DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

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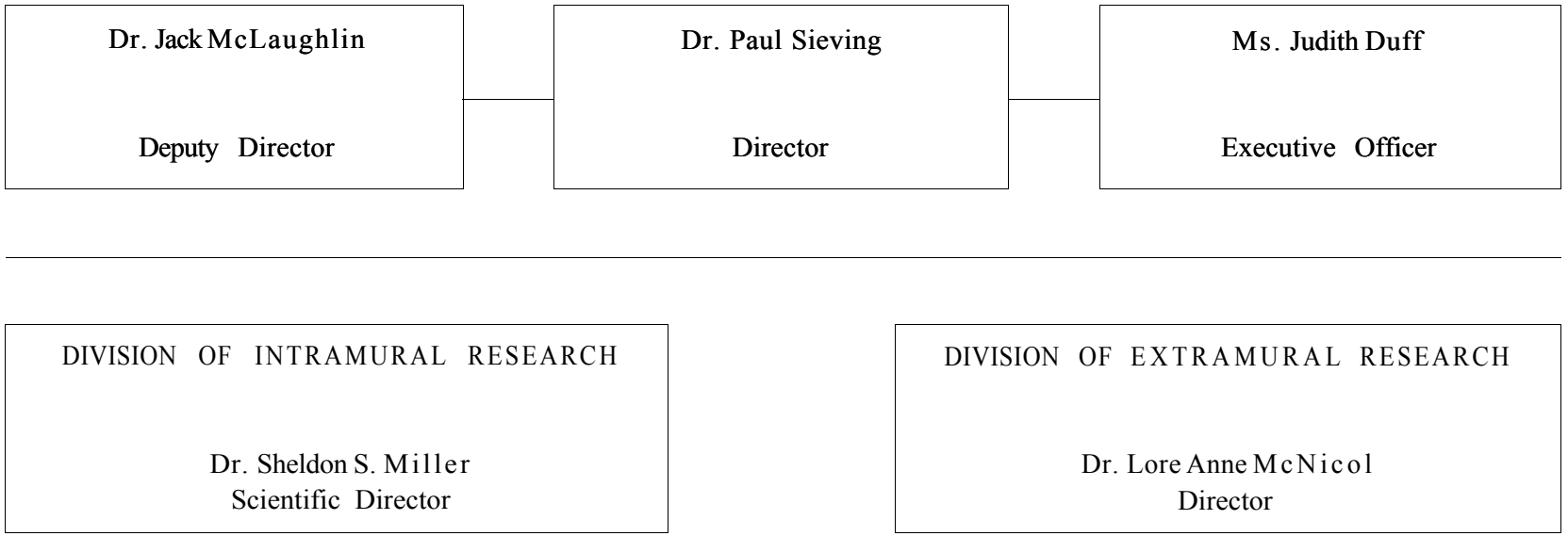
Organization Structure



NATIONAL EYE INSTITUTE

For carrying out section 301 and title IV of the Public Health Service Act with respect to eye diseases and visual disorders, [$674,578,000] *$673,491,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act for Fiscal Year 2005]

Amounts Available for Obligation *If*

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$657,199,000	$674,578,000	$673,491,000
Enacted Rescissions	(4,147,000)	(5,508,000)	0
Subtotal, Adjusted Appropriation	653,052,000	669,070,000	673,491,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(2,090,000)	0	0
Comparative transfer to NIBIB for Radiology Program	(42,000)	0	0
Comparative transfer to Buildings and Facilities	(272,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	2,090,000	0	0
Subtotal, adjusted budget authority	652,738,000	669,070,000	673,491,000
Unobligated Balance, start of year	0	0	0
Revenue from Breast Cancer Stamp *21*	0		
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	652,738,000	669,070,000	673,491,000
Unobligated balance lapsing	(1,000)	0	0
Total obligations	652,737,000	669,070,000	673,491,000

J/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004-$11,871,000 FY 2005 - 13,438,000 FY 2006 - $14,000,000
Excludes $1,216,000 in FY 2004 for royalties.

Justification

National Eye Institute

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended.

Budget Authority:

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
223	$652,738,000	223	$669,070,000	224	$673,491,000	1	$4,421,000

This document provides justification for the FY 2006 activities of the National Eye Institute, including HIV/AIDS activities. A detailed description of the NIH-wide FY 2006 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

Congress created the National Eye Institute (NEI) with the mission to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of individuals who are visually impaired. Inherent in this mission is clinical research across the spectrum of diseases of the eye and disorders of vision, as well as the investigation of the normal tissue and normal visual processes that will help gain a more complete understanding of the abnormal processes that lead to these conditions. These investigations are conducted in hundreds of extramural laboratories and clinics throughout the United States and in the NEI's own intramural facilities in Bethesda, Maryland. The highlights that follow are examples of the research progress that has been made with the investment of Federal funds in NEI-supported research and the direction that research will take over the next year.

Story of Discovery

Using Brain Signals to Drive Prosthetic Devices. Scientists at the California Institute of Technology have taken an important step in the development of a strategy to use the higher-level neural activity of the brain to drive a prosthetic device. Such a strategy would allow paralyzed individuals to use their thoughts to move a device when they can not move their limbs. This project is funded by the National Eye Institute as a Bioengineering Research Partnership grant and has benefited significantly from the participation of engineers both at California Institute of Technology and The Jet Propulsion Laboratory.

For decades, neuroscientists have been working to develop prosthetic devices that are driven by brain signals. Most of this work has been focused on brain activity related to hand trajectory signals recorded from the area of the brain known as the motor cortex, which governs movement. However, because so many movement-related areas of the cortex converge into this one pathway, a prosthetic device based on motor cortical signals might only be' able to perform one task at a time. Moreover, this approach will not work if motor cortical pathways are damaged by disease or injury.

A new, innovative approach by Richard Andersen, Sam Musallam and their colleagues at California Institute of Technology relies on brain signals that initiate movement based on sensory input. Using this method with trained monkeys, the investigators decoded brain signals related to reaching movements to position a cursor on a computer screen.

This breakthrough was first conceived in the mid 1990s when Andersen and colleagues discovered a visual area of the brain called the parietal reach region (PRR) in the parietal cortex of monkeys. The PRR was found to be involved in planning motor movements based on preferences and goals. For example, if given the choice of reaching for an apple or an orange, the PRR would influence the movement based on the monkey's taste preference for fruit. The abstract, high-level nature of the PRR precedes the lower-level brain activity related to motor cortical control of hand trajectories. In 2003, Andersen and collaborators from the University of Western Ontario discovered the PRR in humans.

The discovery of the PRR and its cognitive function led Dr. Andersen to consider creating a neural interface that could decode signals from PRR brain waves, allowing people with paralysis to manipulate prosthetic limbs or robotic devices with their thoughts. Andersen and Musallam created a specially designed, implantable multi-electrode device that connects a brain signal decoder to a computer cursor. The Cal Tech researchers implanted the device in the brains of monkeys and then trained the monkeys to position the cursor on a computer screen at a particular location without actually performing the physical movement.

The researchers created reward motivation experiments where the monkeys were given juice when they engaged PRR brain waves in anticipation of moving a cursor to a specific location on a computer screen. PRR neurons are able to hold a memory of reward and so through repeated cursor movement experiments, the monkeys' PRR learned what movement led to reward. The researchers next manipulated the type, amount and frequency of the juice reward given to the monkeys in a repeated pattern. PRR cell activity was more active before the expected delivery of a preferred juice reward, allowing the researchers to obtain a value signal based on the monkey's reward level. The PRR readings from the neural prosthesis allowed the Cal Tech researchers to decode the value signal to then move the computer cursor based solely on the signals of the PRR.

Until now no one has succeeded in tapping the messages of higher-order neurons involved in planning and motivation for potential use in prosthetics. Although much work exists, this exciting breakthrough offers proof of concept in decoding higher level brain signals to manipulate physical objects. Such an approach might make it possible to operate a number of devices such as robot limbs, wheelchairs, computers and even cars. Additionally, a wide range of higher order brain signals could be interpreted through a prosthetic device to give voice to patients who cannot speak by allowing them to merely think about what they would like to say.

