DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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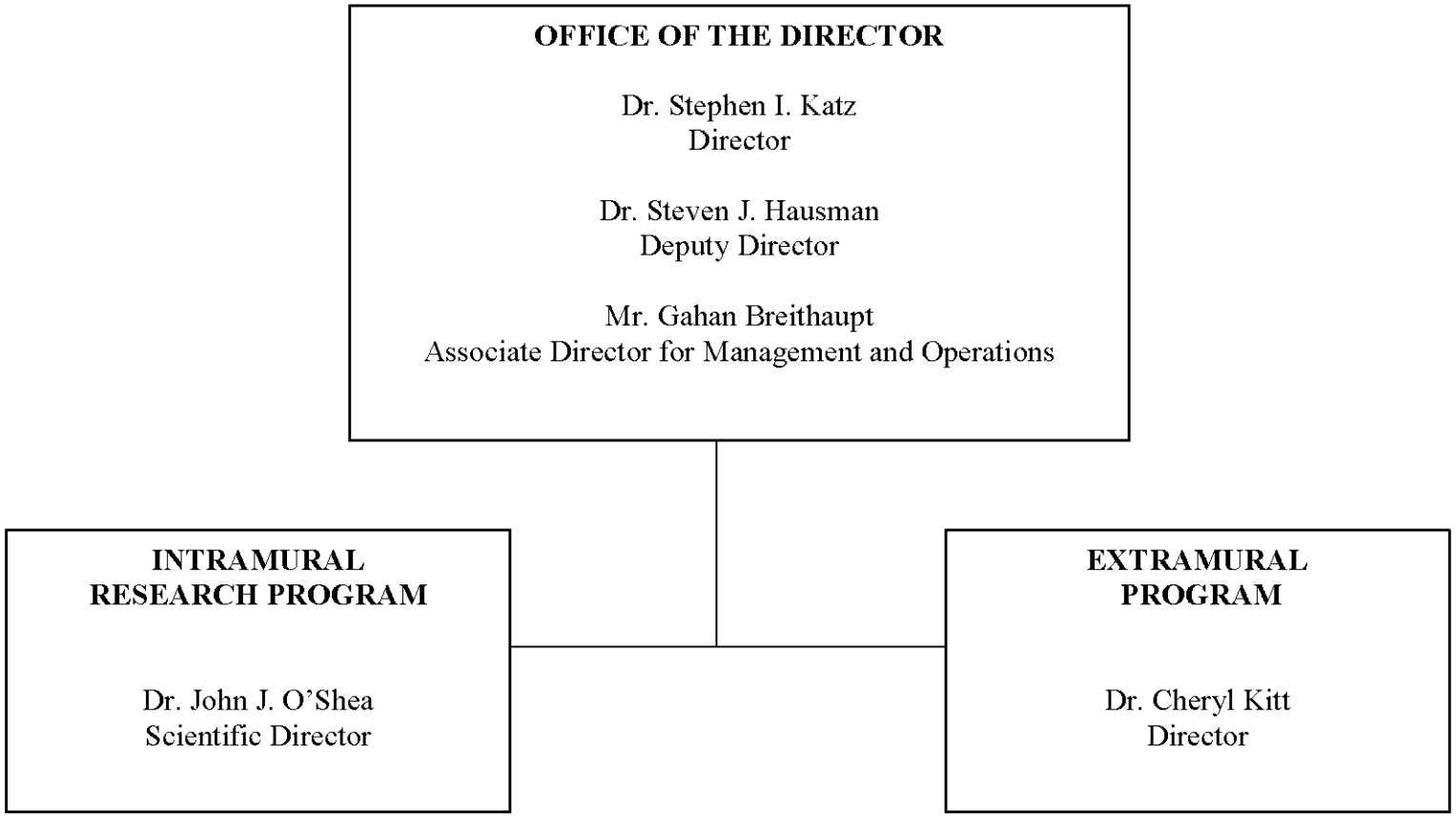
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to Arthritis and Musculoskeletal and Skin Diseases, [$507,932,000] *$504,533,000*.

[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 Arthritis and Musculoskeletal and Skin Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	$515,378,000	$513,063,000	$504,533,000
Enacted Rescissions	(4,221,000)	(5,131,000)	0
Subtotal, Adjusted Appropriation	511,157,000	507,932,000	504,533,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(3,231,000)	(4,539,000)	0
Comparative transfer from OD for NIH Roadmap	3,231,000	4,539,000	0
Subtotal, adjusted budget authority	511,157,000	507,932,000	504,533,000
Unobligated Balance, start of year	0	0	0
Revenue from Breast Cancer Stamp 2/	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	511,157,000	507,932,000	504,533,000
Unobligated balance lapsing	(83,000)	0	0
Total obligations	511,074,000	507,932,000	504,533,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $1,015,000 FY 2006 - $2,000,000 FY 2007 - $$2,000,000
Excludes $5,000 in FY 2006 and $5,000 in FY 2007 for royalties.

Justification

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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

Budget Authority:

FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
212	$511,157,000	212	$507,932,000	213	$504,533,000	+1	-$3,399,000

This document provides justification for the Fiscal Year 2007 activities of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, including HIV/AIDS activities. A more 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

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiologic research, research training, and information programs on many of the more debilitating diseases affecting the American people. Most of these diseases are chronic and many cause life-long pain, disability and disfigurement. These diseases of bones, muscles, joints, and skin affect people of all ages, racial and ethnic populations, and economic strata.

The NIH Roadmap for Medical Research: A major challenge in chronic diseases is the inability to really assess many dimensions of these diseases in objective ways. As part of the Re-Engineering the Clinical Research Enterprise component of the NIH Roadmap for Medical Research, the NIAMS is leading efforts to address this challenge. The NIH is funding six primary research sites and a statistical coordinating center for a network known as PROMIS – the Patient-Reported Outcomes Measurement Information System. The goal is to develop ways to measure patient-reported symptoms such as pain and fatigue and aspects of health-related quality of life across a wide variety of chronic diseases and conditions. Additional information on PROMIS can be found in the NIH Roadmap section of the Congressional Justification.

NIAMS SCIENCE ADVANCES AND NEW INITIATIVES

The NIAMS provides support for research across a broad spectrum of approaches, understanding that the ultimate conquest of diseases always involves basic, animal model, clinical, clinical trial, and prevention research. In most cases, the essential ingredient is the translation: taking the

findings at the research bench and applying them to human disease, and taking observations from the bedside and using them to inform and guide basic research. We are proud of the stories of research progress from NIAMS-funded research, and we continually seek to identify areas of research opportunity and need. What follows are highlights of stories of progress and promise and new scientific initiatives.

HEALTH DISPARITIES

Many of the diseases within the mission of the NIAMS have a disproportionate impact on women and minorities. The NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

Barriers to Treatment Compliance in Economically Challenged Arthritis and Lupus Patients. Researchers supported by the NIAMS have identified some barriers that keep people who are economically disadvantaged as well as people from diverse ethnic backgrounds from complying with their prescribed medical treatments, including fear of side effects, belief that the medicines are not working, problems with the health system environment, and medication costs. Fear of side effects was the most often-mentioned factor – patients were concerned about long-term damage if they continued to take the medications. Some patients expressed concern that the prescribed drugs were not working – either the medications were not providing relief from symptoms or they were concerned because the drugs were not curing the disease. Problems with the health care system included navigating the requirements for Medicaid and the lack of continuity in seeing the same doctor. The financial costs of the medications meant that some people stopped taking their prescribed medications since many of them had little or no medical coverage. Other obstacles included language barriers for some Hispanic patients in this study and a shortage of translators; difficulties in scheduling appointments when patients had sporadic and unpredictable employment; financial difficulties in paying for the appointments; a lack of transportation to get to the appointments; and the severity of their illness on the day of the appointments often made the patients unable to keep appointments. Studies like this provide information on sensitivity to different populations, and are important as we continue to address the issues of health disparities – to identify the many, complex factors that make some populations more vulnerable to diseases within our mission areas.

Lupus Deaths in Minorities. Lupus is one of the many diseases within our mission areas that occurs in increased numbers and often greater severity in women and minorities, and recent reports suggest that lupus deaths may be underestimated in ethnic minorities with low education levels. In epidemiologic studies, higher socioeconomic status has been consistently coupled with lower overall mortality, and specifically with fewer deaths from cardiovascular and cerebrovascular diseases. In race-specific studies, similar associations have been found, but researchers have questioned whether the incidence of lupus-caused deaths follows the same pattern. An investigator in the NIAMS Intramural Research Program, drawing on data from the National Center for Health Statistics, recently studied U.S. deaths in people with lupus over a three-year period. It was determined that in whites of both genders, the incidence of lupus-caused deaths does decrease as socioeconomic status increases. However, in three minority categories -- African American men, African American women and Asian/Pacific Islander women -- the risk of death from lupus was lower among those with lower education levels. This

study also compared the education/mortality link in lupus to that of other causes of death, and found that people with lower educational levels were underrepresented among deaths from lupus for the three minority categories. It is speculated that the under-representation was likely due to under-reporting and under-diagnosis.

Total Knee Replacement in Minorities. Researchers at a NIAMS-supported center undertook an analysis of the epidemiology of total knee replacement in the U.S. Medicare population. There is a real shortage of epidemiologic data in all of our mission areas, and this particular report described the rates of primary and revision total knee replacement and selected outcomes in people in the U.S. who were older than 65. Using Medicare claims and information on total knee replacements in the year 2000, the data showed that the rate of primary knee replacement was lower in African Americans than in whites. It was also lower in those qualifying for Medicaid supplementation than in those with higher incomes. Furthermore, African Americans had higher rates of mortality, readmission, and wound infection after primary knee replacements than whites. In addition, patients who qualified for Medicaid supplementation had high complication rates, particularly after primary knee replacement. While overall the rates of postoperative complications during the 90 days following total knee replacement are low, these data underscore the health disparity challenges that we face in many of our mission areas.

BONE BIOLOGY, BONE DISEASES, AND ORTHOPAEDICS

New Combinations and Sequential Use of Therapies for Osteoporosis. NIH-supported researchers reported seminal findings in 2003 on the use of combination therapies for the treatment of osteoporosis, and they have now taken the original studies to the next stage of investigation – with important results that provide good news for people with osteoporosis. The original study compared the effectiveness of combining the bone-building treatment of parathyroid hormone (PTH) with a drug that slows bone loss (alendronate). The results from two different studies demonstrated that combining injections of PTH with alendronate taken orally produced no significant improvement in bone mineral density compared to administering the drugs individually. In fact, PTH alone increased bone mineral density at least as well as or better than the combination therapy. In the latest study, women taking PTH alone in the first year were given either no drug in the second year or were switched to alendronate. The women receiving no drug after a year of PTH began to lose the bone they had gained during treatment. The women who switched to alendronate in the second year after taking PTH for the first year continued to gain bone, particularly in the spine. These studies demonstrate that the sequential use of PTH as a bone building drug followed by alendronate as an anti-resorptive (or bone conserving) drug maximized the bone gain as measured by bone mineral density.

In a related study in a different laboratory, researchers found that treatment with PTH does not need to be continuous throughout the year. In fact, cyclic treatment with PTH for three months followed by three months of alendronate alone was as effective in stimulating bone gain as the continuous use of PTH for 12 months. Taking 3-month breaks from PTH not only provides cost benefits, but also improves quality of life for patients who do not need to inject the drug every day. Physicians and patients can use the results of both of these studies to strategize for the best therapeutic benefit while minimizing drug use and cost.

Bone Quality. In osteoporosis, bone strength is compromised and affected people have an increased risk of fractures. The term "bone quality" is not well defined, but it is used to describe the diverse factors influencing skeletal health and fracture risk that go beyond the measurement of bone mineral density. Although bone mineral density measurement is among the most useful clinical tools for diagnosing osteoporosis, its limitations have become apparent. Thus, bone quality and skeletal fragility have become critical topics for basic scientists, clinical investigators, and clinicians. The NIAMS partnered with the American Society for Bone and Mineral Research, the French Institute of Health and Medical Research (INSERM), and the NIH National Institute of Biomedical Imaging and Bioengineering, in sponsoring the meeting, "Bone Quality: What Is It and Can We Measure It?" on May 2-3, 2005. This scientific meeting brought together leading scientists from around the world to identify needs and future directions in bone quality research; highlighted basic science, clinical, regulatory (U.S. Food and Drug Administration), and pharmaceutical perspectives; assessed established and new methods for measuring bone quality and explored how to include them in clinical trials; and discussed novel mechanisms to bring together research efforts on bone quality to move this research field forward.

