DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

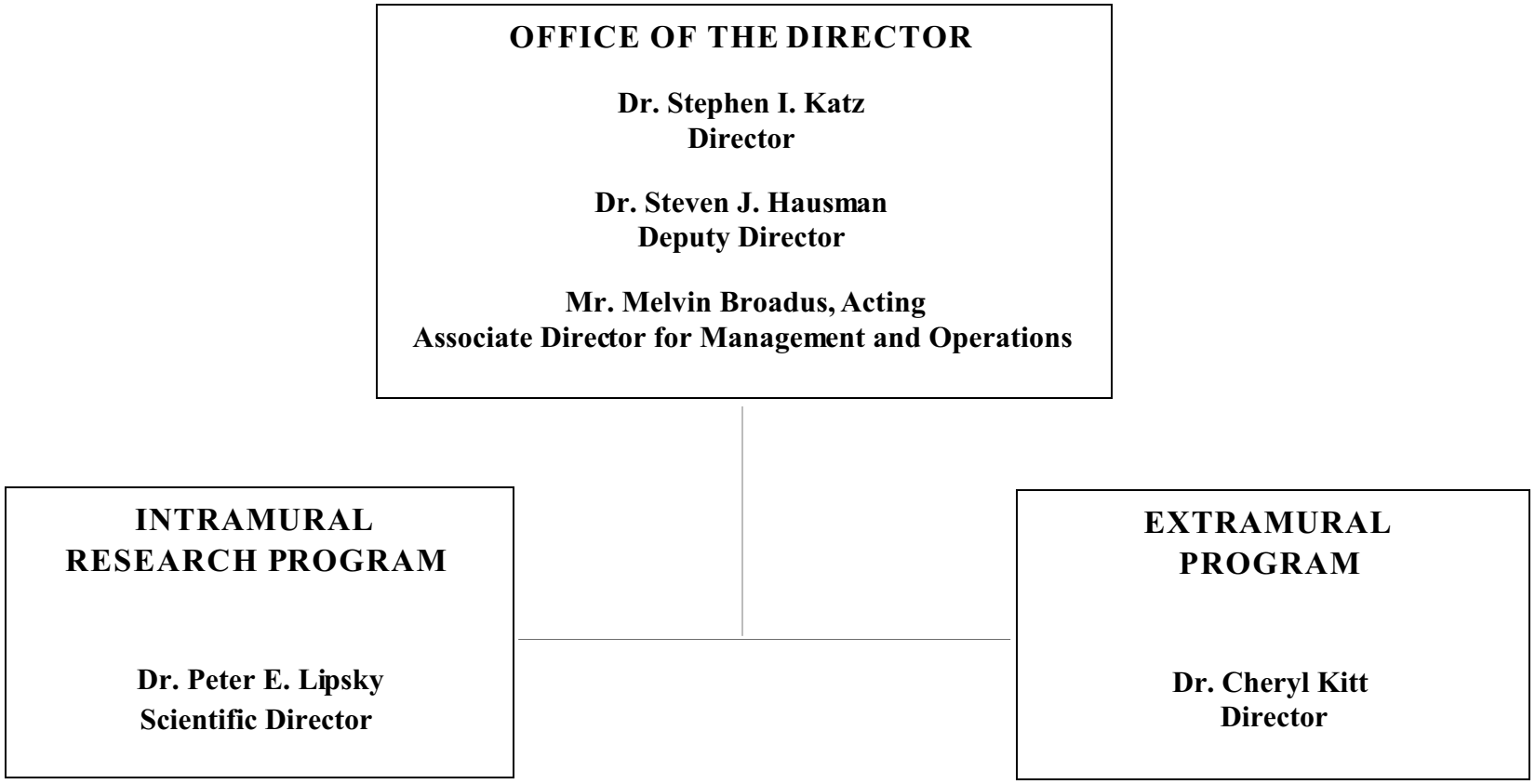
National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 2005 Budget — Page No.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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, [$504,300,000] *$515,378,000*.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2004]

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.
Reauthorizing legislation will be submitted.

Budget Authority:

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
250	$485,611,000	236	$500,908,000	236	$515,378,000		+$14,470,000

This document provides justification for the Fiscal Year 2005 activities of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), including HIV/AIDS activities. Justification of the National Institutes of Health (NIH)-wide FY 2005 AIDS activities can be found in the NIH section entitled Office of AIDS Research (OAR).

INTRODUCTION

Improving daily life is the driving force for the research that we support and conduct at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Virtually every home in America is touched by diseases affecting bones, joints, muscles, and skin. We are committed to advancing understanding, diagnosis, treatment, and prevention of these diseases and disorders that are often chronic and disabling, many of which disproportionately affect women and minority populations.

The stories of research progress and promise below illustrate that support for research across a broad spectrum is essential basic research at the laboratory bench needs to be translated through clinical research to benefit patients. The converse is equally true we count on clinical researchers to stimulate basic studies that will ultimately yield information useful to patient care and disease prevention. The budget increases over the last several years have made a real difference in the research that the NIAMS has been able to support in that we have significantly expanded our support of clinical research and clinical trials. Some of these investments have already borne fruit while others will take several years before we can determine their outcome. Highlights of some recent research advances as well as of ongoing and new initiatives in areas of scientific opportunity follow.

The NIH Roadmap. The NIAMS is an enthusiastic partner in all dimensions of the newly-released NIH Roadmap. We believe much of the basic research our investigators conduct will be greatly facilitated by the focus on basic science in the "Pathways to Discovery" initiatives. Further, because the NIAMS supports research on complex chronic diseases, many initiatives within the "Research Teams of the Future," theme are very relevant to our mission. Specifically,

facilitation of interdisciplinary research can only enhance progress in arthritis, musculoskeletal, and skin research. Finally, we are most enthusiastic about the promise of the multidimensional approach to "Re-engineering the Clinical Research Enterprise." The initiatives in this area will provide many clinical researchers studying diseases of the bones, muscles, joints, and skin access to advanced and novel infrastructure, eliminating the need to create new infrastructure every time a new clinical study is initiated. We expect to enjoy more efficient use of resources and an increased pace of scientific discovery in our clinical research as a result.

NIAMS SCIENCE ADVANCES AND NEW INITIATIVES

An Illustration of Effective Translational Research NIH Researchers Collaborate to Produce a Targeted Immunosuppressive Drug. Ten years ago, researchers in an NIAMS Intramural Research Program laboratory discovered a particular protein, an enzyme known as JAK3, and determined that it is found only in immune system cells. This finding now holds great promise for people undergoing organ transplants as well as for people with the wide range of autoimmune diseases. The importance of JAK3 comes from a long process of research and discovery by the NIH team and their collaborators engaged in basic research that included not only the actual discovery of JAK3, but also demonstrating that this protein was critical for cell signaling resulting in the development of infection-fighting white blood cells. Further research revealed that mutations of the gene that encodes JAK3 in humans is responsible for a form of severe combined immunodeficiency disease (SCID). Researchers then looked to translate these seminal discoveries in basic research to benefit patients with improved, targeted therapies. Because JAK3 is essential for immune cell function, and because its expression is limited to blood cells, researchers predicted that inhibiting JAK3 might be the basis for a new class of drugs that could suppress the immune system. While suppression of the immune system is problematic for most people and results in a whole host of potentially devastating side effects, suppression of the immune system is actually desirable for people who have had organ transplants as well as people who have autoimmune diseases. The researchers then entered into a collaborative research and development agreement with Pfizer in a partnership that enabled Pfizer to develop a new drug. This partnership, involving researchers in the NIAMS Intramural Program, in academia, and at Pfizer, is studying a new immunosuppressive drug, CP-690,550, that holds the promise of avoiding some of the common side effects associated with other currently available medications that curb the immune system. This new drug was tested in mice that had heart transplants and in monkeys that had kidney transplants and, in both cases, animals treated with CP-690,550 survived much longer than untreated animals. None of the treated animals showed signs of typical, serious immunosuppressive side effects. An analysis of the mechanism of action of this new drug revealed that it specifically inhibits the enzyme JAK3, and that inhibiting this enzyme has the effect of suppressing the immune system, while not affecting other systems of the body. This is in contrast to many of the current immunosuppressive drugs that target enzymes found in cells throughout the body, resulting in toxic side effects. This is an illustration of translational research at its best with research findings from basic to clinical investigations. These studies have enabled researchers to design more focused basic research as well as offered the promise of improved, targeted patient care. CP-690,550 is the first protein tyrosine kinase inhibitor to show positive results in primates with respect to regulating immune response. Further animal studies are being conducted to determine if this drug could be used

successfully and safely in humans to prevent the body from rejecting transplanted organs, as well as to treat autoimmune diseases such as lupus, rheumatoid arthritis, and psoriasis.

