

DEPARTMENT OF HEALTH AND HUMAN SERVICES

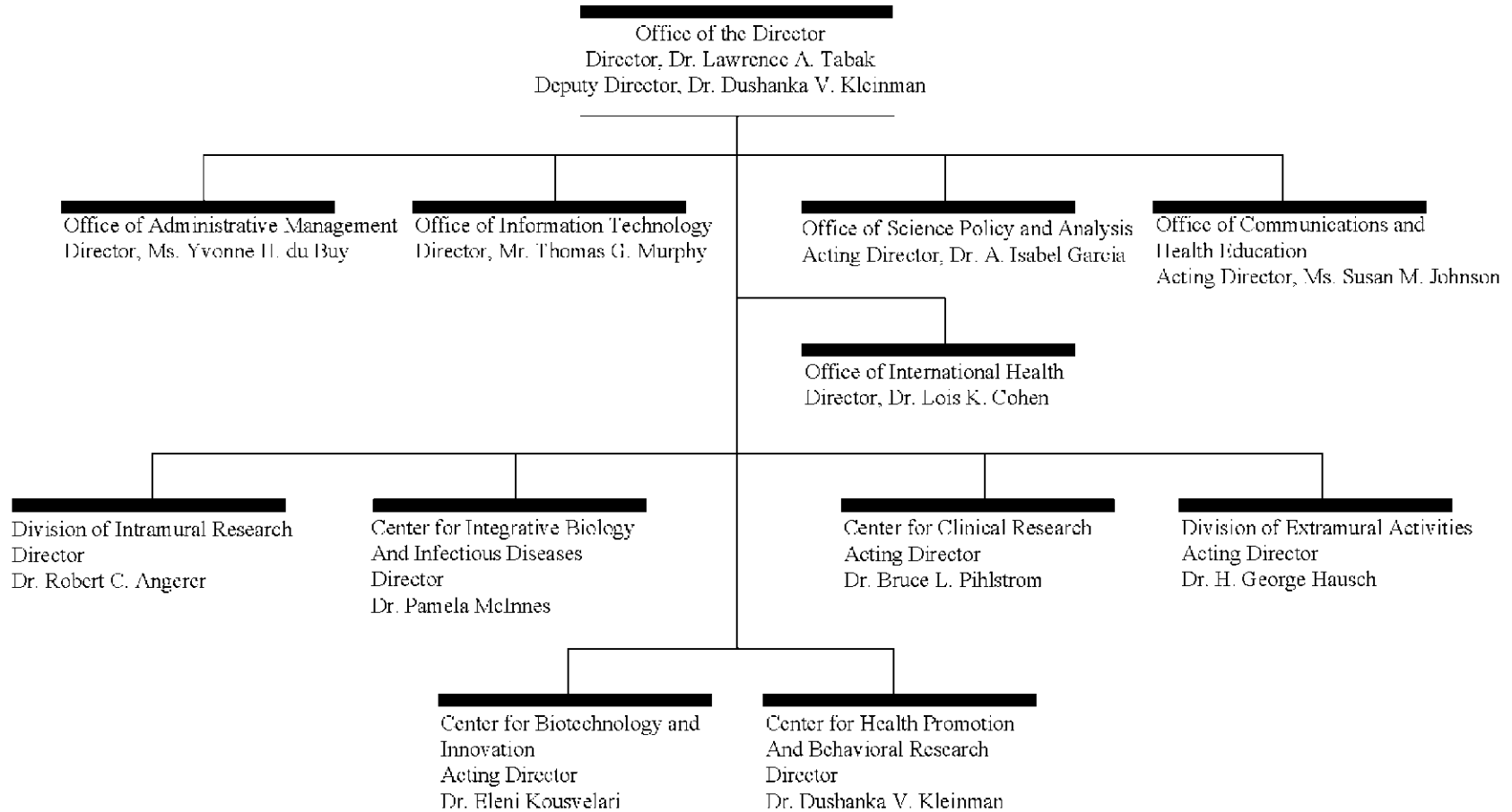
NATIONAL INSTITUTES OF HEALTH

National Institute of Dental and Craniofacial Research

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# NATIONAL INSTITUTES OF HEALTH

## National Institute of Dental and Craniofacial Research



NIDCR-2

**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 [\$393,269,000] \$386,095,000.

[Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2006, as enacted by Public Law (109-149)]

**National Institutes of Health  
National Institute of Dental and Craniofacial Research**

**Amounts Available for Obligation 1/**

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	\$395,080,000	\$393,269,000	\$386,095,000
Enacted Rescissions	(3,251,000)	(3,933,000)	0
Subtotal, Adjusted Appropriation	391,829,000	389,336,000	386,095,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(2,477,000)	(3,479,000)	0
Comparative transfer from OD for NIH Roadmap	2,477,000	3,479,000	0
Subtotal, adjusted budget authority	391,829,000	389,336,000	386,095,000
Unobligated balance lapsing	(6,000)	0	0
Total obligations	391,823,000	389,336,000	386,095,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:

FY 2005 - \$1,065,000    FY 2006 - \$1,500,000    FY 2007 - \$1,360,000

Excludes \$577,000 in FY 2006 and \$577,000 in FY 2007 for royalties.

## Justification

### National Institute of Dental and Craniofacial Research

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

#### Budget Authority

FY 2005		FY 2006		FY 2007		Increase or	
<u>Actual</u>		<u>Appropriation</u>		<u>Estimate</u>		<u>Decrease</u>	
<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>
259	\$391,823,000	261	\$389,336,000	262	\$386,095,000	1	-\$3,241,000

This document provides justification for the Fiscal Year 2007 activities of the National Institute of Dental and Craniofacial Research (NIDCR). A detailed description of NIH-wide Fiscal Year 2007 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)." Detailed information on the NIH Roadmap for Medical Research may be found in the Overview section.

## INTRODUCTION

It is widely accepted that team science will be required to solve the most intractable complex diseases and conditions that face our Nation. The merging of once disparate scientific disciplines is already well under way in dental and oral health research. The NIDCR now supports the first regional oral cancer screening program that integrates highly informative molecular discoveries with traditional screening techniques. This seminal project likely will serve as a template for more effective and potentially life saving early detection programs for oral cancer throughout the United States and Canada. As highlighted below, this research group took an important step forward this year in establishing that some predictive molecular characteristics of early precancerous oral lesions can be integrated with an easy-to-use liquid dye called toluidine blue that has been around since the late 1940s.

The NIDCR is not only fostering greater integration across scientific disciplines, it is leading by example. Also highlighted this year is collaboration between NIDCR intramural scientists with expertise in the basic biology of the salivary glands and a National Cancer Institute scientist with expertise in radiation biology. This merging of scientific interests has established in preliminary animal studies that a compound called Tempol can reproducibly spare the salivary glands during radiation therapy. This represents one of the more promising research leads in years to prevent dry mouth as a potentially debilitating side effect of radiation treatment for head and neck cancer.

### **Story of Discovery: Promising Lead in Preventing Radiation Therapy-Induced Dry Mouth**

One day in 2002, NIDCR scientist Dr. Ana Cotrim faced a logistical dilemma. She needed to test in laboratory rodents whether certain genes experimentally transferred into salivary glands naturally protect against radiation. But her laboratory lacked a radiation-beam-producing machine called an irradiator to allow her studies to proceed. Cotrim mentioned the problem to Dr. Bruce Baum, her lab chief, and he suggested speaking with Dr. James Mitchell, chief of the National Cancer Institute's Radiation Biology Branch. A meeting was arranged, and Mitchell gladly agreed to share his group's irradiator with Cotrim.

That might have been the end of the story, except Mitchell had a special request of his own. A cell biologist by training, Mitchell explained that for the past 18 years he had been studying a synthetic chemical called Tempol, which possesses the unique ability to protect cells against radiation. The chemical already was under evaluation in a human clinical trial to prevent the hair loss that occurs following radiation therapy, and Mitchell asked if the two would be interested in helping him test its radiation-protecting ability in the salivary glands of their rodents. As the three scientists recognized, this was the perfect collaboration: Mitchell was an expert on the pharmacology of Tempol; Cotrim and Baum possessed the needed expertise on the unique biology of the salivary glands.

If their initial research proved promising, the trio also recognized that Tempol might help one day to fill a major need in oncology. Each year, thousands of Americans receive radiation therapy for head and neck cancer, leaving their salivary glands severely damaged and their mouths persistently dry. This irreversible chronic dryness can make normal chewing and swallowing problematic, and leave many patients susceptible to a range of painful oral diseases that may not be correctable while they undergo treatment for their cancer. Although a different radio-protective treatment was recently approved to help spare the salivary glands during radiation therapy, it is unclear whether that compound might also protect the tumor, thereby diminishing the effects of the radiation therapy.

In 2004, after completing a series of studies using mice, Cotrim, Baum, Thompson, and colleagues had their answer: Tempol worked - and how! The group found that Tempol, when injected into the abdomen of mice 10 minutes prior to radiation therapy to the head and neck, provided "significant radioprotection of the salivary glands." In combination with a mouth/nose shield, they characterized protection by Tempol as "essentially complete" at 15 Grays (Gy), a standard measure of absorbed radiation, and greater than 75 percent protective at 17.5 Gy. Critically, Tempol did not protect tumors from radiation. This past year, the scientists followed up with more preclinical data on the most advantageous administration of Tempol, and future clinical trials in people with head and neck cancer are a strong possibility in the future.

