS-3	2	2	2
GS-2	1	1	1
GS-1	0	0	0
Subtotal	323	316	309
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	8	8	8
Senior Grade	0	0	0
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	9	9	9
Ungraded	99	99	99
Total permanent positions	334	323	316
Total positions, end of year	438	431	424
Total full-time equivalent (FTE) employment,end of year	412	414	407
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$137,255	$140,028	$142,128
Average GM/GS grade	10.5	10.5	10.5
Average GM/GS salary	$61,367	$62,794	$63,736

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging
Amounts Available for Obligation 1/

Source of Funding	FY 2002 Actual	FY 2003 Amended President's Budget	FY 2004 Estimate
Appropriation	$893,443,000	$958,155,000	$994,411,000
Enacted Rescissions	(1,176,000)	(0)	---
Subtotal, Adjusted Appropriation	892,267,000	958,155,000	994,411,000
Real transfer to:			
Other HHS Agencies through Secretary's one-percent transfer authority	(965,000)	(0)	(0)
Comparative transfer from:			
Fogarty International Center for International Services Branch	53,000	53,000	0
Comparative transfer to:			
Office of the Director for program changes	(539,000)	(582,000)	(0)
National Institute of Biomedical Imaging and Bioengineering	(0)	(0)	(0)
Subtotal	890,816,000	957,626,000	994,411,000
Subtotal, adjusted budget authority	890,816,000	957,626,000	994,411,000
Unobligated balance lapsing	(20,000)	---	---
Total obligations	890,796,000	957,626,000	994,411,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2002 - $1,674,000 FY 2003 - $2,000,000 FY 2004 - $2,000,000.

Excludes $177,282 in FY 2002 and $979,430 in FY 2003 for royalties.

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
Office of the Director	33	30	30
Intramural Research Program	260	265	261
Office of Administrative Management	29	32	30
Office of Extramural Affairs	31	30	30
Biology of Aging Program	13	13	13
Geriatrics & Clinical Gerontology Program	13	12	12
Behavioral & Social Research Program	15	14	14
Neuroscience & Neuropsychology of Aging Program	18	18	17
Total, NIA	412	414	407
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2000	10.3
2001	10.5
2002	10.5
2003	10.5
2004	10.5

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Mechanism - NonAIDS

MECHANISM	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	908	$422,710,000	976	$464,859,000	960	$472,617,000
Administrative supplements	(125)	14,421,000	(110)	8,126,000	(110)	8,126,000
Full funded	0	$0	0	$0	13	$2,000,000
Single year	395	$133,699,000	415	$145,094,000	446	$159,462,000
Renewal	76	$46,142,000	88	$52,038,000	95	$57,638,000
New	310	$85,337,000	327	$93,056,000	351	$101,824,000
Supplements	9	$2,220,000	0	$0	0	$0
Subtotal, competing	395	133,699,000	415	145,094,000	459	161,462,000
Subtotal, RPGs	1,303	570,830,000	1,391	618,079,000	1,419	642,205,000
SBIR/STTR	65	20,220,000	68	21,492,000	74	23,606,000
Subtotal, RPGs	1,368	591,050,000	1,459	639,571,000	1,493	665,811,000
Research Centers						
Specialized/comprehensive	64	77,563,000	67	82,956,000	67	86,025,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	736,000	0	0	0	0
Comparative medicine	0	538,000	0	0	0	0
Research Centers in Minority Institution	0	0	0	0	0	0
Subtotal, Centers	64	78,837,000	67	82,956,000	67	86,025,000
Other Research						
Research careers	173	20,730,000	180	22,384,000	180	23,212,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	5	2,208,000	5	2,296,000	5	2,431,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	1,240,000	0	1,290,000	0	1,338,000
Other	32	6,590,000	27	5,427,000	27	5,578,000
Subtotal, Other Research	210	30,768,000	212	31,397,000	212	32,559,000
Total Research Grants	1,642	700,655,000	1,738	753,924,000	1,772	784,395,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	59	2,400,000	59	2,489,000	59	2,581,000
Institutional awards	512	18,684,000	512	19,375,000	512	20,092,000
Total, Training	571	21,084,000	571	21,864,000	571	22,673,000
Research & development contracts	72	48,401,000	101	52,696,000	101	54,646,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	257	85,911,000	262	91,961,000	258	94,745,000
Research management and support	152	29,780,000	149	31,861,000	146	32,433,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NIA	409	885,831,000	411	952,306,000	404	988,892,000
(Clinical Trials)		(62,299,000)		(67,000,000)		(69,500,000)