Science Advances and Future Research Directions

Retinal Diseases

The retina is the complex, light-sensitive, neural tissue in the back ofthe eye that contains highly-specialized and metabolically active photoreceptor cells (rods and cones). These cells respond to light by emitting chemical and electrical signals. The signals are received by other retinal cells that process and transmit visual information via the optic nerve to the brain for further processing. The choroid is the underlying layer ofblood vessels that nourish the retina. The retina and choroid are susceptible to a variety ofdiseases that can lead to visual loss or complete blindness. These sight-threatening conditions include age-related macular degeneration, diabetic retinopathy, retinopathy ofprematurity, retinitis pigmentosa, Usher's syndrome, ocular albinism, retinal detachment, uveitis (inflammation), and cancer (choroidal melanoma and retinoblastoma).

Adult bone marrow stem cells in retinitis pigmentosa. A recent NEI-supported study found that eye injections ofbone marrow derived stem cells prevented vision loss in two rodent models of retinitis pigmentosa (RP). RP is the name given to a family ofdiseases that result from harmful mutations in rod photoreceptor cell genes. Rod photoreceptors are the light sensitive cells in the retina that provide peripheral and night vision. RP causes the loss ofthese cells and results in night blindness and loss ofperipheral vision. For reasons that are not entirely understood, the sick and dying rod cells also cause cone photoreceptor cells to die. Cone cells are concentrated in the macula, the center ofthe retina, and provide the sharp visual acuity that allows us to read, recognize faces, and perform detailed tasks that require hand-eye coordination. As the disease progresses patients lose their central vision, resulting in severe visual impairment or total blindness. This study raises the possibility that patients could receive an injection oftheir own bone marrow stem cells to preserve central vision.

The role of inflammation in macular degeneration. Age-related macular degeneration (A M D) is a leading cause ofblindness and visual disability in older age Americans. The inability to prevent the development of A M D and its complications is largely due to a lack ofunderstanding ofthe underlying pathologic mechanisms ofthe disease. Genetic and environmental factors have previously been found to play a role in the disease. Recent NEI-supported studies have found evidence that inflammation may also play a role in the disease. In one study, researchers developed two rodent models ofthe disease that are deficient in either a molecule or a cell receptor involved in recruiting macrophages to inflammatory sites. Macrophages are a part of the immune system that help clear foreign substances from tissue. As these animal models age, they develop pathologic features similar to human A M D . Although further work is needed to determine whether defective macrophage trafficking plays a role in human A M D , these animal models offer new insights into possible mechanisms ofthe disease. The availability ofanimal models ofthe disease w i l l also allow for the testing ofnew intervention strategies. In a second study, NEI-supported researchers found that elevated levels ofa protein associated with inflammation is an independent risk factor for A M D . This study adds further credence to the role ofinflammation in the pathogenesis of A M D and suggests additional avenues for therapeutic intervention.

A Rapid Defense Systemfor the Retina. The body defends itself against bacteria and viruses in part by initiating an innate immune response that activates within minutes after the invasion of an attacking microorganism. Recent studies identified that in the innate immune response, the body recognizes foreign invaders through toll-like receptors (TLRs) that are present on the surface of selected cells within the body. When TLRs are engaged, genes important for an effective host defense, such as those that cause inflammation, are activated. To investigate the role of TLRs in cells ofthe visual system, NEI intramural scientists analyzed TLR expression in human retinal pigment epithelial (RPE) cells. The RPE cell layer provides a barrier between the body's blood supply and the neural retina and is thought to be a basic component of ocular immunity. Previous studies have found that RPE cells are a target of several infectious agents that can lead to vision loss. One particular TLR that defends against viral infection, TLR-3, was found to be highly expressed in these cells. Stimulation of TLR-3 receptors in RPE cells initiated an immune response that included the secretion of interferon beta, a molecule highly effective in inhibiting virus replication. This discovery identifies the central role of the TLR system and the immediate protection mechanisms of the innate immune response within the retina. Learning how the body quickly turns on genes and produces molecules that can protect the retina from invading organisms is crucial to designing augmented responses to viral infections of the retina.

Gene discovery provides new insights into age-related macular degeneration. Late onset diseases like AMD are thought to result in part from sequence variations in genes that confer subtle changes in the proteins they encode. One method of elucidating the genetics underlying the disease is to study genes that cause classically inherited, early onset forms of macular degeneration. These early onset forms share many clinical characteristics of AMD. In a previous NEI-supported study, researchers discovered mutations in the fibulin 3 gene, which cause malattia leventinese, an inherited form of macular degeneration. Like AMD, this disease is characterized by yellowish deposits (known as drusen) under the retina. Drusen deposits are the first clinical manifestations of AMD. Despite the similarity of these diseases, the fibulin 3 gene has not been implicated in AMD. However, fibulin 3 is part of a recently discovered family of genes that are very similar in structure and function. And so, NEI-supported researchers looked at members of the fibulin gene family in patients with AMD to determine whether these genes might play a role in the disease. Of 402 patients, 7 had sequence variations in the fibulin 5 gene that were not present in age-matched controls who did not have the disease. Fibulin 5 encodes an extracellular protein that helps form elastic fibers in skin and blood vessels. These fibers are found in Bruch's membrane, which adjoins the RPE. Although fibulin 5 accounts for a small fraction of AMD, this study is one ofthe first to find genetic sequence variations associated with AMD. Additionally, the study findings suggest that an examination of other genes preferentially expressed in the development and maintenance ofBruch's membrane is warranted.

The effects of zinc supplementation and eye disease on mortality. An analysis by NEI intramural researchers of data collected from the Age-Related Eye Diseases Study (ARED S) established that age-related macular degeneration (AMD) is associated with increased mortality and that zinc supplementation was associated with decreased mortality. ARED S was an NEI-sponsored clinical trial of older-age Americans that found antioxidant supplementation slowed the progression of AMD but not cataracts. Whether physiologic aging explains the associations between ocular disease and mortality or whether there are factors associated with the

development of ocular diseases that are also related to mortality, such as cardiovascular disease, cannot be determined from this study. However, it is possible that factors associated with AMD and cataract development, such as smoking, diet and body mass index, could be responsible for the increased risk of both the ocular diseases and mortality. Based on these and other findings, the NET study authors recommend that a diagnosis of either cataract or AMD might be one more reason to modify life style habits to promote good health. Additionally, the preliminary association between zinc supplementation and decreased mortality in older Americans provides an important direction for future research.

Retinal phenotypes in age-related macular degeneration. One of the performance targets of the NEI Government and Performance Results Act (GPRA) goal of identifying the genes that control the risk for developing age related macular degeneration (AMD) and glaucoma, was to reach consensus on classification standards that can be used to describe the diverse retinal characteristics, or phenotypes, found in macular degeneration. To achieve this, the NEI hosted an *Age-related Macular Degeneration Phenotype Consensus Meeting* on October 29, 2003. The meeting assembled investigators with the largest retinal phenotype collections in the U.S. and abroad. Participants reviewed currently known AMD phenotypes. In most cases, these existing phenotypes are already well classified and described. Much of the current focus is directed toward identifying new AMD phenotypes. Devising and maintaining classification standards is essential to recognize new AMD phenotypes. The identification of new AMD phenotypes will improve diagnostic accuracy, refine treatment protocols, define useful outcome measures for clinical trials, and help direct epidemiology and genetic studies to identify factors that influence various phenotypes.

Immunomodulation in uveitis. Uveitis is an autoimmune disease characterized by inflammation of tissue in the eye. Immunosuppressive agents are used to treat the condition; however, chronic administration of these therapies has many serious and life threatening complications. NEI intramural scientists are working to develop a novel therapy based on reprogramming the immune system, an approach called immunomodulation. Bacterial toxins can alter immune responses when included in small, nontoxic, doses in an immunization protocol. Using a small dose of cholera toxin, the NEI scientists were able to protect a rodent model of uveitis from developing this blinding disease. This study offers proof of concept that immunomodulatory treatments can be a valuable therapy for uveitis.

Targeting the chemokine receptor CXCR3 in Uveitis. NEI researchers have been studying the underlying molecular cause of inflammation in uveitis to develop more effective treatments for the disease. A major component of all inflammatory responses is the migration of immune cells into the affected tissue, a process that is mediated and controlled by a family of signaling molecules called chemokines. These molecules activate the immune system by attaching themselves to immune cell receptors on the cells' surface and then signaling other immune cells to invade the target tissue. The immune cells that migrate first into inflammatory sites are called T-helper cells. The migration of these T-cells toward the target site is facilitated by the chemokine receptor designated "CXCR3". Using an experimental system in which T-cells induce ocular inflammation in mice, scientists at the NEI found a unique pattern of expression of CXCR3 receptors that facilitated this inflammatory response. Most importantly, the NEI researchers found that an antibody that blocks CXCR3 receptors strongly inhibited the development of disease in these animals. The pathogenic process of ocular inflammation in the

mouse is very similar to that in humans and, therefore, the new observations made in this study could be applied for the development of more effective and safer treatments.