Research challenges abound, not only in oral cancer, but also in the fight against temporomandibular joint and muscle disorders, chronic orofacial pain, dry mouth, periodontal disease, dental decay and myriad other oral conditions that collectively affect millions of Americans. These diseases are by nature complex, variable in severity, and sometimes exceedingly difficult to treat. While many of the molecular pieces underlying these conditions have been assembled, solving the totality of these biological puzzles will require greater integration among the life sciences, physical sciences, computer sciences, materials sciences, and other areas of scientific expertise. Each discipline brings its own complementary perspective, suggesting unique approaches to cut through the inherent complexity of a research problem and accelerate discovery.

The NIDCR and the Centers for Disease Control and Prevention last year released the first report in over a decade on the status of the Nation's oral health. These new data, based on a survey representing more than 256 million Americans, show that while the oral health of our Nation continues to improve, there is much work to be done. Improvements included up to 10 percentage points reduction in tooth decay among persons six years of age and older, a 13 percentage point

increase in dental sealants among children and adolescents, and a six percentage point reduction in total tooth loss among older Americans<sup>1</sup>. As rewarding as these results are, many public health challenges await. Tooth decay among pre-school children increased, and unacceptable oral health disparities still remain for too many Americans. Through continued integration, and ultimately, translation of the most promising research findings into widely available new treatments, it stands to reason that future reports will reflect continued gains in our Nation's oral health.

## SALIVARY DIAGNOSTICS

During the past year, several reports in the popular press unveiled a future of saliva-based diagnostic tests. These stories highlighted the painlessness of collecting saliva, the broad range of informative biochemicals such as hormones and biomarkers that are naturally dissolved in the fluid, and the near real-time speed of obtaining results. As promising as these scenarios are, they depend on continued technological progress to more fully integrate the various miniaturized components, automate the testing process, and validate the results to be as good as or better than standard blood tests. Through the continued integration of biology with engineering, physics, and computer sciences, the necessary technological breakthroughs now are coming online, and in recent months preliminary data have been published to begin the process of validating the accuracy and practicality of salivary diagnostics.

### **Science Advance: Microchip Assay for Inflammatory Disease**

A group of NIDCR grantees and colleagues have developed a novel silicon microchip detection system for measuring the levels of various substances in saliva, including DNA, electrolytes, and proteins. The system functions as an automated and fully integrated "lab on a chip." First, the saliva is transported to a designated region of the silicon platform, and then microfluidic structures deliver a series of small-volume reagents for an array of chemical and immunologic reactions. The result of each reaction produces a clear, color-coded fluorescent signal.

Following up on their technological success, the scientists recently reported clinical success in detecting C-reactive protein in human saliva with their microchip assay system. C-reactive protein, a measurable sign of inflammation in serum, is elevated in people with periodontal disease and may be predictive of developing heart disease. In their studies with healthy volunteers and others with periodontal disease, the group demonstrated that the system could measure levels of C-reactive protein in the saliva of those with oral inflammation. Importantly, the scientists also found their microchip had sufficient sensitivity and specificity to detect the protein during the various stages of periodontal disease. These studies mark the initial lab-on-a-chip exploration of proteins in saliva associated with periodontal disease, and they also clear the way for additional comparisons of C-reactive protein levels in healthy people and those with periodontitis, in order to establish baseline parameters indicative of periodontal health and disease. Such parameters will enable clinicians to identify and address periodontal disease earlier in the disease process, using methods that are faster and more comfortable for patients. Traditionally, clinicians have monitored periodontal disease by periodically measuring 168

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<sup>1</sup> Centers for Disease Control and Prevention. Surveillance for dental caries, dental sealants, tooth retention, edentulism, and enamel fluorosis—United States, 1988-94 and 1999-2002. In: Surveillance Summaries, August 26, 2005. MMWR 2005;54(NoSS-3).

different points in the mouth with a small probe to assess the amount of supporting bone lost. The traditional procedure is time consuming, and some patients find it uncomfortable; even more significant, by the time a change can be observed, the damage *i.e.*, bone loss, cannot be reversed.

### **Science Advance: Mitochondrial DNA in Salivary Diagnostics**

Although the DNA double helix in the cell nucleus grabs all of the attention, there is another source of genetic material in our cells. It is the DNA of our energy-generating mitochondria. Scientists have discovered in recent years that alterations in mitochondrial DNA occur in several types of tumors linked to smoking, including head and neck cancer. Building on this earlier work, a team of NIDCR grantees and colleagues hypothesized that people with oral squamous cell carcinoma may have elevated levels of mitochondrial DNA in their saliva, and this elevation would be independent of other possible contributing factors, such as age and how often one smokes. To test this hypothesis, the scientists evaluated levels of two mitochondrial DNA genes called Cox I and Cox II in the saliva of 94 people with oral squamous cell carcinoma and 656 healthy volunteers. Cox I and Cox II, specific forms of the enzyme cyclooxygenase, are known to be involved in the development and growth of head and neck cancer. The group found Cox I and Cox II DNA levels were, on average, significantly higher in those with head and neck cancer compared to the healthy controls, and this difference was independent of other contributory factors. With further investigation they hope to determine the timing and the mechanism by which these changes occur during the development of the cancer. That knowledge can then be used to develop more effective diagnostic tests and therapies.

### **Science Advance: Early Success Using Saliva to Detect Oral Cancer**

NIDCR grantees found they could assay for elevated levels of four distinct cancer-associated molecules in saliva and distinguish with 91 percent accuracy between healthy people and those diagnosed with oral squamous cell carcinoma. This so-called “proof-of-principle” study marks the first report in the scientific literature that distinct patterns of “messenger RNA” not only are measurable in saliva, but also can indicate a developing tumor. Messenger RNA (mRNA) is the molecular intermediate between gene and protein, serving as a chemical record that an individual gene has been expressed.

The scientists noted it may be possible with further refinement of the test, possibly by including additional cancer-linked mRNAs, to attain the necessary 99 to 100 percent accuracy required of commercial diagnostic tests for oral squamous cell carcinoma, the sixth most common cancer in the United States. The researchers noted that currently no biochemical or genetic diagnostic tests are commercially available for oral cancer, and they also suspected RNA patterns in saliva may be informative for other cancers and common diseases.

## **HEAD AND NECK CANCER**

Advances in early diagnosis of head and neck cancers are particularly important to reducing the unnecessary disfigurement and death wrought by this horrific disease. The five-year survival rate for victims of oral and pharyngeal cancers is only 56 percent<sup>2</sup>. These survival rates have not

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<sup>2</sup> American Cancer Society. Cancer Facts and Figures 2003. Atlanta (GA): American Cancer Society; 2003.



changed much in the last 20 years, due in part to the late stage at which many cases are diagnosed.

### Story of Discovery: Toluidine Blue Enters the Molecular Age

April 30, 1949 fell on a Saturday and, for the nation's physicians and scientists, that meant the arrival of their weekly *Journal of the American Medical Association*, or *JAMA*. Today, flipping through this now 56-year-old issue of *JAMA* is like stepping back in medical time, with its descriptions of treatments that were long ago rendered obsolete. But this copy of the journal remains noteworthy today because it contains one of the first - if not the first - published report of a compound called toluidine blue, a liquid form of toloum chloride that had been recently synthesized at the Abbott Laboratories and which today has accumulated over 3,000 citations in the medical literature.

Although this early report features toluidine blue as a potential coagulant for abnormal bleeding, the compound took on a new identity by the late 1960s as a unique chemical dye that could help doctors determine whether or not to biopsy an abnormal growth. As correctly reported at the time, developing tumors retain toluidine blue, producing a stain that is different in hue than that of normal tissue. In areas of the body that are visible, toluidine blue represented a potential breakthrough in identifying tumors very early in their development and eliminating them before they ever turned cancerous.

By the late 1970s, however, the promise had succumbed to controversy, particularly among those who treated oral cancer. Several studies reported that toluidine blue, while nearly perfect in detecting high-grade precancerous lesions, was less reliable in staining those of low grade. Grade refers to a scoring system in which pathologists look through a microscope at a tumor biopsy and, based upon its appearance, characterize its potential to turn cancerous. Some speculated doctors and dentists would miss too many potential cancers if they relied on toluidine blue, with disastrous consequences for their patients.

As the controversy smoldered toward the end of the 20th century, most researchers turned away from toluidine blue to focus on defining the broad molecular characteristics of oral cancer. Today, this ongoing effort has led to the discovery of scores of changes in genes, proteins, and chromosomes that might drive the development of tumors in the mouth. But this growing body of information has raised a new challenge: How can these molecular clues be applied most effectively to diagnose oral cancer—a disease that accrues nearly 30,000 new cases and kills more than 7,000 people each year<sup>3</sup>?

One possibility is to pair these molecular discoveries with toluidine blue. The idea hinges on laboratory work that showed an association in early oral lesions between toluidine blue retention and the presence of cells with distinct, cancer-predisposing chromosomal abnormalities. If correct, it would mark a far more relevant standard to evaluate toluidine blue. Toluidine blue, that is, would not need to be held to the artificially high standard of staining every low grade oral lesion, regardless of whether or not they progress to cancer. It could be held to the more meaningful measure of catching those low-grade lesions in particular that will progress to cancer.

Following up on this lead, this year a group of NIDCR grantees reported results from a clinical study demonstrating that toluidine blue appears to stain the highest risk low-grade lesions. In their study, the grantees monitored 100 patients with oral premalignant lesions for 44 months, allowing the scientists to evaluate over time the possible association of toluidine blue staining and three factors: clinical pathology, several well characterized chromosomal aberrations, and clinical outcome. They found toluidine blue detected 16 of 17 cases of high-grade dysplasia (early alterations in cell structure), and it preferentially stained the oral premalignant lesions with minimal or no dysplasia that had high-risk clinical and molecular attributes. The scientists will now follow up this critical finding in larger clinical studies. But, based on the initial work, the merging of old and new could have a profound impact on the future of more informative molecular-based detection of early oral cancer.