ARTHRITIS AND OTHER RHEUMATIC DISEASES

Progress in Research on Lupus: Serum Antibodies Precede Clinical Findings in Lupus by Many Years. Systemic lupus erythematosus (SLE), or lupus, is a chronic and potentially fatal autoimmune disease, often occurring in women of child-bearing age. It can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. People of all races have lupus; however, African American women are three times more likely to have lupus and are more likely to die from lupus than are white women. African American women also tend to develop the disease at a younger age than white women and develop more serious complications. Lupus is also more common in women of Hispanic, Asian, and Native American descent. Women are nine times more likely to have lupus than are men. Lupus is often difficult to diagnose because of its highly varied and often serious insidious clinical manifestations. A new study funded by the NIH revealed that people diagnosed with lupus have autoantibodies (antibodies against their bodies own tissues) in their blood years before the symptoms of lupus appear. The early detection of these autoantibodies may help in recognizing those who will develop the disease and allow physicians to monitor them before they might otherwise be diagnosed. Lupus and other autoimmune diseases often go untreated for years and are diagnosed only after damage to the body tissues has occurred. Findings such as these, which will help to identify and monitor people who may develop these diseases, are extremely valuable.

Researchers Uncover a Genetic Signature for Lupus. A team of scientists supported by the NIH and the private sector have discovered a genetic "signature" present in some patients with lupus who develop such life-threatening complications as blood disorders, central nervous system damage, and kidney failure. Researchers analyzed thousands of genes in the blood cells of lupus patients and healthy controls. Interestingly, 14 of the thousands of genes studied were linked to a subset of lupus patients with severe disease. These 14 genes, referred to collectively as the IFN (interferon) expression signature, are turned on by the activity of interferon, a complex family of proteins involved in the regulation of immune responses. Patients with severe lupus consistently showed higher expression levels of this IFN signature. Identifying lupus patients at particular risk for severe disease before serious complications arise has enormous implications for the early diagnosis and treatment of this potentially devastating disease. These research results provide strong support for developing new therapies to block IFN pathways in patients with severe lupus, and the pattern of gene expression in blood cells may be useful in identifying patients most likely to benefit from these new therapies. Gene expression profiling in blood cells may also be useful in identifying disease pathways in other autoimmune and inflammatory disorders. The NIAMS partnered with the National Center on Minority Health and Health Disparities, the NIH Office of Research on Women s Health, the Minnesota Lupus Foundation, and the Alliance for Lupus Research in this research.

Genetic Differences Found in African American, European American Lupus Families. After 10 years of collecting genetic information on families with lupus, researchers have found different genetic regions linked to lupus in African Americans and European Americans. This

genetic linkage study may one day help to explain why more African Americans die of lupus and develop more serious complications such as nephritis (kidney failure) compared with people of European descent. These researchers identified a region on chromosome 1 associated with the development of lupus in African American families. They also identified two regions of chromosome 11 associated with lupus in subsets of the African American families. In European American families, they found a genetic linkage to chromosome 4 that contributes to lupus. These results suggest that the genetic origins of lupus may differ in African Americans and European Americans.

Federal Working Group on Lupus. In other news related to lupus, the first meeting of the Federal Working Group on Lupus was held in October 2003. The conference report for the FY 2003 appropriations included language calling on the Office of the Secretary to establish this new group. This working group was established under the leadership of the NIAMS, and it includes representatives from seven NIH components as well as all relevant DHHS agencies and other federal departments having an interest in lupus. The working group will provide a forum for representatives of federal agencies and non-federal organizations with an active interest in lupus research, training, and education to share ideas and information, to identify promising scientific opportunities, and to facilitate novel collaborations. In addition, liaison members from interested health voluntary organizations will be participating in working group meetings and activities, to ensure that broad input and diverse perspectives are incorporated into the working group's deliberations. We will make every effort to harmonize the activities of this working group with the work of existing groups, such as the NIH Autoimmune Diseases Coordinating Committee, to be sure that the new working group complements on-going efforts to promote collaborations relevant to lupus.

Pain and Social Activity in Children with Juvenile Arthritis. Using diary analysis in conjunction with standard clinical testing, researchers have shown that increased anxiety - and, surprisingly, not depressed mood - was significantly associated with increased fatigue and pain frequency and intensity. In addition, the research team found not surprisingly that increased pain and fatigue are linked to reduced participation in school and social activities. Children with juvenile arthritis may have pain that can be intense and disabling, and comprehensive treatment optimizes their ability to fully participate in these activities. In addition to being more aggressive in treating pain with traditional pharmacological therapies, the researchers also recommend including behavior-altering medication and cognitive-behavioral therapy to treat associated anxiety in children with juvenile arthritis. While arthritis pain has been the focus of much research in adults, there is an increasing awareness of the need to focus on pain in children. This study, supported by NIAMS, the Office of Research on Women s Health, and the private sector, has shed new light on this important research topic.

Identification of Pain-Signaling Pathways. Chronic pain is a debilitating feature of fibromyalgia and other musculoskeletal diseases of concern to the NIAMS. A recent study, partly funded by the NIAMS, suggests that a pain-signaling pathway in the brain, modulated by the neurotransmitter GABA, could be a target for a potential therapy for controlling chronic pain. The work showed that signals from the insular cortex (a small region in the forebrain), to the amygdala (a brain area involved in pain, fear and attention) facilitated by GABA may be involved in chronic pain. When the insular cortex sends signals to the amygdala, pain is

experienced; equally, communication between the insular cortex and the locus coeruleus (an area in the hindbrain involved in the stress response) increases pain. The insular cortex uses two different forms of the neurotransmitter GABA $GABA_A$ and $GABA_B$ to communicate with the locus coeruleus and the amygdala, respectively. Thus, it might be possible to inhibit the signals from the insular cortex to the amygdala by manipulating $GABA_B$ levels in the insular cortex, which might benefit patients who experience chronic pain. Most current therapies work from the bottom up, focusing on peripheral areas where the pain is experienced. This research points toward an approach from the top down : blocking the signals from the brain to the peripheral areas affected by pain.