Corneal Diseases

The cornea is the transparent tissue at the front of the eye that serves two specialized functions. The cornea forms a protective physical barrier that shields the eye from the external environment. It also serves as the main refractive element of the eye, directing incoming light onto the lens. Refraction depends on the cornea acquiring transparency during development and maintaining this transparency throughout adult life. Refractive errors such as nearsightedness (myopia), farsightedness (hyperopia) and astigmatism are the most common causes of correctable visual impairment. Corneal disease and injuries are some of the most painful ocular disorders.

Possible new therapeutic insight for corneal ulcers. The epithelial cells of the cornea form a surface barrier that protects the underlying tissues from the external environment. When this layer is damaged, the epithelial cells normally respond quickly to close the wound and reform the barrier. In some cases, however, this response is defective, leading to the formation of persistent and painful corneal ulcers. Development of more effective treatments for this condition has been hampered by the limited information about the cellular and biochemical events that regulate corneal wound closure. This year, scientists at the N E I discovered that an enzyme called Cdk5 plays a central role in regulating the migration of epithelial cells to close corneal wounds. Cdk5 regulates Src, an enzyme which is known to control many aspects of cell movement. They found that overexpression of Cdk5 decreased the activity of the Src enzyme and inhibited cell migration. Conversely, drugs that inhibited Cdk5, promoted the accumulation of Src along the cell membrane, increasing the rate of cell migration and wound closure. These findings suggest a new approach for treating persistent corneal ulcers and other conditions with impaired wound healing. Animal studies are in progress to determine whether inhibitors of Cdk5 can safely be used in the eye to enhance wound healing.

The prevalence of refractive errors. Blurred vision from refractive error such as nearsightedness and farsightedness can be relieved in most cases with spectacles, contact lenses, or refractive surgery. Nevertheless, the high prevalence of refractive errors and the costs of correction make these conditions a substantial public health and economic problem in many parts of the world. The prevalence of refractive error in the United States has not been evaluated since the early 1970s. A recent NEI-sponsored study published prevalence rates for refractive error by combining data from large, high-quality, population-based eye surveys. Based on these data, researchers estimate that refractive errors affect 42.2 million (35.3%) Americans 40 years or older[1].

Lens and Cataract

Cataract, an opacity of the lens of the eye, interferes with vision and is the leading cause of blindness in developing countries. In the U.S., cataract is also a major public health problem. An estimated 26.6 million Americans over age 40 have cataract or have had surgery to remove

[1] The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. Arch Ophthalmol. 122: 495-505, 2004.

the lens opacification. Currently, cataract surgery accounts for 60 percent of vision-related Medicare expenditures. However, by 2020 researchers estimate that 39.6 million Americans will be affected by cataract[2]. The enormous economic burden of cataract will only worsen as the American population ages. The major goals of this program, therefore, are to determine the causes and mechanisms of cataract formation, to search for ways to slow or prevent the progression of cataract, and to develop and evaluate new diagnostic and therapeutic techniques in cataract management.

Lens Borrows Cell Death Enzymes to Maintain Its Structure. The lens is a dense, compact structure containing two cell types: metabolically active epithelial cells and quiescent fiber cells. Throughout life, the lens carries out a process of continued growth with epithelial cells dividing and differentiating into fiber cells. As epithelial cells differentiate into fiber cells they become denuded of organelles such as the nucleus and mitochondria. Elimination of organelles is critical because they would interfere with the refractive index and lead to cataracts. It has been suspected that epithelial cells "borrow" enzymes involved in programmed cell death, or apoptosis, to mediate organelle destruction. Apoptosis is a normal biologic process that guides an orderly destruction of cells that are no longer functional or needed. In a recent study, NEI-supported scientists have shown that specific forms of caspases, a group of protein degrading enzymes critical to dismantling organelles during apoptosis, are also involved in fiber cell formation as well. This study defines a critical step in how fiber cells are formed and will spark further investigation into whether alterations in caspase enzymes play a role in cataract formation.

Protein Integrity May Be Key to Lens Transparency. Age-related cataract formation is believed to result from the complex effects of aging on normal physiological processes. It has long been recognized that lens transparency is due in part to a very high concentration of soluble proteins, the crystallins, within a specialized lens cell, the fiber cell. That there is little turnover of proteins within these cells—an adult lens contains proteins from the earliest stages of embryonic development—makes fiber cell proteins especially susceptible to aging. During aging and cataract formation, lens crystallins tend to coalesce and aggregate, forming complexes which cause light to scatter. Counteracting this tendency is one type of crystallin, a-crystallin, whose job is to prevent the aggregation of proteins. Thus, one hypothesis of cataract formation is that a-crystallin activity decreases as a consequence of age allowing proteins to coalesce into light scattering aggregates that lead to opacification. Recently, a group of NEI scientists found that aging a-crystallm becomes modified by the addition of structures known as phosphate groups. The scientists found that the addition of phosphate groups to strategic places along the cc-crystallin protein altered its structure and increased its propensity to aggregate with other proteins. Rather than preventing lens cell proteins from aggregating, the addition of these phosphate groups becomes part of the problem. This study provides an elegant approach to understanding normal lens physiology and identifying how physiological changes as a result of aging make the lens vulnerable to cataract formation.

[2] Prevalence of cataract and pseudophakia/aphakia among adults in the United States. Arch Ophthalmol 122: 487-494, 2004.

Glaucoma and Optic Neuropathies

Glaucoma is a group of eye disorders that share a distinct type of optic nerve damage, which can lead to blindness. Elevated intraocular pressure (pressure inside the eye) is frequently, but not always, associated with glaucoma. Glaucoma is a major public health problem and the number one cause of blindness in African Americans. Approximately 2.2 million Americans have been diagnosed with glaucoma and the prevalence of the disease will rise to a projected three million by 2020[3]. Most of these cases can be attributed to primary open angle glaucoma, an age-related form of the disease. NEI activities in glaucoma research are directed toward understanding the mechanisms of the disease through basic research, identifying risk factors, and preventing blindness.

Early treatment effective for African Americans with glaucoma. The prevalence of glaucoma is three times higher in African Americans than in non-Hispanic whites. Additionally, the risk of visual impairment is much higher and the age of onset is earlier than in Whites. About 70 percent of glaucoma cases are associated with a history of elevated intraocular pressure (IOP). An NEI-supported follow-up study to the Ocular Hypertension Treatment Study (OHTS) found that early treatment of elevated IOP reduces the risk of developing glaucoma in African Americans. Of the participants in the treatment arm of the study, 8.4 percent developed glaucoma whereas 16.1 percent in the observation group developed the disease. Additionally, the OHTS follow-up study found that certain biological characteristics of the eye including corneal thickness are helpful in predicting who will likely develop glaucoma and who will benefit from therapy.

A mechanism to help explain glaucoma. Glaucoma is a complex disease involving anterior segment tissue, the retina, and the optic nerve. Elevated IOP is believed to be an important factor in the majority of cases of glaucoma. It results from an imbalance in the inflow and outflow of aqueous humor, the fluid that circulates in the anterior segment of the eye. A major breakthrough in the study of glaucoma came with the mapping and identification of a mutant gene which causes an inherited form of glaucoma. This gene encodes a protein, myocilin, found in cells of the trabecular meshwork, the tissue involved in regulating the outflow of the watery fluid between the cornea and the iris at the front of the eye. NEI-supported scientists have now shown that mutant forms of myocilin do not fold properly, resulting in abnormal shaped proteins that clump within the cell. The abnormal protein accumulates within the cell eventually causing the cell to die. As the trabecular meshwork cells die, the outflow tissue becomes dysfunctional. Importantly, the scientists also found that myocilin proteins displayed temperature sensitivity and when the temperature was lowered, they folded properly. Proper folding led to a reversal of the cellular pathology and rescue of the cells thus suggesting a new therapeutic avenue involving some method of cooling treatments to the trabecular meshwork.

[3] Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol 122: 532-538,2004.

