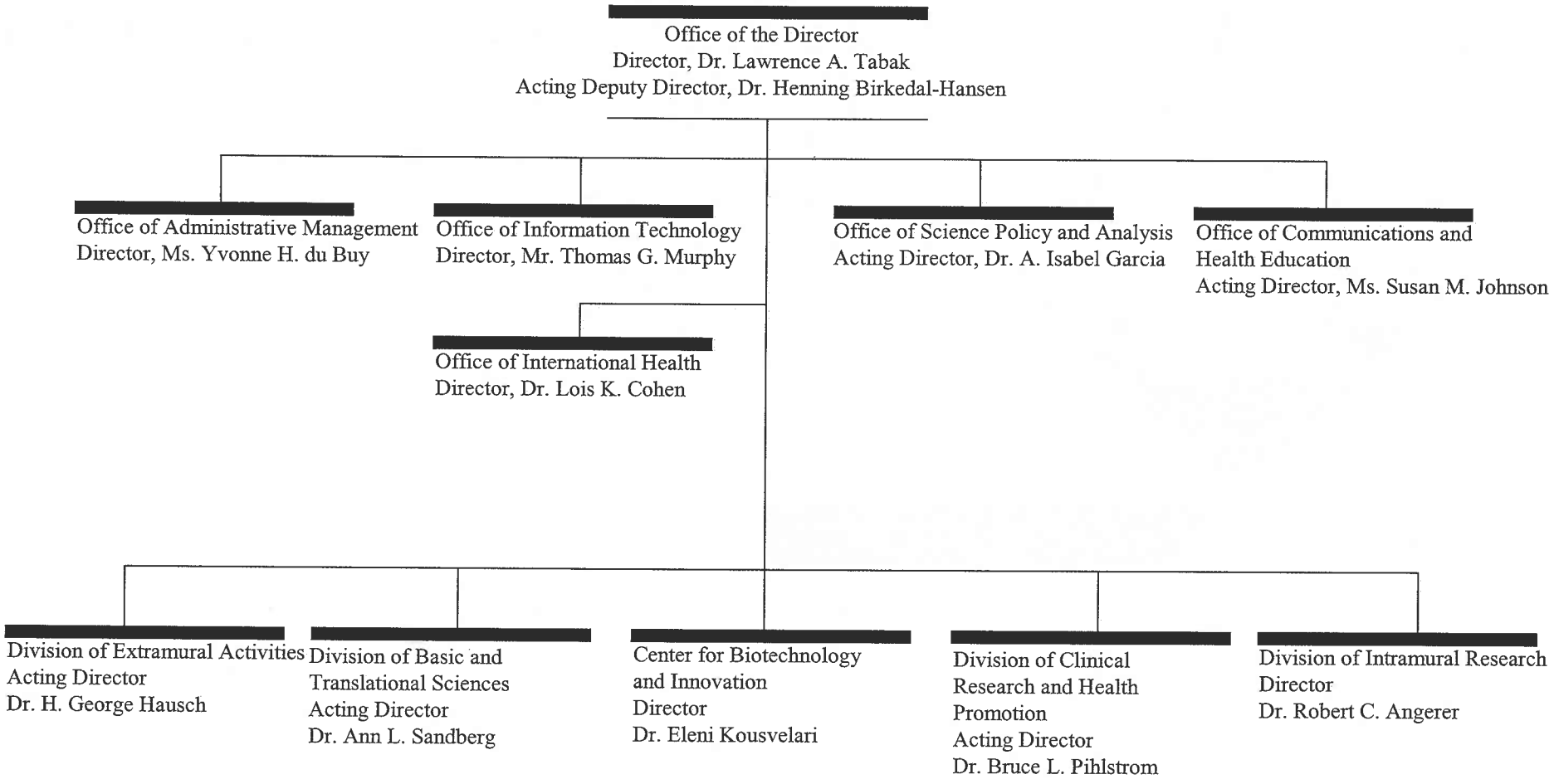
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research



NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research

For carrying out section 301 of the Public Health Service Act with respect to dental and craniofacial diseases [$395,080,000] $393,269,000.

[Department of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act, 2005].

National Institutes of Health
National Institute of Dental and Craniofacial Research

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$385,796,000	$395,080,000	$393,269,000
Enacted Rescissions	(2,514,000)	(3,251,000)	0
Subtotal, Adjusted Appropriation	383,282,000	391,829,000	393,269,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(1,261,000)	0	0
Comparative transfer to NIBIB for Radiology Program	(37,000)	0	0
Comparative transfer to Buildings and Facilities	(197,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	1,261,000	0	0
Subtotal, adjusted budget authority	383,048,000	391,829,000	393,269,000
Unobligated balance lapsing	(8,000)	0	0
Total obligations	383,040,000	391,829,000	393,269,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $1,359,000 FY 2005 - $2,000,000 FY 2006 - $2,000,000
Excludes $350,000 in FY 2005 and $350,000 in FY 2006 for royalties.

Justification

National Institute of Dental and Craniofacial Research

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

Budget Authority

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
257	$383,048,000	266	$391,829,000	266	$393,269,000	--	$1,440,000

This document provides justification for the Fiscal Year 2006 activities of the National Institute of Dental and Craniofacial Research (NIDCR), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

Never before have scientists been able to assemble such a remarkable body of data that define cellular functions in great detail as we have today. Armed with the critical mass of biological information now readily available, the next logical research step is to create teams of life and physical scientists, to sift through these data, and engineer sophisticated, molecular-based tools and treatments to advance public health.

The NIDCR is committed through a variety of new initiatives and ongoing studies to elevate oral health in America to a level previous generations might never have imagined. The NIDCR will soon begin a historic initiative to create, or, more accurately to bioengineer in the laboratory, the first fully functional replacement teeth. While this initiative is scientifically quite ambitious with no previous research model to follow as a guide, it builds on the substantial progress in recent years throughout the life and physical sciences, which suggests that the replacement of teeth is now within reach. If successful, replacement teeth would provide a new, biology-based option for millions of Americans who are missing teeth, particularly young children who do not develop one or more permanent teeth, the most common congenital malformation in humans.

The Institute's investment in the highest quality science already has begun to revolutionize the diagnosis of isolated cleft lip and palate (*i.e.*, clefts occurring in the absence of other birth defects), one of the most common birth defects in the world. This year, Institute grantees and their colleagues reported that, based on a series of DNA sequence variations in and around a certain gene, they can predict whether some parents are more likely than others to produce a second child with isolated cleft lip and palate. With this test and a similar test reported last year, it is now possible to screen for about 15 percent of isolated cleft lip and palate, a possibility that

was virtually unimaginable just a few years ago. These findings and the likelihood of many more to come, raises a host of social, legal, and ethical questions. Already, scientists and practitioners have begun to discuss how best to apply these gene tests to ensure that they truly benefit the families and their children, and more formal considerations should take place in the months and years ahead.

The NIDCR will soon launch an initiative to evaluate the ability of emerging technologies to accurately and reproducibly measure extremely subtle changes in dental enamel that signal the earliest phases of dental caries. While this initiative may sound highly technical, its outcome could play an essential role in transforming dentistry. Treatments with the potential to remineralize tooth surfaces in the very earliest stages of decay, long before a filling is needed, are emerging. In anticipation of the required clinical trials to rigorously evaluate these treatments, NIDCR has launched an initiative to ensure that microscopic changes in a tooth's mineral content can be measured accurately and reproducibly. Through the enabling research, the evaluation of these treatments will be grounded in science, ensuring the greatest possible benefit to the public.

In sum, the findings mentioned above and others highlighted in this document provide strong evidence of the tremendous value of dental research not only to enhance public health but also to bolster the nation's scientific enterprise as a whole. Unlike the body's internal organs, which are difficult to access or image, the mouth is easily accessible. It is clear that in the coming years this combination of accessibility and strong science will lead to significant contributions to our understanding of human biology and to advancing promising areas of study such as gene therapy, tissue engineering, stem cell research, and nanotechnology.

TISSUE ENGINEERING

Over the past decade, researchers have begun sowing the scientific seeds of "regenerative dentistry," a bold attempt to bioengineer teeth and other parts of the mouth that are frequently damaged by disease or injury. To date, laboratories have reported early success in producing tooth enamel, generating dentin, and even reconstructing gum tissues ravaged by disease. Also needed is the knowledge to regenerate the periodontal ligament, the fibrous, net-like hammock that holds our teeth in the jaws. Since the 1970s, scientists have suspected that the periodontal ligament might contain its own unique ligament-producing stem cells. But, for a variety of technical reasons, the search had come up empty, leaving some to wonder whether stem cells could be extracted from such a tiny bit of tissue known to contain a complex mix of cell types.

Science Advance: Human Periodontal Ligament Stem Cells Isolated for the First Time

NIDCR researchers and colleagues isolated human postnatal stem cells for the first time directly from the periodontal ligament. They later transplanted into mice distinct populations or colonies of stem cells cultured in the laboratory and loaded into a growth-promoting mineral (hydroxyapatite) carrier. Most of the colonies produced a dense mixture of cementum, which is the hard tissue of tooth root surfaces, and periodontal ligament, including fibrous structures similar to the so-called Sharpey's fibers that insert into both cementum and bone to hold teeth in place.

If additional animal studies are successful, the scientists hope to evaluate the regenerative ability of these stem cells in people with advanced periodontal (gum) disease, which in severe cases can destroy both the periodontal ligament and surrounding bone leading to tooth loss. Because these stem cells are readily accessible, in theory, people could one day "bank" them after having their wisdom teeth extracted, thus opening the door for regenerative treatment later in life for advanced periodontal disease.

New Initiative: Building a Tooth - Bridging Biology and Material Sciences

Tooth loss has been a serious public health problem in the United States since the days of George Washington and Thomas Jefferson. Despite advances in oral health over the last half century, tooth loss remains a daunting public health problem, particularly among disadvantaged groups and certain racial/ethnic minorities. While dental implants or dentures are often effective replacements, science has progressed to the point that it may be possible to generate replacement teeth from scratch, which would mark a truly historic advance in oral healthcare and in our understanding of human biology.