Two New Initiatives in Osteoarthritis. Osteoarthritis is the most common form of arthritis, and it not only affects millions of Americans today, but it is expected to affect many more people in the future as the number of elderly in our country increases. The NIAMS supports a broad and diverse portfolio of basic and clinical research to improve our understanding of the underlying causes of osteoarthritis, improve the diagnosis and treatment of osteoarthritis, and improve quality of life for affected individuals. This year the NIAMS has targeted two particular areas of opportunity in research on osteoarthritis. The first is the recent launch of a collaborative osteoarthritis biomarkers research network that is currently made up of five grant awardees. This network is structured to facilitate the discovery and development of osteoarthritis biomarkers. Investigators in the network will work collaboratively and share resources for the development, evaluation, and validation of biochemical markers for osteoarthritis onset, severity, progression, and response to treatment. When the NIAMS has sought the advice of leading researchers and professional and lay organizations, there has been widespread support for research that would identify biomarkers of disease for osteoarthritis biological clues to increased susceptibility, early stages of disease, the course of the disease, and the response of people with osteoarthritis to various therapies. The hope is that this collaborative network of leading investigators will speed the process for identifying these critically needed biomarkers so that people at various stages of the disease can be identified before they progress to significant symptoms of pain and joint deterioration.

The second new NIAMS initiative is focused on determining the influences of biomechanics in osteoarthritis. A team of scientists is now conducting three interrelated studies of biomechanical factors that influence cartilage breakdown and inflammation in osteoarthritis. The work is interdisciplinary, involving such disciplines as orthopaedic surgery, immunology, biomedical engineering, and behavioral science. This multidisciplinary approach promotes the exchange of expertise and research findings, and promises a more rapid translation of basic science to clinical therapies and screening and diagnostic techniques. One project will involve laboratory experiments to examine the roles of biomechanical factors on cells and tissue within joints affected by osteoarthritis. A second study will examine the effects of biomechanical factors in a mouse model of osteoarthritis. A third component will seek to develop more effective exercise and weight loss therapies to reduce pain and disability for patients with knee osteoarthritis.

Gout. Gout is one of the most painful rheumatic diseases. It results from deposits of needle-like crystals of uric acid in connective tissue and in the joint space. These deposits lead to inflammatory arthritis, which causes swelling, redness, heat, pain, and stiffness in the joints. A

number of risk factors, including genetics and age, are related to the development of gout. It is more common in men than in women and more common in adults than in children. Because research on gout has not progressed much in the past several years, the NIAMS sponsored a scientific meeting last April on gout and other articular crystal deposition diseases. Scientific opportunities and research gaps were identified and we anticipate releasing a solicitation for research in targeted areas.

Additional areas related to rheumatic diseases that we have targeted for research emphasis include the study of the microcirculation and target organ damage in rheumatic and skin diseases; gene expression studies in arthritis and other areas; high risk research in arthritis and other areas; the role of innate immunity in autoimmune rheumatic diseases; clinical trial outcomes instrument development; and translational cooperative research on pediatric rheumatic and skin immunomodulatory diseases.

MUSCULOSKELETAL BIOLOGY AND MUSCULOSKELETAL DISEASES

***Story of Discovery*: Important New Information in the Treatment of Osteoporosis**: From its inception almost two decades ago, the NIAMS has committed a significant portion of its budget to bone research - including seminal studies on bone biology and ground-breaking research on bone diseases that laid the foundation for understanding normal bone biology as well as determining what goes awry in bone diseases. Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing affected people to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Osteoporosis is the most common of the bone diseases that affect Americans. Although it is the underlying cause of most fractures in older people, the condition is silent and undetected in many cases until a fracture occurs.

With the significant budget increases of the last few years, the Institute was able to launch a study of combination therapies in osteoporosis - a study that industry would never undertake. Patients with osteoporosis may be given therapy to slow down the breakdown of bone or therapy to enhance the bone building process - both with the goal of building up bone mass before fractures occur. The NIAMS undertook studies combining the bone-building treatment parathyroid hormone (PTH) with a drug that slows bone loss (alendronate). The design of these studies is such that the drugs are compared as single treatments as well as in combination, and the head to head comparison is something that the companies who make the drugs would be less inclined to support. The hope was that the combination of these two therapies with different targets of action would optimize osteoporosis treatment and increase bone density more than either therapy would alone. The results of two independent studies (one at an NIAMS Specialized Center of Research) testing bone density in the spine and the hip of postmenopausal women and men with low bone mineral density determined, however, that combining PTH with alendronate actually produced no significant improvement in bone mineral density beyond that produced by the individual drugs. In fact, PTH alone increased bone mineral density at least as well as or better than combination therapy. It is thought now that alendronate, given concurrently with PTH, may reduce the bone-building effects of PTH, and the therapeutic effect of PTH is somewhat diminished when the two agents are combined. Both patients and physicians benefit from knowing how the combination compares to single drug treatment.

These findings could offer important clinical guidance to people at high risk for fractures and to those who treat them. People with osteoporosis have had their treatment options diminished by reports in recent years that the negative consequences of long-term estrogen therapy out-weigh the positive effects on bone. We need more information on safe and effective alternatives for treating osteoporosis. Both of the drugs tested in this project are an important part of the arsenal to treat patients with osteoporosis. NIAMS-supported researchers are pursuing additional research to determine if the optimal effects of these drugs might be achieved by sequential or cyclic therapy, rather than by combining them at the same time. In addition, a comparative study of fracture rates will also

Story of Discovery: **Important New Information in the Treatment of Osteoporosis** *continued*

be initiated to assess drug effectiveness. The NIAMS is continuing its strong commitment to identifying the most beneficial and best tolerated therapies for osteoporosis, and these recent research studies have provided important information on osteoporosis treatment to affected people and their health care providers.

Bone Quality. To date, the best surrogate of bone quality is the measurement of bone mineral density by DXA (dual energy x-ray absorptiometry). However, it is generally agreed that DXA does not really adequately assess bone quality. As a consequence, the NIAMS sponsored a meeting to encourage new approaches to studying and assessing bone quality. One of our goals for this meeting was to stimulate cross-disciplinary collaborations among investigators in the areas of bone mechanics, bone imaging, and clinical medicine. We were pleased to have the participation of so many representatives from the pharmaceutical and imaging companies at this meeting. We plan to foster research and new technology in this area so that better tools can be developed to assess fracture risk. The NIAMS is very interested in stimulating the development of public-private partnerships and initiatives in this important area of bone quality assessment.

In other research related to bone mineral density, a study by an interdisciplinary team of researchers determined that the combination of supervised aerobic, weight-bearing and weight-lifting exercises, three times per week for a year, provided significant improvement in the bone mineral density of postmenopausal women at specific bone sites. The key to reaching the goal of improved bone health is in the intensity of the weight-bearing workout. It is especially noteworthy that this benefit was found for women not taking hormone replacement therapy as well as for women who were taking hormone replacement therapy.

Other researchers in this field have studied bone mineral content and size in young children and determined that the effect of physical activity is amplified by calcium supplementation. This determination that calcium intake can modify the response of bones to exercise holds promise for the ability to create effective exercise programs that include not only exercise, but also optimal calcium intake. Research has demonstrated the importance of building bone mass in young children and adolescents, and this study in young children provides important information on the interaction between calcium and exercise that will be useful to parents, schools, and sports programs for young children.

Similar Outcomes for Limb Reconstruction and Amputation After Trauma. For years it was not known whether amputation or limb reconstruction provided a better outcome for patients who suffered severe trauma to the leg. Recent research reports indicate that individuals who undergo limb reconstruction or amputation following severe trauma to the lower leg fare about the same functionally. The NIAMS-supported study, Lower Extremity Assessment Project (LEAP), is a multicenter initiative that was intended to: (1) compare clinical and functional outcomes for those undergoing amputation versus reconstruction, (2) identify early clinical predictors of successful limb salvage and good functional outcomes, and (3) identify characteristics of the patient and environment that affect functional outcomes and well-being. Despite medical and surgical advances in reconstruction of severely injured legs, patients

undergoing this procedure were more likely than those who had amputations followed by a well-fit prosthesis to experience serious complications requiring re-hospitalization for additional surgery. However, when overall functional outcome was determined by the Sickness Impact Profile (a measure of self-reported health status), there was very little difference between patients in the reconstruction and amputation groups. Fifty-three percent of patients in the amputation group and 49.4 percent of those in the reconstruction group returned to work within two years of their procedure. Neither the severity of fracture and soft-tissue injury nor the presence of other injuries in the same or opposite leg significantly affected the functional outcome. The findings of this study should help surgeons and patients make better-informed decisions when choosing between reconstruction or amputation of a limb that has been severely damaged.