Strabismus, Amblyopia, and Visual Processing

Developmental disorders such as strabismus (misalignment of the eyes) and amblyopia (commonly known as "lazy eye") affect 2-4 percent of the United States population[4,5]. The correction of strabismus is one of the most frequently-performed ophthalmic surgical procedures. In addition to research relevant to strabismus and amblyopia, the NEI supports investigations of irregular eye movements and refractive errors. Three million Americans now have low vision, a term used to describe chronic visual conditions that are not correctable by eye glasses or contact lenses. The NEI also supports research on improving the quality of life of persons with visual impairments by helping them maximize the use of remaining vision and by devising aids to assist those without useful vision.

Dual Approach Enhances Regeneration of the Central Nervous System. A fundamental issue in neuroscience has been the inability of nerve cells to regenerate. If researchers could develop therapies that overcome this limitation, the deleterious effects of many neurologic diseases and central nervous system (CNS) injuries might be reversed or greatly improved. NEI-supported researchers provoked nerve cell regeneration by activating a nerve cell's natural growth capacity and using gene therapy to suppress the effects of growth-inhibiting factors. The researchers injured the optic nerves of rats and then caused an inflammatory reaction in the lens of the eye of the same animal. Previous work has shown that inducing inflammation actually stimulates immune cells called macrophages to release growth factors. These growth factors activate genes in retinal cells causing new nerve fibers (known as axons) to grow into the optic nerve. In an attempt to enhance this growth, the researchers added a gene therapy technique that effectively removed the inhibitory factors that block nerve fiber growth. Although vision was not restored, this combined approach stimulated nerve cell regeneration three times greater than prior attempts. Regeneration of the mature CNS would provide an opportunity to treat blindness and other neurologic diseases.

Effectiveness of vision screening tests for preschoolers evaluated. Healthy vision is an important part of a child's success in school. A great deal of classroom instruction is conveyed visually through books, computer screens and chalkboards. Children who enter school with eye diseases or visual impairments are at a distinct disadvantage when encountering visually-based instruction. Childhood visual impairment can also result in developmental delays, the need for special education programs, social services and a lifetime of irreversible visual impairment. It is estimated that 20 percent of preschool children ages 3-4 have a treatable eye condition[6]. While many states are developing guidelines for preschool screening programs, none of the commonly used vision tests have been evaluated in a research-based environment to establish their effectiveness. Results from the NEI-sponsored Vision in Preschoolers (VIP) Study found that 11 commonly used screening tests vary widely in identifying children with symptoms of common childhood eye conditions such as amblyopia, strabismus, and significant refractive error. When

[4] The evolving concept of amblyopia: a challenge to epidemiologists. Am J Epidemiol 118(2): 192-205, 1983.

[5] Baltimore Vision Screening Project. Ophthalmology 103(1): 105-109,1996.

[6] Comparison of preschool vision screening tests as administered by licensed eye care professionals in the Vision In Preschoolers Study. Ophthalmology 111(4): 637-50, 2004.

the best tests are used by highly skilled personnel in a controlled setting, approximately two-thirds of children with one or more of the targeted disorders were identified. These better tests were able to detect 90 percent of children with the most severe visual impairments. The VIP study will provide state and local agencies with data to select the most effective vision screening exams that are currently available. The VIP study will also help ensure that more children are detected and treated at an early stage when therapy is most effective.

New insights into the causes of strabismus, amblyopia, and neural development: Strabismus is a common eye disorder resulting in improper alignment of the eyes. Although strabismus has a clear tendency to run in families, the underlying genetic mechanisms involved in its pathogenesis are poorly understood. This stems, at least in part, from the complexity of the common strabismus phenotypes and their underlying genetic mechanisms. There are, however, several rare forms of strabismus that are inherited as classic genetic disorders, and are more approachable using current genetic techniques. Uncovering the genetic basis of these rare disorders has the potential to provide insight into the pathogenesis of more common forms of strabismus and to provide a foundation for the development of new interventions and treatments. This year, NEI-funded clinician scientists have identified two genes, *KIF21A* and *ROB03,* which are altered in rare, genetic forms of strabismus. In both cases, strabismus appears to result from developmental defects in neuronal axons that are involved in sending impulses to extraocular muscles. Further study will help target the exact role of these genes in neuronal development and may contribute insight into other forms of strabismus. Additionally, these genes may contribute toward our understanding of repairing motor neuron circuits.

Dopaminergic mechanism found as basis of reward-oriented eye movement. Within the brain, a neuronal network known as the basal ganglia has previously been shown to control behavior. Studies by intramural scientists at the NEI indicate that the basal ganglia also modify saccadic eye movement. Saccadic eye movements are rapid, voluntary eye movements that redirect one's line of sight, allowing the eyes to fix on an object or adjust their vision. With this new insight, researchers have been working to identify where in the visual system saccadic eye movements originate. Because of their proximity to caudate (CD) projection neurons, which are a major origin of eye movement signals in the basal ganglia, dopaminergic (DA) neurons (which release the neurotransmitter dopamine) have been proposed as a candidate neuron for the origination of reward-related input. To study how motivational signals modulate motor signals in the basal ganglia, NEI intramural scientists examined activity of DA neurons and CD projection neurons in monkeys. The NEI researchers devised a visual test, called a one-direction-rewarded task, in which a visual target is presented at random positions, but only one position is associated with a big reward. In three of four monkeys studied, DA neurons responded with excitation to a reward-indicating cue and with inhibition to a no-reward-indicating cue. These results suggest that DA neurons modulate CD neurons to initiate saccadic eye movement in a reward-related manner. It is thought that the basal ganglia is effected in some neurologic diseases, such as Parkinson's, schizophrenia and autism. Further work to elucidate the role of DA and CD neurons in health and disease could lead to important new directions in understanding neurologic illnesses.

Understanding How the Brain Makes Decisions. In the study of the neural basis of decision-making, vision scientists and sensory physiologists traditionally emphasize the effects of sensory stimuli on the outcome of the decision process. Psychologists and economists, however, have long known that one of the most important determinants of the decisions that humans and animals make is the value, or what economists might call the utility, of the options available to them. These impressions develop over time based upon our experience acting in the world and observing the consequences of those actions. How then, is such abstract knowledge about the value of alternatives represented in the brain? To study this phenomenon, NEI-funded scientists studied a visual area of the brain of monkeys called the lateral intraparietal area (LJJP). In these studies, monkeys were trained to play a simple video game in which they had to choose between a red and a green circle that appeared on a computer display. Sometimes the monkey was rewarded for making a choice with something it valued, a squirt of fruit juice, but most of the time it received no reward. The important feature of this game was that choices of the red or green circle resulted in juice rewards with different frequencies which changed unpredictably over time. Remarkably, the investigators found that individual nerve cells in the LIP retain the relative value of the two options from one round of tests to the next, suggesting that these very cells of the visual system participate in encoding the brain's representation of value. Studying how brains actually represent and act on value will provide insights on how humans make decisions. Moreover, many psychiatric disorders are characterized by a disruption in one's ability to correctly value the options that are available. This is very clear in the case of addictive behavior but is also present in more subtle ways in other disorders such as depression and schizophrenia.

Low Vision and Blindness Rehabilitation

Seeing by Touch. Visual impairment is a major public health challenge facing this country. A major approach in overcoming this disability is the development of rehabilitation strategies that rely on other senses such as the tactile nature underlying the Braille reading system. In order to maximize and guide the effective development of these approaches research is underway to determine the extent that other senses can be used to compensate for limited vision. NEI-supported investigators are studying how well visual areas (occipital cortex) of the brain can be utilized by other sensory inputs, like touch, as a means for sensory substitution. The researchers found that the occipital cortex is involved in tactile information processing involving spatial relationships. Furthermore, the ability of the visual cortex to aide in discriminating spatial relationships is not lost in congenitally blind subjects. Such information may be of use in developing rehabilitation technologies for the blind that channel the remaining abilities of the occipital cortex through other senses.