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<sup>3</sup> Ibid.

### **Science Advance: New Lead in Tumor Angiogenesis**

NIDCR supported scientists added a key new piece to the puzzle of how tumor cells induce new blood vessels to form and fuel their abnormal growth, a process called angiogenesis. They found that, in addition to the well-known strategy of secreting proteins to trigger angiogenesis, tumor cells also physically attach to a protein displayed on the surfaces of cells that line the walls of our blood vessels. This physical interaction, like a finger pushing a button, sends a signal within these cells to grow and sprout new capillaries.

The finding has potentially major implications for anti-angiogenic therapy, one of the most intensively pursued areas in cancer research. It suggests a future strategy of blocking not only the secreted molecules, but also the cell-to-cell contact. Moreover, the finding raises the intriguing possibility of directing growth-inhibiting drugs at the normal blood vessel cells to stop angiogenesis. The great appeal of this approach is that it blocks the development of capillaries that would feed the developing tumor at a physical site which is not prone to develop resistance to the therapy, a frequent problem in traditional chemotherapeutic approaches.

### **Science Advance: Cell Surface Enzyme Causes Cancer**

NIDCR scientists and colleagues reported in animal studies that a single, scissor-like enzyme called matriptase can cause cancer. This finding marks the first report of a protein-cleaving enzyme, or protease, on the cell surface that can efficiently trigger the formation of tumor cells.

The scientists noted the exact function of matriptase in healthy human cells remains a bit of a mystery. Previous studies showed that cells comprising the outer lining, or epithelium, of nearly all human organs express the protease. They also suggest that matriptase might play a role in activating other membrane-bound proteins on the cell surface that are involved in signaling basic cellular activities, such as growth and motility, or movement. Unanswered, however, was the question of whether matriptase, when over-expressed and deregulated within the cell, might cause cancer. The scientists produced mice that expressed the human version of the gene in a stable, measurable manner to answer the question. They found that deregulated matriptase sends a strong, versatile pro-growth signal; a key point is that, like a classic oncogene, (cancer-causing gene) matriptase *initiates* the erroneous growth signal. Because of its accessibility on the cell surface, the scientists also noted that, with further study, matriptase may serve as an excellent molecular target to treat cancer.

### **Science Advance: Key Finding in How Tumor Cells Invade Healthy Tissues**

To colonize a healthy tissue, cancer cells must degrade the extracellular matrix that encapsulates it. That means primarily degrading a ubiquitous structural protein called collagen. For decades, researchers have focused on how tumor cells co-opt the body's own protein-degrading machinery to bore through the collagen. What has not been well studied is whether cells within the developing tumor also possess their own internal machinery to carry out the job.

NIDCR scientists and colleagues found that a recently discovered molecule called uPARAP/Endo180 not only is present on the surface of certain cells in a tumor, but it also serves

as a switch that activates an internal process to degrade collagen. In fact, the scientists indicate this internal, or intracellular, pathway appears to play a major role in collagen degradation during tumor invasion. This seminal finding raises an important clinical issue. A number of cancer drugs are under study to prevent collagen degradation through the co-opting of the body's protein-degrading machinery. Is it possible that tumors simply can compensate for the effects of the drugs by activating the intracellular degradation pathway?

## **PAIN AND NEUROSENSORY RESEARCH**

The temporomandibular joints (TMJ) - where the jaw and skull bones meet on both sides of the head - are always in harm's way. The TMJ is readily exposed to absorb blunt force to the head, and, because of its essential role in opening the mouth, the joint must absorb and process continuous mechanical stress throughout the day from chewing, talking, clenching, and even grinding one's teeth at night. Given this heavy daily wear and tear, an estimated 10 million Americans today live with temporomandibular joint and muscle disorders (TMJMD), a group of at least 20 distinct pathologic conditions, which disproportionately affect women. Many additional individuals suffer from other chronic craniofacial pain pathologies such as trigeminal neuralgia.

NIDCR has long been a leader in the area of pain research and management. By spanning the areas of basic, translational and clinical research, NIDCR's pain research encompasses a broad array of scientific areas – from basic studies of the biology of pain to research on novel approaches to manage chronic and acute pain. Thus, it is natural that NIDCR pain and neuroscience research interfaces with two important NIH-wide initiatives. One is the **NIH Pain Consortium**, composed of representatives of NIH Institutes and Centers that support pain research and jointly led by NIDCR, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute for Nursing Research (NINR). In addition to member Institutes' grants for pain research, recent activities included a conference on Women and Pain and a Science Writer's Seminar on pain. A second program, the **NIH Blueprint for Neuroscience Research**, is a new initiative formed by 15 Institutes and Centers working collaboratively to fund large, innovative neuroscience research projects at NIH. Initiatives on neurodegeneration, which are planned for FY 2007, will be of interest to NIDCR researchers studying chronic orofacial pain disorders such as temporomandibular joint disorders.

### **New Initiative: Temporomandibular Joint and Muscle Disorders - Pathophysiological Mechanisms Linking Comorbid Conditions**

Scientists long have noted that studying TMJMD can be problematic because many patients also battle co-existing chronic illnesses that contribute to, and often mimic, some of the symptoms of TMJMD. These painful conditions include: fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, irritable bowel syndrome, migraine headache, atypical facial pain, and trigeminal neuralgia. Further complicating the research, scientists know little about the underlying molecular and pathological mechanisms that link the symptoms of these associated conditions with TMJMD. Once these mechanisms are delineated, scientists will have a clearer view of the pathophysiology of these conditions, an understanding that is essential in learning to design targeted and more effective treatments for people with TMJMD.

This initiative will determine the fundamental causes of several painful conditions that are known to occur concurrently in people with TMJMD. By defining the underlying causes of these associated conditions, it will be possible to focus more clearly on their contributory role in the development, course, and persistence of TMJMD.

### **Science Advance: Genetics of Pain Perception**

Over the years, scientists have identified a handful of human genes that are involved in pain perception. One is catecholamine-O-methyltransferase, or COMT, an enzyme that inactivates a certain type of nerve signaling compound called a neurotransmitter. NIDCR scientists, grantees, and colleagues recently recruited 202 healthy female volunteers at risk for TMJMD. The researchers analyzed the COMT gene sequence of each volunteer and discovered three common changes in the chemical structure, or spelling, of the gene. These changes, consisting of shared combinations of several repeated chemical “phrases” along the gene sequence, are called haplotypes. Importantly, the three haplotypes correlated with each volunteer’s baseline sensitivity to pain. The three haplotypes were designated: low pain sensitivity, average pain sensitivity, and high pain sensitivity.

After following 170 of the volunteers for many months, the researchers determined that those who had a low-sensitivity-to-pain haplotype were more than two times *less* likely to develop TMJMD. In addition, those with the low-sensitivity haplotype had much higher levels of COMT enzymatic activity compared to the other haplotypes - an observation consistent with animal studies in which inhibition of COMT produced “a profound increase in pain sensitivity.” The challenge now is to pursue this initial work and further define its diagnostic and prognostic usefulness for the treatment of TMJMD.

### **Science Advance: Scientists Decode Bitter Taste**

Obesity, which is recognized as a growing health problem, is a complex condition. One gap in our knowledge that may help address obesity is a thorough understanding of how we taste our foods. The ability to sense bitter substances is one of five fundamental qualities of human taste, alerting us to noxious or even potentially toxic substances. In previous work, NIDCR scientists established that specialized protein receptors on the tongue and palate known as T2R receptors initiate the sensation that our brain recognizes as bitterness. Now the scientists and their colleagues have further decoded the molecular wiring involved in the process. The researchers reported that T2R receptor proteins not only are sufficient and necessary to detect bitter compounds, they vary between mouse and man. This evolutionary diversity helps to explain the differences in bitter taste responses between the species. The next step in the investigation was to determine the mechanism by which the T2R receptors confer the bitter sensation. When mice were engineered to express T2R receptors in sweet sensing cells, they became strongly attracted to the resulting “bitter” taste. Conversely, those that expressed the T2R receptor normally were averse to the same bitter taste that the specially bred sweet-sensing mice found so appealing. This finding illustrates that whether a compound tastes bitter or sweet is not a property of the molecule or even of the receptors that it activates, but rather because it activates a specific class of taste receptor cells that are hard-wired in the nervous system to elicit a specific sensation and

reaction. This discovery may lead to the logical design of new compounds designed to modify taste, for example, in designing non-caloric sweeteners, sweeteners that can improve dental health or compounds that can block the intensely bitter taste associated with many medications.

## ORAL BIOFILM

To date, researchers have identified over 400 different bacteria in the oral biofilm, also known as plaque, but they estimate this number may represent just over half of the microbial species there. This shortfall is due to the fact that many of these microbes cannot be cultivated in the laboratory or recovered in pure form. This makes it extremely difficult to understand how the biofilm functions as an intact community or to identify the subsets of microbes that interact to cause oral infections. As molecular-based techniques have matured in recent years, scientists have begun to make progress in completing the full roster of microbes that inhabit the oral biofilm, essential information in learning to fight periodontal disease, tooth decay, and other common oral conditions.