Markers of Fracture Risk in Older Persons. Elevated levels of the amino acid homocysteine have long been associated with an increased risk of cardiovascular disease, including heart attack and stroke. But a new research study suggests that high homocysteine levels also may be linked to the development of osteoporosis and related fractures. Investigators measured blood homocysteine levels and screened for hip fracture over a 16- to 19-year period in nearly 2,000 older (over 59) Framingham Osteoporosis Study participants. Analyses revealed that men and women with the highest homocysteine levels were at greater risk for hip fracture than those with the lowest levels. The risk was increased fourfold in men and twofold in women, and it was independent of other risk factors for fracture, such as age and weight. It is not clear from the study whether homocysteine has a direct effect on bone and fracture or whether it serves as a marker for something else. But this latest research shows that elevated homocysteine levels are emerging as an important risk factor for hip fractures in older persons. Since folic acid and other B vitamins in the diet can manipulate homocysteine, this may suggest a new therapeutic approach to reducing the risk of hip fractures in the elderly.

Basic Genetic Studies in Osteoporosis. Although scientists know that many genes influence bone mass and thus osteoporosis risk, identifying specific genes has been challenging – especially in humans, who are genetically diverse. By using laboratory mice, whose bone physiology is similar to humans, however, NIAMS-supported researchers have been able to locate a gene that not only influences bone density in mice, but also provides new insight into how to preserve bone mass in people. These researchers identified the gene, called alox15, while working with two strains of mice that have very different bone mineral densities. Variations in the gene, they discovered, account for a significant part of that difference. While scientists have known of the gene for some time, it was never recognized as important for the skeleton. Instead, it was known to be involved in the metabolism of certain fats and was believed to play a role in heart disease and other health problems. Because there are two genes in people with activities similar to that of alox15, scientists believe that one or both of these genes might be targets for treatment of osteoporosis. Also, the discovery of alox15's influence on bone mass suggests that a previously unsuspected metabolic pathway could be important for skeletal health. By further

studying this pathway, scientists may find additional clues for preventing osteoporosis and the resulting fractures.

Progress in the Development of a Genetic Treatment for Osteogenesis Imperfecta. Scientists supported by the NIAMS have made an important step toward using gene therapy to treat severe cases of osteogenesis imperfecta (OI), a genetic disease in which bone is fragile and highly vulnerable to fracture. Severe cases of OI can lead to serious bone malformation and even death. Most cases of OI are due to mutations in the gene that produces a protein called type I collagen, which forms a network of fibers in bone and provides much of its strength. Everyone has two versions of the gene, so mutations that simply inactivate one version usually produce mild cases. But when mutations result in an abnormal collagen molecule, the mutant collagen can interact with normal collagens, disrupting the fiber network and drastically reducing the strength of bone. The scientists reasoned that by turning off the affected genes in these more severe patients, they could transform them into milder cases. They tested their theory in cultured cells from bone marrow, where bone-forming cells normally arise, by infecting the cells with harmless viruses specially modified to inactivate a gene. The greatest challenge in this process was to target the viruses to the collagen gene, avoiding the inactivation of normal genes with other functions. Using cells from OI patients with severe forms of the disease, the scientists were able to correctly target the collagen gene with the modified virus in 90 percent of the cells into which the viruses were inserted. Just as important, cells in which the mutant collagen gene was inactivated were shown to produce normal collagen and retain the ability to develop into mature bone-forming cells in culture. Although this approach to gene therapy is not yet ready for testing in humans, advances like this bring scientists closer to being able to repair genetic errors, not just for OI, but also for many other diseases that are due to the activity of abnormal genes. This may enable those born with genetic errors to escape lifelong and often devastating consequences.

Outcomes Following Severe Leg Injuries. Severe injuries of the legs as the result of pedestrian and motor vehicle accidents continue to be common, costly, and disabling public health problems. This is especially true for those leg injuries that put individuals at risk of losing their legs. A study conducted several years ago – the Lower Extremity Assessment Project (LEAP) -- provided prediction tools to be used by patients and providers in making treatment decisions, and demonstrated that patients treated with amputation and those treated with reconstruction had similar functional outcomes at two years following severe limb-threatening injuries. The most recent study assessed the functional outcomes 7 years following these treatments, and assessed whether previously determined risk factors had an impact on functional outcomes at 7 years. Patient characteristics that were significantly associated with poorer long term outcomes included: older age, female gender (physical functioning only), non-white race, lower education level, living in a poor household, current or previous smoking, low self-efficacy, and health status before the injury. The LEAP study is one of the first long-term, and largest prospective assessments of outcome following major lower leg injuries. These long-term results confirmed the investigative team's previous conclusions that efforts to improve the rate of successful reconstructions have merit. The long-term outcomes found in this study suggest that reconstruction of severe lower leg injuries below the knee joint is a goal for trauma centers. Regardless of the treatment option, however, long-term functional outcomes for both amputation and reconstruction groups are poor, underscoring the significant public-health impact of major

leg trauma. Additional studies are needed on the post-acute-care services that address other conditions that affect optimal recovery. Clinical interventions that can reduce limb complications and the need for hospital readmission should also be determined.

Importance of Surgical Experience in the Outcomes of Total Knee Replacement. A research team analyzed almost 81,000 claims of Medicare patients who had primary or revision total knee replacement between January 1 and August 31, 2000. The results suggest a positive relationship between surgeons and hospitals performing a high volume of total knee replacements and the outcomes for these interventions. The study found that patients of surgeons who perform 50 or more total knee replacements per year had a lower incidence of morbidity and postoperative complications than those whose doctors do 12 or less. Also, hospitals in which 200 or more total knee replacements are performed per year demonstrated similar positive outcomes in contrast to facilities that do less than 25 of these procedures per year. The data were adjusted for age, gender, co-morbid conditions, Medicaid eligibility (which is a marker of low income) and arthritis diagnosis. The findings of this study are consistent with those reported previously on associations between procedure number and outcome for hip replacements. Arthritis is a major contributor to impairment of daily functions and disability in affected people, and it accounts for significant numbers of hospitalizations and health care costs in the elderly. Total joint replacements are a major advance in the treatment of joint deterioration and, if successful, make a significant difference in quality of life of patients. Studies like this most recent report on the positive relationship between outcome of total joint replacements performed by surgeons and in hospitals with high volumes of these procedures can help to guide patients in their decisions to undergo this life-changing surgery and improve overall costs and clinical outcomes.

Development of Promising New Polymers for Cartilage Repair. Cartilage is a tissue that lacks capacity for self repair. However, recent multidisciplinary studies by biologists, engineers, physicians, and other are providing new strategies for treating degenerative cartilage that may result in treatments for articular cartilage lesions. Researchers funded by the NIAMS have developed a class of injectable materials based on a biodegradable polymer OPF (oligo-polyethylene glycol fumarate) for cartilage tissue engineering. These are synthetic, biodegradable, and biocompatible polymers that can be injected into a site with a defect and crosslinked *in situ* under physiological conditions that eliminate the need for invasive surgery. Short-term studies in experimental animals demonstrated excellent tissue filling and integration resulting from implantation of these materials into cartilage defects. The polymers were also designed to deliver bioactive molecules, such as growth factors, as well as cells, such as chondrocytes or progenitor cells to cartilage lesions to enhance tissue repair. Early results show that chondrocytes remain viable, proliferate, and synthesize cartilage matrix components in these polymer gels. Taken together, these results indicate that OPF gels are promising materials for cell delivery in cartilage repair strategies.

OSTEOARTHRITIS

The Osteoarthritis Initiative. The NIAMS partnered with the National Institute on Aging, several other NIH components, and three pharmaceutical companies in establishing the Osteoarthritis Initiative, a public-private partnership aimed at developing clinical research

resources that support the discovery and evaluation of biomarkers and surrogate endpoints for osteoarthritis clinical trials. For the first time, a public-private partnership is bringing together new resources and commitments to help find biological markers for the onset and progression of osteoarthritis. Recruitment of participants is actively underway, and by the end of FY 2005, more than 3,800 participants have been recruited. One year follow-up measurements have been carried out on over 1,000 participants, and will continue for the next 4 years. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification. This consortium serves as a model for future endeavors that link the public and private sectors.

Mechanical Influences on the Induction of Osteoarthritis-related Biomarkers. The influences of biomechanical factors on biomarker production are not well understood, and two separate basic research laboratories explored these influences. The first study was on the role of mechanical stress on biomarker release from normal cartilage. It showed that mechanical stress in the ranges experienced from normal to intense physical activity increased the turnover of cartilage and the release of biomarkers from the tissue and varied with the magnitude of applied stress. This suggests that mechanical stress regulates turnover of molecules in the cartilage extracellular matrix. The second study examined release of cartilage- and bone-derived biomarkers in college athletes undergoing high-intensity training (rowers, cross-country runners, and swimmers) and in non-athlete controls. Analyses of urinary biomarkers suggest that rowers undergo the highest bone turnover and runners the highest cartilage turnover. These results suggest that biomarkers can vary between individuals involved in different types of physical activities. While the mechanisms involved in these processes are not fully understood, these studies indicate that mechanical stress is a variable that can increase the production and release of osteoarthritis-related biomarkers. This research has practical significance in that the interpretation of biomarker analyses from osteoarthritis patients will need to take into account the type and extent of physical activity of the patients.

The Importance of Self-management of Osteoarthritis. When patients understand and feel that they have some control over their chronic disease, the course of their disease is often improved. In this latest study, we learned that improvement can be made in the self-management of osteoarthritis when spouses provide help. The intervention that was tested used spouse-assisted coping skills training and exercise training to improve physical fitness, pain coping, and self-efficacy in patients with osteoarthritis of the knee. The results from this study suggest that a combination of both spouse-assisted pain coping skills training and exercise training leads to more improvements than could be achieved with either intervention alone.

Acupuncture and Knee Osteoarthritis. The NIAMS joined with the National Center for Complementary and Alternative Medicine in a study that revealed that acupuncture relieves pain and improves function in knee osteoarthritis, and it serves as an effective complement to standard care. This study is the longest and largest randomized, controlled phase 3 clinical trial of acupuncture ever conducted. This is the first time that a clinical trial with sufficient rigor, size, and duration has shown that acupuncture reduces the pain and functional impairment of osteoarthritis of the knee. These results also indicate that acupuncture can serve as an effective addition to a standard regimen of care and improve quality of life for knee osteoarthritis sufferers.

RHEUMATOID ARTHRITIS AND LUPUS ERYTHEMATOSUS

A Genetic Variation was Found to Double the Risk of Rheumatoid Arthritis. Scientists have long suspected that autoimmune diseases such as rheumatoid arthritis result from a combination of genetic and environmental factors. Now a NIAMS-funded research team has identified a specific genetic variation, called a single nucleotide polymorphism or SNP, that increases rheumatoid arthritis risk twofold. The SNP is located within a gene that codes for a particular enzyme that is known to be involved in controlling the activation of white blood cells called T cells that play an important role in the body's immune system. Under normal conditions, the enzyme works as a negative regulator: it inactivates a specific signaling molecule which, in turn, interrupts the communications and keeps immune cells from becoming overactive. However, in cases where the SNP is present in one or both copies of a person's genes for this enzyme, the team found that the negative regulation by the enzyme appears to be inefficient, allowing T cells and other immune cells to respond too vigorously, causing increased inflammation and tissue damage. The implications of this finding go beyond a better understanding of rheumatoid arthritis risk. It may also help explain why different autoimmune diseases tend to run in families, since this gene variant is also found in diabetes and lupus.