Quality of Life for People with Low Back Pain. Participation in a self-management program decreases symptoms associated with low back pain and increases confidence in managing low back pain symptoms for inner city patients, according to a recent study funded by NIAMS and the Department of Veteran Affairs. Researchers followed inner city patients participating in either a self-management program or in standard care. The researchers found that those individuals participating in the self-management program reported less anxiety and depression, less low back pain, less fear of physical activity and movement, and more confidence in managing back pain symptoms. There is a high prevalence of back pain in the United States, and additional research on reducing back pain disability especially in socioeconomically vulnerable patients is needed. Self-management strategies show promise as a tool to improve the quality of life for selected individuals who experience acute low back pain.

Insights into the Interaction of Bone and the Immune System. Many bones in the skeleton are partially hollow, and are filled with marrow. The marrow is the source of the many types of infection-fighting cells of the immune system, and also of the cells that produce and break down or resorb bone. In spite of this close relationship between bone and the immune system, much is still unknown about the nature of bone/immune interactions. Evidence is accumulating that similar biochemical signals are important in both bone and the immune system. Under certain conditions, cells of the immune system can influence the activities of bone cells. However, it remains unclear how important such interactions are for skeletal health and disease. Several avenues of study have revealed significant parallels and interactions between bone and the immune system. One group discovered that bone cells have a particular protein called CD40 on their surfaces. This suggested that the bone cells might interact with CD40's partner protein, called CD40L, which is known to prevent the death of immune cells called dendritic cells. In experiments, investigators found that CD40L did prevent the death of bone cells that normally occurs in the presence of a drug used to suppress the immune system. This is potentially important because increased cell death rates among bone cells are observed under a variety of conditions that lead to bone loss. A second research group focused on a particular protein called RANKL, which is important for both bone and the immune system. Mice that lack RANKL have both immune defects and a condition called osteopetrosis, caused by an absence of bone-resorbing cells, called osteoclasts. Osteopetrotic bones lack a marrow space, and grow slowly. Using genetic engineering techniques, investigators created a mouse in which RANKL was produced only by immune cells. In these mice, osteoclasts were present and the marrow space was restored, but the growth defects persisted. Thus, immune cells can provide the RANKL

necessary for osteoclast development, but only in certain parts of the skeleton. Finally, researchers have identified new factors in the complex chain of events that links estrogen deficiency with bone loss. In mice, estrogen deficiency leads to a stimulation of immune cells, increasing production of several proteins that promote bone resorption. Similar events may contribute to post-menopausal bone loss in women, leading to osteoporosis. Taken together, these studies provide a growing body of evidence that suggests that bone/immune interactions must be taken into account in the design of therapies. For example, bone loss induced by immuno-suppressive drugs (used in organ transplantation, and to treat some rheumatic diseases) is a serious clinical problem. Targeting drugs to CD40 on bone cells could prevent the death of these cells, preventing bone loss. Conversely, if immune cells are involved in bone loss, targeting drugs to specific immune functions may provide new preventive therapies for osteoporosis arising from a variety of causes.

Total Joint Replacement: Researchers have reported significant progress in the whole field of joint replacement, including three recent findings: The first study focused on the long-term results of total hip replacement performed in young adults. Total hip replacement has been previously shown to be a highly successful treatment for end-stage arthritis in older adults with severe pain and limited functions. With this success has come the gradual expansion of the indications for total hip replacement to younger adults (50 years old and younger). Unlike older adults, the indications for total hip replacement in these younger patients is usually arthritis that results from hip dysplasia, trauma or infection. Because of their age and greater activity level, this group of patients places unique stresses on these artificial joints, which may predispose such patients to increased wear and premature artificial joint failure. To alleviate this concern, porous coated implants have been designed, in which the patient s own bone grows into pores (holes) in the surface of the implant to hold it in place. Conventional total hip replacements have implants that are cemented into the end of the femur and into the pelvis. The NIAMS supported a 25 to 35-year follow-up of patients who received conventional total hip replacements that were cemented. All individuals were less than 50 years old when surgery was performed, and all surgeries were performed by the same surgeon in the same hospital. The results from this study were that less than one-third of the original total hip replacements had to be revised or removed, while more than two-thirds of the original group who had a total hip replacement were functioning well at the latest follow-up. This study confirms that a well performed conventional total hip replacement (cemented) provides excellent results in patients less than 50 years old with isolated disease in one or both hips. Additional research is needed to further compare the results of cemented versus porous coat implant total hip replacements.

The second study in this area determined that the timing of total joint replacement affects clinical outcomes among patients with osteoarthritis of the hip or knee. While analyses have established that total hip replacement and total knee replacement are both highly successful and cost-effective procedures for end-stage joint disease, the influence of the timing of these two procedures on patient outcomes had not been previously examined. Researchers at an NIAMS-supported Multidisciplinary Clinical Research Center studied patients undergoing elective total hip replacement or total knee replacement for osteoarthritis and followed them for 2 years postoperatively. Patients were characterized as high function or low function before surgery. Improvements in pain and function were constant after six months. However, patients who were in the low function group before surgery had a higher level of pain and lower level of function

than patients who were in the high function group before surgery. So although the surgery reduced pain and improved function, these were not improved to the same degree as those in the pre-operative high function group. This study suggests that patients operated upon earlier in the course of functional decline have better outcomes. The improvements in functional status are seen in six months and persist through 24 months. This observation supports a strategy to intervene earlier with total joint replacement in patients with lower extremity osteoarthritis.

The third study identified risk factors for hip replacement in women. Using information from participants enrolled in the Nurses Health Study who received a hip replacement to treat hip osteoarthritis, researchers examined several risk factors including body mass index, use of hormone therapy after menopause, age, alcohol consumption, physical activity and cigarette smoking. Of these potential risk factors, only body mass index and age were associated with needing hip replacement. Participants with a high body mass index showed double the risk for having a hip replacement compared with low body mass index participants. Those individuals who had a high body mass index at age 18 had five times the risk for receiving a hip replacement while those women age 70 and older were nine times more likely to have a hip replacement compared with those under age 55. This is one of the first long-term prospective studies to show an association between a modifiable risk factor and osteoarthritis. Results suggest that reducing weight may improve quality of life and decrease health care costs related to osteoarthritis. The NIAMS partnered with the National Cancer Institute and the Arthritis Foundation in supporting this study.

In other news related to joint replacements, approximately 300,000 total knee replacements are performed each year in the United States for end-stage arthritis of the knee joint, and reports in the orthopaedic literature indicate that total knee replacements have shown outstanding success. Despite this success, some controversies exist. To address these controversies, to review the current state of the science, and to identify directions for future research, the NIH (with the NIAMS as the sponsoring institute) held a Consensus Development Conference on Primary Total Knee Replacement on December 8-10, 2003. Six questions formed the basis of the panel s deliberations: (1) what are the current indications and outcomes for primary total knee replacement? (2) how do specific characteristics of the patient, material, and design of the prosthesis and surgical factors affect the short-term and long-term outcomes of primary total knee replacement? (3) are there important perioperative interventions that influence outcomes? (4) what are the indications, approaches, and outcomes for revision total knee replacement? (5) what factors explain disparities in the utilization of total knee replacement in different populations? And (6) what are the directions for future research? We look forward to the report from this meeting and the recommendations it will provide for the best ways to address areas of research opportunity.