### **Science Advance: Chronic Periodontitis Involves More Oral Bacterial Species Than Previously Thought**

For most of the 20th century, scientists extracted plaque from periodontal infections, placed it in a culture dish, and then compared the bacterial species that grew to those grown when the sample was taken from a healthy donor. This research led to the paradigm that a small subset of bacteria in the mouth, most notably gram-negative species of bacteria, such as *Porphyromonas gingivalis*, probably causes periodontal disease. However, some have begun to question this paradigm, and have suggested that many more bacterial species are involved than was traditionally believed. A team of NIDCR grantees recently added important new data to bolster this line of thinking.

NIDCR-supported researchers employed open-ended molecular based techniques - that is, cataloguing a broad array of the bacteria present, not just the known species - to compare the subgingival bacteria of a group of fifteen people in good oral health with another group of fifteen who had moderate to severe periodontitis. After identifying a total of 274 bacterial species in the samples, including six that were previously unidentified, the scientists found that 60 percent of these bacteria were from species that have not as yet been successfully grown in culture, meaning studies a decade or more ago would have missed them completely. The group also noticed that the bacterial profiles of healthy and diseased periodontal plaque donors differed in unexpected ways. Looking at the level of bacterial genera - clusters of related species - the researchers found several associations among the gram positives, rather than the gram negatives usually thought to be important in disease. They also noted that several of the newly identified bacteria outnumbered *P. gingivalis* and other species traditionally thought to play a role in periodontal disease. Taken together, these data suggest that chronic periodontitis is the result of global perturbation of the oral bacterial ecology rather than a site-specific microbial shift in the area of periodontal pocketing.

## **Science Advance: Study Finds Direct Association between Cardiovascular Disease and Periodontal Bacteria**

In the early 20th century, scientists proposed that oral bacteria shed from chronic gum infections, enter the circulatory system, and possibly contribute to diseases of the heart and other body organs. This concept, known as the “focal infection theory,” fell out of fashion by the 1940s, and then resurfaced four decades later with the publication of new data proposing a link. Since then, a major sticking point in advancing the research has been simply how to pursue the hypothesis. Lacking the scientific tools to track oral bacteria in the body over several decades to determine if they directly trigger heart disease, most previous studies pursued indirect evidence. Conspicuously missing has been a large, well-designed study that in some way directly evaluates the role of the oral pathogens themselves.

In one of the first large, well-designed studies on the subject, an NIDCR grantee and colleagues reported that older adults who have higher proportions of four periodontal-disease-causing bacteria inhabiting their mouths also tend to have thicker carotid arteries, a strong predictor of stroke and heart attack. These data mark the first report of a direct association between cardiovascular disease and bacteria involved in periodontal disease, an inflammation of the gums that affects to varying degrees an estimated 200 million Americans. The researchers caution, however, that the findings are not proof that the bacteria cause cardiovascular disease, directly or indirectly. They noted that the more than 650 people in the study had their oral bacteria and carotid thickness evaluated at the same point in time, making it impossible to determine which comes first - the periodontal disease or thickening of the carotid artery. The scientists now are monitoring the participants over time in hopes of answering this question.

## **Science Advance: Important Clue into How Oral Bacteria Might Contribute to Endocarditis**

Endocarditis is a sometimes life-threatening infection of the inner surface of the heart and/or its valves. Of the approximately 15,000 cases of endocarditis reported each year in the United States, many likely arise when bacteria that naturally attach to our teeth are displaced and pass into the bloodstream during a dental procedure, flossing, or even chewing food. These microbes while relatively harmless in the mouth, have an affinity for damaged endothelial cells or blood clots in the heart, where they attach, multiply, and form larger bacterial colonies that trigger the endocarditis. Scientists have shown that immune cells called monocytes are prominently found in early inflammatory lesions linked to endocarditis. What has been puzzling is that the monocytes tend to disappear from the lesions over time without becoming macrophages, scavenging immune cells formed from monocytes that remove debris from tissues, such as the damaged, bacteria-laden cells linked to endocarditis.

In studies with the well-known oral bacterium *Streptococcus mutans*, a team of NIDCR grantees showed that the usual monocyte-macrophage transformation rarely occurs. Instead, infected monocytes become dendritic cells, a type of immune cell that initiates an inflammation-producing immune response upon interaction with this bacterium. This finding indicates that changes in a person's normal immune response that are mediated by oral streptococci can contribute to endocarditis. It also suggests that an effective future strategy to treat endocarditis

might involve learning to turn off the destructive immune response and/or reprogram the monocytes to produce macrophages to clear away the disease-causing bacterial colonies from the heart.

## ORAL IMMUNOLOGY

Researchers have long recognized the involvement of oral bacteria in causing periodontal disease, tooth decay, and other common dental conditions. However, identifying the oral bacteria that are destructive to oral health is really just the first step in a much more complex research process. One must also know precisely how these oral microbes interact with our immune cells to spark the sometimes chronic inflammation of our gums, information that will point to specific proteins (for example, the C-reactive protein described earlier in this document) to target for improved periodontal therapy. As laboratory tools have improved in recent years, tremendous progress has been made to fill in the molecular details of this interaction, resulting in a range of discoveries with application not only to conditions in the mouth but throughout the body.

### **Science Advance: Anti Inflammatory Role of Omega-3 Fatty Acids Elucidated**

Most Americans have listened to news stories extolling the anti-inflammatory health benefits of a diet rich in oily fish, such as salmon and mackerel, and their constituent polyunsaturated fat, omega-3 fatty acids. Left unanswered is the question of *how* omega-3 fatty acids protect against periodontitis, heart disease, arthritis, and other inflammatory conditions. A team of NIDCR grantees and their colleagues recently answered part of that question. They discovered that our bodies break down omega-3 fatty acids to yield important byproducts called resolvins, a newly discovered class of dietary fat. The scientists found that the subtype resolvin E1, in particular, helps to stop the migration of certain immune cells to sites of inflammation, thereby modulating the severity of (that is to say, *resolving*) the immune response. This is important, because many serious diseases (including periodontal and heart diseases as described earlier in this document) are thought to be the result of an overly exuberant response to inflammation by our bodies. Previously, the researchers found that aspirin also seems to prompt our bodies to produce resolvins. The scientists say they now are trying to develop large scale production methods for synthetic versions of resolvin E1 to enable larger scale studies that might elucidate additional information on mechanisms of action of this newly-discovered class of fatty acids, optimal therapeutic dosing levels for humans, etc., and possibly one day, to create medications for use in people with diseases caused or exacerbated by inflammatory response mechanisms.

### **New Initiative: Ontogeny of Host Innate Immune Recognition of, and Response to, Oral Microbes**

At birth, our mouths contain hundreds of distinct bacteria, viruses, fungi, and other microbes. Some are potentially disease causing, but most are so-called “commensals.” The commensals obtain food and other benefits from inhabiting the mouth, but, in general, they neither harm nor help their human host. Many scientists have wondered why our innate immune system, which serves as our frontline defense against microbes throughout our lives, allows commensals to inhabit the mouth. The answer appears to be that commensals and the innate immunity that protects our oral mucosa, or gums, have co-evolved to ensure neither adversely affects the well

being or survival of the other. The molecular basis for human-commensal mutualism is one of the fundamental questions in contemporary immunology, and this natural interaction is related to the longstanding quest for an explanation of how our innate immune system distinguishes self from non-self. For dental researchers, this question is particularly interesting because the innate immune system possesses the remarkable ability to discriminate between commensals and oral pathogens, even though many microbes display common structural motifs on their surfaces. By further clarifying the cellular and molecular mechanisms that underlie this discriminatory process, it may be possible in the future to target oral pathogens with greater specificity to prevent or treat periodontal disease, oral candidiasis, and tooth decay.

This initiative will define the cellular and molecular mechanisms involved in innate immune recognition over a lifetime. It will encourage research that explores which molecules on oral microbes are recognized by the innate immune system, how the system responds when it interacts with these microbes, and the contribution of saliva to this immunological process. At the same time, the initiative will foster studies to determine whether subtle genetic differences in a person's DNA might influence the immune response to oral microbes, and what the connection is between our innate recognition of oral microbes and acquired immunity.

## **DENTAL MATERIALS**

Virtually every American remains at risk for tooth decay. As a result, the disease continues to be a prominent public health problem. In fact, tooth decay remains the single most common chronic childhood disease - five times more common than asthma and seven times more common than hay fever<sup>4</sup>. For more than 40 years, dentists have placed tooth-colored dental composites into decayed teeth as an alternative to the traditional silver-colored amalgam restorations. However, most dental composites today still utilize the original matrix-forming molecules as their structural backbone. Despite steady progress in learning how to better formulate and cure, or harden, composites in a damaged tooth - particularly in larger back, or posterior, teeth - dentists still encounter the same basic laws of chemistry that confronted the inventor of composites. That is, a large composite filling shrinks, and stresses the tooth to which it is bonded. The accumulated stress increases the chances that the composite will need to be replaced prematurely and/or that the decayed tooth will crack, requiring more extensive repair. Given the seemingly unsolvable nature of the problem, innovative approaches are essential to introduce alternative methods that have the potential to propel the science of materials and restorative dentistry forward.

### **Science Advance: Promising New Polymer and Dental Material Discovered**

Merging physics, chemical engineering, and materials science, NIDCR grantees and colleagues have developed a cross-linked polymer that reversibly cleaves its chemical backbone to allow for rapid stress relief during the curing process. Remarkably, the polymer does so without any degradation of its mechanical properties. The polymer mixture consists of two substances that

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<sup>4</sup> U.S. Department of Health and Human Services. *Oral Health in America: A Report of the Surgeon General Executive Summary*. Rockville, MD. 2000, p.2.



produce a rubbery network. In addition to its potential usefulness in addressing problems with shrinkage of dental materials, this process may also be applied to a vast array of other biomedical or industrial applications for which the control or elimination of stress is critical.