Increased Risk of Heart Disease in Rheumatoid Arthritis. Individuals with rheumatoid arthritis appear to have an increased risk of cardiovascular morbidity and mortality. A large, population-based study included individuals who first fulfilled diagnostic criteria for rheumatoid arthritis between 1955 and 1995, and age- and sex-matched controls who did not have rheumatoid arthritis. It was determined that patients with rheumatoid arthritis had a significantly higher risk of myocardial infarction ("heart attack") prior to meeting diagnostic criteria for rheumatoid arthritis than those without rheumatoid arthritis. Patients with rheumatoid arthritis were also less likely to have symptoms of angina, were likely to receive coronary artery bypass surgery, and had significantly higher risk of sudden cardiac death. Together, these findings indicate that the presentation of coronary heart disease differs markedly between those with rheumatoid arthritis and those without. In addition, patients with rheumatoid arthritis had twice the risk of developing congestive heart failure. These findings have implications for an inflammation-based etiology of heart disease, as well as implications for the detection and prevention of coronary heart disease and congestive heart failure in patients with rheumatoid arthritis.

A Cancer Drug Holds Promise as a Treatment for Lupus. Preliminary studies that were partly funded by the NIAMS show that the cancer medication rituximab may someday be an effective treatment for lupus. In a study of adults with lupus that was clinically active despite treatment, just one injection of rituximab eased symptoms for up to a year or more. Several participants were able to reduce or completely stop their regular lupus medications. Rituximab, which is FDA-approved for the treatment of patients with lymphoma, works by lowering the number of the immune system's B cells. In lymphoma, the body makes too many B cells. In lupus, there are usually lower-than-normal numbers of B cells, but the B cells that do exist overreact or react inappropriately toward the body's own tissues. As a result, the disease can damage many body organs and systems including the joints, skin, blood and blood vessels, kidney, lungs and brain. In this study, researchers reported that all of the lupus patient participants in whom rituximab reduced B cell levels experienced significant reduction in

symptoms. Furthermore, the side effects from rituximab were minimal and even reactions to the infusion – a side effect of the drug seen in lymphoma – were not seen in the lupus patients. While current lupus treatments work by suppressing the entire immune system, rituximab selectively targets the B cells that are at the root of the problem. In doing so, it may not only be more effective than other medications, it may also be less toxic. But more studies are needed to better understand its effectiveness and safety and to better determine its role in lupus treatment. The researchers are currently planning another multicenter study that will help address those issues.

A Common Virus Can Trigger Lupus. For some time, scientists have suspected that the Epstein-Barr virus or EBV -- the virus that causes infectious mononucleosis -- may be related to the development of lupus in certain people. A recent study partly supported by the NIAMS helps confirm the connection. Researchers studied changes in the blood of people who later developed lupus, and were able to identify when people with lupus began to make the autoantibodies that damage target tissues. For many, the antibodies were first produced in response to EBV infection, as evidenced by antibodies to the virus. In genetically predisposed people, antibodies to a portion of the EBV protein cross-reacted with a piece of a protein in the body called Ro. Later studies showed that the same phenomenon occurred in rabbits injected with this same portion of the EBV protein. Although EBV infection has been implicated as a cause of lupus, proving an association has been difficult for a number of reasons. One reason is that most people are infected with EBV at some point and relatively few develop lupus. The Department of Defense repository that was used for this study allowed these researchers to identify military personnel who developed lupus and then look at their blood samples taken a decade or more before symptoms started. These researchers were able to identify the first changes in the blood that led to the disease. This study provides new insight into how lupus begins, and it also has implications for treating or even preventing the disease through vaccinations against EBV or other mechanisms that could prevent or block the autoimmune response.

Hormone Therapy is Not Associated with Severe Lupus Flares. Women with lupus may experience the benefits of postmenopausal hormone therapy (HT) without an increased risk of severe disease flares, according to a major study funded by the NIAMS. In a 16-center study of menopausal women, those taking a standard regimen of hormone therapy had no statistically significant increased risk of severe flares compared to those taking a placebo. Women in the HT group were, however, about 20 percent more likely to have a mild-to-moderate flare, which included new or worsening skin rashes, mouth ulcers, hair loss, aching or inflammation of the joints (arthritis), or fluid around the heart or lungs. None of these mild-to-moderate flares resulted in the need for high-dose steroids or hospitalizations. In recent years, long-term use of HT has been questioned because of risks of cardiovascular disease and some estrogen-dependent cancers. Yet short-term therapy is still widely used and beneficial for some of the unpleasant effects of menopause, as well as for preventing osteoporosis. Women with lupus who are taking cyclophosphamide (a drug that suppresses damaging inflammation of the disease) are especially prone to early and severe effects of menopause, and it may be that HT can provide a particular benefit for these women. Traditionally, doctors have not prescribed HT in women with lupus for fear that increasing the level of female hormones in the body might increase disease activity. This fear arose in part from the fact that lupus is far more common in women and that it typically begins during the childbearing years when female hormone levels are at their peak. This study

provided important reassurances, but further investigation of HT is needed to determine the most appropriate candidates for therapy. Some women may be biologically predisposed to flares in response to hormones, and in the future there may be ways to determine who is at greatest risk of flares before initiating treatment. It is important for doctors and patients to carefully consider expected benefits balanced with possible risks in deciding whether to use HT in any women.

MUSCLE BIOLOGY AND MUSCLE DISEASES

Scientists Come a Step Closer to New Treatment for Muscular Dystrophy. One form of muscular dystrophy -- Duchenne muscular dystrophy (DMD) – is a severe form of the disease, and few people with DMD live past their early 20s. Researchers have recently shown that injecting a fragment of a protein called heregulin improves the structure and function of muscles of mice that develop a disease similar to DMD. After injecting these mice with the heregulin fragment for three months, the mechanical properties of their muscles were improved, and they showed fewer sites of muscle degeneration and less muscle inflammation than those injected with an inert saline solution alone. Previous research suggested that heregulin works by increasing the body's production of another muscle protein, utrophin, which is structurally and functionally similar to dystrophin. In laboratory animals, utrophin is produced in high levels before birth, but decreases to low levels by adulthood. By increasing utrophin production, scientists found they could halt muscle degeneration related to dystrophin deficiency in mice. It was suspected that utrophin would serve as a substitute for deficient dystrophin, and the latest research suggests that this is the case. Successful treatments for muscular dystrophy are being actively pursued through a number of research avenues, and additions to the candidate therapeutic approaches – such as this one – improve the chances of discovering ways to incrementally improve the lives of those affected by this devastating disease.

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. The NIAMS has teamed with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Child Health and Human Development (NICHD), and the Muscular Dystrophy Association in funding a consortium of Centers of Excellence for research on muscular dystrophy. Three of these Centers were established in 2003, and – in addition to their research components -- they are required to make core resources or services available to the national muscular dystrophy research community. In FY 2005, 3 additional Centers were established, bringing the total number to 6. The interactions of the Centers and their service to the research and patient care communities are coordinated by a steering committee with representatives from each of the Centers, NIH program staff and a lay member who is a parent of a child with muscular dystrophy. The diseases studied by these Centers include Duchenne/Becker Muscular Dystrophy, Myotonic Dystrophy, Facioscapulohumeral Dystrophy, Limb-Girdle Muscular Dystrophy and others. Approaches at the Centers include basic and clinical studies of the mechanisms of the diseases, translational research on gene therapy, stem cell therapy, molecular and pharmacological treatments, as well as clinical studies of gene therapy and pharmacological treatments. These Centers are intended to serve as focal points of research, collaboration, and training for the MD scientific and patient care communities.

Postnatal Muscle-derived Stem Cells for Muscle Repair and Regeneration. The repair and regeneration of muscle due to injury, disease, or contraction-induced damage is an important

public health issue. Fortunately, muscle contains cell types and cellular environments that contribute to the regenerative capacity of this tissue. The NIAMS is supporting a number of studies aimed at understanding the mechanisms by which these cells and environmental cues effect repair. Stem cells have been isolated and cloned from postnatal muscle (muscle-derived stem cells, MDSCs) and they exhibit the abilities to differentiate efficiently into muscle and other lineages. An important issue for researchers to consider is whether MDSCs have the capacity to proliferate to the levels necessary to regenerate muscle tissue with high mass. A NIAMS-supported laboratory has developed a method for isolating MDSCs from young mice. In recent work, these researchers tested the hypothesis that colonies of MDSCs could be expanded in tissue culture to create the number of cells that would be necessary for the treatment of muscle diseases. They also tested whether these cells retained the ability to form muscle tissue and did not give rise to tumors when reintroduced into the mice. These investigators found that colonies of MDSCs could be expanded for more than 200 doublings, which would theoretically provide enough cells for any clinical application. Furthermore, at up to about 200 doublings, the cells retained the ability to synthesize muscle-specific proteins and to develop muscle cell morphology, both in culture and when transplanted into mouse muscle tissue. The treatment of muscle diseases such as muscular dystrophies with stem cells will require several significant obstacles to be overcome. This NIAMS-funded work demonstrates that MDSCs can be expanded in culture to the level necessary, and a high percentage of the cells can become muscle. This level of expansion in culture, while maintaining the ability to differentiate, was previously attributed only to embryonic stem cells or cells in the bone marrow. While questions remain regarding the potential use of MDSCs for the treatment of diseased muscle, researchers are pursuing these promising findings from an animal model to determine if similar cells are present in human muscle.

Workshop on the Burden of Muscle Diseases. The NIAMS and the NIH Office of Rare Diseases sponsored a workshop on the burden of muscle diseases on January 26-27, 2005. Speakers and attendees included muscle disease clinicians and researchers, health economists, epidemiologists, representatives of patient advocacy groups, and patients and their families. There were 100 registered attendees representing universities and institutions across the U.S., Canada and the United Kingdom. Also represented were several national and international voluntary health organizations and five agencies of the U.S. Government. The participants in this workshop identified existing data on the economic and psychosocial burdens of muscle diseases on patients, families, and societies, with a focus on the muscular dystrophies, and recommended strategies for developing new information sources.

SKIN BIOLOGY AND SKIN DISEASES

Advances in Understanding Psoriasis. Psoriasis is a chronic skin disease characterized by scaling and inflammation. It occurs when skin cells rapidly pass from their origin below the surface of the skin and pile up on the surface before they have a chance to mature. Usually this movement (also called turnover) takes about a month, but in psoriasis it may occur in only a few days. Three recent studies funded by the NIAMS are helping scientists and doctors to understand how the inflammatory skin disease psoriasis behaves at the molecular level, and what role genes play in predisposing people toward this disease. In the first study, researchers investigated the role of both genes and the environment in psoriasis, psoriatic arthritis and atopic dermatitis, another inflammatory skin condition. The researchers found some similarities in

genetic susceptibility for psoriasis and atopic dermatitis. As for psoriatic arthritis – a condition in which inflamed joints produce symptoms of arthritis for patients who have or will develop psoriasis – they found that the presence of modifier genes can indicate which people with psoriasis are also at risk for psoriatic arthritis. Working at the molecular level, in the second study researchers developed an animal model to investigate the molecular basis of psoriasis. Psoriasis is a disorder of the immune system. Normally, a type of white blood cell called a T cell helps protect the body against infection and disease. However, in psoriasis, these T cells are put into action by mistake, and they become so active that they trigger other immune responses, which lead to inflammation and rapid turnover of skin cells. Using the model, the scientists were able to demonstrate how the proliferation of T cells is key to the formation of psoriatic lesions. They also demonstrated the role of a molecule known as "tumor necrosis factor-alpha" – a molecule that mediates the development of psoriatic lesions, and its production can result in T cell proliferation. In other research at the molecular level, the third team of researchers used psoriasis as a model disease to develop a way of identifying autoantigens for autoimmune diseases -- autoantigens are substances found naturally within the body and can trigger an immune response. Psoriasis is an ideal model disease for this kind of study because it is common, and because affected tissue is readily accessible. By studying the role of autoantigens in psoriasis, the researchers were able to better understand how autoantigens are recognized by T cells, and how autoreactive T cells give rise to autoimmune disease. The investigators found 11 potential autoantigens, but focused on 3 that were likely to be related to psoriasis and were associated with significant reactions in patients. Taken together, these three studies provide important information on what causes psoriasis, who gets it and how it can be treated.