MUSCLE BIOLOGY AND MUSCLE DISEASES

Reversing Muscle Degeneration. The broad fields of muscle biology and muscle diseases are active areas of research, and there are many exciting advances to highlight in these areas. One example is the recent report from scientists who have discovered how to reverse muscle degeneration in a mouse model of Duchenne muscular dystrophy. Researchers devised a way to

revitalize wasting muscle by using a special carrier to introduce the missing dystrophin gene into the diseased muscle tissue. Using a strain of mouse that lacks the dystrophin gene, researchers injected affected muscles with the missing gene, using a special adenovirus vector, or carrier. The muscles became more able to resist injury and muscle function was restored. Such techniques could eventually lead to gene therapies for patients with Duchenne muscular dystrophy once it is possible to provide gene delivery to all of the muscles in the body.

Faulty Gene is Key to Understanding Myotonic Dystrophy. Researchers have succeeded in linking the gene defect in myotonic dystrophy to its biological malfunction. Their findings emphasize how misreading of a gene can lead to improper conduction of electrical impulses in skeletal muscle. Two different studies were completed. The first examined tissue samples from skeletal muscle in patients with myotonic dystrophy, and the results revealed that extra genetic material caused by the defect in the DNA sequence affects the chloride channels that control muscle relaxation. The second study measured electrochemical muscle impulses in a mouse model of the disease. The results indicated that the genetic defect affects the conductance of electrical signals, resulting in delayed muscle control. People with myotonic dystrophy have the normal gene with additional information that interferes with the translation of proteins. While further study still needs to be done, these findings are a key step in understanding the causes of this type of muscular dystrophy.

Facioscapulohumeral Muscular Dystrophy Study Shows Chromosomal Variation. NIAMS-supported scientists have found that people with facioscapulohumeral muscular dystrophy (FSHD) have an exclusive association with one of the two different forms, or alleles, of the chromosomal region linked to the disease. Scientists examined the alleles 4qA and 4qB in people with FSHD and in controls. The alleles occurred with roughly equal frequency in the control group, but in the FSHD group, the affected allele was always of the 4qA type. This research may lead to a better understanding of the role of genetics in people with FSHD.

NIAMS Scientists Find Biochemical "Switch" Directs Muscle Building. Scientists may soon be able to influence muscle formation more easily as a result of research conducted in the NIAMS Intramural Research Program. These researchers along with collaborators in California and Italy have found that inhibitors of the enzyme deacetylase can switch the pathway of muscle precursor cells (myoblasts) from simply reproducing themselves to becoming mature cells that form muscle fibers (myotubules). It has been known for some time that deacetylase prevents the skeletal muscle gene from being expressed, and inhibits myoblasts from forming muscle. This research team has found that under certain conditions, deacetylase inhibitors (DIs) in myoblasts enhance muscle gene expression and muscle fiber formation. Knowledge of how DIs act against deacetylase is providing important insights on potential ways to correct problems that occur during embryonic muscle development. This research may also lead to methods to induce muscle growth, regeneration, and repair in adults.

Muscular Dystrophy Initiatives. The NIH has been actively engaged in implementing the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (the MD-CARE Act), to boost research and training related to all forms of muscular dystrophy. In September 2002, NIH issued a Request for Applications (RFA) entitled Muscular Dystrophy Cooperative Research Centers, and in October 2003, following peer review of the submitted

applications, NIH announced plans to establish three new centers. The NIAMS, the National Institute of Child Health and Human Development (NICHD), and the National Institute of Neurological Disorders and Stroke (NINDS) are each funding one center at up to $1 million in direct costs per center per year for five years. The centers are based at the University of Pittsburgh (funded by NIAMS); the University of Washington, Seattle (funded by NICHD); and the University of Rochester, New York (funded by NINDS). Researchers at the three centers will conduct studies on Duchenne, myotonic, and facioscapulohumeral muscular dystrophies, and will investigate therapeutic approaches including stem cell and gene therapy.

In a novel collaboration, the Muscular Dystrophy Association (MDA) has agreed to commit up to $1.5 million to enhance research activities at each of the three Centers funded by NIH ($500,000 per center per year for three years). The NIAMS, NINDS, and NICHD signed a Memorandum of Understanding (MOU) with the MDA in May 2003 to formalize this partnership. The principal investigators of each center have been invited by the MDA to apply for these supplemental funds, and the MDA expects to make awards in early January 2004.

The NIAMS will continue to work collaboratively with NINDS and NICHD on the Centers program. As required in the "Muscular Dystrophy Cooperative Research Centers" solicitation, a steering committee to ensure overall coordination of the program is being formed, and will include the scientific program officers from NIAMS, NINDS, and NICHD, the principal investigators of each center, a bioethicist, and a lay member. However, the Centers program is only one of the many ways that NIH is working to further MD research and training. All three institutes are represented on the Muscular Dystrophy Coordinating Committee (MDCC), which held its first meeting in July 2003, and the group is currently in the process of developing a research and education plan for MD. The plan will highlight opportunities for future research and training initiatives, and identify road blocks to progress in this area. In recent years, the three institutes have worked together to co-sponsor initiatives and workshops on MD. All three institutes also participate in the NIH MD Research Task Force to help guide efforts to intensify research and training related to muscular dystrophy. It is important that NIH use its resources to support a wide range of activities on MD, including support for the new centers program. Such a multi-faceted approach will likely yield the most significant advances in understanding and treating the muscular dystrophies.

SKIN BIOLOGY AND SKIN DISEASES

Identification of the Genetic Basis of Predisposition for Vitiligo and Other Autoimmune Diseases. Generalized vitiligo is a common autoimmune disorder characterized by loss of pigment in patches on the skin and hair. It often clusters in families allowing for genetic analysis. In addition, vitiligo is often seen in individuals who have multiple autoimmune diseases. It is a potentially socially devastating disease particularly in more darkly pigmented individuals and races. Thus, an understanding of the susceptibility and the mechanism for the development of vitiligo should facilitate research into prevention and treatment. A group of investigators studied families gathered from both the United States and the United Kingdom, and analyzed multiple family members who were affected by vitiligo. Linkage to a particular location on chromosome 1 established this as the major susceptibility site for vitiligo. The same investigators also used their large population base to look at the coexistence of other

autoimmune diseases and vitiligo in these families. They demonstrated that within the same family there were likely to be multiple members with vitiligo as well as other individuals with autoimmune thyroid disease, pernicious anemia, Addison s disease, systemic lupus erythematosus, and inflammatory bowel disease. Many of these autoimmune diseases can be severe both in terms of the general health of the individual and in terms of psychological and social impact. Understanding the genetic basis as well as the environmental triggers that may lead to the development of vitiligo is important in prevention and treatment.

Understanding the Molecular Events in the Development and Progression of Melanoma. Melanoma is the most severe skin disease with regard to mortality, accounting for approximately half of all deaths from skin disease. Scientists are striving to understand the molecular events involved in the transformation of normal pigment cells of the skin to melanoma cells and the early progression of melanoma. A group of investigators, recognizing that certain atypical moles predisposed individuals to the development of melanoma, studied these cells in culture and added genes to turn on a particular protein (MAPK). The introduction of this activated gene resulted in the development of factors involved in melanoma invasion and metastasis, indicating that this pathway is probably important in melanoma development. This new understanding may facilitate the design of therapeutic interventions to suppress this pathway. Recognition of the molecular pathways that result in malignant transformation of melanocytes into melanoma cells and the spread of melanoma should facilitate the design of better methods for identifying the disease in its earliest stages as well as the design of better therapeutic interventions.