Health Disparities

NEI Study Finds High Prevalence of Eye Disease Among Latinos. Census 2000 data indicate that 12.5 percent of residents in the United States, or 35 million people, are Latino. Based on these data, it is estimated that by the year 2025, 61.4 million Latinos will live in this country, making this the fastest growing minority population. However, there is little available data to ascertain the prevalence and severity of major eye diseases in this population. Results from the NEI-sponsored *Los Angeles Latino Eye Study* (LALES) suggest that Latinos have some of the highest rates of visual impairment and blindness in the United States. The prevalence of visual impairment and blindness in Hispanics increased with age and women were more frequently affected than men. From a socio-economic perspective, Latinos who were unemployed,

divorced or widowed, or less educated had increased rates of visual impairment and blindness. Almost a quarter of the LALES population had diabetes; a rate that is twice that of Caucasians. Half of those diagnosed with diabetes had signs of diabetic retinopathy. The prevalence of glaucoma was also high (4.3 percent) and increased dramatically with age. About 10 percent had early signs of AMD. Lastly, one in five adult Latinos had cataract. These prevalence statistics, coupled with the socio-economic data from LALES concerning the factors that negatively influence access to health care, will aide public health professionals in devising strategies to target at-risk populations for screening and treatment.

NIH Roadmap

Re-engineering the clinical research enterprise. One of the major themes for the NIH Roadmap is aimed at accelerating and strengthening the clinical research process. A major component of the NEI mission is to support the highest quality "clinical research aimed at increasing our understanding of the eye and visual system m health and disease and developing the most appropriate means of prevention, treatment, and rehabilitation." The NEI continues to foster a partnership with the vision research community in the conduct of well-designed, multicenter, clinical trials and to support the conduct of such trials as institute priorities.

Two initiatives under the Re-engineering the Clinical Research Enterprise theme are particularly important and relevant to the research priorities of the NEI. The NIH Multidisciplinary Clinical Research Workforce Training Program initiative will train a cadre of Clinical Research Associates to meet the growing needs of translational research across the country. Under the Clinical Research Networks and the National Electronics Clinical Trials and Research (NECTAR) Network initiatives, common data standards and software tools for protocol preparation, Institutional Review Board (IRB) management, and adverse event reporting are being developed. This initiative will also ease the burden of clinical trial recruitment by focusing on clinical trial investigator networks that include community-based physicians. The NEI and vision research community have anticipated these opportunities by creating networks such as the Pediatric Eye Disease Investigator Group (PEIDG), composed of 60 participating sites with over 120 pediatric ophthalmologists and optometrists from academic and private practice, and by the newly launched Diabetic Retinopathy Clinical Research Network. Continuation and expansion of these initiatives should facilitate and hasten the translation of research discoveries from the laboratory to the clinic for the benefit of those afflicted with a range of disorders and diseases.

New Initiatives

National Health and Nutrition Examination Survey (NHANES) Vision Component Expansion. The NEI collaborated with the National Center for Health Statistics to develop a vision component for NHANES in support of the vision objectives in Healthy People 2010. After collection of baseline data through 2004, the vision component of the 2005-2006 survey will be expanded to include revised questions to capture better information on severe visual impairment, as well as extending the vision-related quality of life questions to ages 20 and older (compared to those 50 and older for NHANES 1999-2004). The NEI is planning further extension of the survey to 2007-2008 to help develop stable national estimates of vision impairment, the extent of

uncorrected but correctable refractive errors, the methods selected by study participants to correct their diagnosed refractive error, and the impact of vision on quality of life activities. This survey will also allow assessment of the impact of Healthy People 2010 on the vision health of the Nation. Additionally, the Centers for Disease Control and Prevention (CDC) is requesting that a retinal component be added to the vision component for 2005-2006. CDC expects to continue the retinal component in 2007-2008, and having vision and retinal data available on the same study participants makes both components more comprehensive.

Innovations in Management and Administration

NEI Strategic Planning Activities. The NEI recently updated its *Strategic Plan for Health Disparities*. The plan has been placed on the NEI website for public review and comment at: http://www.nei.nih.gov/strategicplanning/disparities_draft.asp. Although eye diseases and conditions are neither found exclusively nor nearly exclusively in minority or health disparities populations, some eye diseases and conditions have a greater prevalence in minority populations and result in increased blindness or visual impairment compared to other populations. These include glaucoma, diabetic retinopathy, cataract, and refractive errors. For this draft plan, the areas of research priority related to health disparities that were identified in the NEFs latest strategic plan, the *National Plan for Eye and Vision Research,* were extracted. These areas were used to revise and update the NEI strategic plan for addressing health disparities. In addition, the NEFs activities as a co-lead agency for the new focus area on Vision and Hearing in the Department's Healthy People 2010 are highlighted.

The NTH Neuroscience Blueprint

Overview - The Blueprint is a framework to enhance cooperation among fifteen NTH Institutes and Centers that support research on the nervous system. Over the past decade, driven by the science, the NIH neuroscience Institutes and Centers have increasingly joined forces through initiatives and working groups focused on specific disorders. The Blueprint builds on this foundation, making collaboration a day-to-day part of how the NIH does business in neuroscience. By pooling resources and expertise, the Blueprint can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community.

FY 2005 - For fiscal year 2005, the Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives, with the participation of all Blueprint Institutes, include an inventory of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of ongoing gene expression database efforts. For example, NEI will be a participant in coordinating an expansion of the ongoing Gene Expression Nervous System Atlas, or GENSAT, project to include the eye, ear, and other parts of the nervous system. GENSAT is designed to help answer a wide range of questions about how the brain develops, works, and goes wrong, including how the visual system develops in health and disease, its basis for normal function and the genetic basis for diseases. NEI will participate in an expansion of

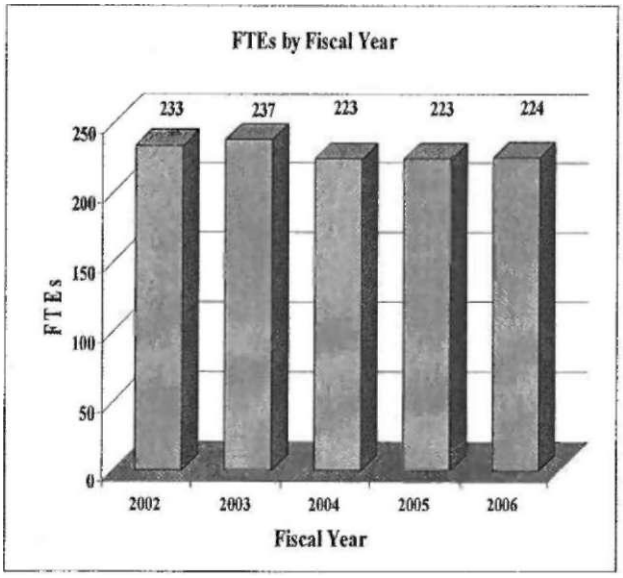
training activities emphasizing the basis for disease conditions in the visual system and coordinating efforts in trans-NIH training activities in neurodegenerative conditions ofthe nervous system.

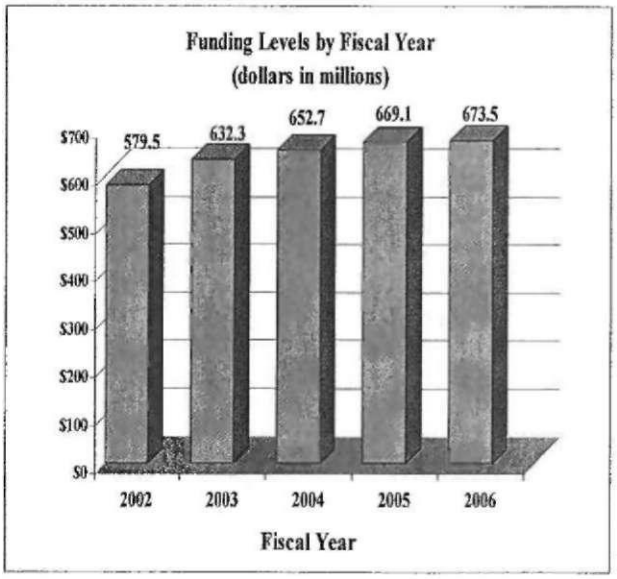
FY 2006 - Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of neuroscience research. Blueprint initiatives for FY 2006 will include systematic development of genetically engineered mouse strains of critical importance to research on nervous system and its diseases and training in critical cross cutting areas such as neuroimaging and computational biology. For example, NEI will participate with other Institutes in an initiative to provide specialized neuroscience resources. These Core Centers will provide a wide range of facilities from animal models and imaging facilities to gene sequencing and screening centers, and will provide vision researchers with access to shared facilities essential for research progress.