Understanding the Nature of Regeneration and Stratification of the Epidermis. The outer layer of skin, the epidermis, provides the barrier function of the skin, excluding harmful microbes and retaining body fluids. NIH-funded basic researchers focused on asymmetric cell divisions that promote stratification and differentiation of mammalian skin, and gave us a new view of how skin is able to create layers of different cell types at the same time that it is forming a continuously self-renewing protective barrier. Working with genetically engineered mouse embryos, these researchers found that the epithelium starts as a single layer of dividing cells attached to a dense meshwork of proteins called the basement membrane. The basement membrane provides growth-signaling molecules to the dividing cells and separates the epidermis from the underlying tissue. As development proceeds, the epithelium begins to stratify to ultimately form a multilayered protective barrier through asymmetric cell division. This is a mechanism that can be described as one mother cell dividing into two distinctly different daughter cells. When these underlying skin cells divide, they actually divide both laterally and perpendicularly: one daughter cell remains attached to the basement membrane and the other daughter cell moves outward. During the course of division, the factors that promote cell growth are partitioned off in the cell that remains at the basement membrane. Other factors, which may be involved in the production of the barrier in skin, are confined to the outward-moving cells. These outward-moving cells eventually make it to the skin's surface where they provide a protective barrier until they are sloughed off or scraped off and replaced by new cells. During all of this development of the barrier dimension of the skin, the cells at the basement membrane continue to divide asymmetrically to form these two different daughter cells. Interestingly, this process continues in adult epidermis also. The next step in these studies is looking at which genes are necessary in the process. These fundamental studies of normal skin and the

mechanisms by which cells form and rebuild tissue have significant implications for understanding the many different disorders of the skin that result when the normal mechanism goes awry -- with implications for skin cancer, psoriasis, and many other skin diseases.

Vitiligo Reveals Earlier Onset and Greater Risk for Other Autoimmune Diseases. Vitiligo is an autoimmune disease in which white patches develop on the skin because of the loss of pigment production within the skin. It can be psychologically devastating especially for people of color. The exact mechanism of pigment cell loss is still not completely clear. Statistically, vitiligo is associated with other autoimmune diseases including autoimmune thyroid disease, pernicious anemia, Addison's disease, and lupus. These other autoimmune diseases occur at greater frequency in relatives of patients with vitiligo even when those relatives do not have vitiligo. A NIAMS-supported research team has been studying familial vitiligo for a number of years. They have established a large cohort of patients and families and are investigating both the genetic basis for the disease and the genes associated with autoimmune disease predisposition as well. Using data from these studies in vitiligo families, the researchers were able to demonstrate not only the previously known association with autoimmune thyroid disease, pernicious anemia, Addison's disease and lupus but also the association within these families with rheumatoid arthritis, psoriasis and adult onset insulin-dependent diabetes mellitus. All of these diseases were found in greater frequency in the extended families of those with vitiligo. The form of vitiligo that demonstrated this association is generalized vitiligo with early onset as distinct from the other forms of vitiligo. The genetic basis for both vitiligo and the multiple autoimmune disease susceptibility continues to be investigated. The ability to recognize which subgroups of vitiligo may be associated with a higher incidence of a wide variety of autoimmune diseases in the family is an important finding that may allow for early diagnosis which can lead to better treatment. In addition, the further genetic analysis of these individuals and families should provide clues to the underlying susceptibility to these diseases, with the ultimate goal of being able to prevent and/or more effectively treat vitiligo and other autoimmune diseases.

STORY OF DISCOVERY: The Genetic and Molecular Basis of Pseudoxanthoma Elasticum.
Pseudoxanthoma Elasticum (PXE) is a systemic, inherited, connective tissue disease that involves the elastic tissue in the skin, eyes, and cardiovascular system. It can result in severe and even fatal health problems or may be much milder and more difficult to identify. It is often not visible early in life but, in more severe cases, may manifest in childhood. For a long time, PXE had been considered to be a genetic disorder of a structural component in elastic fibers. But with the discovery of the gene that is defective in the disease, it became apparent that PXE is actually a metabolic disorder in which the structural component is secondarily affected. A consortium of investigators worked together to uncover the gene underlying PXE several years ago. PXE was found to be caused by a mutation in a gene termed ABCC6, which encodes for a protein that underlies multiple drug resistance in microorganisms, but appears to have the function of transporting materials through the membrane of human cells. In other research, affected individuals from 4 families were studied to determine the specific genetic defects underlying the disease in each family. The 4 families were from different ethnic backgrounds, yet the specific defect in all 4 families was exactly the same. The fact that all 4 families had the identical defect implied that possibly the same mechanism of mutation leads to this uniformity of mutation in different families. The recognition that this is a metabolic disease offered new hope for the development of treatment based on metabolic modifications, potentially including such things as diet manipulation or drug therapy. The isolation of the gene and the cataloging of the gene defects underlying the disease enabled researchers to design studies aimed at the early identification of affected individuals. The goal is to be able to institute treatment before the development of signs or symptoms of the disease and, ultimately, early enough to prevent such signs and symptoms from ever developing.

In recent work reported in 2005, investigators applied the findings that identified the gene underlying PXE to create an animal model in which the ABCC6 gene was ablated. They demonstrated that these mice did not express the protein normally encoded for by the gene in the liver or kidney. At autopsy there was profound mineralization of several tissues in these animals including the skin, arterial blood vessels and the retina, which parallels the findings in the human disease. Only animals carrying 2 copies of the mutated gene showed these effects. Those animals having one normal and one abnormal gene were completely normal. This also parallels PXE in humans. Interestingly, the earliest abnormal finding in the animal model was in modified hair of the vibrissae (whiskers), where mineralization was noted as early as five weeks of age. There have been no systematic examinations of hair in PXE in humans, but this may provide an area of further investigation. If the human parallels the mouse in this area as well, it may provide an easier-to-obtain early indication of whether an individual in an affected family will develop the disease later in life. The availability of animal models allows researchers to undertake studies that reveal the mechanisms of disease in humans. It is anticipated that this animal model will be very useful in further investigation of the underlying disease mechanisms in PXE. This animal model provides a test bed for evaluating potential therapeutic interventions, and it also provides a general model for mineralization studies seen in other diseases with vascular and ocular degeneration.

INFORMATION DISSEMINATION

An important dimension of our mission includes a comprehensive program of information dissemination to patients and to their health care providers. Research advances are of limited value if they never reach the arena of health care, and they miss the goal of improving public health for all Americans. We are also committed to making our information accessible to the vast and diverse populations affected by the diseases within our mandate.

Outreach to American Indian and Alaska Native Communities. The NIAMS, in an effort to expand its ability to reach out to the American Indian and Alaska Native communities, established a Trans-NIH Working Group comprised of representatives of the NIAMS, NIA, NICHD, and National Institute of Dental and Craniofacial Research (NIDCR). This Working Group determined that it was important to understand what the NIH community was doing to reach these populations. On November 1, 2005, these institutes held a workshop, "Taking Action: Health Promotion and Outreach with American Indians and Alaskan Natives," to provide a primer and "lessons learned" for NIH staff involved in health education, communications, and public liaison work. This workshop provided participants with a greater understanding of community analysis, including demographics, geography, and health status; influences on health behavior, including culture, values, and traditions; access, including health care providers and systems; and lessons learned from other NIH health promotion programs. This workshop was an initial step for the Working Group, and outcomes from the workshop may include collaborations between the Working Group members and a larger conference as well as publication opportunities.

Information in Spanish. The NIAMS has launched a new series of "fast facts" in Spanish called "Esenciales," meaning "essentials." This publication series is a transadaptation of the original English-language series developed for consumers using an easy-to-read format. The format uses plain-language techniques to deliver concise and easy-to-understand health information. In FY 2005, we have 10 Spanish fast facts in production: the subjects include gout, rheumatoid arthritis, acne, psoriasis, rosacea, vitiligo, scoliosis, growth plate injuries, fibromyalgia, and sprains and strains. In addition, the "Osteoartritis: Resumen" in Spanish was updated and reposted on the NIAMS website. The production of another Spanish-language publication was started in FY 2005: "Information for Patients About Paget's Disease of Bone."

Curriculum Supplement for Middle School Students. In collaboration with the NIH Office of Science Education, the NIAMS developed a curriculum supplement for middle school students called "Looking Good, Feeling Good: From the Inside Out," to be released in early 2006. The supplement highlights NIAMS scientific research on rheumatic, musculoskeletal, bone, and skin diseases, and provides students with the opportunity to learn how these systems contribute to health and well-being.

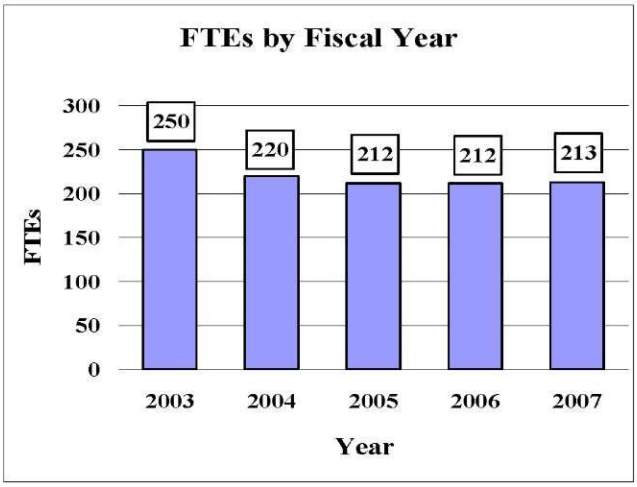
CONCLUSION

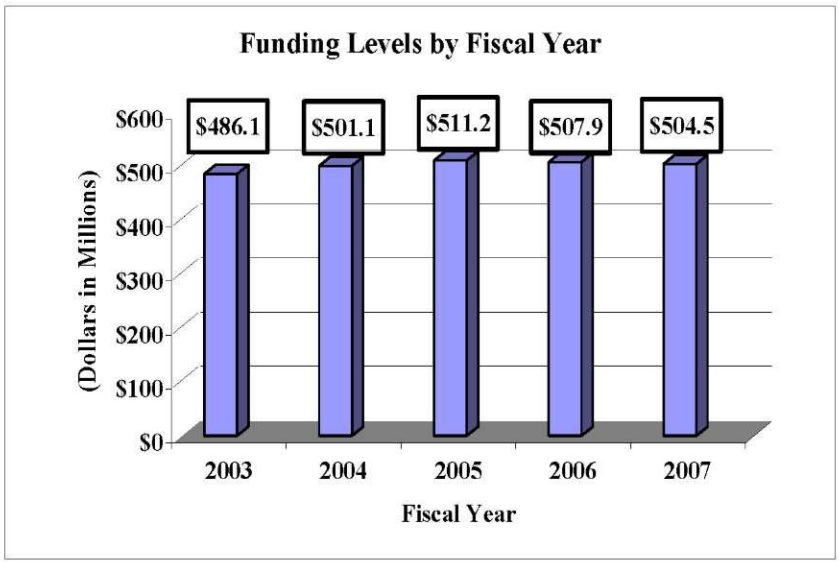
The stories above are by no means inclusive of all the progress that has been made through our investments in research. NIAMS-supported researchers are uncovering important pieces of the research puzzle and launching initiatives to take advantage of emerging areas of science. Our goal is to expand and enhance research so that benefits are realized by all Americans. We are striving to improve our understanding of the fundamental biology of bones, joints, muscles, and skin; determine the changes that cause these life processes to go awry in diseases; improve diagnosis and treatments; and ultimately, prevent the extensive and diverse array of diseases within our mission. Medical research has already made a genuine difference in the length and quality of life, and the investments we are making in research today will have a significant effect on our generation and generations that follow. We are investing in the future health of our nation, and American people of all ages and population groups will benefit from these investments.