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Budget Authority by Object

	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	414	407	(7)
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$140,028	$142,128	$2,100
Average GM/GS grade	10.5	10.5	0.0
Average GM/GS salary	$62,794	$63,736	$942
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$85,106	$86,382	$1,276
Average salary of ungraded positions	93,590	94,994	1,404
OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$20,400,000	$20,800,000	$400,000
11.3 Other than Full-Time Permanent	8,800,000	9,000,000	200,000
11.5 Other Personnel Compensation	1,040,000	1,060,000	20,000
11.7 Military Personnel	800,000	820,000	20,000
11.8 Special Personnel Services Payments	5,600,000	5,700,000	100,000
Total, Personnel Compensation	36,640,000	37,380,000	740,000
12.1 Civilian Personnel Benefits	7,700,000	7,850,000	150,000
12.2 Military Personnel Benefits	400,000	410,000	10,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**44,740,000**	**45,640,000**	**900,000**
21.0 Travel & Transportation of Persons	1,170,000	1,200,000	30,000
22.0 Transportation of Things	177,000	181,000	4,000
23.1 Rental Payments to GSA	6,000	6,000	0
23.2 Rental Payments to Others	2,400,000	2,450,000	50,000
23.3 Communications, Utilities & Miscellaneous Charges	2,600,000	2,670,000	70,000
24.0 Printing & Reproduction	670,000	690,000	20,000
25.1 Consulting Services	1,450,000	1,500,000	50,000
25.2 Other Services	15,500,000	15,800,000	300,000
25.3 Purchase of Goods & Services from Government Accounts	48,971,000	50,700,000	1,729,000
25.4 Operation & Maintenance of Facilities	12,850,000	13,290,000	440,000
25.5 Research & Development Contracts	29,400,000	30,500,000	1,100,000
25.6 Medical Care	420,000	430,000	10,000
25.7 Operation & Maintenance of Equipment	1,900,000	1,960,000	60,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**110,491,000**	**114,180,000**	**3,689,000**
26.0 Supplies & Materials	8,700,000	8,960,000	260,000
31.0 Equipment	6,500,000	6,800,000	300,000
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	780,171,000	811,633,000	31,462,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	1,000	1,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**912,886,000**	**948,771,000**	**35,885,000**
Total Budget Authority by Object	**957,626,000**	**994,411,000**	**36,785,000**

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Aging		$774,194		$832,867		$866,279		$33,412
Subtotal, Extramural research		774,194		832,867		866,279		33,412
Intramural research	260	86,842	265	92,898	261	95,699	(4)	2,801
Res. management & support	152	29,780	149	31,861	146	32,433	(3)	572
Total	412	890,816	414	957,626	407	994,411	(7)	36,785

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2003 Amount Authorized	2003 Amended President's Budget	2004 Amount Authorized	2004 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$935,762,000	Indefinite	$971,738,000
National Institute on Aging	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	21,864,000	b/	22,673,000
Total, Budget Authority				957,626,000		994,411,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1995 2/	$433,701,000	$431,198,000	$433,198,000	$432,698,000 3/
Rescission				(332,000)
1996	455,823,000 2/	453,917,000	439,778,000 2/	453,917,000
Rescission				(346,000)
1997	461,541,000 2/	484,375,000	470,256,000 2/	484,806,000 4/
1998	495,202,000 2/	509,811,000	520,705,000	519,279,000
1999	554,391,000 2/5/	565,574,000	596,521,000	596,521,000
Rescission				(395,000)
2000	612,599,000 2/	651,665,000	680,332,000	690,156,000
Rescission				(3,667,000)
2001	721,651,000 2/	790,299,000	794,625,000	786,039,000
Rescission				(285,000)
2002	879,961,000	873,186,000	909,174,000	893,443,000
Rescission				(313,000)
2003	958,155,000			
2004	994,411,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

3/ Excludes enacted administrative reductions of $233,000, $2,000, and $140,000.

4/ Excludes enacted administrative reductions of $241,000.

5/ Reflects a decrease of $1,679,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Summary of Changes

2003 Amended President's Budget				$957,626,000
2004 Estimated Budget Authority				994,411,000
Net change				36,785,000
	2003 Amended President's Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$30,043,000		$421,000
b. Annualization of January 2003 pay increase		30,043,000		234,000
c. January 2004 pay increase		30,043,000		462,000
d. One extra day of pay		30,043,000		115,000
e. Payment for centrally furnished services		10,863,000		218,000
f. Increased cost of laboratory supplies, materials, and other expenses		51,992,000		774,000
Subtotal				2,224,000
2. Research Management and Support:				
a. Within grade increase		14,697,000		254,000
b. Annualization of January 2003 pay increase		14,697,000		114,000
c. January 2004 pay increase		14,697,000		227,000
d. One extra day of pay		14,697,000		56,000
e. Payment for centrally furnished services		3,589,000		72,000
f. Increased cost of laboratory supplies, materials, and other expenses		13,575,000		199,000
Subtotal				922,000
Subtotal, Built-in				3,146,000