### **New Initiative: Nanocomposite Materials for Dental Restorations**

Nanotechnology stands out as one of the most promising areas of modern science. It involves the manipulation of matter at dimensions of roughly 1 to 100 nanometers (a nanometer is one billionth of a meter) to handcraft, atom by atom, unique molecules with novel applications, an idea that was hard to imagine just a generation ago. Preliminary work indicates that, on the nanoscale, dental researchers can more strategically influence the overall process of matrix formation and thereby enhance the structural integrity of composite dental materials.

Building on this initial work and its important potential benefits to dentistry and public health, the NIDCR will launch an initiative to produce a new generation of nanocomposite materials with enhanced adhesive bonding to the tooth surface, improved durability, better aesthetics, and maximum biocompatibility. The initiative will spur research to fabricate optimal nanoparticles as the structural building blocks for nanocomposites, create novel dental nanomaterials with greater wear resistance, evaluate the interaction of oral tissues with nanocomposites, produce novel nanofillers to act as key strengthening additives to composites, and evaluate the overall biocompatibility of the nanostructure materials.

## **DENTAL ENAMEL**

The developmental biology of dental enamel remains one of nature's most intriguing mysteries. The tissue starts to form in the tooth bud not as the hard, white substance so familiar to us in the mirror, but as a soft, protein-rich matrix specked with mineral crystals called hydroxyapatite. When a tooth finally erupts through the gums, nearly all of the original matrix has disappeared, leaving few clues to how its dominant protein, called amelogenin, orchestrates the mineralization process in the tooth bud. Solving this developmental mystery will be critical in learning to make artificial enamel, a vital step in one day engineering replacement teeth.

### **Science Advance: From Matrix to Microribbons**

A team of NIDCR grantees and colleagues offered an intriguing structural glimpse into how amelogenin might orchestrate enamel deposition. They found in laboratory studies that amelogenin forms into spherical balls that in turn, assemble into long beaded chains. Because of their thin, ribbon-like appearance, the scientists called the chains "microribbons." The scientists next dipped the microribbons into a mineralizing calcium-phosphate solution to determine whether they possess the structural integrity to serve as protein scaffolds for the mineralization process. The result: the microribbons yielded ordered hydroxyapatite crystals with similar orientation to those formed in enamel. This marks the first time that scientists have assembled amelogenin into ordered structures, mineralized them, and shown that the spherical balls, called nanospheres, are responsible for the ordered crystal growth that is essential to proper enamel formation, information that will be absolutely essential to understanding how enamel is formed in the tooth bud, and furthering the NIDCR's ongoing goal to engineer the human tooth.

## **Science Advance: Measuring Toughness of the Dentin-Enamel Junction**

Nature has brilliantly engineered our teeth to transfer mechanical stresses, such as chewing, to a thin, supportive region below the surface of the tooth, where our bony dentin and rigid enamel meet. This biologically complex region, known as the dentin-enamel junction, or DEJ, has captured the interest of dental researchers in hopes of better characterizing its stress-resistant capacity and its unique ability to prevent developing cracks in the outer enamel from spreading throughout the tooth and causing fractures. Despite the long-term research interest, largely missing from the scientific literature has been a comprehensive and technologically sophisticated analysis of structural variations and stress resistance across the DEJ, information that would greatly benefit the dental community. NIDCR grantees and colleagues recently provided this broad structural analysis and, based on their data, offered a new estimate of the toughness of the DEJ, characterizing the region as up to 10 times tougher than enamel but 75 percent less tough than dentin. They also concluded that a tooth's ability to stop the spread of cracks resides in the mantle dentin, *i.e.*, the original layer of dentin laid down at the time of initial tooth formation, not in properties of the DEJ. This essential baseline information will allow academia and industry to develop dental products that better correspond to the structural dynamics of the tooth and therefore function better in the mouth. This knowledge may contribute to finding solutions to the “cracked tooth syndrome”, a problem that is becoming increasingly common among graying baby boomers.

### **NIH ROADMAP**

The Roadmap's three broad initiatives—*New Pathways to Discovery*, *Research Teams of the Future*, and *Re-Engineering the Clinical Research Enterprise* are synergistic with many recent and planned NIDCR activities, and the Institute directly supports awards under several Roadmap initiatives. For example, NIDCR participated in the development of the Roadmap Interdisciplinary Clinical Predoctoral (T32) Program; as a result, a number of the grantees include direct involvement of dental schools. Eighty percent (four out of five) of the recently awarded Multidisciplinary Clinical Research Career Development Programs grants involve dental school collaboration. Additionally, NIDCR directly supported awards for Supplements for Methodological Innovations in the Behavioral and Social Sciences.

Studies such as those 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, the Roadmap initiative on *Interdisciplinary Research Teams of the Future* enables NIDCR's ongoing inter- and multidisciplinary efforts to expand and develop new approaches to research. This initiative's support of translational research and NIDCR-supported activities such as the recent “Pathway to Product Development” meeting are mutually reinforcing.

We anticipate that a number of dental schools will participate in the NIH Clinical and Translational Science Award (CTSA), a Roadmap initiative to catalyze the development of a new discipline of clinical and translational science. Their partnership and collaboration with schools of medicine, nursing, pharmacy, osteopathy, public health, engineering, and other

clinically related entities is intended to create a new academic home for clinical and translational research that will capture, translate, and disseminate new scientific advances for the benefit of all Americans.

The scientific goals of the initiative *Building Blocks, Biological Pathways and Networks* 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. 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. The NIH *Nanomedicine Roadmap Initiative* will be instrumental to NIDCR efforts on "Building the Tooth: Bridging Biology and Material Sciences." For this initiative a biomimetics approach will be used to identify, at the nanoscale, the building blocks needed if we are to build a tooth and its associated structures.

Through these and similar efforts, the NIDCR is pleased to join with its sister Institutes to further the trans-NIH goal of boosting the resources and technologies needed for 21st century biomedical science.

#### **INNOVATIVE MANAGEMENT AND ADMINISTRATION**

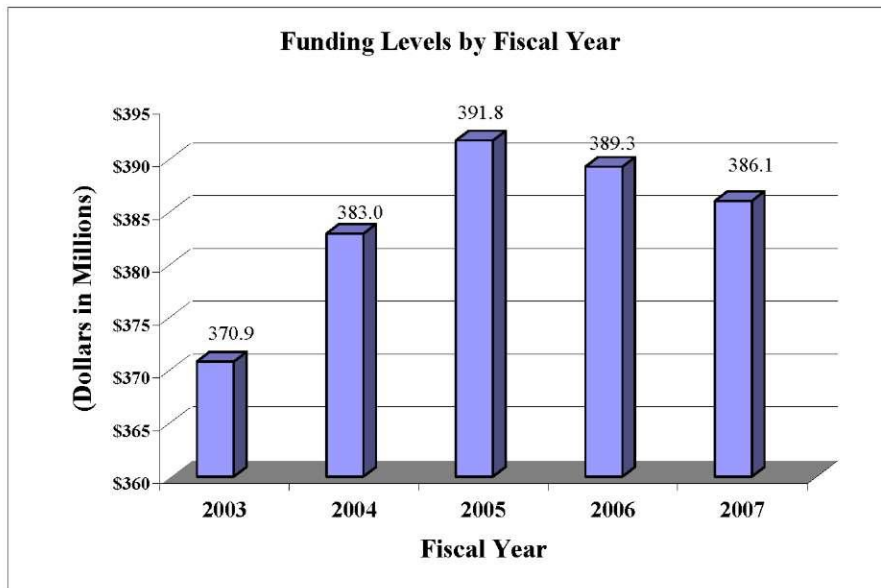
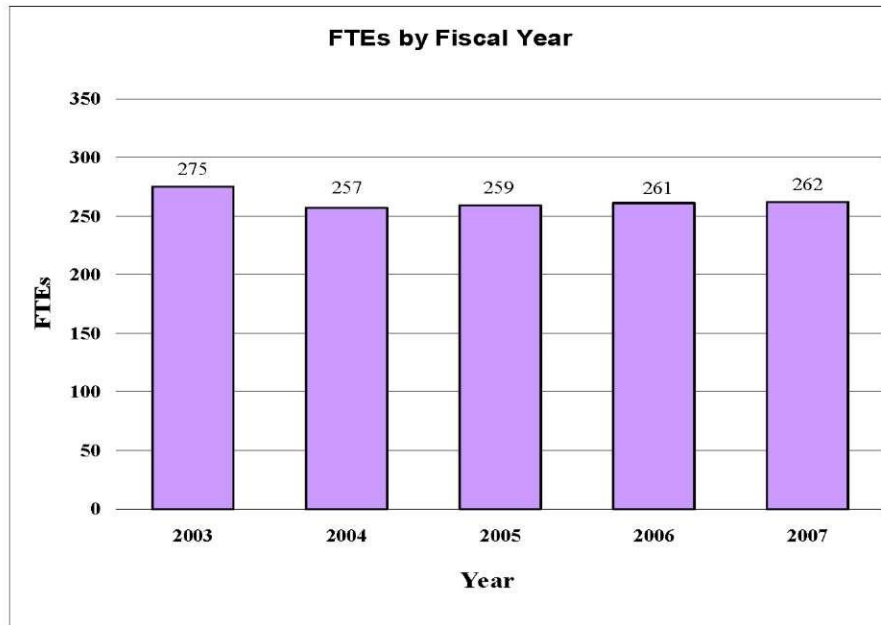
To ensure that the Institute's research agenda appropriately focuses on our mission, NIDCR has established a rigorous and more immediate science planning and priority setting process that feeds into the well-established annual budget process. These efforts are supported by a well-managed information technology infrastructure that relies on NIH enterprise IT systems and utilizes the latest technology to conduct business electronically. One example of NIDCR's foresight in electronic business management lies in the relatively new SCORE system that integrates data on all Institute grants and contracts, and is designed to provide easy and rapid retrieval of information needed to respond to requests from a variety of government and public sources. NIDCR is actively engaged with other Institutes in implementing Grants.gov to receive and process grant applications. NIDCR's IT investment is protected by its long-standing best practice of 100 percent patch management of commodity desktop computers, and patch management for non-commodity computers in all cases where it is practical to do so.