BUDGET POLICY

The Fiscal Year 2007 budget request for the NIAMS is $504,533,000, a decrease of $3,399,000 and 0.7 percent over the FY 2006 Appropriation. Included in the FY 2007 request is NIAMS' support for the trans-NIH Roadmap initiatives, estimated at 1.2% 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 NIAMS are shown in the graphs below. Note that as the result of several administrative restructurings in recent years, FTE data is 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 $306,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NIAMS has committed to a programmatic increase for an award, such increases will be provided.

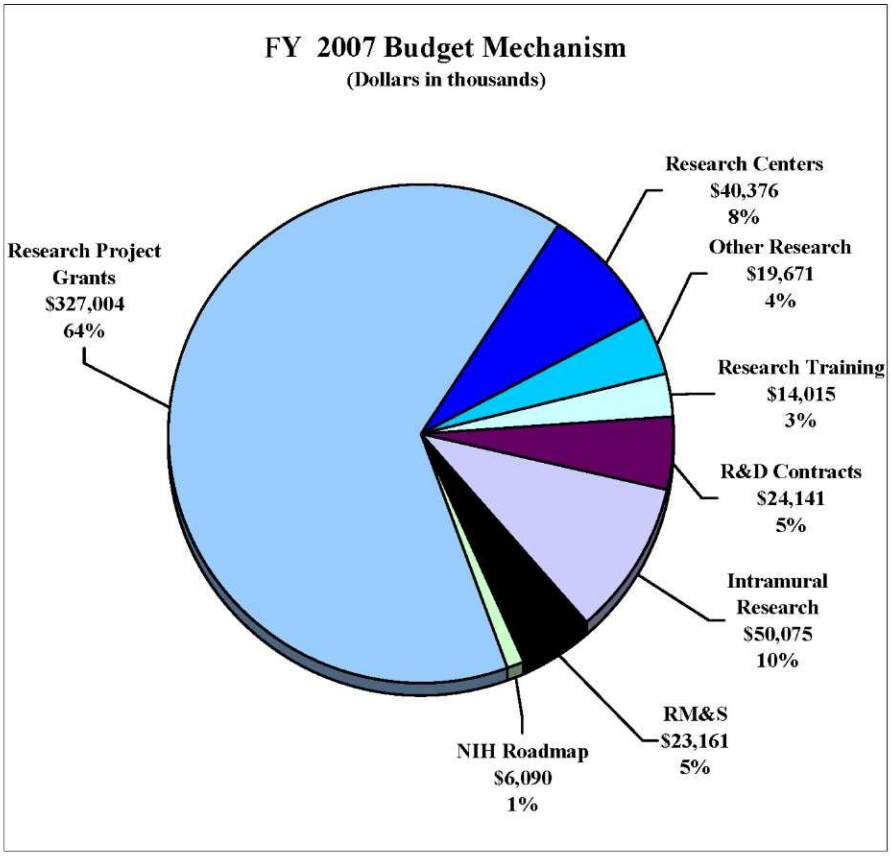
NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIAMS, $360 thousand will be used to support 4 awards for the new K/R "Bridges to Independence" program.

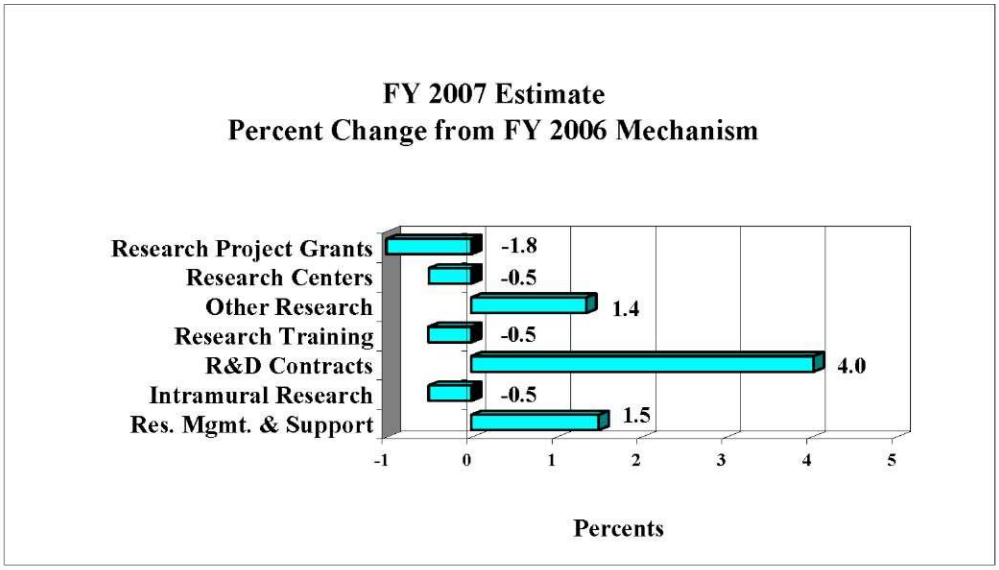
NIAMS will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $866,000 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 38 research centers, 165 other research grants, including 137 career awards, and 68 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by 1.5 percent.

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





NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Mechanism - Total

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	741	$249,225,000	744	$246,721,000	740	$247,132,000
Administrative supplements	(28)	1,515,000	(28)	1,528,000	(28)	1,520,000
Competing:						
Renewal	75	27,143,000	73	26,500,000	218	24,193,000
New	165	46,157,000	161	45,060,000	0	41,150,000
Supplements	4	1,542,000	4	1,501,000	0	1,375,000
Subtotal, competing	244	74,842,000	238	73,061,000	218	66,718,000
Subtotal, RPGs	985	325,582,000	982	321,310,000	958	315,370,000
SBIR/STTR	55	11,929,000	52	11,658,000	51	11,634,000
Subtotal, RPGs	1,040	337,511,000	1,034	332,968,000	1,009	327,004,000
Research Centers:						
Specialized/comprehensive	38	40,638,000	38	40,579,000	38	40,376,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	38	40,638,000	38	40,579,000	38	40,376,000
Other Research:						
Research careers	137	15,857,000	137	16,145,000	137	16,424,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	3	892,000	3	882,000	3	878,000
Other	34	1,921,000	25	2,381,000	25	2,369,000
Subtotal, Other Research	174	18,670,000	165	19,408,000	165	19,671,000
Total Research Grants	1,252	396,819,000	1,237	392,955,000	1,212	387,051,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	47	2,131,000	45	2,112,000	45	2,101,000
Institutional awards	270	12,111,000	261	11,974,000	260	11,914,000
Total, Training	317	14,242,000	306	14,086,000	305	14,015,000
Research & development contracts	67	23,526,000	67	23,206,000	68	24,141,000
(SBIR/STTR)	(0)	(27,000)	(0)	(49,000)	(0)	(49,000)
	FTEs		FTEs		FTEs	
Intramural research	131	50,634,000	131	50,327,000	131	50,075,000
Research management and support	81	22,705,000	81	22,819,000	82	23,161,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
NIH Roadmap for Medical Research	0	3,231,000	0	4,539,000	0	6,090,000
Total, NIAMS	212	511,157,000	212	507,932,000	213	504,533,000
(Clinical Trials)		(32,146,000)		(31,825,000)		(31,510,000)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Activity

(dollars in thousands)

ACTIVITY	FY 2005 Actual FTEs	FY 2005 Actual Amount	FY 2006 Appropriation FTEs	FY 2006 Appropriation Amount	FY 2007 Estimate FTEs	FY 2007 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Arthritis and Musculoskeletal and Skin Diseases		$434,587		$430,247		$425,207		($5,040)
Subtotal, Extramural research		434,587		430,247		425,207		(5,040)
Intramural research	131	50,634	131	50,327	131	50,075	0	(252)
Res. management & support	81	22,705	81	22,819	82	23,161	1	342
Cancer Control & Prevention	0	0	0	0	0	0	0	0
NIH Roadmap for Medical Research	0	3,231	0	4,539	0	6,090	0	1,551
Total	212	511,157	212	507,932	213	504,533	1	(3,399)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes

FY 2006 Estimate				$507,932,000
FY 2007 Estimated Budget Authority				504,533,000
Net change				(3,399,000)
	FY 2006 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$17,444,000		$240,000
b. Annualization of January 2006 pay increase		17,444,000		136,000
c. January 2007 pay increase		17,444,000		295,000
d. One less day of pay		17,444,000		0
e. Payment for centrally furnished services		9,160,000		137,000
f. Increased cost of laboratory supplies, materials, and other expenses		23,723,000		470,000
Subtotal				1,278,000
2. Research Management and Support:				
a. Within grade increase		9,183,000		161,000
b. Annualization of January 2006 pay increase		9,183,000		72,000
c. January 2007 pay increase		9,183,000		157,000
d. One less day of pay		9,183,000		0
e. Payment for centrally furnished services		3,796,000		57,000
f. Increased cost of laboratory supplies, materials, and other expenses		9,840,000		196,000
Subtotal				643,000
Subtotal, Built-in				1,921,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes--continued

CHANGES	FY 2006 Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	744	$248,249,000	(4)	$403,000
b. Competing	238	73,061,000	(20)	(6,343,000)
c. SBIR/STTR	52	11,658,000	(1)	(24,000)
Total	1,034	332,968,000	(25)	(5,964,000)
2. Research centers	38	40,579,000	0	(203,000)
3. Other research	165	19,408,000	0	263,000
4. Research training	306	14,086,000	(1)	(71,000)
5. Research and development contracts	67	23,206,000	68	935,000
Subtotal, extramural				(5,040,000)
	FTEs		FTEs	
6. Intramural research	131	50,327,000	0	(1,530,000)
7. Research management and support	81	22,819,000	1	(301,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Buildings and Facilities		0		0
11. NIH Roadmap for Medical Research	0	4,539,000	0	1,551,000
Subtotal, program	212	507,932,000	1	(5,320,000)
Total changes			1	(3,399,000)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	212	213	1
Full-time equivalent of overtime & holiday hours	0	0	0
Average ES salary	$153,700	$157,540	$3,840
Average GM/GS grade	11.0	11.0	0.0
Average GM/GS salary	$75,500	$77,386	$1,886
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$72,850	$74,670	$1,820
Average salary of ungraded positions	$108,340	$111,046	$2,706

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$12,103,000	$12,692,000	$589,000
11.3 Other than Full-Time Permanent	5,856,000	6,121,000	265,000
11.5 Other Personnel Compensation	351,000	366,000	15,000
11.7 Military Personnel	156,000	163,000	7,000
11.8 Special Personnel Services Payments	3,113,000	3,209,000	96,000
Total, Personnel Compensation	21,579,000	22,551,000	972,000
12.0 Personnel Benefits	4,904,000	5,104,000	200,000
12.2 Military Personnel Benefits	144,000	151,000	7,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**26,627,000**	**27,806,000**	**1,179,000**
21.0 Travel & Transportation of Persons	652,000	622,000	(30,000)
22.0 Transportation of Things	201,000	191,000	(10,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	0	0	0
23.3 Communications, Utilities & Miscellaneous Charges	464,000	443,000	(21,000)
24.0 Printing & Reproduction	280,000	278,000	(2,000)
25.1 Consulting Services	1,670,000	1,578,000	(92,000)
25.2 Other Services	5,649,000	5,417,000	(232,000)
25.3 Purchase of Goods & Services from Government Accounts	38,291,000	38,341,000	50,000
25.4 Operation & Maintenance of Facilities	2,351,000	2,234,000	(117,000)
25.5 Research & Development Contracts	19,564,000	20,130,000	566,000
25.6 Medical Care	442,000	420,000	(22,000)
25.7 Operation & Maintenance of Equipment	1,241,000	1,181,000	(60,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**69,208,000**	**69,301,000**	**93,000**
26.0 Supplies & Materials	5,492,000	5,226,000	(266,000)
31.0 Equipment	2,490,000	2,387,000	(103,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	397,979,000	392,189,000	(5,790,000)
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	0	0	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**476,766,000**	**470,637,000**	**(6,129,000)**
NIH Roadmap for Medical Research	**4,539,000**	**6,090,000**	**1,551,000**
Total Budget Authority by Object	**507,932,000**	**504,533,000**	**(3,399,000)**