Gene Therapy of Epidermolysis Bullosa. Epidermolysis Bullosa (EB) is a group of severe hereditary blistering skin diseases. Many of them are fatal either early in infancy or in childhood or young adulthood, and the less severe forms may be disabling for affected individuals. Gene therapy for permanent correction of various forms of EB is the ultimate goal. One challenge is the potential complications of viral based DNA transfer. A new method of nonviral transfer of normal genes to correct the EB defect has been investigated by NIAMS-supported researchers. They have been able to demonstrate sustained correction of the abnormality in affected cells that demonstrate the defect. Thus, this potentially safer form of gene transfer may eventually result in genetically based treatments for these affected children. Another research group was also able to demonstrate the use of genetically corrected cells to facilitate the healing of wounds in one form of severe EB (recessive dystrophic EB) that usually results in severe deformity and death in early adulthood. In this particular strategy the cells providing the normal gene and gene product were fibroblasts (cells normally present in the deeper layers of skin) rather than the cells of the epidermis (the outer layer of skin) that are usually thought to be the prime target of the disease. This methodology potentially provides a better way to heal the wounds of EB of this type, although it is not a permanent or long lasting cure. These studies indicate progress in providing potential treatments, both curative very early in life or palliative to reverse the major skin defects later in life in different forms of Epidermolysis Bullosa. They also provide evidence for the success of potentially safer methods of gene therapy in the treatment of skin and other diseases.

The Genetic Basis of Psoriasis. Psoriasis is one of the most common skin diseases. It can be mild or quite severe. When severe, it has a major adverse impact on an individual s ability to conduct the normal activities of daily living and can be disabling. There are many treatments for psoriasis, but none of them is without significant risks. Many new treatments are becoming

available, particularly for more severe disease. An improved understanding of the molecular and genetic basis of the disease would allow more rational treatments to be designed. One of the major thrusts in understanding psoriasis is looking for genes common to multiple members of the same family in whom psoriasis is prevalent. Using familial clusters of psoriasis, a group of investigators has demonstrated that a particular area of human chromosome 17 is where susceptibility for psoriasis exists, at least in some families. This study needs to be confirmed in other larger groups before it can be determined whether it is a common or major susceptibility determinant for the disease. Using gene arrays, a multicenter clinical study was undertaken to demonstrate which mediators and markers were activated in diseased skin as compared to normal skin of people with psoriasis and normal controls. The results indicate that immune T-cells, as well as other immunologic cells that reside in the skin called dendritic cells, demonstrate a pattern of inflammatory mediators that sustain the psoriatic skin type. It appears that multiple components of the immune system are activated in developing the disease pattern that we recognize as psoriasis. Once we understand the genes that are involved, we will have a better idea of the gene products that drive the skin to produce psoriasis. This will give us a better approach to designing specific therapeutic interventions that will minimize or eliminate the abnormal skin appearance, but are less detrimental to the overall immune system.

INFORMATION DISSEMINATION

The NIAMS remains committed to a comprehensive program of information dissemination to patients and to their health care providers. We work closely with our many voluntary and professional societies to both learn their needs and views and to disseminate our research findings to them. We have also targeted our information to particular areas of need (including Lupus: A Patient Care Guide for Nurses and Other Health Professionals and "The Many Shades of Lupus") and to diverse populations (including printed information and our toll-free information line in Spanish). We will continue to build and strengthen these relationships with the community and will strive to make our information accessible to the vast and diverse populations affected by the diseases within our scientific mission. We are very proud of the new arm of our information dissemination efforts the NIAMS Spanish-language home page. A new Spanish-language Web site has been launched to provide information about research and health education on diseases of bones, muscles, joints, and skin. The NIAMS has developed En Español (In Spanish) as a tool to reach out to the growing Hispanic/Latino population through the Institute's home page. En Español, launched during Hispanic Heritage Month, provides vital information about health, research, grants, and available clinical trials on the NIAMS Web site as well as information about the Institute's leadership and budget. The new Web site offers an opportunity to learn more about the NIAMS mission and how it is implemented through research and other initiatives to improve the health of the nation.

CONCLUSION

The 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 of bones, muscles, joints, and skin are chronic and many cause life-long pain, disability, or disfigurement. They afflict millions of Americans, cause tremendous human suffering, and cost the United States economy billions of dollars in health care and lost

productivity. These diseases affect people of all ages, racial and ethnic populations, and economic strata. Researchers supported by the NIAMS are using powerful research tools to acquire and apply new knowledge to studies of some of the most challenging diseases affecting Americans today. Many of these diseases have troubled patients for decades, but each year significant discoveries bring researchers closer to fully understanding, diagnosing, treating, and ultimately preventing these common, disabling, costly, and chronic diseases, which greatly compromise quality of life. This was a productive year for NIAMS-supported investigators who reported significant progress in their research studies. In the future, the Institute plans to build on these advances and launch initiatives to pursue the most promising research opportunities and needs with the continuing goal of advancing the scientific enterprise and improving public health.

BUDGET POLICY

The Fiscal Year 2005 budget request for the NIAMS is $515,378,000, an increase of $14,470,000 and 2.9 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request, is NIAMS s support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIAMS are shown in the graphs below. Note that the Fiscal Year 2001 FTE figure is not comparable to the figures in the succeeding years due to NIH s consolidation of its Human Resources function in FY 2003.

NIH s highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product deflator. The NIAMS is providing an average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NIAMS will support 296 pre- and postdoctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 38 research centers, 174 other research grants, including 56 clinical career awards, and 67 R&D contracts. Intramural Research and Research Management and Support receive increases to support increased pay and estimated inflationary increases in FY 2005.

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

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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

FY 2004 House Appropriations Committee Report Language (H. Rpt. 108-188)

Item

Lupus - The Committee encourages NIAMS to enhance its research efforts on lupus through all available means, as appropriate, to improve understanding of the disease and lead to advances in treatment. There are five areas in which research may yield important new insights, including susceptibility, pathogenesis, inflammation and damage, clinical assessment and therapy. In addition, the Committee encourages NIAMS to facilitate efforts to validate biomarkers for lupus. In recent years, the lupus research community has identified a number of biologic molecules that may serve as effective markers of disease risk, disease activity or severity, clinical features of the disease, or response to potential therapies. Collaborative approaches to research on biomarkers could lead to the development of promising new drugs, and ease the way to approval of these ~~agents by the FDA. (p. 79)~~

Action taken or to be taken

The NIAMS is enhancing its research activities in lupus through a multitude of efforts. Several recent NIAMS-funded research discoveries have significant implications for the clinical assessment and treatment of lupus. For example, a team of scientists supported by NIAMS and other components of the NIH including the National Institute of Allergy and Infectious Diseases, the National Center on Minority Health and Health Disparities, and the Office of Research on Women s Health discovered a genetic signature present in some patients with lupus who develop life-threatening complications such as blood disorders, central nervous system damage, and kidney failure. After analyzing thousands of genes in the blood of patients with lupus, researchers found 14 of those genes were linked to a subset of lupus patients with severe ~~dise~~ase. These findings provide strong support for developing new therapies to block the affected pathways in patients with severe lupus, as well as for identifying patients most likely to benefit from these new therapies. Another research highlight was the recent discovery that people diagnosed with lupus have autoantibodies (proteins that attach to the body s healthy tissue by mistake) in their blood years before the symptoms of lupus appear. Early detection of autoantibodies may help in predicting who will develop this disease, as well as allowing physicians to monitor patients earlier in the disease process. In the area of childhood lupus, the NIAMS recently initiated a large, controlled study to assess the ability of statins (cholesterol-lowering agents) in preventing or delaying progression of cardiovascular disease in children with lupus. This research study involves 20 centers from the Pediatric Rheumatology Research Network in establishing the largest cohort of pediatric lupus patients ever prospectively studied.