Last, to assure that we support research endeavors that truly reflect the Institute's mission, we continue to have a robust evaluation program. Currently, an evaluation of NIDCR's portfolio in oral health disparities research is underway and evaluations of our portfolio in craniofacial anomalies and the newly-funded General Dental Practice-Based Research Networks initiative are in the design phase.

## Budget Policy

The Fiscal Year 2007 budget request for the NIDCR is \$386,095,000, a decrease of \$3,241,000 and 0.8 percent from the FY 2006 Appropriation. Included in the FY 2007 request is NIDCR's support for the trans-NIH Roadmap initiatives, estimated at 1.2 percent of the FY 2007 budget request. 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. Note that as the result of several administrative restructurings in recent years, FTE data are non-comparable.



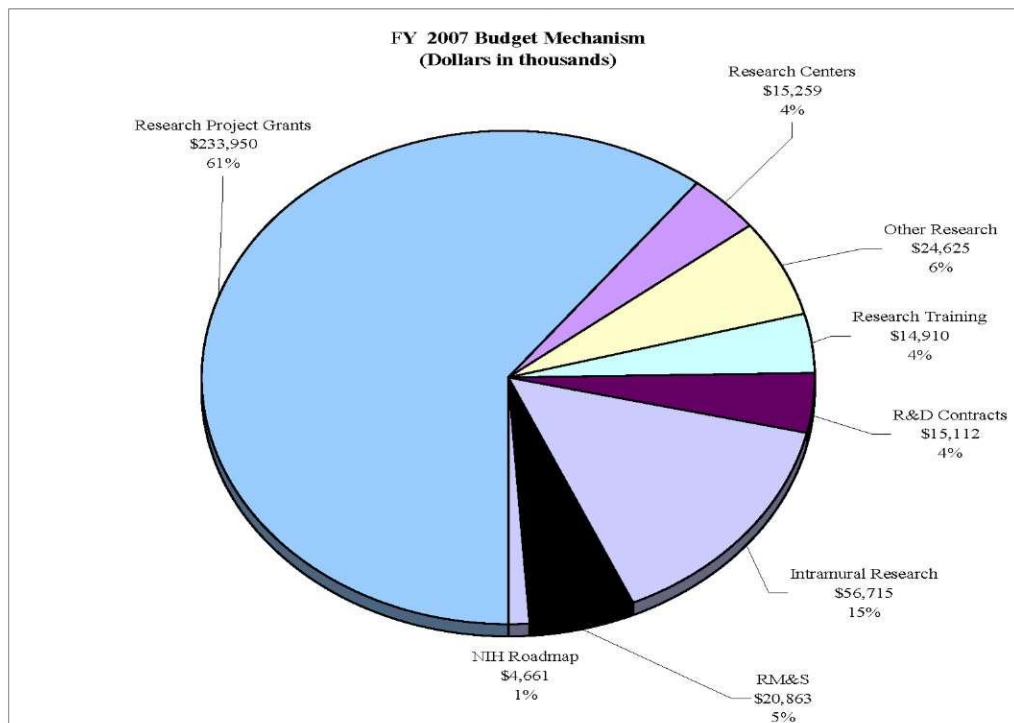
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be \$321,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NIDCR has committed to a programmatic increase for an award, such increases will be provided.

NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIDCR, \$450,000 will be used to support 5 awards for the new K/R "Bridges to Independence" program.

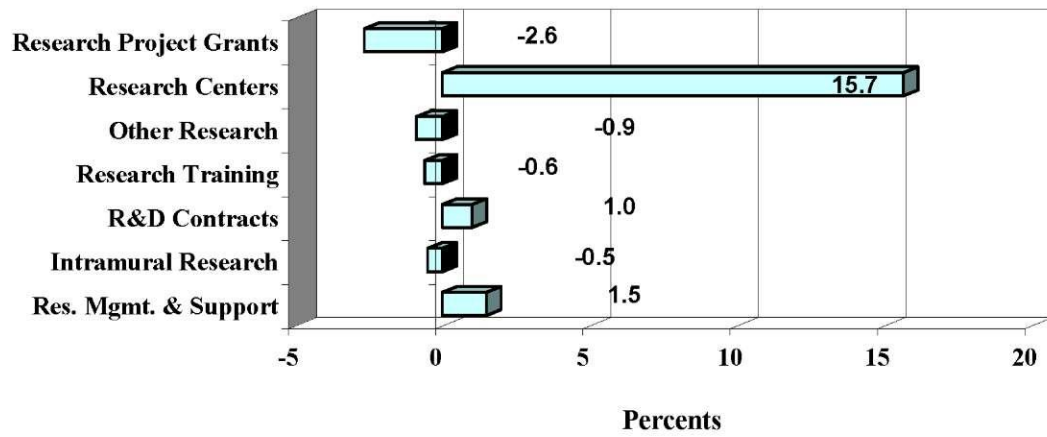
NIDCR will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes \$647,000 to support this project.

In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels. The FY 2007 request includes funding for 8 research centers, 117 other research grants, including 90 career awards, and 17 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by 1.5 percent. To cover the cost of pay increases, NIDCR will decrease the amounts budgeted for other cost categories such supplies, equipment, and services.

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



**FY 2007 Estimate  
Percent Change from FY 2006 Mechanism**



**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

Budget Mechanism - Total

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects:						
Noncompeting	488	\$175,577,000	481	\$173,080,000	451	\$170,693,000
Administrative supplements	(19)	1,593,000	(16)	1,950,000	(14)	750,000
Competing:						
Renewal	37	14,534,000	37	14,412,000	35	13,728,000
New	142	42,833,000	140	42,461,000	134	40,449,000
Supplements	0	0	0	0	0	0
Subtotal, competing	179	57,367,000	177	56,873,000	169	54,177,000
Subtotal, RPGs	667	234,537,000	658	231,903,000	620	225,620,000
SBIR/STTR	39	8,380,000	34	8,400,000	34	8,330,000
Subtotal, RPGs	706	242,917,000	692	240,303,000	654	233,950,000
Research Centers:						
Specialized/comprehensive	7	12,156,000	10	13,104,000	8	15,168,000
Clinical research	0	89,000	0	90,000	0	91,000
Biotechnology	0	15,000	0	0	0	0
Subtotal, Centers	7	12,260,000	10	13,194,000	8	15,259,000
Other Research:						
Research careers	95	12,939,000	91	12,500,000	90	12,350,000
Other	37	11,937,000	30	12,344,000	27	12,275,000
Subtotal, Other Research	132	24,876,000	121	24,844,000	117	24,625,000
Total Research Grants	845	280,053,000	823	278,341,000	779	273,834,000
Research Training:	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>	
Individual awards	31	1,290,000	29	1,200,000	28	1,160,000
Institutional awards	331	14,618,000	311	13,800,000	309	13,750,000
Total, Training	362	15,908,000	340	15,000,000	337	14,910,000
Research & development contracts (SBIR/STTR)	20 (0)	15,180,000 (19,000)	17 (0)	14,961,000 (0)	17 (0)	15,112,000 (0)
Intramural research	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>	
Intramural research	173	57,766,000	171	57,000,000	172	56,715,000
Research management and support	86	20,445,000	90	20,555,000	90	20,863,000
NIH Roadmap for Medical Research		2,477,000		3,479,000		4,661,000
Total, NIDCR	259	391,829,000	261	389,336,000	262	386,095,000
(Clinical Trials)		(107,015,000)		(107,287,000)		(107,317,000)

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

**Budget Authority by Activity**  
**(dollars in thousands)**

ACTIVITY	FY 2005		FY 2006		FY 2007		Change	
	Actual		Appropriation		Estimate			
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
<u>Extramural Research:</u>								
Oral Diseases and Disorders Research		\$311,141		\$308,302		\$303,856		(\$4,446)
Subtotal, Extramural research		311,141		308,302		303,856		(4,446)
Intramural research	173	57,766	171	57,000	172	56,715	1	(285)
Res. management & support	86	20,445	90	20,555	90	20,863	0	308
NIH Roadmap for Medical Research	0	2,477	0	3,479	0	4,661	0	1,182
<b>Total</b>	<b>259</b>	<b>391,829</b>	<b>261</b>	<b>389,336</b>	<b>262</b>	<b>386,095</b>	<b>1</b>	<b>(3,241)</b>