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$12,103,000	$12,692,000	$589,000
Other Than Full-Time Permanent (11.3)	5,856,000	6,121,000	265,000
Other Personnel Compensation (11.5)	351,000	366,000	15,000
Military Personnel (11.7)	156,000	163,000	7,000
Special Personnel Services Payments (11.8)	3,113,000	3,209,000	96,000
Total Personnel Compensation (11.9)	**21,579,000**	**22,551,000**	**972,000**
Civilian Personnel Benefits (12.1)	4,904,000	5,104,000	200,000
Military Personnel Benefits (12.2)	144,000	151,000	
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**26,627,000**	**27,806,000**	**1,179,000**
Travel (21.0)	652,000	622,000	(30,000)
Transportation of Things (22.0)	201,000	191,000	(10,000)
Rental Payments to Others (23.2)	0	0	0
Communications, Utilities and Miscellaneous Charges (23.3)	464,000	443,000	(21,000)
Printing and Reproduction (24.0)	280,000	278,000	(2,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	1,670,000	1,578,000	(92,000)
Other Services (25.2)	5,649,000	5,417,000	(232,000)
Purchases from Govt. Accounts (25.3)	12,631,000	12,650,000	19,000
Operation & Maintenance of Facilities (25.4)	2,351,000	2,234,000	(117,000)
Operation & Maintenance of Equipment (25.7)	1,241,000	1,181,000	(60,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**23,542,000**	**23,060,000**	**(482,000)**
Supplies and Materials (26.0)	5,492,000	5,226,000	(266,000)
Subtotal, Non-Pay Costs	30,631,000	29,820,000	(811,000)
Total, Administrative Costs	**57,258,000**	**57,626,000**	**368,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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

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

Item

Scleroderma - The Committee is encouraged by NIAMS's continued interest in scleroderma, a chronic and progressive disease that predominantly strikes women. Scleroderma is disfiguring and can be life-threatening, and effective treatments are lacking. The Committee encourages NIAMS to continue to collaborate with other institutes, including NHLBI, NIAID, NIDDK, and NIDCR, and through the NIH Autoimmune Coordinating Committee to generate additional research opportunities for scleroderma that may assist to identify genetic risk factors and the development of safe and effective treatments. (p. 87)

Action taken or to be taken

Scleroderma is a symptom of a group of diseases that involve the abnormal growth of connective tissue which supports the skin and internal organs. In some forms of scleroderma, hard, tight skin is the extent of this abnormal process. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as the heart, lungs, and kidneys. NIAMS will continue to seek collaborations across NIH to promote and advance all areas of scleroderma research. In particular, NIAMS will continue to be an active member of the Autoimmune Diseases Coordinating Committee, working closely with committee members from NIAID, NHLBI, NIDDK, NIDCR, and other government organizations to better understand what causes the disease and to help develop more effective therapies.

Through molecular, cellular, and genetic research, NIAMS-supported researchers are closing in on the variety of factors involved in scleroderma. NIAMS is funding several studies seeking to identify the immune mechanisms that lead to scleroderma. For example, NIAMS-supported researchers have created a mouse model to examine the cross-talk between immune cells and fibroblasts, cells that form the connective tissues in the body. These researchers have been able to prevent skin hardening in the mouse model by using latency-associated peptide, a specific inhibitor of transforming growth factor beta, a molecule involved in the increased production of collagen – the major protein of the body's connective tissue. This research will add to the body of knowledge that can be used for the development of more effective diagnostic tools and immune-system-based therapies for scleroderma.

Other studies are investigating the genetic basis of scleroderma, seeking to identify the genes that contribute to the increased collagen production. NIAMS-supported researchers are also working to determine the roles of specific autoantibodies involved in the development and progression of

different forms of scleroderma. Comparisons with autoantibodies found in lupus patients are informative in this study, and may lead to a deeper understanding of both diseases. Additionally, NIAMS-supported researchers are working to identify accurate biomarkers for the blood vessel damage associated with scleroderma. This study seeks ways of predicting pulmonary hypertension and other severe blood vessel consequences in patients with scleroderma.

Item

Burden of skin diseases - The Committee notes the release of the recent report, Burden of Skin Diseases, which supports evidence gathered at the September 2002 workshop on the burden of skin diseases sponsored by NIAMS. Based on these findings, the Committee encourages NIAMS to continue to strengthen the research portfolio on skin disease. The Committee also recommends that NIAMS consider potential partnerships with the skin disease research community to address the challenges outlined by the Burden of Skin Diseases findings. (p. 88)

Action taken or to be taken

NIAMS recognizes the burden of skin diseases report that was recently released by two leading professional organizations interested in skin research. As noted, many of the recommendations included in this report overlap with the results from the Workshop on the Burden of Skin Diseases, which was sponsored by NIAMS in September 2002. As an initial step in addressing the needs identified at this meeting, NIAMS-supported researchers are examining existing skin disease databases which could be used to address disease burden. Results from this study will guide next steps in identifying needs and developing future research endeavors, including potential partnerships between organizations, from both the public and private research sectors.

In other research efforts, NIAMS-supported researchers are working to identify the role of genes in the development of skin diseases in order to improve diagnostic, treatment and prevention options. For example, researchers are investigating genetic influence on the development of psoriasis, psoriatic arthritis, and atopic dermatitis, three diseases which can be both physically and psychologically devastating for patients. Researchers recently discovered similarities in genetic susceptibility for psoriasis and atopic dermatitis. As for psoriatic arthritis, the researchers found that the presence of modifier genes can indicate which individuals with psoriasis are also at risk for psoriatic arthritis. Additionally, other NIAMS-supported researchers working at the molecular level have developed a mouse model of psoriasis to examine the underlying mechanisms of disease, including genetics, and to explore novel treatment options. Taken together, these studies provide important information on what causes psoriasis, who gets it, and how it can be treated.

Other NIAMS-supported researchers have been studying familial vitiligo and its association with other autoimmune diseases in order to determine who is at risk for developing the disease. Using data from these families, the researchers were able to demonstrate not only the previously known association with autoimmune thyroid disease, pernicious anemia, Addison's disease and lupus but also an association with rheumatoid arthritis, psoriasis and adult onset insulin-dependent diabetes mellitus. Results from these studies could provide clues to disease development and progression enabling researchers to develop improved diagnostic, treatment and prevention

options that would decrease the burden of disease and improve the quality of life of patients and their families.

Item

Psoriasis – Psoriasis is a chronic, immune-mediated disease that affects between 5.8 and 7.5 million Americans. The Committee recommends that NIAMS support additional research into this serious disease, both to identify the several genes believed to play a role in psoriasis pathogenesis, as well as to support additional clinical research on current and potential therapies for psoriasis and psoriatic arthritis. (p. 88)

Action taken or to be taken

Psoriasis is a chronic skin disease characterized by scaling and inflammation. Individuals with psoriasis may experience significant physical discomfort and some disability. People with moderate to severe psoriasis may feel self-conscious about their appearance and have a poor self-image that stems from fear of public rejection and psychosexual concerns. To this end, NIAMS funds a variety of research aimed at uncovering the cellular and molecular processes that contribute to the development of psoriasis and psoriatic arthritis, developing more effective treatments, and expanding our knowledge of genes that play a role in the development of these diseases in order to help increase the quality of life for patients.

Three recent NIAMS-funded studies are helping scientists and doctors to understand how psoriasis and psoriatic arthritis behaves at the molecular level and what role genes play in predisposing people toward these diseases. For example, NIAMS-supported researchers have found some similarities in genetic susceptibility for psoriasis and atopic dermatitis, another inflammatory skin disease. As for psoriatic arthritis, the researchers found that the presence of modifier genes can indicate which people with psoriasis are also at risk for psoriatic arthritis.

Other NIAMS-supported researchers have developed an animal model to demonstrate how the proliferation of T cells – cells that help to protect the body against infection and disease – is key to the formation of psoriatic lesions. The researchers also demonstrated the role of a molecule involved in the inflammation process, known as tumor necrosis factor alpha, in the development of psoriatic lesions and T cell growth. In another study, a team of scientists used psoriasis as a model disease to develop a way of identifying autoantigens (substances found naturally within the body that can trigger an immune response) for autoimmune diseases. The investigators found three autoantigens that were likely to be related to psoriasis and were associated with significant reactions in patients.

Item

Vitiligo treatment for children - Vitiligo is an environmental and genetic auto-immune disease of unknown origin which affects about three to six million Americans. Almost fifty percent develop the disease in childhood, with the median age of onset at four years of age. In its most severe forms, patients have milky white patches covering wide-spread areas of the body due to the loss of pigment in these areas. Especially for young children, the physical pain caused by severe

burns from the harmful effects of sunlight and the emotional pain caused by people confusing vitiligo with an infectious disease diminish the quality of a patient's life. There are no FDA-approved treatments for children. The Committee encourages NIAMS to enhance research efforts through all appropriate mechanisms to identify the causes of this disease and develop pediatric treatment options for vitiligo. (p. 88)

Action taken or to be taken

Vitiligo is a disease in which white patches develop on the skin because of the loss of pigment production within the skin, and it is especially psychologically devastating in people of color. Children whose parents have the disorder are more likely to develop vitiligo; however, most people with vitiligo do not have a family history of the disorder. NIAMS-supported researchers are studying familial vitiligo in order to examine the genetic basis for the disease.

Statistically, vitiligo is associated with other autoimmune diseases. These other autoimmune diseases occur at greater frequency in relatives of patients with vitiligo even when those relatives do not have vitiligo themselves. Using data from a large cohort of patients and families, NIAMS-supported researchers are investigating the genes associated with the predisposition for vitiligo and other autoimmune diseases. The researchers have been able to demonstrate not only the previously known association with autoimmune thyroid disease, pernicious anemia, Addison's disease, and lupus but also association within families with rheumatoid arthritis, psoriasis and adult onset insulin-dependent diabetes mellitus. All of these diseases were found in greater frequency in the extended families of those with vitiligo.

The form of vitiligo that demonstrated this association was generalized vitiligo which has an earlier onset and is distinct from the other forms of the disease. The ability to recognize which subgroups of vitiligo may be associated with a higher incidence of autoimmune diseases in the family is an important finding that may allow for earlier diagnosis which can lead to better treatment options, particularly for younger patients. In addition, the further genetic analysis of patients and their families should provide clues to the underlying susceptibility to these diseases.

Item

Marfan Syndrome - The Committee commends NIAMS and its collaborative efforts with other institutes to provide support of research on Marfan syndrome, a life-threatening, progressive and degenerative genetic disorder which is characterized by aortic aneurysms, orthopedic disabilities and ocular manifestations which can result in blindness. Years of investment in basic research are ready to be translated to clinical studies of drug therapies with the potential of reversing many of the life-threatening and disabling symptoms of Marfan syndrome. These drug therapies may also prove to benefit people with other connective tissue disorders. The Committee encourages NIAMS to support clinical trials of new drug therapies through all available mechanisms, as appropriate. (p. 88)

Action taken or to be taken

Marfan syndrome is a heritable condition in which connective tissue is defective and does not function appropriately. It is caused by a mutation in the gene that determines the structure of fibrillin, a protein that is an important part of connective tissue. Because connective tissue is found throughout the body, the disease can affect many body systems, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs. Marfan syndrome affects men, women, and children, and has been found among people of all races and ethnic backgrounds.

NIAMS continues to support a multi-site translational research program in Marfan syndrome. The long-term goal of this program is to develop treatment strategies for individuals with Marfan syndrome and related disorders of connective tissue. Researchers are studying genetically engineered mouse models of Marfan syndrome to uncover the abnormal cellular activities that contribute to this disorder, and they will translate this new knowledge into more effective therapies. The program utilizes a comprehensive and multidisciplinary approach that integrates the scientific interest and expertise of four leading laboratories in this and related research fields.