The NIDCR began an initiative that will catalyze the first "meeting of the minds" from the biological and materials sciences to draft science-based blueprints from which to bioengineer complete, fully functional replacement teeth. Based upon these blueprints, work will commence to build the first replacement teeth. The crucial first steps will be to: identify existing gaps in our knowledge of tooth formation; pursue viable solutions from throughout the biological and physical sciences to bridge these gaps; and, based on these comprehensive analyses, formulate blueprints from which to design a complete tooth. Relying on the best of these blueprints, interdisciplinary teams of scientists will begin the process of engineering replacement teeth. It is possible that these investigations will initially yield functional replacement parts, such as enamel, dentin or periodontal ligament, but the ultimate goal is complete tooth regeneration.

Science Advance: Stem Cells from Fat Tissue Heal Large Cranial Wounds

Surgical reconstruction of craniofacial bone malformations and injuries continues to be a necessary and thriving practice in the United States. In 2001, over 20,000 procedures were performed to repair skeletal damage of the face due to car accidents, workplace injuries, and other trauma-related causes at a total cost to the nation of $400 million[1]. While many Americans benefit greatly from these surgeries, those with large wounds to their face or skull still present significant medical challenges. One reason is that bone tends not to reform well and/or rapidly enough to repair large craniofacial wounds, leaving many people disfigured even after multiple surgeries. Recently, researchers have discovered that adult stem cells naturally present in fat tissue can be stimulated under laboratory conditions, and without tedious genetic or other growth-promoting manipulations, to generate large amounts of bone-producing cells. While these findings are encouraging, the next step is to evaluate whether these cells, known as adipose-derived adult stromal cells, or ADAS, can indeed heal large wounds in rodents, a key early test in evaluating their clinical viability for people.

[1] Steiner C, Elixhauser A, and Schnaier J, The healthcare cost and utilization project: an overview, Eff. Clin. Pract. 5, 143-151, 2002.

NIDCR grantees implanted growth-assisting synthetic scaffolds into adult mice with large (4mm) wounds in the crowns of their heads. The scaffolds were seeded with bone-producing cells derived from the ADAS cells. After 12 weeks, they found the implanted cells had contributed from 84 to 99 percent of all new bone formation, and, in some areas of the wound, had produced the complete bridging of bone with high-quality mineralized tissue. While more research is needed before this strategy will be ready for evaluation in people, this study nevertheless marks an important step forward. These studies show not only that ADAS-derived cells have the potential to heal large wounds in animals, but also emphasize that these cells have many advantages over other types of adult stem cells. ADAS cells are available in abundant quantities, they can be harvested using a minimally invasive procedure, they proliferate well in culture, and they differentiate into bone cells in a reproducible manner than requires no complicated genetic or growth-promoting manipulations.

CLEFT LIP AND PALATE

Each year, thousands of infants are born in the United States with cleft lip and/or cleft palate. Though the condition is usually correctable with multiple surgeries, families undergo tremendous emotional and economic hardship during the process, and children often require many additional services, including complex dental care and speech therapy. The isolated form accounts for about 70 percent of all cleft lip and palate cases, and is one of the most common birth defects in the world. Among Caucasians, the condition occurs in an estimated one in every 1,000 live births, and the frequency seems to be even higher in some Asian countries.[2]

Story of Discovery: From Genes to Tests for Isolated Cleft Lip and Palate

In the mid 1980s, as researchers became more adept at identifying genes involved in causing inherited diseases, several laboratories went on the hunt for the gene involved in Van der Woude Syndrome (VWS). First described in the 1860s, VWS accounts for about 2 percent of all cases of cleft lip and palate, occurring in approximately one of every 33,000 live births[3]. Children with the syndrome are born with any of four characteristic birth defects: pits, or small indentations, in the lower lip, cleft lip, cleft palate, and undeveloped tooth buds.

Shortly thereafter, NIDCR grantee Jeffrey Murray and his colleagues at the University of Iowa narrowed the search to a specific region of chromosome 1, the first step in finding the gene. But, in trying to pinpoint the precise location of the defect, the scientists eventually ran into technical difficulties that stalled their studies for several years. In 2001, the researchers caught a break when a visiting graduate student in Murray's laboratory spoke on the telephone to a colleague in her native Brazil, and the colleague happened to mention that he had just seen so-called 'monozygotic twins,' of whom one had van der Woude and the other did not. Murray and colleagues immediately became excited, hypothesizing that the twins were genetically identical with one exception: the affected twin would have a change in the VWS gene. Shinji Kondo, a post-doctoral fellow in Murray's lab, then sequenced the relevant portions of DNA from the twins, and in 2002, they discovered a syndrome-causing deletion in a gene called IRF6. According to Murray, the discovery was especially interesting because it could very possibly lead him and his colleagues to genes involved in "non-syndromic" cleft lip and palate, one of the most common birth defects in the world. As Murray noted at the time, "Since there is so much

[2] : Vanderas, AP: Incidence of cleft lip, cleft palate, and cleft lip and palate among races: a review Cleft Palate J 24 : 216 – 225, 1987.

[3] Burdick AB: Genetic epidemiology and control of genetic expression in van der Woude syndrome. J Craniofac Genet Dev Biol Suppl. 2:99-105, 1986.

clinical overlap between the two, we expect that similar genes and maybe even the same genes will be involved in the non-syndromic form."

While studying the structure of the IRF6 gene, the group noticed a sequence variation that they thought might play a role in causing isolated clefts. Such variations, called single nucleotide polymorphisms, or SNPs, occur about every 1,000 bases in our DNA and are generally considered to be harmless. What interested them about this specific SNP is that it caused an amino acid change, substituting an isoleucine for the normal valine, precisely where the IRF6 protein attaches to other substrates. They reasoned the isoleucine insertion might somehow hamstring the protein's normal biological activities during tissue and organ development. Fueling their suspicions was the fact that the normal valine is tightly conserved from fish to humans, meaning if the valine were trivial, it may have been altered in species along the evolutionary ladder with greater frequency.

To test their hypothesis, the scientists turned to their collaborators in Europe, South America, and Asia, providing a pool of 1,968 families - or about 8,000 people - in 10 countries with a history of isolated clefts. Rarely do research studies have such a broad international flavor, but, as Murray noted, the rate of isolated clefts in some parts of the world, such as the Philippines, Brazil, and China, is even higher than in the United States. "We wanted to see whether the variation could be found across multiple ethnic and ancestral groups," he said. "Or, was it confined to a single population?"

The researchers found that the isoleucine variation was indeed present at a low but measurable level in all of the populations. This allowed the group to ask the next question: Was their original hypothesis correct? To their complete surprise, the answer was no. "What we found is that the valine was over-transmitted in those with clefts," said Murray. "That was actually a puzzle and remains so a little bit because it's both the ancestral and common sequence, which is found in 97 percent of Europeans. What we strongly believe is happening is the valine serves as a marker for some other mutation nearby within the gene that's really doing the deed," he continued. "In a sense, the valine is hitchhiking with the actual mutation."

At this point, the researchers stepped back and looked more broadly at the gene and flanking regions of the chromosome. They identified a total of 36 SNPs, both within and outside the gene, and nine of these variations seemed to be associated with clefting. They assembled the individual variations into a haplotype, or a stretch of several variations spaced out like signposts along a gene or chromosome. The scientists soon discovered that this particular haplotype is over-transmitted in some families with isolated clefts, suggesting a predictive association with the birth defect, and this was true in the populations from The Philippines, Denmark, and the United States.

Based on a detailed analysis of 1,316 families, the scientists estimated that the risk of parents with this haplotype having a second child with isolated cleft lip and palate is about 12 percent. Because Murray and others found in 2003 that mutations in another gene account for about 2 percent of all cases of isolated clefts, researchers in the field now can collectively screen for about 15 percent of isolated cleft lip and palate. "These studies show that we've reached a point where it's possible to take blood samples from parents, test certain genes, and determine whether their risk for a second child with cleft lip or palate is, say, 1 or 20 percent," said Murray. "That was an impossibility just a few years ago, and it shows just how rapidly research into cleft lip and palate is progressing."

DENTAL CARIES

Despite dramatic reductions in tooth decay in the United States over the past 50 years, dental caries remains a significant public health problem, particularly among lower socioeconomic groups and certain racial/ethnic groups[4]. In recent years, experimental treatments have emerged from our nation's laboratories with the potential either to prevent the demineralization process that characterizes caries or to remineralize areas of early decay. However, the necessary clinical

[4] U. S. Department of Health and Human Services. Oral Health in America: A Report of the Surgeon General. Rockville, MD, p. 2, 2000.

trials to evaluate the safety and efficacy of these potentially revolutionary treatments in people have been slowed by a lack of scientifically validated imaging technologies to measure their therapeutic effects.

New Initiative: New Technologies for Clinical Assessment of Enamel Demineralization

The NIDCR will launch an initiative to validate the effectiveness of high-resolution, real-time clinical imaging technologies and their ability to measure accurately the demineralization and remineralization of tooth enamel. Some of the technologies that will be evaluated include: fiber optic transillumination, digital imaging fiber optic transillumination, electrical conductivity measurement, quantitative light fluorescence, alternating current impedance spectroscopy, multi-photon imaging, infrared thermography, infrared fluorescence, optical coherence tomography, ultrasound, and terahertz imaging.

If these emerging technologies can be shown to accurately measure enamel mineralization, they would greatly facilitate clinical trials of revolutionary treatments to prevent or reverse tooth decay. The initiative will stimulate much needed validation studies, including the application and refinement of new technologies for accurate and early assessment of tooth surface demineralization, the development of appropriate reference standards and validation protocols for them in caries research, and rapid implementation of proven technologies in future caries clinical trials.

ORAL BIOFILM

Biofilms are sticky, mat-like microbial communities that typically consist of hundreds of distinct organisms that cooperate with each other to adapt to changes in their environment and ensure their mutual survival. These complex microbial communities are found throughout nature and most parts of the human body, including the mouth, where they can cause tooth decay, periodontal diseases, and other oral diseases. To date, researchers have identified over 400 bacteria in the oral biofilm, but they estimate this number may represent only about half of the microbes there. This shortfall has made it extremely difficult to understand how these microbial communities function as a unit or identify the subsets of microbes that interact to cause oral infections. The NIDCR has begun supporting an innovative, three-year study to compile the first full catalogue of genes found in oral biofilms. The study, which will yield many tens of thousands of new genes – exceeding the number found in the landmark Human Genome Project - will also attempt to detect unique patterns of genes and gene expression within these bacterial communities that are predictive of periodontal diseases, a leading cause of tooth loss that affects millions of Americans[5]. Once found, these telltale patterns could lead one day to far earlier and more precise diagnosis and treatment of these diseases. All of this biological information will be stored in a searchable online database that is accessible, free of charge, to researchers worldwide. The database also will be home to an ambitious attempt to sort through the genes with sophisticated computer software and reassemble the genomes, or complete set of genes, for all of the organisms in the oral biofilms. If successful, this would mean the entire genomes of bacteria that scientists previously could not grow or study in the laboratory would now be available for

[5] Dye BA, Vargas CM: The use of a modified CPTIN approach to estimate periodontal treatment needs among adults aged 20-79 years by socio-demographic characteristics in the United States, 1988-1994. Community Dent Health 2002 Dec; 19(4):215-23.

research. The project will involve an increasingly popular technique called *metagenomics*, which has been used in recent years to study various environmental biofilms. The NIDCR investigation marks the first time that this approach has been undertaken for biomedical research on humans.