**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

**Summary of Changes**

FY 2006 Estimate		\$389,336,000		
FY 2007 Estimated Budget Authority		386,095,000		
Net change		(3,241,000)		
CHANGES	FY 2006 Appropriation		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		\$21,401,000		\$311,000
b. Annualization of January 2006 pay increase		21,401,000		168,000
c. January 2007 pay increase		21,401,000		358,000
d. One less day of pay		21,401,000		0
e. Payment for centrally furnished services		9,980,000		150,000
f. Increased cost of laboratory supplies, materials, and other expenses		25,619,000		484,000
Subtotal				1,471,000
2. Research Management and Support:				
a. Within grade increase		10,219,000		168,000
b. Annualization of January 2006 pay increase		10,219,000		80,000
c. January 2007 pay increase		10,219,000		171,000
d. One less day of pay		10,219,000		0
e. Payment for centrally furnished services		3,484,000		52,000
f. Increased cost of laboratory supplies, materials, and other expenses		6,852,000		122,000
Subtotal				593,000
Subtotal, Built-in				2,064,000

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

**Summary of Changes--continued**

CHANGES	FY 2006 Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	481	\$175,030,000	(30)	(\$3,587,000)
b. Competing	177	56,873,000	(8)	(2,696,000)
c. SBIR/STTR	34	8,400,000	0	(70,000)
Total	692	240,303,000	(38)	(6,353,000)
2. Research centers	10	13,194,000	(2)	2,065,000
3. Other research	121	24,844,000	(4)	(219,000)
4. Research training	340	15,000,000	(3)	(90,000)
5. Research and development contracts	17	14,961,000	17	151,000
Subtotal, extramural				(4,446,000)
6. Intramural research	<u>FTEs</u> 171	57,000,000	<u>FTEs</u> 1	(1,756,000)
7. Research management and support	90	20,555,000	0	(285,000)
11. NIH Roadmap for Medical Research	0	3,479,000	0	1,182,000
Subtotal, program	261	389,336,000		(5,305,000)
Total changes			1	(3,241,000)

**NATIONAL INSTITUTES OF HEALTH  
National Institute of Dental and Craniofacial Research**

**Budget Authority by Object**

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	261	262	1
Full-time equivalent of overtime & holiday hours	0	0	0
Average ES salary	\$154,786	\$157,340	\$2,554
Average GM/GS grade	11.1	11.1	0.0
Average GM/GS salary	\$75,880	\$77,133	\$1,253
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	\$99,104	\$100,740	\$1,636
Average salary of ungraded positions	103,500	105,208	1,708
<b>OBJECT CLASSES</b>	<b>FY 2006 Appropriation</b>	<b>FY 2007 Estimate</b>	<b>Increase or Decrease</b>
Personnel Compensation:			
11.1 Full-Time Permanent	\$12,713,000	\$13,238,000	\$525,000
11.3 Other than Full-Time Permanent	8,204,000	8,634,000	430,000
11.5 Other Personnel Compensation	305,000	314,000	9,000
11.7 Military Personnel	728,000	748,000	20,000
11.8 Special Personnel Services Payments	3,540,000	3,668,000	128,000
<b>Total, Personnel Compensation</b>	<b>25,490,000</b>	<b>26,602,000</b>	<b>1,112,000</b>
12.0 Personnel Benefits	5,671,000	5,943,000	272,000
12.2 Military Personnel Benefits	459,000	472,000	13,000
13.0 Benefits for Former Personnel	0	0	0
<b>Subtotal, Pay Costs</b>	<b>31,620,000</b>	<b>33,017,000</b>	<b>1,397,000</b>
21.0 Travel & Transportation of Persons	628,000	640,000	12,000
22.0 Transportation of Things	116,000	109,000	(7,000)
23.1 Rental Payments to GSA	390,000	370,000	(20,000)
23.2 Rental Payments to Others	0	0	0
23.3 Communications, Utilities & Miscellaneous Charges	0	0	0
24.0 Printing & Reproduction	321,000	313,000	(8,000)
25.1 Consulting Services	1,271,000	1,211,000	(60,000)
25.2 Other Services	3,021,000	2,854,000	(167,000)
25.3 Purchase of Goods & Services from Government Accounts	40,125,000	40,654,000	529,000
25.4 Operation & Maintenance of Facilities	504,000	473,000	(31,000)
25.5 Research & Development Contracts	4,572,000	3,689,000	(883,000)
25.6 Medical Care	511,000	480,000	(31,000)
25.7 Operation & Maintenance of Equipment	701,000	659,000	(42,000)
25.8 Subsistence & Support of Persons	0	0	0
<b>25.0 Subtotal, Other Contractual Services</b>	<b>50,705,000</b>	<b>50,020,000</b>	<b>(685,000)</b>
26.0 Supplies & Materials	6,196,000	5,824,000	(372,000)
31.0 Equipment	2,540,000	2,397,000	(143,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	293,341,000	288,744,000	(4,597,000)
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	0	0	0
44.0 Refunds	0	0	0
<b>Subtotal, Non-Pay Costs</b>	<b>354,237,000</b>	<b>348,417,000</b>	<b>(5,820,000)</b>
<b>NIH Roadmap for Medical Research</b>	<b>3,479,000</b>	<b>4,661,000</b>	<b>1,182,000</b>
<b>Total Budget Authority by Object</b>	<b>389,336,000</b>	<b>386,095,000</b>	<b>(3,241,000)</b>

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

**Salaries and Expenses**

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
<b>Personnel Compensation:</b>			
Full-Time Permanent (11.1)	\$12,713,000	\$13,238,000	\$525,000
Other Than Full-Time Permanent (11.3)	8,204,000	8,634,000	430,000
Other Personnel Compensation (11.5)	305,000	314,000	9,000
Military Personnel (11.7)	728,000	748,000	20,000
Special Personnel Services Payments (11.8)	3,540,000	3,668,000	128,000
<b>Total Personnel Compensation (11.9)</b>	<b>25,490,000</b>	<b>26,602,000</b>	<b>1,112,000</b>
Civilian Personnel Benefits (12.1)	5,671,000	5,943,000	272,000
Military Personnel Benefits (12.2)	459,000	472,000	
Benefits to Former Personnel (13.0)	0	0	0
<b>Subtotal, Pay Costs</b>	<b>31,620,000</b>	<b>33,017,000</b>	<b>1,397,000</b>
Travel (21.0)	628,000	640,000	12,000
Transportation of Things (22.0)	116,000	109,000	(7,000)
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities and Miscellaneous Charges (23.3)	0	0	0
Printing and Reproduction (24.0)	321,000	313,000	(8,000)
<b>Other Contractual Services:</b>			
Advisory and Assistance Services (25.1)	1,271,000	1,211,000	(60,000)
Other Services (25.2)	3,021,000	2,854,000	(167,000)
Purchases from Govt. Accounts (25.3)	24,200,000	23,919,000	(281,000)
Operation & Maintenance of Facilities (25.4)	504,000	473,000	(31,000)
Operation & Maintenance of Equipment (25.7)	701,000	659,000	(42,000)
Subsistence & Support of Persons (25.8)	0	0	0
<b>Subtotal Other Contractual Services</b>	<b>29,697,000</b>	<b>29,116,000</b>	<b>(581,000)</b>
Supplies and Materials (26.0)	6,191,000	5,819,000	(372,000)
<b>Subtotal, Non-Pay Costs</b>	<b>36,953,000</b>	<b>35,997,000</b>	<b>(956,000)</b>
<b>Total, Administrative Costs</b>	<b>68,573,000</b>	<b>69,014,000</b>	<b>441,000</b>

## NATIONAL INSTITUTES OF HEALTH

### National Institute of Dental and Craniofacial Research

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

##### FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

##### Item

***Dental Abnormalities*** - The Committee encourages NIDCR to continue its support of research aimed at the health of oral mineralized tissues. This includes studying the role of genetic factors and the potential for cell-based and pharmacological therapy and early screening for osteoporosis. Additionally NIDCR is urged to continue research on fibrous dysplasia/McCune Albright syndrome and to focus on the dental abnormalities associated with Paget's disease. (p. 65)

##### Action Taken or to be Taken

The NIDCR is committed to supporting research aimed at improving oral health and has established several regional dental practice-based research networks which, over the next seven years, will engage practicing dentists and their academic partners in conducting clinical studies related to prevention and treatment strategies for oral diseases including caries and periodontal diseases that involve oral mineralized tissues. NIDCR continues to support studies of proteomics and gene-environment interactions to define the risk factors responsible for predisposing some individuals to these oral diseases.

NIDCR-supported scientists are actively engaged in identifying and characterizing the role of genetic factors in diseases of tooth development and of supporting tissues. Genetic analysis has identified genes that are important for the form and function of oral hard tissues (tooth enamel and dentin, bone, temporomandibular joint), and developed mouse models that serve as a basis for the study of human disease. For example, a protein was identified that is critical for enamel formation in mice, and recently two mutations in the corresponding protein were identified in human patients with abnormal enamel formation. A related protein was found to be critical for proper shape of the skull, bone formation, molar eruption and formation of the temporal mandibular joint. Other animal models indicate that several bone matrix proteins control the activity of growth factors important to maintenance of hard tissues such as bone and dentin and that their absence results in osteoarthritis of the temporal mandibular joint. A recent study showed that mice that lack a cell-signaling factor are highly susceptible to periodontal bone loss caused by infection from oral bacteria. Continued development and study of such models will provide a greater understanding of how to better manipulate hard tissue cells for repair and regeneration, and provide targets for pharmacological therapies.

NIDCR-supported investigators are also studying the potential of stem or progenitor cells collected from various adult tissue sources, such as bone marrow, baby teeth, wisdom teeth, fat, and muscle to repair craniofacial, oral and dental tissues. Investigators have reported that stem cells isolated from muscle were able to repair a bone defect in the skull. Preclinical studies of the use of bone marrow cells for bone regeneration have recently been completed, and NIDCR researchers are preparing to apply these techniques to patients with large skull defects due to trauma.