The Institute is also actively supporting research to identify and validate biomarkers for lupus. For example, the Institute s extramural program supports the Autoimmune Biomarkers Collaborative Network, a group that is using cutting edge technologies, such as gene expression profiling with DNA microarrays, to develop biomarkers for lupus. These new technologies may assist in the diagnosis of lupus, help physicians better guide and manage therapy, and provide information on the course of disease for lupus patients. In the fall of 2003, the NIAMS intramural program held a meeting with experts from the lupus research community to discuss how to establish new strategies for developing and validating biomarkers for lupus. These biomarkers will be used in clinical settings to facilitate the process of making new therapies available to patients. Participants included clinical and basic scientists from the lupus research community, as well as representatives of the NIH, the Food and Drug Administration, and voluntary organizations.

The NIAMS is also enhancing research efforts on lupus through a new Federal Working Group on Lupus, the purpose of which is to exchange information and coordinate Federal efforts in lupus research and education. This group complements the NIH Autoimmune Diseases Coordinating Committee (ADCC) which recently developed a comprehensive research plan for autoimmune diseases, including lupus. The new Lupus Working Group is comprised of representatives from all relevant DHHS agencies and other Federal departments having an interest in lupus. The NIAMS was chosen to lead this new Working Group, which held its first meeting in the fall of 2003.

Also in the fall of 2003, national leaders in lupus research came together to discuss the latest scientific opportunities at the Lupus Today: Research Into Action scientific conference. As a co-sponsor for this conference, the NIAMS invited leading lupus researchers to gather to discuss the latest scientific discoveries and what they mean for the current and future management of lupus. Panel discussions included: the future of lupus clinical trials, patient participation in clinical trials, and how lupus affects minority populations. Other topics covered at the conference included childhood lupus, cardiovascular lupus, and neuropsychiatric lupus. Information on cutting edge clinical trials involving stem cell therapy and high dose cytoxan was also presented.

Lupus is a key area in the NIAMS focus on health disparities. The Institute s Health Partnership Program is working with community leaders and organizations in the African American and Hispanic/Latino communities in Washington, D.C., to develop a model community-based initiative for addressing disparities in rheumatic diseases, including lupus. In addition, the Institute recently released a solicitation for applications on innovative approaches to eliminating health disparities in rheumatic, musculoskeletal, and skin diseases. This solicitation will encourage the development of new approaches to addressing the high prevalence of rheumatic diseases such as lupus in minority populations.

Item

Bone diseases **-** The Committee urges NIAMS to explore new avenues for cell- and gene-based therapies for the treatment of bone and cartilage diseases, such as osteoporosis, Paget s disease, and osteogenesis imperfecta, as well as identify new targets for enhancing bone formation and blocking bone destruction. (p. 79)

Action taken or to be taken
Stem cell research is an area of cutting edge scientific inquiry that provides new opportunities for researchers and clinicians working in a variety of fields. In June 2000, the NIAMS and the National Institute on Aging held a workshop to identify new opportunities in basic and applied stem cell research, and to promote the orderly and optimal development of the field and the development and use of therapeutic interventions. As a result of this meeting, NIAMS issued a request for applications (RFA) aimed at exploring basic and applied stem cell research for arthritis and musculoskeletal diseases. In 2002, NIAMS announced the funding of five new projects in response to this solicitation, including several that have important implications for bone and cartilage diseases such as osteoporosis, Paget s disease, and osteogenesis imperfecta (OI). These studies include work to better understand the growth factors and hormones that influence how stem cells develop, which could point the way to new therapies for bone diseases; efforts to evaluate the potential for regeneration or repair of bone marrow using mouse stem cells in an animal model of OI; and investigations of programmed cell death and how that process generates a form of stem cells that are a factor in maintaining adult bone mass.

Current research in Paget s disease and other areas across bone research will facilitate the development of cell- and gene-based treatments for many disorders. For example, NIAMS continues to support a number of projects investigating the viral and genetic factors contributing to Paget's disease, including a multi-component research program aimed at understanding the causes of Paget's disease. Four related projects, integrated within a single program, will examine several factors that contribute to the development of the disease. A key component is the creation of a new strain of mice, based on the long-suspected role of measles virus infection in Paget's disease, that exhibits bone abnormalities resembling the human disease. Additionally, in October 2003, the NIAMS collaborated with the NIH Office of Rare Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases to sponsor the First International Symposium on Osteopetrosis, a condition present at birth in which the bones are overly dense. At this Symposium, recent findings were presented, identifying the genetic defects that cause most instances of this disease. Such information will be crucial in developing new cell- and gene-based therapies for osteopetrosis, which arises from defects in the cells that normally remove old cartilage and bone as the skeleton grows.

Known as brittle bone disease, OI arises from mutations in the two genes that make type I collagen, a protein important to bones and skin. The mutations can cause the body to make either too little or poor-quality type I collagen. Individuals with OI have bones that fracture easily, low muscle mass, and joint and ligament laxity. In the Fall of 2000, NIAMS partnered with the National Institute on Aging and the National Institute of Child Health and Human Development and released a request for applications (RFA) entitled New Research Strategies in Osteogenesis Imperfecta. This RFA was built on recommendations that were made at the scientific meeting in September of 1999 that was co-sponsored by the NIAMS, the NIH Office of Rare Diseases, the Osteogenesis Imperfecta Foundation, and the Children's Brittle Bone Foundation, to identify ways to expand the scope of research on OI. NIAMS announced the funding of four new projects in response to this solicitation to support research activities ranging from cutting-edge gene and cell therapies to testing drug treatments in animal models. NIAMS also partnered with the National Heart, Lung, and Blood Institute in early 2002 to issue an RFA entitled Research on Heritable ~~Disorders of Connective T~~issue. This RFA was designed to stimulate research to better

understand the disease progression of heritable disorders of connective tissue, such as OI, and to develop innovative treatment strategies. In the fall of 2002, the NIAMS announced the funding of eight new projects in response to this solicitation, including several that may have implications for OI. These new projects will complement on-going work on OI.

Item
Duchenne muscular dystrophy - Duchenne is a degenerative and fatal form of muscular dystrophy that usually takes its victims in their late teens or early twenties. The only treatment is the long-term use of steroids, which delays the progression of the disease but has many unwanted side effects. The Committee considers this a very important area of research and urges NIAMS, along with NINDS and NICHD, to work to enhance the research efforts into Duchenne muscular dystrophy. (p. 79)

Action taken or to be taken
The NIH has been actively engaged in implementing the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (the MD-CARE Act), to boost research and training related to all forms of muscular dystrophy, including Duchenne MD. In September 2002, NIH issued a request for applications (RFA) entitled Muscular Dystrophy Cooperative Research Centers, and in October 2003, following peer review of the submitted applications, NIH announced plans to establish three new centers. NIAMS, NICHD, and NINDS are each funding one center at up to $1 million in direct costs per center per year for five years. The centers are based at the University of Pittsburgh (funded by NIAMS); the University of Washington, Seattle (funded by NICHD); and the University of Rochester, New York (funded by NINDS). Researchers at the three centers will conduct studies on Duchenne, myotonic, and facioscapulohumeral muscular dystrophies, and will investigate therapeutic approaches including stem cell and gene therapy. In fiscal year (FY) 2004, NIH plans to re-issue the solicitation for cooperative research centers, and expects to fund up to two additional meritorious centers in FY 2005.