Science Advance: *Archaea* Contribute to Periodontal Diseases

Archaea are unicellular organisms that resemble bacteria but are evolutionarily distinct. Among the three recognized groups of *Archaea* are the methanogens, whose name derives from their ability to synthesize methane gas for energy in anaerobic environments (*i.e.*, environments without oxygen), including areas of the mouth such as periodontal pockets. Several studies have reported previously that methanogens are present in the mouths of people with chronic gum, or periodontal, infections. While interesting, these findings did not definitively link the methanogenic *Archaea* to the actual infections, leaving unanswered whether these organisms contribute to chronic periodontal disease, a condition that affects an estimated 35 percent of all adults in America[6]. If so, this would mark the first report in the medical literature of *Archaea* playing a role in human disease.

NIDCR grantees and colleagues detected methanogenic *Archaea* in 36 percent of people with chronic periodontitis. The scientists showed that the more abundant the methanogenic *Archaea* were within the periodontal lesions, the more severe the infections tended to be. Conversely, they found that the relative abundance of the *Archaea* decreased as the lesions improved with treatment. This report provides the first clear evidence that *Archaea* can contribute to human disease. Because *Archaea* also have been isolated from biofilms in the human gut and vagina, these findings point to an obvious need to study their possible contributions to other chronic inflammatory conditions. Although the exact role of *Archaea* in periodontal disease remains to be elucidated, the researchers hypothesized that the *Archaea* may benefit from a symbiotic microbial relationship at the site of infection, possibly growing on fermented byproducts released by other oral pathogens. If correct, in people with *Archaea*-positive periodontal disease, it may be possible to develop treatments that interfere with this symbiotic relationship and perhaps slow the infection.

Science Advance: Scientists Finish Sequence of Oral Pathogen

In the late 1600s, Antonie van Leeuwenhoek, the renowned "father of microbiology," peered through a microscope and noticed an unusual thread-like oral spirochete, a type of free-living bacterium that would later receive the name *Treponema denticola*. More than 300 years later, a team of NIDCR grantees finished assembling the complete 2.8 million bases, or units of DNA, of Van Leeuwenhoek's microbe. Although microbial genomes are now routinely sequenced, this organism could prove particularly interesting. *T. denticola* is associated with periodontal diseases, and previous studies indicate *T. denticola* aggregates in the mouth with *Porphyromonas gingivalis*, which has long been suspected as one of the main causes of periodontal diseases. Because the genome of *P. gingivalis* already has been fully sequenced, the *T. denticola* genome will allow scientists to more systematically study how these oral pathogens interact to cause

[6] Albandar JM, Brunelle JA, and Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1988-1994. J. Periodontol. 70:13-29, 1999.

disease. Such studies could provide precise molecular clues on where to target new and potentially more effective therapies to prevent periodontal diseases. *T. denticola* could serve as ideal prototype organisms to study the biology of spirochetes in general, which include human pathogens such as *Treponema pallidum*, which causes syphilis, and *Borrelia burgdorferi*, the source of Lyme disease. With the full DNA sequence of *T. denticola*, the scientific community now has an excellent point of reference to study the biology of spirochetes, allowing them to define their basic biology, as well as compare the evolutionary adaptations that allow *T. denticola* and other organisms to survive in their own unique environment.

Science Advance: Protein from Oral Pathogen Can Clear Medical Devices

Most people do not expect to get sick after being admitted to the hospital. But hospital-acquired infections from bacteria-laden catheters are fairly common, with thousands of catheter-related bloodstream infections occurring in U.S. hospitals each year[7]. One of the main culprits is *Staphylococcus epidermidis*, a bacterium that inhabits the skin and mucous areas, such as the nose and mouth. When a catheter is inserted into the body, *Staph. epidermidis* can produce a sticky slime that enables it to attach firmly to the instrument, grow into an adherent layer called a biofilm, and ultimately spread throughout the body. *Staph. epidermidis* is resistant to many antibiotics, and doctors say they have few tools to thwart this ubiquitous bacterium from invading catheters.

NIDCR grantees discovered in laboratory studies that a novel enzyme from an oral bacterium can stop *Staph. epidermidis* from attaching to hard surfaces. The researchers showed that pre-coating catheters with the enzyme, called dispersin B, prevented the formation of a *Staph. epidermidis* biofilm. This preventive activity lasted for at least a month and showed no signs of enzymatic breakdown, which would make it easy to store the precoated catheters in hospitals until they are needed. With further development, the enzyme could be applied to coat catheters or other medical devices, potentially saving the American healthcare system millions of dollars each year. It similarly could be applied to established biofilms to detach the bacterium from hard surfaces and/or consequently make it more sensitive to conventional antibiotic therapy. The researchers also are pursuing whether dispersin B adversely affects other bacterial pathogens.

PAIN RESEARCH

People often think of "pain" as a general term to describe anything that ails them. In truth, pain represents a spectrum of sensation, with different types of nerve and supportive cells interacting to communicate different aspects of the experience. Because of its vast, web-like complexity of sensory inputs and outputs, pain can be extremely difficult to target and effectively treat, especially among the estimated 34 million adults with chronic pain conditions[8]. Opioid-based analgesics, the mainstay of current treatments for moderate to severe chronic pain, cannot provide universal relief, and other treatments are nonselective and/or can cause serious side effects. These shortcomings have produced a tremendous need for novel approaches to pain management that, in combination with new and existing treatments, provide a broader range of relief from pain.

---

[7] Darouiche R, Device-associated infections: A macroproblem that starts with microadherence. Clin. Infect. Dis. 33: 1567-1572, 2001.

[8] Foley KM, Gelband H (eds): Improving Palliative Care for Cancer, Washington, D. C., National Academy Press, 2001.

New Initiative: The Role of Neuronal/Glial Cell Interactions in Orofacial Pain Disorders

Sizeable gaps exist in our understanding of some of the most basic cells involved in the pain process. Prime examples are the glial cells, of which there are three basic types: microglia, oligodendrocytes, and astrocytes. For decades, scientists assumed that glial cells primarily played a supportive role in the central nervous system and had no direct influence on the transmission of sensory signals to the brain. But, as more powerful analytical molecular tools have emerged in recent years, scientists now realize that glial cells play a far more participatory role in pain than was previously appreciated. With this new awareness, it becomes imperative to better define the biology of these cells and their roles in regulating certain aspects of nervous system function.

The NIDCR will launch an initiative that will stimulate needed research into the basic biology of glial cells and their interactions with neurons in causing orofacial pain disorders, such as temporomandibular joint disorders. The initiative will encourage multidisciplinary studies in the following areas: (1) how activated glial cells (astrocytes and microglia) influence neurons in the actual biochemical transmission of pain in experimental pain models, (2) defining the mechanisms by which activated neurons signal the spinal cord, brain, and peripheral glial cells, (3) identifying proteins and signaling pathways within glial cells that maintain chronic pain states, (4) defining the neuronal proteins and pathways that glial cells activate, and (5) discovering novel therapeutic targets on activated glial cells. Based on this broad investigative approach, key aspects of the pain process will be more clearly defined, pointing the way to unique and highly specific molecular targets for drug development.

Story of Discovery: Variation on an Ancient Theme

More than 2,000 years ago, the Roman physician, Euphorbius, was among the first to tout the medicinal qualities of a spiny, cactus-like plant called *Euphorbia resinifera*. Native to a remote region of Morocco, the plant contained a milky juice, which was dried into a resin and was widely prescribed as an irritant to counteract a range of problems from lethargy to snake bites. As the centuries passed, E. resinifera lapsed into historical obscurity, until a team of scientists in the mid 1970s identified its active, irritating compound, which they gave the tongue-twisting name of resiniferatoxin, or RTX. Among pain researchers, RTX soon became a popular laboratory tool because of its unique ability to bind to a much-studied protein called vanilloid receptor 1 (VR1), which is displayed on the surface of certain types of heat-pain-sensing neurons. RTX attaches to VR1, and, like opening a window, prompts a brief influx of calcium ions through a channel, or pore, but only in those cells that manufacture the ion channel.

In 2001, Mike Iadarola and his colleagues at NIDCR published data showing the RTX-induced flow of calcium can overdose, seriously disable, and ultimately kill these neurons. Because nerve cells in the peripheral nervous system first transmit their signals to the spine, where they then are processed and routed onward to the brain, their finding raised an intriguing therapeutic scenario: The cell bodies of these peripheral neurons bundle together in groups near the spine, called dorsal root ganglia. If RTX were applied directly to the ganglia, the scientists knew that they could selectively delete specific neurons that express large amounts of the VR1 protein on their surface. By doing this, they wondered whether they could also permanently turn off their chronic pain signals, which are involved in severe arthritis, peripheral neuromas, trigeminal neuralgia, and advanced cancer?

As reported this year, Iadarola and colleagues performed a series of experiments in rats that showed a single injection into the trigeminal ganglion, which supplies sensation to the face, or into the cerebrospinal fluid that bathes the dorsal root ganglia, which supply sensation to the body, most likely deleted permanently a type of nerve cell called C-fiber neurons. The same held true when they injected the drug into multiple ganglia that connect to the tail and hind legs. In both experiments, rats maintained their normal motor function as well as their ability to respond to other sensory stimuli, such as warm and very hot thermal stimulation and a mechanical pinch, an indication that

RTX had only affected C-fiber neurons. "This showed us that the deficit in terms of overall pain sensation was probably minimal," said NIDCR scientist Zoltan Olah, one of the inventors of the technology. "What were lost were the C-fiber neurons, which confer that sense of aching, chronic pain."