As one example of the research being conducted by this consortium, researchers are using mouse models of Marfan syndrome in order to identify the molecular and cellular events responsible for the development and progression of aortal aneurysm, a common consequence of the disease. The goal of this study is to discover a basis for drug-based treatments of aneurysm in patients with Marfan syndrome. Another related study examining the molecular level is investigating the role of transforming growth factor-beta (TGF-beta, a signaling protein which regulates the activity of osteoblasts and osteoclasts) and its connection with the deficiency of fibrillin-1 that is characteristic of Marfan syndrome. If it can be determined that the lack of fibrillin-1 causes the overproduction of TGF-beta, resulting in some of the symptoms of Marfan syndrome, these studies may lead to new treatments based on blocking TGF-beta activity.

Item

Tuberous sclerosis complex (TSC) - TSC is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the skin. The Committee encourages NIAMS to support programs examining the molecular and cellular basis of dermatological lesions in TSC as well as the development of non-surgical treatments for skin manifestations. (p. 88)

Action taken or to be taken

NIAMS actively participates in the Trans-NIH Tuberous Sclerosis Coordinating Committee which is led by NINDS and includes representatives from other NIH components such as NCI, NIDDK, NIMH, NHLBI, NICHD, NIGMS and the NIH Office of Rare Diseases. Other participating organizations include the Department of Defense and the Tuberous Sclerosis Alliance. Members of the Coordinating Committee have reviewed and discussed the research portfolios of the participating organizations, including relevant ongoing clinical trials, in order to identify potential research partnerships and opportunities for targeted initiatives on tuberous sclerosis complex.

Recently, NINDS, NIDDK, NIMH, NIAMS, and NCI partnered with the Tuberous Sclerosis Alliance to release a program announcement focused specifically on tuberous sclerosis complex. The solicitation encouraged applications designed to broaden the base of knowledge related to the disease including the identification of new therapeutics. NIAMS encourages highly meritorious applications in mission-related research that is directly related to tuberous sclerosis complex including the development of non-surgical treatment options for the associated skin manifestations of the disease.

Item

Mucopolysaccharidosis (MPS) - The Committee encourages NIAMS to work collaboratively with NIDDK in an effort to achieve a greater understanding of the bone and joint lesions in MPS disorders. The committee supports NIAMS research addressing the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored, and potential therapeutic approaches to treating these debilitating aspects of MPS and related disorders. (p. 88)

Action taken or to be taken

Mucopolysaccharidosis (MPS) is an inherited metabolic disorder that causes a variety of musculoskeletal problems including bone and joint irregularities resulting in short stature, stiff joints and curvatures of the spine. Progressive physical disability can result from these manifestations and neurological problems can also occur if nerves become compressed. Although treatments for these symptoms are available, there is currently no cure for the disease.

NIAMS is committed to advancing the understanding, diagnosis, treatment, and prevention of a broad range of bone and joint diseases. Currently, NIAMS supports a number of research programs designed to examine these diseases at the cellular and molecular levels and to utilize animal models in order to better understand the genetic aspects of disease. Advances in many of these areas could provide valuable insight into the development and progression of MPS. NIAMS would welcome highly meritorious applications relevant to our research mission that address the musculoskeletal issues associated with MPS. In order to facilitate this process and to identify appropriate research areas, NIAMS staff has meet with representatives of NIDDK and NINDS, as well as representatives of MPS patient advocacy groups, to consider opportunities for collaboration across the NIH.

Item

Osteogenesis Imperfecta The Committee commends NIAMS for its support of promising gene-targeting stem cell research that could represent a potential cure for osteogenesis imperfecta and encourages continued support of this research. (p. 89)

Action taken or to be taken

Osteogenesis imperfecta (OI) is a genetic disorder characterized by bones that break easily, often from little or no apparent cause. OI is caused by a genetic defect that affects the body's production of collagen, the major protein of the body's connective tissue. In OI, a person has either less collagen or a poorer quality of collagen than normal, leading to weak bones that fracture easily.

The NIAMS supports several projects which focus on new and innovative treatment options for OI. NIAMS-funded scientists have developed a method of inactivating affected genes in cells from patients with severe forms of OI. These cells were shown to produce normal collagen and retain the ability to develop into mature bone-forming cells. Although this therapy will require further testing, it holds the promise of reducing the burden of disease. Advances like this bring scientists significantly closer to being able to repair genetic errors, not just for OI, but for many other diseases that are due to the activity of abnormal genes.

Other researchers are utilizing a mouse model of OI to evaluate the potential use of stem cells derived from bone marrow to facilitate the repair and regeneration of bone. The study seeks to test the idea that stem cells from normal donor mice, when infused into mice with OI, will contribute to the growth of healthy bone. This study may lead to the development of better treatments for genetic and non-genetic diseases of bone.

Additionally, NIAMS-supported scientists continue to investigate the molecular basis of OI and the use of new medications to treat it. For example, researchers are examining the chemical basis for the unique structure of collagen. This research will provide new insight into the interaction of collagen with other proteins, and could ultimately lead to the creation of collagen substitutes and collagen-based biomaterials with important therapeutic applications.

Item

Osteopetrosis – The Committee encourages NIAMS to increase support of research on models, methods, and modalities to increase bone formation and alter bone remodeling, and address the impact of aging, genetics, obesity, inactivity and exercise on bone at molecular, cellular, and tissue levels. NIAMS is encouraged to work with NICHD and NIDDK to strengthen research on the genetics and new treatments for the rare disorder osteopetrosis. (p. 89)

Action taken or to be taken

NIAMS supports a broad range of research on bone to better understand what causes the various forms of bone disease and to help develop more effective therapies. For example, researchers have been able to locate a gene that not only influences bone density in mice, but also provides new insight into how to preserve bone mass in humans. By locating relevant bone formation pathways, scientists may find additional clues to the prevention of bone diseases such as osteoporosis and resulting fractures.

NIAMS-supported researchers are also investigating a number of animal and cellular models of bone resorption, the process in which old bone is broken down and removed by specialized cells. The overall goal of these studies is to discover novel mechanisms in the control pathways that are relevant to bone health and disease. Identification of the molecular mechanisms of these pathways may reveal additional therapeutic targets that can be pursued to improve the clinical treatment of a variety of bone diseases.

Osteopetrosis is a group of congenital bone diseases that are characterized by an increase in skeletal mass resulting from inadequate bone breakdown. In osteopetrosis, the cells that break down bone (osteoclasts) usually are either fewer in number or are ineffective in breaking down bone, leading to dense but fragile bones. To date, the precise genetic control of osteoclast function remains inadequately understood. Improved treatment of bone disease awaits additional investigation into the complex control mechanisms that balance the formation and breakdown of bone. NIAMS supports a broad portfolio of bone research, including studies examining osteopeterosis, and would welcome opportunities to work with other components of the NIH with similar interests.

Recent studies have shown that certain mutations in the chloride channel cause a specific form of osteopetrosis, Type 2 autosomal dominant osteopetrosis or ADO2, but up to 1/3 of subjects with the same mutation remain unaffected carriers. This has led to the search for both environmental causes as well as other genes that modify the response to the mutation. New research involving eight multi-generational families with ADO2 has revealed that modifier genes may control the expression of the disease and determine its onset and severity. The identification of these modifier genes may provide further insight into the mechanism of this disease, but also may suggest new therapeutic targets for this and other metabolic bone diseases.

Item

Lupus - The Committee is aware that the discovery of lupus susceptibility genes may be a prerequisite to developing exciting new therapies for lupus and ultimately a way to prevent and cure the disease. Advanced new technologies make finding these genes less expensive and more feasible than ever before. The Committee is also aware that new consortia within the lupus community have been formed to facilitate genetic research. The Committee urges the Institute to strengthen its work in support of the collection of DNA, serum, genotyping and subject information from lupus patients, their family members and healthy unrelated controls so that the identification of the relevant genes can be explained. (p. 89)

Action taken or to be taken

For over 10 years, NIAMS has supported the Lupus Registry and Repository, a core facility dedicated to collecting and characterizing information from patients and their family members. The registry currently includes 624 pedigrees; 287 of these include multiple cases that are especially useful for genetic linkage analyses. DNA, plasma, and serum samples are available to researchers across the country and currently provide patient information to more than 28 other lupus-related projects. Additionally, NIAMS provides support for the Research Registry for Neonatal Lupus. This registry provides material for basic research on the causes of this disease,

tracks important epidemiological data such as incidence, and facilitates family counseling. Data from both registries, as well as other ongoing genetics studies, will facilitate development of improved methods of diagnosis, prevention, and treatment.

NIAMS-supported researchers continue to make a significant impact on the landscape of lupus research. For example, a recent study supported by NIAMS and NIAID helps confirm the connection between lupus and the Epstein-Barr virus (EBV), particularly in those individuals with a genetic predisposition for the disease. Using information from the Department of Defense repository, researchers studied changes in the blood of people who later developed lupus, and were able to identify when people with lupus began to make the autoantibodies that damage target tissues. In people genetically predisposed to lupus, antibodies to a portion of the EBV protein cross-reacted with a piece of a protein in the body called Ro. This study provides new insight into how lupus begins, and it also has implications for treating or even preventing the disease.

Other researchers are examining new and existing treatment options for patients with lupus. For example, preliminary studies that were partly funded by the NIAMS show that the cancer medication rituximab may someday be effective against lupus. In a study of adults with lupus that was clinically active despite treatment, just one injection of rituximab eased symptoms for up to a year or more. While current lupus treatments work by suppressing the entire immune system, rituximab selectively targets the B cells – white blood cells that produce proteins called antibodies – that are at the root of the problem.

Additionally, women with lupus may experience the benefits of postmenopausal hormone therapy without an increased risk of severe disease flares, according to a major study funded by the NIAMS. In a 16-center study of menopausal women, those taking a standard regimen of hormone therapy had no statistically significant increased risk of severe flares compared to those taking a placebo. Women in the hormone therapy group were, however, about 20 percent more likely to have a mild-to-moderate flare. None of these mild-to-moderate flares resulted in the need for high-dose steroids or hospitalizations.

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

Item

Bone Formation and Remodeling - The Committee encourages NIAMS to increase support of research on models, methods and modalities to increase bone formation and alter bone remodeling, and address the impact of aging, genetics, obesity, inactivity and exercise on bone at molecular, cellular, and tissue levels. NIAMS should work with NICHD and NIDDK to expand research on the genetics and new treatments for the rare disorder osteopetrosis. (p. 133)

Action taken or to be taken

Please refer to page NIAMS-34 of this document for NIAMS' response to this significant item regarding osteopetrosis.

Item

Burden of Skin Diseases - The Committee notes the release of the recent report, `Burden of Skin Diseases', which supports evidence gathered at the September 2002 workshop on the burden of skin diseases sponsored by NIAMS. Based on these findings, the Committee urges NIAMS to continue to expand the research portfolio on skin disease. The Committee also encourages that NIAMS consider potential partnerships with the skin disease research community to address the challenges outlined by the "Burden of Skin Diseases" findings. (p. 133)

Action taken or to be taken

Please refer to page NIAMS-29 of this document for NIAMS' response to this significant item regarding burden of skin diseases.

Item

Duchenne Muscular Dystrophy - The Committee continues to be concerned with the amount of time taken by NIAMS to complying with the MD Care Act. The Committee encourages the NIAMS to increase research for Duchenne Muscular Dystrophy. The Committee further requests that NIAMS coordinate with NINDS on timelines for translational research, a consensus conference and the strategic plan. (p. 133)

Action taken or to be taken

NIAMS, along with NINDS and NICHD, continues to actively work with both public and private organizations to respond to the major provisions of the MD-CARE Act. For example, NIAMS has been an integral component of the ongoing activities of the Muscular Dystrophy Coordinating Committee (MDCC). The MDCC has overseen the development of the Muscular Dystrophy Research and Education Plan for the NIH and the new Action Plan for the Muscular Dystrophies. The Action Plan, which refines the goals of the Research and Education Plan, has been designed to serve as a comprehensive document for the entire muscular dystrophy research and education community to use when developing future research activities related to the detection, diagnosis, treatment and prevention of all types of muscular dystrophy. The final draft of the Action Plan was presented to the MDCC on November 9, 2005, for review and comment. Once approved, the Action Plan will be available to the public.