A group of NIDCR-supported researchers are investigating whether biomarkers can be identified in human saliva that would indicate bone loss from the jaw. Oral bone loss is often associated with osteoporosis, and further complicated by gum diseases. These biomarkers may represent a convenient screening method for early screening for generalized osteoporosis.

NIDCR clinical researchers are currently engaged in five active protocols for the study and treatment of fibrous dysplasia of bone, a genetic disease whereby normal bone and bone marrow are replaced with fibrous tissue and defective bone. Patients often have additional hormonal disorders, which worsen the bone disease. Recently, NIDCR investigators determined that these patients often over-produce a newly discovered hormone that causes loss of phosphate, an essential molecule for bone mineral. Current studies aim to determine how this hormone works, and are evaluating several different therapies for controlling the hormonal imbalances. A long-term study of these patients has enabled physicians to personalize their clinical management plans leading to improved prognosis and quality of life, and is leading to evidence-based changes in the standard of care.

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 attributed to the malfunction of cells that destroy bone, osteoclasts. The NIDCR supports research on the activities and functions of these cells, and continues to pursue bone specimens from Paget's disease patients in order to determine cellular and molecular defects of bone marrow cells.

#### 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.

#### 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 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 tests with miniaturized power supplies, reagent cartridges, miniaturized laser-induced fluorescence detector, and control hardware to detect 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.

In FY 2005 the NIDCR issued a request for applications (RFA) to continue the program for another five years to promote the fabrication and validation of a prototype portable device containing integrated electronic components that would manage introduction of saliva samples, preprocessing, detection, and analysis. Discussions have been initiated between NIDCR and NCI program staff regarding validation of oral cancer biomarkers present in saliva.

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. So far about 637 proteins in fluid obtained directly from a salivary gland, and 530 in saliva itself have been identified.

Moreover, the NIDCR has awarded a contract to develop an international research registry for Sjögren's syndrome, an autoimmune disease. This registry houses well-characterized biological specimens, including saliva, from patients and healthy controls in five countries. Samples are provided to investigators who are studying different stages of the disease to determine the feasibility of new diagnostic tests for Sjögren's syndrome.

#### FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

##### Item

***Dental Abnormalities*** - NIDCR is encouraged to continue its support of research aimed at the health of oral mineralized tissues. This includes studying the role of genetic factors and the potential for cell-based and pharmacological therapy and early screening for osteoporosis. Additionally, NIDCR is urged to continue research on fibrous dysplasia/McCune Albright syndrome and to focus on the dental abnormalities associated with Paget's disease. (p. 103)

### Actions Taken or to be Taken

Please refer to page 29 of this document for NIDCR's response to this significant item regarding Dental Abnormalities.

### Item

***Temporomandibular Joint Disorders [TMJ]*** - The Committee agrees with and is encouraged by recent public statements by NIH officials that because of past and current investments in research and patient registries, the field is now ready to support a substantial new research investment in this complex set of disorders. The Committee therefore strongly urges that NIDCR take its appropriate leadership role in a substantially expanded effort to complete the research needs and opportunities agenda outlined in the June 2005 NIH TMJ Report to Congress. As noted previously, the Committee expects NIDCR to continue to collaborate and coordinate with all relevant ICs.

Because patient advocacy groups are often the best sources of information about affected populations and have established mechanisms for communicating with them, the Committee urges NIDCR to regularly consult with the TMJ Association and other relevant groups as it develops and operates its patient registry activities. In addition, the Committee urges NIDCR to fund an effort to categorize and analyze the symptoms of people with TMJ disorders that are collected in a patient advocacy group database, in an effort to enhance future TMJ research agendas. (p. 103)

### Actions Taken or to be Taken

The National Institute of Dental and Craniofacial Research (NIDCR) continues to provide leadership in temporomandibular joint and muscle disorders (TMJMD) research through the NIH's TMJMD Interagency Working Group and, particularly, through the active development of its own extramural grant and contract portfolio. Since the inception of the TMJDIWG, funding by NIH ICs other than NIDCR has increased from \$308,000 in FY1999 to \$5.3 million in FY2004. Over this same period, NIDCR's commitment to TMJMD research has remained consistently high, growing from \$10.5 million in FY1999 to \$11.4 million in FY2004. During FY2005, the NIDCR issued two Requests for Applications (RFA), developed a third one that may lead to a trans-NIH activity, and funded a major prospective evaluation and risk assessment of orofacial pain, representing more proactive solicitation of research than any other Institute or Center at NIH. One RFA, *Pathobiology of Temporomandibular Joint Disorders*, resulted in 24 applications, ten of which were on the topic of TMJMD and all of which were funded. Applications for the other RFA, *The Role of Neuronal/Glial Cell Interactions in Orofacial Pain Disorders*, were due in November 2005 and the Institute already has 25 letters of intent.

The NIDCR recognizes the value of input from patients on a variety of issues relevant to Institute's mission. In this regard, we sponsor an annual meeting of the leadership of all patient advocacy groups whose membership benefits from the research activities of the Institute. In addition, leaders of the two TMJMD patient advocacy groups are fully participating members of the TMJMD Interagency Working Group. The Institute has funded two grants to support the TMJ Association's scientific meetings, one in 2003 titled "Joint and Muscle Dysfunction of the



Temporomandibular Joint” and the other in 2005 titled “Advancing Diagnostic Approaches for TMJ Diseases and Disorders.” In addition, the Institute was instrumental in disseminating the proceedings of these conferences, published in *TMJ Science*, to dental schools and oral health researchers. Finally, the Director of NIDCR encourages and engages in regular one-on-one meetings with the leaders of the two TMJMD patient advocacy groups. Moreover, the Assistant to the Director has arranged individual meetings between the President of the TMJ Association and extramural program staff as well as Directors of several other Institutes and the Director of the Office of Research on Women’s Health.

Patient advocates provide input into certain ongoing research projects funded by NIDCR by participating as members of steering committees. For example, the President of the TMJ Association serves on the steering committee of the jaw implant registry funded by the NIDCR at the University of Minnesota. This study involves collaborations between the University of North Carolina at Chapel Hill, The University of Florida, The University of Maryland, The State University of New York at Buffalo and Battelle. The purpose of this systematic prospective study of more than 3000 individuals is to provide information to physicians and dentists about the causes of TMJMD and who is likely to be affected by this disease. Not surprising, this study will produce data much more powerful and useful than that contained in the TMJ Association, or any non-scientifically generated database on patients insofar. It will also provide systematically collected longitudinal information about symptoms and their development as well as biological information from each participant. An unbiased picture of the time course of overt symptom development can emerge from these data along with the possibility of developing biomarkers and risk factors for TMJMDs.

**NATIONAL INSTITUTES OF HEALTH  
National Institute of Dental and Craniofacial Research**

**Authorizing Legislation**

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	\$374,336,000	Indefinite	\$371,185,000
Craniofacial Research	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	15,000,000		14,910,000
<b>Total, Budget Authority</b>				<b>389,336,000</b>		<b>386,095,000</b>

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

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

**Appropriations History**

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation <u>1/</u>
1998	190,081,000 <u>2/</u>	209,403,000	211,611,000	209,415,000
1999	214,559,000 <u>2/ 3/</u>	228,961,000	233,588,000	234,338,000
Rescission				(155,000)
2000	225,709,000 <u>2/</u>	257,349,000	267,543,000	270,253,000
Rescission				(1,442,000)
2001	263,075,000 <u>2/</u>	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	393,269,000	405,269,000	393,269,000
Rescission				(3,933,000)
2007	386,095,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

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

3/ Reflects a decrease of \$590,000 for the budget amendment for Bioterrorism

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

**Detail of Full-Time Equivalent Employment (FTEs)**

OFFICE/DIVISION	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	13	14	14
Office of Administrative Management	14	14	14
Office of Information Technology	6	8	8
Office of Science Policy and Analysis	6	7	7
Office of Communications and Health Education	8	8	8
Office of International Health	2	1	1
Division of Intramural Research	173	171	172
Center for Integrative Biology and Infectious Diseases	8	8	8
Center for Clinical Research	6	6	6
Division of Extramural Activities	15	16	16
Center for Biotechnology and Innovation	3	3	3
Center for Health Promotion and Behavioral Research	5	5	5
<b>Total</b>	<b>259</b>	<b>261</b>	<b>262</b>
FISCAL YEAR	Average GM/GS Grade		
2003	10.8		
2004	10.8		
2005	11.1		
2006	11.1		
2007	11.1		

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Dental and Craniofacial Research**

**Detail of Positions**

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	2	2	2
Total - ES Salary	\$302,316	\$309,572	\$314,680
GM/GS-15	17	16	16
GM/GS-14	26	26	26
GM/GS-13	16	16	16
GS-12	26	27	27
GS-11	23	24	24
GS-10	1	1	1
GS-9	18	18	18
GS-8	6	6	6
GS-7	11	11	11
GS-6	9	9	9
GS-5	2	3	3
GS-4	0	2	2
GS-3	1	1	1
GS-2	1	1	1
GS-1	1	1	1
Subtotal	158	162	162
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	6	6	5
Senior Grade	1	1	1
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	8	8	7
Ungraded	89	99	100
Total permanent positions	172	173	174
Total positions, end of year	257	264	265
Total full-time equivalent (FTE) employment, end of year	259	261	262
Average ES level	ES-4	ES-4	ES-4
Average ES salary	\$151,158	\$154,786	\$157,340
Average GM/GS grade	11.1	11.1	11.1
Average GM/GS salary	\$74,102	\$75,880	\$77,133