The group then applied the technique to dogs, whose owners had brought them into nearby veterinary hospitals with severe pain from arthritis and cancer. "We were very encouraged to see a long-term therapeutic benefit that did not diminish with the progression of the disease," said Iadarola. "When a cancer progresses, you often have to increase the dose of conventional pain medications, such as opiate analgesics, which can produce alterations of consciousness, activity level, and other severe side effects that can impair overall quality of life." Based on these data, Iadarola said the RTX technique has tremendous potential in veterinary care. But the group's ultimate goal is to move the treatment into early stage clinical trials in the near future for people with severe chronic pain.

SALIVARY GLANDS

For many serious health conditions, early detection offers the best hope for cure. However, many individuals obtain a diagnosis only after they experience symptoms, and then it may be too late. Saliva and other oral fluids reflect serum levels of substances that may be useful for diagnostic applications, such as drugs, hormones, immunoglobulins, and toxic molecules. Saliva is easy to collect and poses none of the risks, fears, or "invasiveness" of blood tests. Miniaturization of the "lab on a chip" may allow placement of the detection device directly in the mouth, making sample collection unnecessary. NIDCR is supporting an exciting initiative aimed at determining the efficacy of salivary diagnostics to monitor health and disease. It is envisioned that by 2013, it will be possible to fabricate inexpensive technologies for the diagnosis of systemic and oral diseases in the privacy of one's own home. If successful, this line of research could yield improved detection for a number of diseases as well as dramatically reduce the cost and risk associated with blood test-based diagnostics. Working in partnership with colleagues in industry and academia, scientists are already using microchip technology to develop salivary diagnostic tests that can be applied to a variety of conditions, including AIDS, oral infections, and potential agents of bioterror. During the next phase of this initiative, NIDCR plans to support research that will complete the fabrication of a portable, automated microfluidics-based diagnostic device, validate the device, provide feasibility analysis of large-scale manufacture and test the device in clinical settings.

For decades, most biologists have subscribed to the idea that glands in the body either secrete proteins into the bloodstream, called endocrine secretion, or channel them outward through a duct, for example, to the mouth or to the intestine, called exocrine secretion. But, according to the dogma, they cannot do both. Salivary glands are an exception to the rule. They not only secrete proteins into saliva then into the mouth in an exocrine manner, but also secrete proteins into the bloodstream in an endocrine fashion. This dual secretory feature has made the salivary glands an intriguing, though often overlooked, target for gene therapy experiments. In theory, the salivary glands could be used to treat oral and systemic conditions or even single-protein deficiency disorders, such as Type I diabetes mellitus, human growth hormone deficiency, and erythropoietin-responsive deficiencies. The great potential advantage of gene therapy is that only one gene delivery infusion is needed, instead of multiple injections, making it less expensive and potentially easier to tolerate for patients. Additionally, therapeutic genes injected into the salivary gland could provide a higher local concentration of medication than is possible with general injections into blood or muscle.

Science Advance: Gene-Expression System Produces Stable Release of Growth Hormone

Although gene therapy has shown much promise over the past decade, one of its major challenges continues to be controlling the expression of a transplanted gene once it has been delivered into a cell. As many scientists already have reported, transplanted genes may switch off prematurely, or, in some cases, they might not turn off fast enough, causing an undesirable overproduction of its replacement protein. One way around this problem is to control the expression of the transplanted gene with a system controlled by a small molecule, for example rapamycin, a well-characterized drug that is frequently taken by organ transplant patients. As scientists have envisioned the strategy, they stitch a chemical switch next to the gene that only rapamycin (or derivative) molecules can control. Upon administration of the drug, the gene will turn on leading to protein production.

A team of NIDCR scientists succeeded in getting the so-called "rapamycin gene-activation" system to work in the salivary glands. The scientists showed that the production of human growth hormone (hGH) and its secretion into the saliva of rats could be induced, or activated, with rapamycin at least three times in 16 days. They found only a small amount of hGH in the blood compared to saliva, showing the salivary gland released this protein in the same manner as the pituitary gland normally does.

Science Advance: Gene Vector Performs Well in Animal Studies

Two years ago, NIDCR scientists constructed a new version of a gene-carrying vehicle, or vector, which functioned well in the salivary glands of mice for several weeks. Most significantly, the vector - a stripped down, bioengineered version of the harmless adeno-associated virus (AAV) - had done so without triggering a sustained immune response, a common setback in gene therapy experiments. Left unanswered, however, was whether the AAV gene vector could keep up the good work for several months or a year.

NIDCR scientists found that the AAV vector performed extremely well in the salivary glands of mice for at least one year. The vector carried the gene for human erythropoietin, a hormone produced primarily in the kidneys to stimulate the production of red blood cells. After injecting the vector into the submandibular salivary glands, they began to detect a gradual increase in serum levels of the human erythropoietin over the first 12 weeks, a sign that the salivary gland was producing the hormone and pumping it into the bloodstream. Thereafter, serum levels of the human erythropoietin remained relatively stable to the 54-week mark. Importantly, they detected no signs of an adverse immune response in the salivary glands. These results clear the way scientifically to begin work in larger animals, which would allow the scientists to better scale the likely therapeutic dosage for humans for possible clinical trials.

New Initiative: Sjögren's Syndrome as a Model for Complex Diseases

Sjögren's syndrome is a systemic autoimmune disorder that involves any or all of the following symptoms: dry mouth, dry eyes, and rheumatoid arthritis. The syndrome affects perhaps as many as four million Americans and disproportionately occurs in women at a ratio of nine to one[9]. Because its cause is not well understood, highly specific and detailed diagnostic criteria

[9] Fox, RI, et al. Evolving concepts of diagnosis, pathogenesis, and therapy of Sjogren's syndrome. Curr. Opin

are lacking. In fact, people typically live with the syndrome's ill effects from six to 10 years before receiving the diagnosis. Just as significantly, no effective treatment is now available to control or reverse the underlying causes of Sjögren's syndrome. For those with oral complications, their salivary glands develop varying degrees of autoimmune damage, leading to reductions in their normal flow of saliva. This places them at greater risk for caries and mucosal infections such as candidiasis and dysphagia. They also must cope with the daily irritation of a dry mouth with its adverse effects on chewing, swallowing, and even speaking.

The NIDCR will organize an initiative to explore the complex biological and environmental interactions that trigger Sjögren's syndrome. A strong emphasis also will be placed on developing novel diagnostic, preventive, and therapeutic tools for the condition. Recent advances in genomics, proteomics, combinatorial chemistry and other areas of science now make possible comprehensive studies of complicated conditions like Sjögren's syndrome. This initiative will employ these and other emerging technologies to elucidate the multifactorial etiology of the syndrome. Among the issues addressed will be: identifying genetic risk factors in humans, developing appropriate animal models, determining the initiating events that trigger the syndrome, teasing out its immunological aspects, identifying biological markers of developing disease, and generating relevant outcome measures for clinical trials of new therapeutics that treat all manifestations of Sjögren's syndrome. Because Sjögren's syndrome is recognized as an outstanding "model" to study complex disease, the knowledge gained from this initiative could have broader application for understanding the biological and environmental interactions underlying other complex conditions.

HEAD AND NECK CANCER

Head and neck cancer is diagnosed in an estimated 38,500 Americans each year and about 11,000 will die from this disease[10]. Patients whose cancers are detected and treated early have a much better chance of survival and suffer less treatment-related damage than patients whose disease is diagnosed at a late stage. Unfortunately, many head and neck cancers are not detected early, resulting in poor prognosis and, in many cases, needless disfigurement or death.

Science Advance: Human Papillomavirus and Risk of Head and Neck Cancer

Previous research has identified a link between the presence of human papillomavirus (HPV) and the risk for developing head and neck cancer. This finding opens up the possibility of using HPV as an independent predictor of risk for this malignancy. Following up on this lead, NIDCR-supported scientists used an oral rinse to recover cells that normally are shed in the mouth. They examined the presence of oncogenic, or high-risk, HPV in the cells of head and neck cancer patients and compared them with persons of similar age and gender without the disease. They found that high-risk HPV types were detected in the oral cells from 23 percent of cancer patients compared to only 11 percent of the control subjects. In addition, the researchers showed that the HPV type detected in the oral cells was similar to the HPV type detected in the tumor tissue at the time of diagnosis. This finding suggests that detecting HPV from oral cells collected at the time of diagnosis but before treatment may be predictive of an HPV-related head

---

Rheumatol 10: 446-456, 1998.

[10] U. S. Department of Health and Human Services. NCI Fact Book. Bethesda, MD, p. C-2, 2003.

and neck cancer. Findings that HPV high-risk types can be detected from oral exfoliated cells from an oral rinse are noteworthy and might eventually lead to the development of a screening test to prevent oral cancer or to detect the disease during its earliest stages.

Science Advance: Scientists Discover Role of Protein in Tumor Cell Invasion

Scientists have recognized that bone sialoprotein (BSP) is elevated in the tumors and blood of people with breast and certain other developing cancers, a rise that sometimes can be associated with the spread of cancer cells throughout the body. What has remained unclear is exactly how BSP might play a role in this process.

NIDCR researchers and colleagues reported for the first time that BSP forms a complex with two other proteins, possibly enabling cancer cells to better degrade the tissue that surrounds them and break free from tumors. From there, the cells can distribute throughout the body and colonize other tissues, a process called metastasis. The discovery could mark this protein complex as a potential target to prevent tumor metastasis. Although the data are based on laboratory work, the scientists said they provide a viable target to explore the molecular dynamics of metastasis and potentially to intervene in the cancer process. It is estimated that 350,000 people die with bone metastases annually in the United States[11]. If people at high risk of bone metastases can be identified early, treatment with bisphosphonate therapy, which suppresses the degradation of bone induced by tumor cells, can be initiated immediately. The scientists also noted that their data have potential to be applied to the dental clinic, where this protein complex could be used to distinguish between suspicious oral lesions and aggressive early tumors.

DENTAL IMPLANTS

Since their introduction in North America over 20 years ago, dental implants have become associated with a variety of designs, types, and surgical protocols. However, few clinical trials have been conducted that adequately compare the various surgical and prosthetic protocols, their success in different locations of the mouth, the potentially compromising effects of systemic disease, and patient outcomes over time.