As part of the MD-CARE Act, NIH was authorized to establish centers of excellence for muscular dystrophy. Currently, NIAMS provides support for two of the six existing Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. Taken together, the six Centers provide expertise, infrastructure and resources focused on major questions about muscular dystrophy. NIH staff work closely with representatives from each Center to promote collaborations between Centers and to provide guidance and continued evaluation of research goals and progress.

NIAMS continues to develop its muscular dystrophy portfolio, including projects focused on translational research. Building on recent basic biology advances in the muscular dystrophies,

NIAMS-supported researchers are exploring treatment options for degenerative muscle diseases including pharmacological, and gene- and cell-based therapies. NIAMS-supported researchers are working to identify and test potential drugs used to block the enzymes that cause muscle degeneration, and pharmacological methods to promote muscle growth. Additionally, NIAMS supports several other translational research projects aimed at developing and testing recombinant viruses engineered to be vehicles for the delivery of therapeutic genes that may block or reverse muscle degeneration. In collaboration with NINDS, the NIAMS will soon release a set of two program announcements to further advance NIH-supported translational research in the muscular dystrophies. Specifically, these initiatives will implement a broad-based translational research program of exploratory/developmental research projects and cooperative agreements with the goal of developing new and more effective treatments.

Item

Lupus - The Committee recognizes lupus is a serious, complex, debilitating chronic autoimmune disease that can cause inflammation and tissue damage to virtually any organ system in the body and impacts between 1.5 and 2 million individuals. This autoimmune disorder affects the skin, bones, joints, connective tissue and vital organs. The Committee is disappointed with the pace of research regarding lupus and strongly urges the Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases to expand and intensify research and related activities with respect to lupus. (p. 133)

Action taken or to be taken

Please refer to pages NIAMS-35 of this document for NIAMS' response to this significant item regarding lupus.

Item

Marfan Syndrome - The Committee commends NIAMS and its collaborative efforts with other Institutes to provide vital research on Marfan syndrome, a life-threatening, progressive and degenerative genetic disorder that is characterized by aortic aneurysms, painful orthopedic issues, pulmonary issues and ocular manifestations. Years of basic research are ready to be translated into a clinical trial for a drug therapy that may potentially prevent and reverse many of the life-threatening aspects of this syndrome. In addition, it may help many of the disabling characteristics not only of Marfan syndrome but also of other connective tissue disorders. The Committee urges NIAMS to support this effort through all available mechanisms, as deemed appropriate. (p. 134)

Action taken or to be taken

Please refer to pages NIAMS-31 of this document for NIAMS' response to this significant item regarding Marfan syndrome.

Item

Mucopolysaccharidosis [MPS] - The Committee encourages the NIAMS to work collaboratively with NIDDK in an effort to achieve a greater understanding of the underlying pathophysiology of bone and joint lesions in MPS disorders, the gene mutations and substrates that are stored, and potential therapeutic approaches to treating these debilitating aspects of MPS and related disorders. (p. 134)

Action taken or to be taken

Please refer to page NIAMS-33 of this document for NIAMS' response to this significant item regarding mucopolysaccharidosis.

Item

Osteogenesis Imperfecta.--The Committee commends NIAMS for its support of the promising gene targeting stem cells research that represents a potential cure for osteogenesis imperfecta and encourages continued support of this research. (p. 134)

Action taken or to be taken

Please refer to pages NIAMS-34 of this document for NIAMS' response to this significant item regarding osteogenesis imperfecta.

Item

Osteoporosis – The Committee urges the study of genetics of osteoporosis including, studies to determine the causes of variation in peak bone mass and rates of bone loss and therapies to lower fracture risk in patients at high risk for osteoporotic fractures. (p. 134)

Action taken or to be taken

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures. Although scientists know that many genes influence bone mass and thus osteoporosis risk, identifying specific genes has been challenging – especially in humans, who are genetically diverse.

NIAMS supports several studies examining the genetic determinants of the material properties of bone including bone mineral density (BMD) and bone quality in both human and animal models. BMD is the most widely used measure in the assessment of osteoporosis and fracture risk and is very valuable clinically; however, there are some limitations to using BMD alone for either genetic studies or for the assessment of fracture risk. Cutting edge imaging, as well as biomarker research, is currently exploring other characteristics of bone that may inform studies of skeletal health and fracture risk. Discovery of the genes essential for optimal bone quality would offer tremendous insight into overall bone strength. These studies also have the potential to lead to new developments in the prevention and treatment of osteoporosis.

In recent studies, NIAMS-supported researchers have been able to locate a gene that not only influences bone density in mice, but also provides new insight into how to preserve bone mass in people. These researchers identified the gene, called alox15, while working with two strains of mice that have very different bone mineral densities. Variations in the gene account for a significant part of that difference. While scientists have known of the gene for some time, it was never recognized as important to the skeleton. The discovery of alox15's influence on bone mass suggests that previously unsuspected metabolic pathways could be important for skeletal health. By further studying this pathway, scientists may find additional clues to the prevention of osteoporosis and the resulting fractures.

In addition to the research previously mentioned, NIAMS recently sponsored the meeting, Bone Quality: What Is It and Can We Measure it?, in May 2005. This scientific meeting brought together leading scientists from around the world to identify needs and future directions in bone quality research; highlighted basic science, clinical, regulatory, and pharmaceutical perspectives. Participants assessed established and new methods for measuring bone fragility as well as how to facilitate their inclusion in clinical trials; and they discussed novel mechanisms to bring together research efforts on bone quality to move this research field forward. The NIAMS partnered with the American Society for Bone and Mineral Research, the French Institute of Health and Medical Research (INSERM), and the NIH National Institute of Biomedical Imaging and Bioengineering in sponsoring this meeting.

Item

Paget's Disease- The Committee urges NIAMS to study the role of genes and the underlying abnormal functioning of cells involved in bone breakdown in Paget's disease patients. Further research is needed on the role the bone microenvironment plays in the development of Paget's disease and the molecular processes involved. (p. 134)

Action taken or to be taken

Paget's disease is a chronic disorder that can result in enlarged and misshapen bones. The excessive breakdown and formation of bone tissue causes affected bone to weaken – resulting in bone pain, fractures, and arthritis in the joints near the affected bones. The underlying causes of Paget's disease are complex, and are still poorly understood. Likely contributing factors include chronic infection with certain viruses and inherited predisposition to develop the disease in some families. However, it is clear that a key feature of the disease is excessive numbers and activity of osteoclasts, the cells that are responsible for bone breakdown.

NIAMS supports an integrated multi-project program of research into the biological mechanisms underlying the development of Paget's disease. These efforts have shown that osteoclast precursors from people with Paget's disease are unusually sensitive to dihydroxyvitamin D3 (Vitamin D3). This form of the vitamin is normally present in the body and is important for a number of metabolic processes. The normal levels of Vitamin D3 that are present do not stimulate formation of osteoclast cells. However, when the cells from people with Paget's disease are exposed to the same levels of Vitamin D3, they readily form osteoclasts. In recent

work, investigators have identified components of the molecular machinery responsible for this hyper-responsiveness to Vitamin D3 in individuals with the disease, one of which is a protein called the vitamin D receptor (VDR). VDR has been studied for many years and a number of drugs, called VDR antagonists, have been developed that block the action of VDR in cells. Investigators have now tested one of these VDR antagonists in cultures of bone marrow cells from people with Paget's disease. They found that the VDR antagonist effectively prevented the stimulation of osteoclast formation by Vitamin D3. This suggests that VDR antagonists could be useful in the treatment of Paget's disease.

Other NIAMS-supported investigators are seeking to identify the genetic basis of a disease in which myopathy (muscle damage) is associated with Paget's disease. This work may reveal previously unsuspected biochemical pathways that can contribute to the development of Paget's disease. Other NIAMS-supported researchers are employing a variety of molecular and cellular techniques, as well as transgenic animal models, to provide new insights into the mechanism of osteoclast formation. Improved understanding of the regulation of bone breakdown may provide novel targets for the development of pharmaceutical agents aimed at preventing bone destruction associated with bone disorders such as Paget's disease.

Item

Psoriasis - Ten to 30 percent of psoriasis patients develop psoriatic arthritis, a painful and potentially destructive joint disease. The Committee urges NIAMS to support additional genetic research to identify the genes responsible for psoriasis susceptibility, basic research to understand the mechanism of disease and clinical research to identify new safe and effective therapies for these diseases. (p. 134)

Action taken or to be taken

Please refer to page NIAMS-30 of this document for NIAMS' response to this significant item regarding psoriasis.

Item

Scleroderma - The Committee is encouraged by NIAMS's continued interest in scleroderma, a chronic and progressive disease that predominantly strikes women. Scleroderma is disfiguring and can be life-threatening, and effective treatments are lacking. The Committee encourages NIAMS to continue to collaborate with other Institutes, including NHLBI, NIAID, NIDDK, NIDCR, and through the NIH Autoimmune Coordinating Committee to generate additional research opportunities for scleroderma that may assist to identify genetic risk factors and the development of safe and effective treatments. (p. 134)

Action taken or to be taken

Please refer to pages NIAMS-28 of this document for NIAMS' response to this significant item regarding scleroderma.

Item

Tuberous Sclerosis Complex - Tuberous sclerosis complex, or TSC, is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the skin. The Committee is encouraged that NIAMS is participating in a Trans-NIH Tuberous Sclerosis Coordinating Committee, and strongly encourages NIAMS to continue to assist the clinical research community in the development of standardized protocols for skin assessment and the development of pilot clinical trials. (p. 135)

Action taken or to be taken

Please refer to page NIAMS-32 of this document for NIAMS' response to this significant item regarding tuberous sclerosis complex.

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

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	$493,846,000	Indefinite	$490,518,000
Musculoskeletal and Skin Diseases	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	14,086,000		14,015,000
Total, Budget Authority				507,932,000		504,533,000

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

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1998	258,932,000 2/	265,458,000	268,210,000	274,760,000
1999	290,176,000 2/ 3/	296,688,000	304,320,000	308,164,000
Rescission				(204,000)
2000	309,953,000 2/	333,378,000	350,429,000	351,840,000
Rescission				(1,872,000)
2001	363,479,000 2/	400,025,000	401,161,000	396,604,000
Rescission				(144,000)
2002	443,565,000	440,144,000	460,202,000	448,865,000
Rescission				(617,000)
2003	485,851,000	485,851,000	489,324,000	489,324,000
Rescission				(3,181,000)
2004	502,778,000	502,778,000	505,000,000	504,300,000
Rescission				(3,234,000)
2005	515,378,000	515,378,000	520,900,000	515,378,000
Rescission				(4,221,000)
2006	513,063,000	513,063,000	525,758,000	513,063,000
Rescission				(5,131,000)
2007	504,533,000			

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 $877,000 for the budget amendment for Bioterrorism

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	52	52	52
Extramural Programs	29	29	30
Intramural Research Program	131	131	131
Total	212	212	213
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research			
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2003	10.7
2004	11.4
2005	11.0
2006	11.0
2007	11.0

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	2	2	2
Total - ES Salary	$298,438	$307,400	$315,808
GM/GS-15	16	16	16
GM/GS-14	17	17	18
GM/GS-13	26	26	26
GS-12	20	20	20
GS-11	17	17	17
GS-10	0	0	0
GS-9	12	12	12
GS-8	12	12	12
GS-7	15	15	15
GS-6	3	3	3
GS-5	5	5	5
GS-4	1	1	1
GS-3	2	2	2
GS-2	0	0	0
GS-1	0	0	0
Subtotal	146	146	147
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	1	1	1
Senior Grade	1	1	1
Full Grade	0	0	0
Senior Assistant Grade	1	1	1
Assistant Grade	0	0	0
Subtotal	3	3	3
Ungraded	58	58	58
Total permanent positions	148	148	149
Total positions, end of year	209	209	210
Total full-time equivalent (FTE) employment,end of year	212	212	213
Average ES salary	$149,219	$153,700	$157,540
Average GM/GS grade	11.0	11.0	11.0
Average GM/GS salary	$73,303	$75,500	$77,386

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis and Musculoskeletal and Skin Diseases

New Positions Requested

	FY 2007		
	Grade	Number	Annual Salary
Health Scientist Administrator	GS-14	1	$99,645
Total Requested		1	