Budget Policy

The Fiscal Year 2006 budget request for the NEI is $673,491,000, an increase of $4,421,000 and 0.7 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NEFs support for the trans-NIH Roadmap initiatives, estimated at 0.89% ofthe FY 2006 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

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





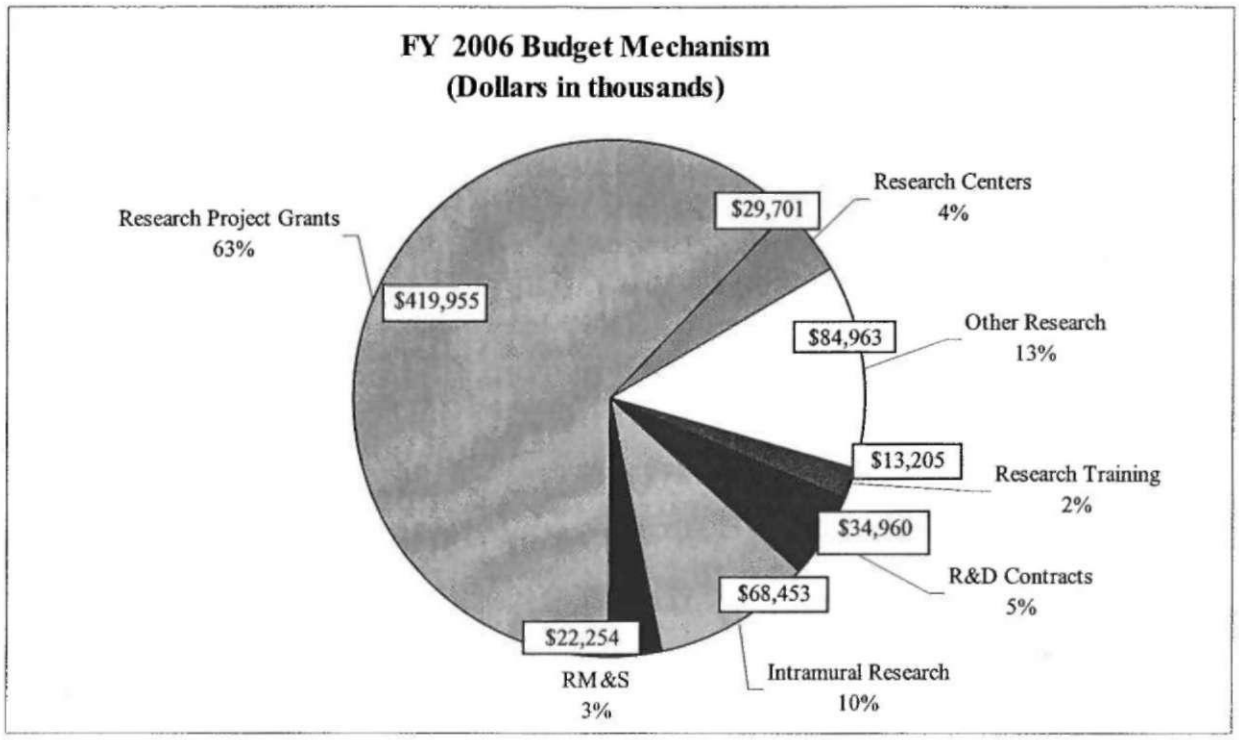
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $327,000 in FY 2006. While no inflationary increases are provided for direct, recurring costs in non-competing RPG's, where the NEI has committed to a programmatic increase in an award, such increases will be provided.

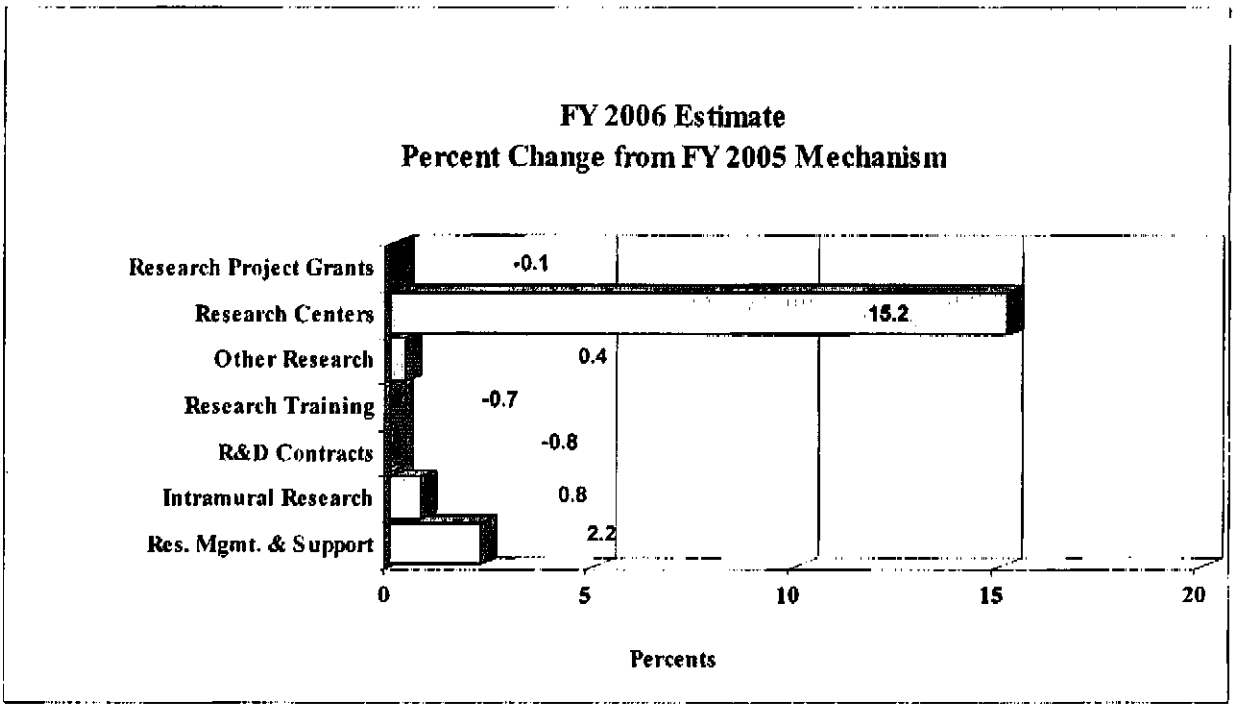
Advancement in medical research is dependent on attracting, training, and retaining the best and the brightest individuals to pursue careers in biomedical and behavioral research. In the FY 2006 request, most stipend levels for individuals supported by the Ruth L. Kirschstein National Research Service Awards are maintained at the FY 2005 levels. To help prevent the potential attrition of our next generation of highly trained post-doctoral trainees, stipend levels for post-docs with 1-2 years of experience are increased by 4.0 percent. This will bring these stipends closer to the goal NIH established for post-doc stipends in March, 2000. In addition, individual post-doctoral fellows will receive an increase of $500 in their institutional allowance for rising health benefit costs. The need for increased health benefits is particularly acute for these post-doctoral trainees, who, because of their age and stage of life are more likely to have family responsibilities. The NIH believes that it is important to properly support and adequately compensate those who are participating in these training programs, so that the programs can continue to attract and retain the trainees most likely to pursue careers in biomedical, behavioral and clinical research.

The FY 2006 request includes funding for 47 research centers, 186 other research grants, including 73 clinical career awards, and 59 R & D contracts. Intramural Research and Research Management and Support receive increases of 0.5 percent, the same as the NIH total increase.

NEI is participating in the NIH Neuroscience Blueprint. The FY 2006 request includes $4,400,000 for a variety of Neuroscience Blueprint initiatives, including neuroscience cores, training initiatives, and the Neuromouse project.