New Initiative: Clinical Research on Osseointegrated Dental Implants

The NIDCR will begin an initiative to expand the body of high quality, scientific evidence that is available to patients and practitioners on the successful implantation of osseointegrated dental implants. Patients and practitioners would benefit greatly from a series of clinical trials that explore these critical issues and provide objective scientific data to better inform their choices. This initiative will compare outcomes of the various surgical and prosthetic protocols now used in the field. Examples include immediate versus delayed placement, implant placement following various types of osseous grafting, immediate functional loading versus delayed functional loading, and implant needs in children who have congenitally missing teeth or suffer developmental disabilities. Another area of opportunity is the assessment of the influence of systemic diseases, such as osteoporosis and diabetes, on success rates. Lastly, studies will be conducted to evaluate patient preferences and quality of life compared to other prosthetic methods, such as dentures, for restoring the dentition.

[11] Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer 2002;2:584-593

HIV INFECTION AND HIV-RELATED OPPORTUNISTIC INFECTION

Oral complications of HIV infection have been recognized since the onset of the AIDS epidemic and remain a significant public health problem, affecting an estimated 30 to 80 percent of HIV-positive individuals[12]. These complications include: oral tumors, oral candidiasis, oral viral infections, salivary gland disorders, and oral ulcerations. These conditions can be quite painful and directly contribute to a loss of appetite and wasting in individuals who develop AIDS.

New Initiative: Protein Profiles of the Oral Mucosal Tissues in the Context of HIV/AIDS

The NIDCR will support an initiative to characterize changes in protein profiles and protein-protein interactions within the oral mucosa following HIV exposure and disease. The oral mucosa is more resistant to HIV infection than other mucosal sites in the body. This is of great interest scientifically because most HIV infections initiate in mucosal tissues. If the anti-HIV factors in the oral mucosa can be elucidated more clearly, the new knowledge could lead to novel strategies to combat the virus and fight oral and other AIDS-related opportunistic infections. As a critical first step in this direction, this initiative will support studies that comprehensively catalogue the patterns of protein expression in healthy oral mucosa and under varying degrees of HIV resistance and infection. Because the oral mucosa is exposed to myriad external factors, ranging from immune cells to changes in oral pH, it is likely that the onset of oral HIV infection involves a convergence of internal and external factors. This initiative will employ proteomic strategies to explore these complex biological interactions and better define the process of HIV resistance and infection.

New Initiative: Research on Oral Manifestations of HIV-Related Immunosuppression

Traditionally, research into the oral manifestation of HIV infection has involved a single scientific discipline or one-time multidisciplinary collaborations. However, given the biological complexity of these oral complications, a more dedicated teaming of researchers from complementary areas of science could greatly accelerate the pace of discovery and ultimately the development of improved treatments.

The NIDCR will launch an initiative that will enable multidisciplinary scientific teams to study the oral manifestations and complications associated with HIV/AIDS-related immunosuppression. This initiative will seed the formation of several multidisciplinary teams to pursue projects within a related biological theme. This approach will expand the number of investigators interested in oral AIDS and has the potential to attract distinguished scientists from an array of disciplines.

NIH ROADMAP

- The initiative *Building Blocks, Biological Pathways and Networks* -- seeks to create a better "toolbox" for researchers, including innovative ways for capturing real-time images of molecular and cellular events that occur in the human body. The scientific goals of this

[12] Patton LL, McKaig R, Strauss R, Rogers D, Enron JJ Jr., "Changing prevalence of oral manifestations of human immunodeficiency virus in the era of protease inhibitor therapy," Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90:299-304, 2000.

initiative are closely linked to NIDCR's efforts to identify the full complement of genes, proteins and protein networks that are expressed in both oral cancer and periodontal disease. Advances in proteomic analysis platforms will be crucial for NIDCR to achieve its goal of defining the salivary proteome -- a key step in the Institute's long-term goal to use oral fluids for diagnostic purposes. The *Molecular Libraries and Molecular Imaging* initiative may accelerate NIDCR's progress in defining the molecular pathways of pain reception and in identifying new therapeutic targets to manage chronic pain.

- The *Interdisciplinary Research Teams of the Future* initiatives will stimulate new mechanisms to facilitate the conduct of multi- and interdisciplinary research. NIDCR's work, particularly in areas such as Sjögren's syndrome, cleft lip and palate, ectodermal dysplasia, cancer, chronic pain, and infectious diseases has traditionally included researchers from many disciplines. Ongoing studies, designed to determine the linkages between oral infections and systemic conditions, such as preterm birth and cardiovascular events, have required collaborations among physicians, dentists and nurses. By integrating several disciplines in a more systematic way, this Roadmap initiative will enable NIDCR's ongoing inter- and multidisciplinary efforts to expand and develop new approaches to research.

- The *Re-engineering Clinical Research* initiative will promote the creation of better integrated networks working on clinical research that include community-based health care providers. The integration of dentists in this new clinical research infrastructure is key, given that certain systemic conditions such as diabetes, Sjögren's syndrome, HIV/AIDS and osteoporosis have important oral symptoms, manifestations or complications. NIDCR's General Dental Practice-Based Networks in time, will link with existing medical networks supported through the Roadmap initiative to provide additional patients, professional expertise, and integration of resources for conducting research across a broad spectrum of health care specialties. These practice-based dental networks will, upon the completion of the NIH Roadmap "Networks/NECTAR" feasibility studies, position the dental research community to participate in the next stage of related Roadmap initiatives.

- Nanotechnology involves the creation and use of materials and devices at the level of molecules and atoms. Researchers have developed powerful tools to extensively categorize the parts of cells in vivid detail, yet many questions remain to build "nano" structures that are compatible with living tissues and can safely operate inside the body. The NIH *Nanomedicine Roadmap Initiative* will be instrumental to NIDCR's efforts by providing extensive information about the physical properties of intracellular structures that will inform us about how biology's molecular machines are built.

- Finally, the NIDCR is directly supporting awards under several of the Roadmap initiatives, including those for Short Programs for Interdisciplinary Research Training and Supplements for Methodological Innovations in the Behavioral and Social Sciences.

THE NIH NEUROSCIENCE BLUEPRINT

Overview -- The Blueprint is a framework to enhance cooperation among fourteen NIH 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.

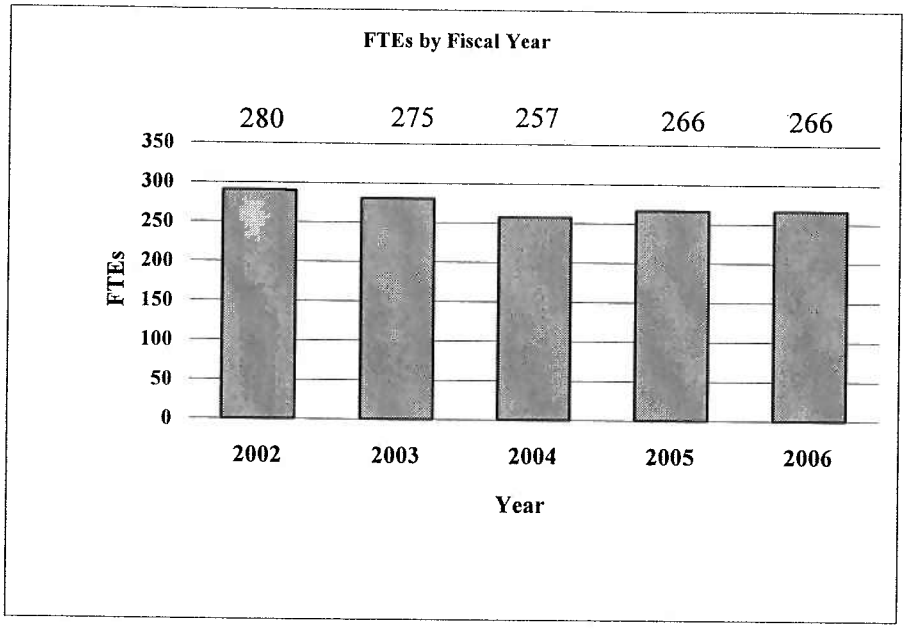
FY2005 -- For fiscal year 2005, the Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives, with the participation of all Blueprint Institutes, 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.
NIDCR funded neuroscience researchers will be able to take advantage of the Gene Expression Nervous System Atlas (GENSAT) project since genes important in pain processing in the trigeminal ganglion will be recommended for inclusion in the expansion of this initiative. Participation in this initiative will help to increase NIDCR grantees' understanding of the function and regulation of proteins involved in chronic pain disorders. NIDCR trainees will benefit from supplements to existing training grants that will include course work on Neurobiology of Disease. The themes of neurodegeneration and neuroplasticity are common to many diseases of the nervous system including chronic pain, which can be considered a neurological disease.

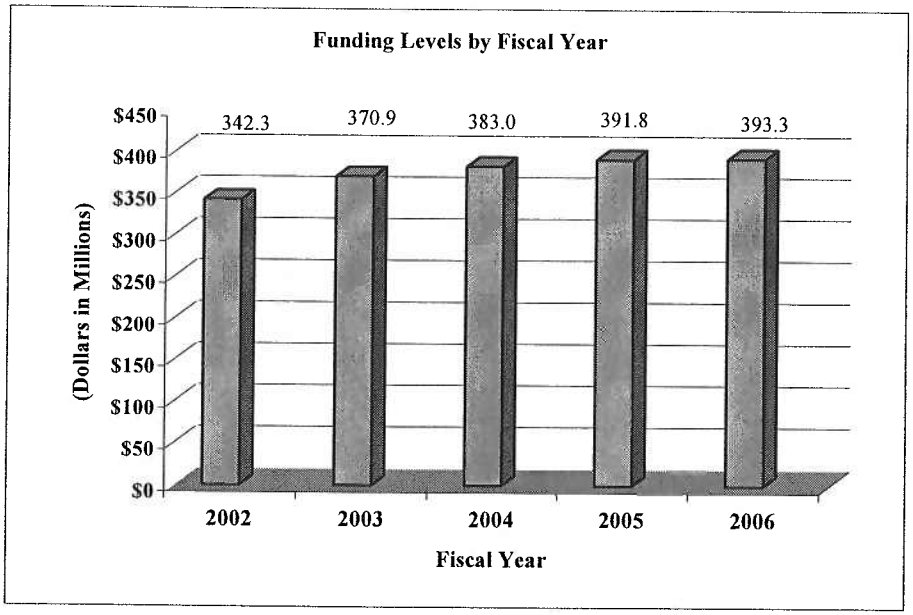
FY2006 -- Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of neuroscience research. Blueprint initiatives for fiscal year 2006 will include systematic development of genetically 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. NIDCR funded neuroscientists will benefit from the cross-Institute training programs in neuroimaging and computational neuroscience. These areas of emphasis are important to those grantees studying chronic pain conditions and temporomandibular joint disorders. An expansion of the research cores grant program will allow NIDCR grantees to utilize these facilities and establish collaborative projects with other neuroscientists. This expansion will also allow for cross fertilization of research between dental researchers and other institutional departments. NIDCR neuroscientists will benefit from the Neuromouse Project since genes involved in pain processing will be recommended for inclusion in knock-out studies envisioned for this initiative.

Budget Policy

The Fiscal Year 2006 budget request for the NIDCR is $393,269,000, an increase of $1,440,000 and 0.4 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NIDCR's support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the 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 NIDCR are shown in the graphs below.





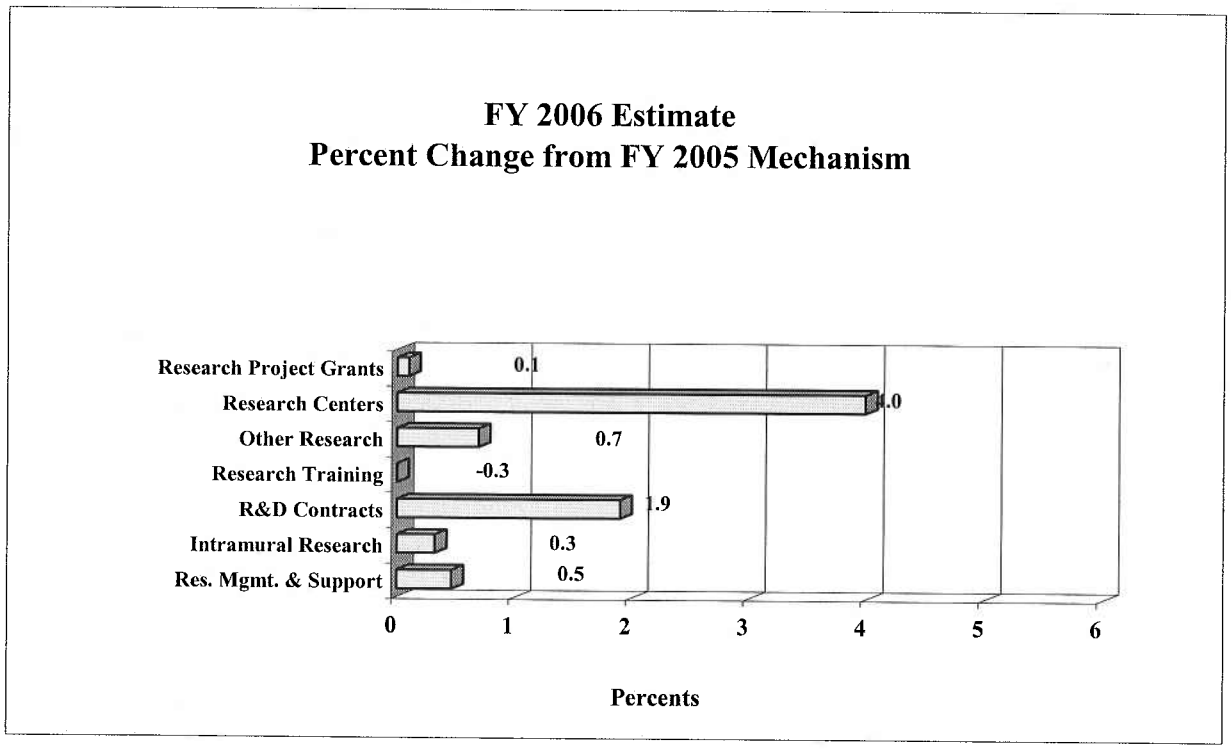
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. The average cost of competing RPGs will be held at the FY2005 level. There will be no inflationary increases for direct, recurring costs in noncompeting continuation RPGs.

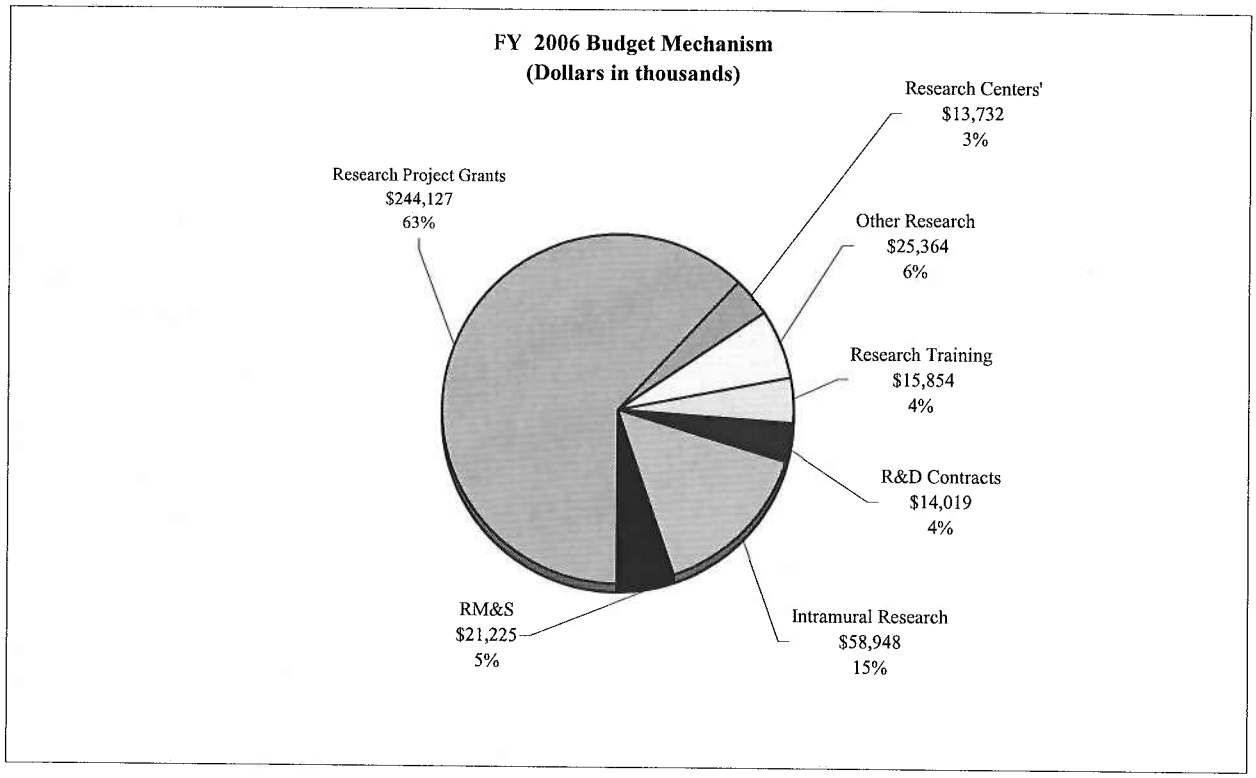
Advancement in medical research is dependent on attracting the best and the brightest to pursue careers in biomedical research. In the Fiscal Year 2006 request, stipend levels for post-doctoral

recipients supported through the Ruth L. Kirschstein National Research Service Awards will increase by 4.0% for those with 1-2 years of experience, with all other stipends remaining at the FY2005 levels. NIH will also provide an increase of $500 per post-doctoral fellow, for increased health insurance costs. NIDCR will support 350 pre- and postdoctoral trainees in full-time training positions.

The Fiscal Year 2006 request includes funding for 8 research centers, 118 other research grants, including 16 clinical career awards, and 17 R&D contracts. Intramural Research receives a 0.3 percent increase and Research Management and Support receives a 0.5 percent increase which is the same as the NIH total increase. NIDCR is participating in the NIH Neuroscience Blueprint. The FY2006 request includes $100,000 for a variety of Neuroscience Blueprint initiatives, including neuroscience cores, training initiatives, and the Neuromouse project."

The mechanism distribution by dollars and percent change follows:




FY 2006 Budget Mechanism
(Dollars in thousands)
Research Centers'
$13,732
3%
Other Research
$25,364
6%
Research Training
$15,854
4%
R&D Contracts
$14,019
4%
Intramural Research
$58,948
15%
RM&S
$21,225
5%
Research Project Grants
$244,127
63%

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research

Budget Mechanism - Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	468	$167,433,000	490	$176,129,000	496	$176,949,000
Administrative supplements	(12)	601,000	(14)	806,000	(14)	750,000
Competing:						
Renewal	45	15,587,000	40	14,334,000	40	14,196,000
New	167	47,969,000	148	43,953,000	146	43,528,000
Supplements	2	252,000	2	232,000	2	229,000
Subtotal, competing	214	63,808,000	190	58,519,000	188	57,953,000
Subtotal, RPGs	682	231,842,000	680	235,454,000	684	235,652,000
SBIR/STTR	35	8,281,000	34	8,436,000	34	8,475,000
Subtotal, RPGs	717	240,123,000	714	243,890,000	718	244,127,000
Research Centers:						
Specialized/comprehensive	7	12,613,000	7	12,955,000	8	13,387,000
Biotechnology	0	160,000	0	250,000	0	345,000
Subtotal, Centers	7	12,773,000	7	13,205,000	8	13,732,000
Other Research:						
Research careers	91	12,041,000	87	12,301,000	90	12,454,000
Cooperative clinical research	0	50,000	0	0	0	0
Biomedical research support	0	7,000	0	9,000	0	11,000
Other	28	12,645,000	27	12,879,000	28	12,899,000
Subtotal, Other Research	119	24,743,000	114	25,189,000	118	25,364,000
Total Research Grants	843	277,639,000	835	282,284,000	844	283,223,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	24	907,000	27	1,064,000	27	1,064,000
Institutional awards	311	14,015,000	324	14,842,000	323	14,790,000
Total, Training	335	14,922,000	351	15,906,000	350	15,854,000
Research & development contracts	17	15,369,000	17	13,757,000	17	14,019,000
(SBIR/STTR)	(0)	(16)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	173	54,054,000	176	58,756,000	176	58,948,000
Research management and support	84	21,064,000	90	21,126,000	90	21,225,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, NIDCR	257	383,048,000	266	391,829,000	266	393,269,000
(RoadMap Support)		(1,027,000)		(2,461,000)		(3,513,000)
(Clinical Trials)		(20,320,000)		(20,674,000)		(20,684,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Oral Diseases and Disorders Research		$307,930		$311,947		$313,096		$1,149
Subtotal, Extramural research		307,930		311,947		313,096		1,149
Intramural research	173	54,054	176	58,756	176	58,948	0	192
Res. management & support	84	21,064	90	21,126	90	21,225	0	99
Total	257	383,048	266	391,829	266	393,269	0	1,440