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





Budget Mechanism - Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	891	$286,522,000	909	$300,032,000	895	$305,179,000
Administrative supplements	(86)	8,085,000	(88)	8,339,000	(88)	8,285,000
Competing:						
Renewal	144	53,180,000	129	49,050,000	121	46,201,000
New	180	50,034,000	164	47,128,000	156	44,390,000
Supplements	0	0	0	0	0	0
Subtotal, competing	324	103,214,000	293	96,178,000	277	90,591,000
Subtotal, RPGs	1,215	397,821,000	1,202	404,549,000	1,172	404,055,000
SBIR/STTR	73	16,031,000	72	15,855,000	72	15,900,000
Subtotal, RPGs	1,288	413,852,000	1,274	420,404,000	1,244	419,955,000
Research Centers:						
Specialized/comprehensive	40	23,804,000	41	24,766,000	46	28,514,000
Clinical research	0	200,000	0	200,000	0	200,000
Biotechnology	0	272,000	1	426,000	1	591,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	396,000	0	396,000	0	396,000
Subtotal, Centers	40	24,672,000	42	25,788,000	47	29,701,000
Other Research:						
Research careers	59	11,055,000	71	13,114,000	73	13,380,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	92	61,748,000	95	63,983,000	95	63,983,000
Biomedical research support	0	12,000	0	16,000	0	18,000
Minority biomedical research support	0	0	0	0	0	0
Other	25	11,102,000	18	7,546,000	18	7,582,000
Subtotal, Other Research	176	83,917,000	184	84,659,000	186	84,963,000
Total Research Grants	1,504	522,441,000	1,500	530,851,000	1,477	534,619,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	74	3,355,000	74	3,439,000	74	3,439,000
Institutional awards	257	9,414,000	260	9,853,000	260	9,766,000
Total, Training	331	12,769,000	334	13,292,000	334	13,205,000
Research & development contracts	57	34,197,000	59	35,237,000	59	34,960,000
(SBIR/STTR)	(0)	(31,000)	(0)	(31,000)	(0)	(31,000)
	FTEs		FTEs		FTEs	
Intramural research	165	64,681,000	159	67,923,000	159	68,453,000
Research management and support	58	18,650,000	64	21,767,000	65	22,254,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, NEI	223	652,738,000	223	669,070,000	224	673,491,000
(RoadMap Support)		(2,243,000)		(4,230,000)		(6,023,000)
(Clinical Trials)		(58,969,000)		(60,266,000)		(60,507,000)

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual FTEs	FY 2004 Actual Amount	FY 2005 Appropriation FTEs	FY 2005 Appropriation Amount	FY 2006 Estimate FTEs	FY 2006 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Vision Research		$569,407		$579,380		$582,784		$3,404
Subtotal, Extramural research		569,407		579,380		582,784		3,404
Intramural research	165	64,681	159	67,923	159	68,453	0	530
Res. management & support	58	18,650	64	21,767	65	22,254	1	487
Total	223	652,738	223	669,070	224	673,491	1	4,421

Summary of Changes

FY 2005 Estimate				$669,070,000
FY 2006 Estimated Budget Authority				673,491,000
Net change				4,421,000
	FY 2005 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$21,454,000		$328,000
b. Annualization of January 2005 pay increase		21,454,000		198,000
c. January 2006 pay increase		21,454,000		370,000
d. One less day of pay		21,454,000		(84,000)
e. Payment for centrally furnished services		10,723,000		54,000
f. Increased cost of laboratory supplies, materials, and other expenses		35,746,000		1,084,000
Subtotal				1,950,000 .
2. Research Management and Support:				
a. Within grade increase		7,921,000		140,000
b. Annualization of January 2005 pay increase		7,921,000		73,000
c. January 2006 pay increase		7,921,000		137,000
d. One less day of pay		7,921,000		(31,000)
e. Payment for centrally furnished services		4,461,000		22,000
f. Increased cost of laboratory supplies, materials, and other expenses		9,385,000		613,000
Subtotal				954,000
Subtotal, Built-in				2,904,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Summary of Changes—continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	909	$308,371,000	(14)	$5,093,000
b. Competing	293	96,178,000	(16)	(5,587,000)
c. SBIR/STTR	72	15,855,000	0	45,000
Total	1,274	420,404,000	(30)	(449,000)
2. Research centers	42	25,788,000	5	3,913,000
3. Other research	184	84,659,000	2	304,000
4. Research training	334	13,292,000	0	(87,000)
5. Research and development contracts	59	35,237,000	0	(277,000)
Subtotal, extramural				3,404,000
	FTEs		FTEs	
6. Intramural research	159	67,923,000	0	(1,420,000)
7. Research management and support	64	21,767,000	1	(467,000)
Subtotal, program		669,070,000		1,517,000
Total changes	223		1	4,421,000

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	223	224	1
Full-time equivalent of overtime & holiday hours	0	0	0
Average ES salary	$151,000	$154,500	$3,500
Average GM/GS grade	12.5	12.5	0.0
Average GM/GS salary	$87,400	$89,400	$2,000
Average salary, grade established by act of July 1, 1944(42 U.S.C. 207)	$67,400	$68,950	$1,550
Average salary of ungraded positions	114,900	117,600	2,700

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$14,420,000	$14,979,000	$559,000
11.3 Other than Full-Time Permanent	6,373,000	6,617,000	244,000
11.5 Other Personnel Compensation	655,000	680,000	25,000
11.7 Military Personnel	65,000	67,000	2,000
11.8 Special Personnel Services Payments	2,554,000	2,651,000	97,000
Total, Personnel Compensation	24,067,000	24,994,000	927,000
12.0 Personnel Benefits	5,243,000	5,445,000	202,000
12.1 Military Personnel Benefits	65,000	67,000	2,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**29,375,000**	**30,506,000**	**1,131,000**
21.0 Travel & Transportation of Persons	815,000	814,000	(1,000)
22.0 Transportation of Things	93,000	92,000	(1,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	11,000	11,000	0
23.3 Communications, Utilities & Miscellaneous Charges	489,000	496,000	7,000
24.0 Printing & Reproduction	421,000	427,000	6,000
25.1 Consulting Services	725,000	719,000	(6,000)
25.2 Other Services	5,903,000	5,895,000	(8,000)
25.3 Purchase of Goods & Services from Government Accounts	56,398,000	56,224,000	(174,000)
25.4 Operation & Maintenance of Facilities	1,491,000	1,481,000	(10,000)
25.5 Research & Development Contracts	16,577,000	16,456,000	(121,000)
25.6 Medical Care	253,000	251,000	(2,000)
25.7 Operation & Maintenance of Equipment	3,113,000	3,094,000	(19,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**84,460,000**	**84,120,000**	**(340,000)**
26.0 Supplies & Materials	4,911,000	4,871,000	(40,000)
31.0 Equipment	4,352,000	4,330,000	(22,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	544,143,000	547,824,000	3,681,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	0	0	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**639,695,000**	**642,985,000**	**3,290,000**
Total Budget Authority by Object	**669,070,000**	**673,491,000**	**4421,000**

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$14,420,000	$14,979,000	$559,000
Other Than Full-Time Permanent (11.3)	6,373,000	6,617,000	244,000
Other Personnel Compensation (11.5)	655,000	680,000	25,000
Military Personnel (11.7)	65,000	67,000	2,000
Special Personnel Services Payments (11.8)	2,554,000	2,651,000	97,000
Total Personnel Compensation (11.9)	**24,067,000**	**24,994,000**	**927,000**
Civilian Personnel Benefits (12.1)	5,243,000	5,445,000	202,000
Military Personnel Benefits (12.2)	65,000	67,000	2,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**29,375,000**	**30,506,000**	**1,131,000**
Travel (21.0)	815,000	814,000	(1,000)
Transportation of Things (22.0)	93,000	92,000	(1,000)
Rental Payments to Others (23.2)	11,000	11,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	489,000	496,000	7,000
Printing and Reproduction (24.0)	421,000	427,000	6,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	725,000	719,000	(6,000)
Other Services (25.2)	5,903,000	5,895,000	(8,000)
Purchases from Govt. Accounts (25.3)	36,777,000	36,757,000	(20,000)
Operation & Maintenance of Facilities (25.4)	1,491,000	1,481,000	(10,000)
Operation & Maintenance of Equipment (25.7)	3,113,000	3,094,000	(19,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**48,009,000**	**47,946,000**	**(63,000)**
Supplies and Materials (26.0)	4,890,000	4,850,000	(40,000)
Subtotal, Non-Pay Costs	54,728,000	54,636,000	(92,000)
Total, Administrative Costs	**84,103,000**	**85,142,000**	**1,039,000**

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS'

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-636)

Item

Gene therapy - The Committee is aware of progress made in demonstrating the effectiveness of gene therapy to reverse and cure several retinal diseases, including diabetic retinopathy, macular degeneration, and retinopathy of prematurity. Diabetic retinopathy and macular degeneration are leading causes of blindness and visual disability in the United States, with an additional 165,000 people losing their vision each year due to these disorders. Additionally, each year more than 500 infants are blinded by retinopathy of prematurity. This gene therapy intervention has been successfully demonstrated in laboratory animals. The Committee encourages the Institute to facilitate clinical trials in primates and humans to further validate gene therapy interventions to reverse and cure retinal diseases, (p. 87)

Action taken or to be taken

NEI actively supports research on gene therapy for retinal diseases. NEI is updating and re-issuing a Program Announcement, "Collaborative Research on Therapy for Visual Disorder," soliciting applications for therapeutic research that involves a biological intervention, such as gene- or cell-based therapy or pharmacological approaches. This program makes resources available to collaborative research teams to address scientific, technical, and clinical questions beyond the capabilities of any one research group.