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Summary of Changes

FY 2005 Estimate				$391,829,000
FY 2006 Estimated Budget Authority				393,269,000
Net change				1,440,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$20,741,000		$298,000
b. Annualization of January 2005 pay increase		20,741,000		195,000
c. January 2006 pay increase		20,741,000		363,000
d. One less day of pay		20,741,000		(83,000)
e. Payment for centrally furnished services		10,156,000		51,000
f. Increased cost of laboratory supplies, materials, and other expenses		27,859,000		381,000
Subtotal				1,205,000
2. Research Management and Support:				
a. Within grade increase		10,492,000		173,000
b. Annualization of January 2005 pay increase		10,492,000		99,000
c. January 2006 pay increase		10,492,000		184,000
d. One less day of pay		10,492,000		(42,000)
e. Payment for centrally furnished services		3,145,000		16,000
f. Increased cost of laboratory supplies, materials, and other expenses		7,489,000		82,000
Subtotal				512,000
Subtotal, Built-in				1,717,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Summary of Changes--continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	490	$176,935,000	6	$764,000
b. Competing	190	58,519,000	(2)	(566,000)
c. SBIR/STTR	34	8,436,000	0	39,000
Total	714	243,890,000	4	237,000
2. Research centers	7	13,205,000	1	527,000
3. Other research	114	25,189,000	4	175,000
4. Research training	351	15,906,000	(1)	(52,000)
5. Research and development contracts	17	13,757,000	17	262,000
Subtotal, extramural				1,149,000
	FTEs		FTEs	
6. Intramural research	176	58,756,000	0	(1,013,000)
7. Research management and support	90	21,126,000	0	(413,000)
Subtotal, program	266	391,829,000		(277,000)
Total changes			0	1,440,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	266	266	0
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$147,480	$150,024	$2,544
Average GM/GS grade	10.8	10.8	0.0
Average GM/GS salary	$70,946	$72,170	$1,224
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$94,848	$96,484	$1,636
Average salary of ungraded positions	95,997	97,653	1,656

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$13,250,000	$13,793,000	$543,000
11.3 Other than Full-Time Permanent	7,556,000	7,866,000	310,000
11.5 Other Personnel Compensation	202,000	207,000	5,000
11.7 Military Personnel	798,000	816,000	18,000
11.8 Special Personnel Services Payments	3,500,000	3,579,000	79,000
Total, Personnel Compensation	25,306,000	26,261,000	955,000
12.0 Personnel Benefits	5,330,000	5,549,000	219,000
12.1 Military Personnel Benefits	571,000	584,000	13,000
13.0 Benefits for Former Personnel	26,000	26,000	0
Subtotal, Pay Costs	**31,233,000**	**32,420,000**	**1,187,000**
21.0 Travel & Transportation of Persons	785,000	785,000	0
22.0 Transportation of Things	115,000	112,000	(3,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	0	0	0
23.3 Communications, Utilities & Miscellaneous Charges	478,000	460,000	(18,000)
24.0 Printing & Reproduction	310,000	293,000	(17,000)
25.1 Consulting Services	1,090,000	1,049,000	(41,000)
25.2 Other Services	2,706,000	2,630,000	(76,000)
25.3 Purchase of Goods & Services from Government Accounts	41,897,000	41,810,000	(87,000)
25.4 Operation & Maintenance of Facilities	1,192,000	1,164,000	(28,000)
25.5 Research & Development Contracts	3,007,000	3,160,000	153,000
25.6 Medical Care	420,000	410,000	(10,000)
25.7 Operation & Maintenance of Equipment	856,000	832,000	(24,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**51,168,000**	**51,055,000**	**(113,000)**
26.0 Supplies & Materials	5,780,000	5,645,000	(135,000)
31.0 Equipment	3,900,000	3,801,000	(99,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	298,059,000	298,697,000	638,000
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	**360,596,000**	**360,849,000**	**253,000**
Total Budget Authority by Object	**391,829,000**	**393,269,000**	**1,440,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$13,250,000	$13,793,000	$543,000
Other Than Full-Time Permanent (11.3)	7,556,000	7,866,000	310,000
Other Personnel Compensation (11.5)	202,000	207,000	5,000
Military Personnel (11.7)	798,000	816,000	18,000
Special Personnel Services Payments (11.8)	3,500,000	3,579,000	79,000
Total Personnel Compensation (11.9)	**25,306,000**	**26,261,000**	**955,000**
Civilian Personnel Benefits (12.1)	5,330,000	5,549,000	219,000
Military Personnel Benefits (12.2)	571,000	584,000	
Benefits to Former Personnel (13.0)	26,000	26,000	0
Subtotal, Pay Costs	**31,233,000**	**32,420,000**	**1,187,000**
Travel (21.0)	785,000	785,000	0
Transportation of Things (22.0)	115,000	112,000	(3,000)
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities and Miscellaneous Charges (23.3)	478,000	460,000	(18,000)
Printing and Reproduction (24.0)	310,000	293,000	(17,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	1,090,000	1,049,000	(41,000)
Other Services (25.2)	2,706,000	2,630,000	(76,000)
Purchases from Govt. Accounts (25.3)	25,983,000	25,534,000	(449,000)
Operation & Maintenance of Facilities (25.4)	1,192,000	1,164,000	(28,000)
Operation & Maintenance of Equipment (25.7)	856,000	832,000	(24,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**31,827,000**	**31,209,000**	**(618,000)**
Supplies and Materials (26.0)	5,778,000	5,643,000	(135,000)
Subtotal, Non-Pay Costs	39,293,000	38,502,000	(791,000)
Total, Administrative Costs	**70,526,000**	**70,922,000**	**396,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research

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

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

Item

Scleroderma – The Committee is encouraged by NIDCR's interest in scleroderma, a chronic and progressive disease that predominantly strikes women. Scleroderma is disfiguring and life-threatening; and effective treatments are lacking. Scleroderma is often associated with a number of dental and craniofacial complications. The most major and common problems are xerostomia and microstomia. Additional concerns are increased frequency of caries, periodontal disease, fibrotic changes, fungal infections, telangectasia and bone resorption of the mandible. Additional research is needed to develop safe and effective treatments and to identify the cause or causes of the serious complications of scleroderma. (p. 72)

Action Taken or to be Taken

The NIDCR, an active member of the NIH Autoimmune Diseases Coordinating Committee (ADCC), recognizes that scleroderma patients face many challenges. The Institute would welcome receipt of high-quality grant applications relevant to the oral and craniofacial complications associated with this chronic disease.

Item

Saliva - The Committee is aware that research on saliva has progressed rapidly and holds the potential to be an inexpensive non-invasive diagnostic tool for early detection of breast cancer, osteoporosis, hepatitis, HIV, and Sjögren's disease. The Committee encourages NIDCR to work cooperatively with NCI and other appropriate institutes in pursuing research initiatives on the development of saliva as a diagnostic tool. (p. 72)

Action Taken or to be Taken

In 1999 the NIDCR started a dialogue with National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases, (NIAID), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), which led to a workshop on salivary-based diagnostic technologies and an initiative in this area thereafter. As a result of this initiative, the NIDCR has launched a program for the development of saliva-based diagnostic technologies. Some of the investigators in the program are focusing on the fabrication of a portable device for oral fluid-based diagnostics. It integrates microchip-based immunoassays with miniaturized power supplies, reagent cartridges, miniaturized laser-induced

fluorescence detector, and control hardware for the detection of biomarkers associated with oral and systemic diseases, such as cardiovascular disease. Other investigators focus on the development of an integrated micro-fluidics platform. This device will be able to detect HIV, hepatitis, early signs of breast and oral cancers, various hormones, or monitor patients undergoing kidney dialysis. The NIDCR is planning to continue the program for another five years to promote the fabrication and validation of these platforms. It is at that stage that the Institute will consult with other Institutes, including NCI, for clinical evaluation of these technologies.

In order to complement the Salivary-Based Diagnostic Technologies program, particularly the validation of diagnostic technologies, in FY 2004, the NIDCR created a program to catalogue and characterize the proteins present in human saliva (the human salivary proteome), including potential biomarkers for oral and systemic diseases, such as cancer and autoimmune diseases. This effort will identify all protein components in human saliva, as well as their natural variants and complexes; develop a molecular "tool box" for the isolation and functional characterization of salivary proteins; and, establish a bioinformatics environment for the dissemination of salivary proteome data to the wider scientific community. These studies will help to create the "periodic table" of the salivary proteins, and provide baseline data for a point of comparison to detect even subtle changes in the composition of saliva among people with or at risk for various diseases.

Moreover, the NIDCR has awarded a contract to develop an international research registry for Sjögren's syndrome. It will house well-characterized biological specimens, including saliva, from patients and healthy controls in five countries. This registry will provide the needed saliva samples at different stages of disease to determine the feasibility of developing novel diagnostic tests for Sjögren's syndrome.

Item

Biology of bone – The Committee encourages NIDCR to continue to conduct research into the basic biology of bone cells and bone matrix and their roles in bone turnover and regeneration. The Committee also urges NIDCR to pursue research into the role of genes and other agents in restoring skeletal tissue and causing skeletal disorders, including fibrous dysplasia and dental abnormalities in Paget's disease patients. (p. 72)

Action Taken or to be Taken

NIDCR-supported scientists are actively engaged in research related to bone repair and regeneration, and will continue to follow many research avenues with the goal of understanding the basis for skeletal disorders. As a prime example of recent work on bone regeneration, scientists reported that progenitor cells isolated from fat could be coaxed in mice into becoming bone-forming cells. The study further showed that these cells could grow and contribute to new bone formation that repaired a large defect in the skull. This approach may ultimately provide a convenient and technically feasible therapy in repairing bone defects and injuries.

Other NIDCR researchers are studying how bone cells sense and respond to biochemical and biomechanical signals from the bone matrix. They have discovered that the bone matrix synergizes with growth factors to control the expression of genes important for bone growth.

Studies are underway to decipher the mechanism of this synergy. This information will help us better understand basic bone biology, and will equip us with the ability to better manipulate the bone cells for repair and regeneration.