Item

Juvenile diabetes - The Committee is aware of the serious problem of retinopathy in individuals with juvenile diabetes and encourages NEI to continue to collaborate with other institutes on efforts to identify the genes for diabetic retinopathy, by collecting and analyzing human samples and by developing animal models of diabetic retinopathy, (p. 88)

Action taken or to be taken

NEI is collaborating with the National Institute of Diabetes and Digestive and Kidney Diseases (NLDDK) in a Request for Applications (RFA), "Surrogate Endpoints for Diabetic Microvascular Complications." This RFA solicits basic and clinical research applications to develop biochemical, cellular, physiologic or genetic surrogate endpoints that can be used to predict risk in the microvascular complications of diabetes. Diabetic retinopathy is among the most serious of these complications. NEI is continuing its collaboration with NLDDK on the Family Investigation of Neuropathy of Diabetes (FIND) study. NEI is funding the costs of eye exams for patients enrolled in FIND which is a genetic and genomic investigation of patients with diabetic kidney disease. The development and utilization of animal models of diabetic retinopathy in the development and testing of new or improved treatments is an active area of investigation.

Item *

Ocular albinism. - Ocular albinism is a hereditary, blinding disease that causes severely distorted vision in children. Victims, who are usually boys and receive the defective gene from their mother, experience nystagmus, photophobia, lack of stereoscopic vision, strabismus, and other symptoms which deny these children normal vision. In recent years, research has made great strides in the search for improved diagnostic tools and treatments. Recently, the OA1 gene, responsible for most cases of the disease, was identified, and a diagnostic screening test was created to help women determine if they are at risk of passing the disease on to their children. As researchers move closer to understanding how this disease works and developing potential treatments that could improve the vision of children with the condition, the Committee requests NEI to be prepared to report on advances in research on ocular albinism in the fiscal year 2006 hearing, (p. 88)

Action taken or to be taken

The protein product of the ocular albinism gene OA1 has been shown to be a specific kind of biological receptor called GPCR for G-protein coupled receptors. With this discovery, work focuses on identifying the specific molecule that binds to and activates this GPCR. Additionally, using genetic technology a mouse model has been produced by knocking out the OA1 gene to produce an animal model that has many of the eye characteristics of ocular albinism. When tested under laboratory conditions for vision changes, the animals showed a reduced ability to respond to light. Use of gene transfer technology to re-introduce a normal OA1 gene back into these animals resulted in partial rescue of visual function. This suggests that it may be feasible to use gene therapy to restore limited vision in younger patients with ocular albinism. NEI will be prepared to report on advances in research on ocular albinism at the FY 2006 hearings.

Item

Diabetic retinopathy - The Committee encourages NIBIB to collaborate with NEI on the development and application of scanning technologies that will be affordable and accessible to allow for early detection of diabetic retinopathy, (p. 99)

Action taken or to be taken

NEI is cooperating with the National Institute for Biomedical Imaging and Bioengineering (NIBIB) in a Request for Applications, "Non-Invasive Imaging for Diabetic Retinopathy," that seek to develop, apply, and evaluate noninvasive technology that is practical, affordable, and accessible so that patients with diabetes can benefit from remote site disease screening.

NEI continues to fund the Diabetic Retinopathy Clinical Research Network (DRCR.net). The DRCR.net is designed to support the development and implementation of a collaborative nationwide network dedicated to facilitating multicenter clinical research on diabetic retinopathy. It also supports the identification, design, and implementation of multi-center clinical research imtiatives while incorporating standardization of multiple study procedures and integration of information technology for evaluation of promising new therapies.

FY 2005 Senate Appropriations Committee Report Language (H. Rpt 108-345)

Item

Diabetic Retinopathy - The Committee commends N E I for establishing the Diabetic Retinopathy Clinical Research Network, which serves to expedite the evaluation of new approaches to address vision-related complications of diabetes. The Committee encourages N E I to continue to expand upon its efforts to detect, prevent and treat diabetic retinopathy by collaborating with NIB IB on the development and application of scanning technologies that will be highly affordable and widely accessible to allow for early detection, (p. 133)

Action taken or to be taken

Please refer to page NEI-28 of this document for N E F s response to this significant item regarding diabetic retinopathy.

Item

Gene Therapy - The Committee is aware of progress made in demonstrating the effectiveness of gene therapy to reverse and cure several retinal diseases, including diabetic retinopathy, macular degeneration, and retinopathy of prematurity, diabetic retinopathy and macular degeneration are leading causes of blindness and visual disability in the United States, with an additional 165,000 people losing their vision each year due to these disorders. Additionally, each year more than 500 infants are blinded by retinopathy of prematurity. Since gene therapy intervention has been successfully demonstrated in laboratory animals, the Committee urges the Institute to facilitate clinical trials in primates and humans to further validate gene therapy interventions to reverse and cure retinal diseases, (p. 133)

Action taken or to be taken

Please refer to page NEI-27 of this document for N E F s response to this significant item regarding gene therapy.

Item

Juvenile Diabetes - The Committee is aware of the serious problem of retinopathy in individuals with juvenile diabetes, and it encourages the N E I to continue to collaborate with other institutes on efforts to identify the genes for diabetic retinopathy by collecting and analyzing human samples and by developing animal models of diabetic retinopathy, (p. 134)

Action taken or to be taken

Please refer to page NEI-27 of this document for N E F s response to this significant item regarding juvenile diabetes.

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Eye Institute	Section 41B	42§285b	indefinite _^	> $655,778,000	Indefinite	> $660,286,000
National Research Service Awards	Section 487(d)	42§288	*af*	13,292,000		13,205,000
Total, Budget Authority				669,070,000		673,491,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1
1997	$310,072,000 *2/*	$333,131,000	$315,948,000	$332,597,000 3/
1998	330,955,000 2/	354,032,000	357,695,000	355,691,000
1999	373,198,000 *2/*	383,447,000	395,261,000	395,857,000
Rescission	0	0	0	(262,000)
2000	395,935,000 2/4/	428,594,000	445,172,000	452,706,000
Rescission				(2,406,000)
2001	462,776,000 2/	514,673,000	516,605,000	510,611,000
Rescission				(153,000)
2002	571,126,000	566,725,000	614,000,000	581,366,000
Rescission				(653,000)
2003	625,666,000	625,666,000	637,290,000	637,290,000
Rescission				(4,142,000)
2004	652,738,000	648,299,000	657,199,000	657,199,000
Rescission	0	0	0	(4,147,000)
2005	671,578,000	671,578,000	680,300,000	674,578,000
Rescission	0	0	0	(5,508,000)
2006	673,491,000			

1 Reflects enacted supplemental, rescissions, and reappropriations.

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

3/ Excludes enacted administrative reductions of $138,000.

4/ Reflects a decrease of $ 1,158,000 for the budget amendment for bioterrorism.

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	33	33	33
Division of Intramural Research	165	159	159
Division of Extramural Research	25	31	32
Total	223	223	224
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2002	11.8
2003	12.2
2004	12.4
2005	12.5
2006	12.5

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	2	2	2
Total - ES Salary	$291,200	$302,000	$309,000
GM/GS-15	36	36	37
GM/GS-14	21	21	21
GM/GS-13	27	25	25
GS-12	29	29	29
GS-11	23	23	23
GS-10	3	3	3
GS-9	8	8	8
GS-8	10	8	8
GS-7	2	2	2
GS-6	1		
GS-5	1		
GS-4			
GS-3			
GS-2			
GS-1			
Subtotal	161	155	156
Grades established by Act of July 1,1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade			
Senior Grade	1	1	1
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	1	1	1
Ungraded	70	70	70
Total permanent positions	167	161	162
Total positions, end of year	234	228	229
Total full-time equivalent (FTE) employment,end of year	223	223	224
Average ES salary	$145,600	$151,000	$154,500
Average GM/GS grade	12.4	12.5	12.5
Average GM/GS salary	$84,262	$87,400	$89,400