Scientists recently discovered a major bone regulatory factor that is responsible for maintaining the activity of the mature bone cells. In a mouse model in which the gene for a major bone regulatory factor was inactivated, the mice have delayed bone formation, deficient bone mineral and low bone mass. Such features are reminiscent of conditions seen in patients with a skeletal disorder called Coffin-Lowry Syndrome. Work will continue on the role of this gene and its interactions with other genes in bone development.

Clinical researchers are currently engaged in five active protocols for the study and treatment of fibrous dysplasia of bone, a disease caused by a mutation in a specific protein. With this mutation, normal bone and bone marrow are replaced with fibrous tissue and defective bone. Patients often have additional hormonal disorders, which exacerbate the severity of the bone disease. Scientists are evaluating several different treatments for efficacy in treating the bone disease and in controlling the hormonal imbalances. Patients are also being evaluated for dental abnormalities. By studying these patients long term, doctors can adjust and personalize clinical management plans for the patients to improve their prognosis and quality of life.

Paget's disease can weaken any part of the skeleton, including the jawbone, and may therefore lead to dental problems such as loose teeth. The condition is caused by aberrant bone turnover and is in part, attributed to malfunctioning of bone resorbing cells called osteoclasts. The NIDCR supports research on the activities and functions of these cells. Furthermore, NIDCR scientists have initiated studies to obtain bone specimens from Paget's disease patients in order to determine the molecular defects in bone cells.

Item

Mucolipidosis Type IV – The Committee urges NIDCR to continue its efforts to create a strain of mice which has the same genetic characteristics as that of humans with this debilitation genetic disorder. This research offers promise for the eventual development of treatments or cures for this and similar genetic disorders in humans. (p. 72)

Action taken or to be taken

In FY 2002, NIDCR initiated a research project to create a mouse disease model with a defective mucolipidosis IV gene to mimic the human disease. In collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) researchers, NIDCR intramural researchers have been making significant progress in FY 2004 by generating and characterizing mouse embryonic stem cell lines with a targeted defect in the mucolipidosis IV (ML-IV) genetic locus. One of these cell lines has now been used to generate a founder mouse line that harbors this altered ML-IV locus. The next step is to characterize the inheritance of the ML-IV gene mutation in the progeny of a second generation of mice. Once a mouse line with inherited defects in this gene is obtained, it will be tested for its effectiveness in mimicking this human genetic defect. It is

expected that these efforts will eventually provide a mouse model for testing potential therapeutic approaches to treating this debilitating human genetic disorder.

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

Item

Saliva as a Diagnostic Tool - In recent years dental scientists have learned that the oral fluids in the mouth contain a cornucopia of information about the condition of the various systems of the body. Of particular interest is the potential to develop a diagnostic test for early detection of breast cancer. The Committee recognizes that considerable clinical research must be done before a test can be approved for use by health care professionals so that the women of this country will have a simple non-invasive, inexpensive procedure to alert them to the risk of breast cancer. The Committee urges the Institute to advance the field of salivary diagnostics. (p. 109)

Action Taken or to be Taken

The NIDCR is planning to continue its salivary-based diagnostic technologies program for another five years. At that time, it is expected that the investigators will finalize the integration of the individual fluidics platforms and the fabrication of portable, fully integrated, and miniaturized micro-fluidic diagnostic systems that can diagnose multiple analytes of oral and systemic disease and disorders and address the important objectives of the validation of these diagnostic devices. Clearly, this program has the potential to provide the technological advances needed for rapid, reliable, non-invasive identification of biomarker signature patterns indicative of local and systemic health status, particularly in regards to the early diagnosis of diseases such as breast and oral cancer.

Item

Scleroderma – The Committee is encouraged by NIDCR's interest in scleroderma, a chronic and progressive disease that predominantly strikes women. Scleroderma is disfiguring and life-threatening; and effective treatments are lacking. Scleroderma is often associated with a number of dental and craniofacial complications. The most major and common problems are xerostomia and microstomia. Additional concerns are increased frequency of caries, periodontal disease, fibrotic changes, fungal infections, telangectasia and bone resorption of the mandible. Additional research is needed to develop safe and effective treatments and to identify the cause or causes of the serious complications of scleroderma. (p. 109)

Action Taken or to be Taken

Please refer to page 30 of this document for NIDCR's response to this significant item regarding Scleroderma.

Item

Skeletal Disorders – The Committee encourages NIDCR to continue to conduct research into the basic biology of bone cells and bone matrix and their roles in bone turnover and regeneration. The Committee also urges NIDCR to pursue research into the role of genes and other agents in restoring skeletal tissue, and skeletal disorders – including fibrous dysplasia and dental abnormalities in Paget's disease patients.

Action Taken or to be Taken

Please refer to page 31 of this document for NIDCR's response to this significant item regarding Biology of bone.

Item

Systemic Health Risks and Oral Health – The association between oral health and systemic health has been a topic of NIDCR funded research projects for many years. Early results from several studies indicate that there is a link between oral bacterium and preterm births. Still another report has shown a connection between gum disease and heart attacks, regardless of whether the patient uses tobacco. The Committee encourages further research to identify the connection between oral disease and systemic disorders. (p. 109)

Action taken or to be taken

Bacteria grow in everyone's mouth and are the primary cause of periodontal (gum) disease. Moreover, bacteria in the mouths of people with gum disease or inflammatory biochemicals from infected gums may gain access to the blood stream and cause disease in other parts of the body.

Animal studies and epidemiologic surveys have linked periodontal (gum) disease with preterm delivery and low birth weight. To see if this link may also occur in humans, the NIDCR is currently funding human studies investigating the possible link between oral bacteria and preterm birth. These studies will determine if oral bacteria can be spread via the blood stream to the birth canal of pregnant women and determine if this spread of bacteria may be related to premature birth and fetal growth.

Furthermore, preliminary data indicate that dental treatment for periodontal disease may reduce the incidence of preterm birth. The NIDCR is supporting two multicenter phase III clinical trials to address these issues. These clinical trials will jointly recruit approximately 2,600 women in the second trimester of pregnancy who have periodontitis and randomize them to either immediate intensive periodontal treatment or to this treatment after the birth of their child. The primary outcome variables in these trials are gestational age at birth and low birth weight.

According to the U.S. Surgeon General's report on Oral Health, released in 2000, preterm birth and low birth weight are considered to be the leading perinatal problems in the United States. Despite major efforts to improve diagnosis and prevention of preterm birth, it remains a foremost

cause of neonatal morbidity and mortality. Preterm birth is more likely to affect minority women who have disparities in health care. The total cost of initial care for the US population of neonates is estimated at $10.2 billion annually. If NIDCR trials demonstrate that periodontal therapy has a positive effect reducing preterm birth and/or low birth weight, it could have enormous public health implications in terms of neonatal mortality, morbidity, and cost savings.

Similar to preterm birth, several epidemiological studies have examined the association between dental health status and the risk of cardiovascular events. For example, Arbes et al. evaluated the association between periodontal disease and coronary heart disease and found that the odds for having had a heart attack increased with the severity of periodontal disease. Since periodontal disease is common in the population (75 percent of the population is affected by mild forms and 20-20 percent by more severe forms), it may account for a significant portion of the proposed infection-associated risk for cardiovascular disease.

Currently, the NIDCR is funding several studies of possible relationship between periodontal diseases and cardiovascular disease including preliminary clinical trials to determine if dental treatment for periodontal disease will have an effect on vascular disease and markers of inflammation. An example of one study that the NIDCR has been supporting is a pilot study of periodontal therapy in patients at risk for cardiovascular events to generate information on how to produce the most effective design for a definitive study. With the appropriate infrastructure and procedures developed, a future definitive phase III clinical trial of the relationship between periodontal infection and cardiovascular disease can be conducted.

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

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	$375,923,000	Indefinite	$377,415,000
Craniofacial Research	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	15,906,000	b/	15,854,000
Total, Budget Authority				391,829,000		393,269,000

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 of Dental and Craniofacial Research

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1997	$174,463,000 2/	$195,596,000	$190,184,000 2/	$195,825,000 3/
1998	190,081,000 2/	209,403,000	211,611,000	209,415,000
1999	214,559,000 2/4/	228,961,000	233,588,000	234,338,000
Rescission				(155,000)
2000	225,709,000 2/	257,349,000	267,543,000	270,253,000
Rescission				(1,442,000)
2001	263,075,000 2/	309,007,000	309,923,000	306,448,000
Rescission				(173,000)
2002	341,898,000	339,268,000	348,767,000	343,327,000
Rescission				(178,000)
2003	374,319,000	374,319,000	374,067,000	374,067,000
Rescission				(2,431,000)
2004	382,396,000	382,396,000	386,396,000	385,796,000
Rescission				(2,514,000)
2005	394,080,000	394,080,000	399,200,000	395,080,000
Rescission				(3,251,000)
2006	393,269,000			

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 $172,000.
4/ Reflects a reduction of $590,000 for the budget amendment for bioterrorism research.

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	15	14	14
Office of Administrative Management	13	14	14
Office of Information Technology	6	7	7
Office of Science Policy and Analysis	5	6	6
Office of Communications and Health Education	9	8	8
Office of International Health	3	2	2
Division of Extramural Activities	14	16	16
Division of Basic and Translational Sciences	8	8	8
Center for Biotechnology and Innovation	1	3	3
Division of Clinical Research and Health Promotion	10	12	12
Division of Intramural Research	173	176	176
Total	257	266	266

FISCAL YEAR	Average GM/GS Grade
2002	10.6
2003	10.8
2004	10.8
2005	10.8
2006	10.8

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental and Craniofacial Research

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	2	2	2
Total - ES Salary	$286,996	$294,460	$299,539
GM/GS-15	18	16	16
GM/GS-14	26	26	26
GM/GS-13	13	13	13
GS-12	24	27	27
GS-11	22	22	22
GS-10	2	2	2
GS-9	17	18	18
GS-8	7	7	7
GS-7	17	11	11
GS-6	11	11	11
GS-5	3	3	3
GS-4	2	2	2
GS-3	1	1	1
GS-2	1	1	1
GS-1	1	1	1
Subtotal	165	161	161
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	7	7	7
Senior Grade	1	1	1
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	9	9	9
Ungraded	98	99	99
Total permanent positions	178	175	175
Total positions, end of year	274	271	271
Total full-time equivalent (FTE) employment,end of year	257	266	266
Average ES salary	$143,498	$147,480	$150,024
Average GM/GS grade	10.8	10.8	10.8
Average GM/GS salary	$69,030	$70,946	$72,170