In a novel collaboration, the Muscular Dystrophy Association (MDA) has agreed to commit up to $1.5 million to enhance research activities at each of the three Centers funded by NIH ($500,000 per center per year for three years). The NIAMS, NINDS, and NICHD signed a Memorandum of ~~Understanding (MOU) with~~ the MDA in May 2003 to formalize this partnership. The principal investigators of each center have been invited by MDA to apply for these supplemental funds, and MDA expects to make awards in early January 2004.

NIAMS will continue to work collaboratively with NINDS and NICHD on the Centers program. As required in the "Muscular Dystrophy Cooperative Research Centers" solicitation, a steering committee to ensure overall coordination of the program is being formed, and will include the scientific program officers from NIAMS, NINDS, and NICHD. However, the Centers program is ~~only~~ one of the many ways that NIH is working to further MD research and training. All three institutes are represented on the Muscular Dystrophy Coordinating Committee (MDCC), which held its first meeting in July 2003, and the group is currently in the process of developing a research and education plan for MD. In recent years, the three institutes have worked together to co-sponsor initiatives and workshops on MD. All three institutes also participate in the MD Research Task Force to help guide efforts to intensify research and training related to muscular

dystrophy. It is important that NIH use its resources to support a wide range of activities on MD, including support for the new centers program. Such a multi-faceted approach will likely yield the most significant advances in understanding and treating the muscular dystrophies.

Item
Scleroderma - The Committee encourages NIAMS to collaborate with other Institutes, including NHLBI, NIDDK, and NIDCR, to generate additional research opportunities for scleroderma to identify genetic risk factors and safe and effective treatments. (p. 80)

Action taken or to be taken
Scleroderma is an autoimmune disease a broad category of diseases in which the body s immune system attacks the body s own tissues as if they were foreign invaders causing significant damage to target organs. In some forms of scleroderma, hard, tight skin is the extent of the disease. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as heart, lungs, and kidneys.

The field of autoimmunity is currently exploding with activity and newly launched initiatives. Many NIH Institutes, including NIAMS, NHLBI, NIDDK, and NIDCR are active members of the NIH Autoimmune Diseases Coordinating Committee (ADCC), which is led by the National Institute of Allergy and Infectious Diseases. The ADCC provides a forum for coordinating research efforts for autoimmune diseases and brings together various stakeholders including the NIH, CDC, FDA, HRSA, AHRQ, and other public and private organizations. The Committee recently developed a comprehensive research plan for autoimmune diseases, including scleroderma.

The plan is based on the premise that information learned from studying one autoimmune disease will provide valuable information for all autoimmune diseases. The plan highlights research opportunities likely to have the greatest impact on accelerating discovery of treatments or cures. Research opportunities highlighted include identifying the genetic and environmental risk factors for developing autoimmune diseases, and developing a centralized clinical research network to conduct multi-institutional clinical trials.

Approximately 80 percent of scleroderma patients will eventually develop some degree of lung involvement, which causes significant morbidity and mortality in scleroderma patients. In collaboration with the NIAMS, the NHLBI is supporting a multi-center clinical trial to evaluate the efficacy of oral cyclophosphamide in stabilizing or improving lung function in scleroderma patients who have active lung inflammation (alveolitis). Thirteen medical centers in the United States began enrolling patients in September 2000 and will complete enrollment within the next few months. The Steering Committee for this study is planning a second treatment trial that would evaluate other immunosuppressive drugs for improving the secondary pulmonary hypertension that causes scleroderma patients to develop heart failure. The NHLBI also supports investigator-initiated research on the molecular mechanisms that contribute to the development of

pulmonary fibrosis in scleroderma patients, and funds numerous projects that address various aspects of pulmonary hypertension, myocardial and pulmonary fibrosis, and cardiac arrhythmias.

A new NIAMS funded project is using a unique sample set lung tissue from scleroderma patients undergoing lung transplant surgery, as well as lung tissue from unused donor lungs to facilitate investigation into the cellular changes that cause the hardening of the lungs. Another new NIAMS-funded study is uncovering the cellular activities inside the blood vessels in scleroderma patients. In collaboration with the Office of Research on Women s Health, NIAMS funds research aimed at uncovering the cellular and molecular processes that contribute to the development of scleroderma.

The NIDDK participates in efforts to enhance progress in scleroderma by conducting basic research on the biology of the gastrointestinal tract, as well as translational research on gastroesophageal reflux disease (GERD), one of the most common gastrointestinal manifestations of scleroderma. Similar NIDDK-supported fundamental and clinical research on renal disease may provide the foundation for developing better treatments for kidney involvement in scleroderma. Furthermore, the NIDCR would welcome receipt of high-quality applications relevant to the dental and craniofacial complications associated with scleroderma.

The NIAMS supports several projects which focus on new and innovative treatment options for patients with scleroderma including: a multicenter trial to test type 1 collagen as a treatment for localized forms of scleroderma; ultraviolet phototherapy; and stem cell transplantation. In addition, behavioral scientists supported by the Institute have found that managing pain and depression may lead to improved functioning and quality of life for patients with scleroderma.

The NIAMS has taken a leadership role in generating research opportunities for scleroderma by supporting a national Scleroderma Family Registry and DNA Repository. The overall objective of this registry is to identify genes that influence susceptibility to the disease. The repository collects and stores genetic material (DNA) and blood serum from scleroderma patients and their families and serves as a national resource to scientists studying the genes associated with scleroderma. The NIAMS facilitates the transfer of basic research findings into clinical practice by supporting large-scale centers of research. For example, NIAMS supports two specialized centers of research (SCORs) in scleroderma one at the University of Texas Health Science Center and one at the University of Tennessee. These SCORs focus only on scleroderma, and they serve as a national resource for researchers studying scleroderma. The NIAMS also supports a new multidisciplinary clinical research center with a special focus on lupus and scleroderma in African Americans. In the area of childhood rheumatic diseases, the NIAMS supports a multidisciplinary clinical research center focused on juvenile scleroderma and other pediatric rheumatic diseases.

Item

Vitiligo treatments for children - The Committee urges NIAMS to enhance research efforts through all available mechanisms, as appropriate, to identify the causes of this disease and develop pediatric treatment options for vitiligo. (p. 80)

Action taken or to be taken

Vitiligo is a pigmentation disorder in which melanocytes (the cells that make pigment) in the skin, the mucous membranes, and retina (inner layer of the eyeball) are destroyed. As a result, white patches of skin appear on different parts of the body. The hair that grows in areas affected by vitiligo usually turns white. In the United States, 2 to 5 million people have the disorder. ~~Ninety~~-five percent of people who have vitiligo develop it before their 40th birthday.

The NIAMS supports a variety of projects examining the cause of vitiligo including genetic studies of vitiligo or other hereditary diseases of pigmentation, with the aim of discovering the genes that cause or predispose individuals to develop the disease. The Institute also supports a number of grants investigating the normal process of melanin (pigment that determines skin color) production and delivery from the melanocyte to the keratinocyte (primary cell of the skin).

Research indicates that vitiligo appears to be more common in people with other autoimmune disorders (conditions in which a person s immune system reacts against the body s own organs or tissues). The NIAMS supports an extensive portfolio addressing autoimmune disorders and advances in this area will benefit the development of treatment and prevention strategies for autoimmune-related skin diseases, such as vitiligo, for both children and adults.

While vitiligo affects all races and both sexes equally, the psychological and social consequences are particularly profound in people of color who have the disease. Not only is the individual affected, but burden of disease can extend to the family, the workplace, and society as a whole. To this end, in September 2002, NIAMS sponsored the "Workshop on the Burden of Skin Disease. A diverse group of investigators and patients discussed the elements that comprise the burden of skin diseases and their impact on public health and daily living; current knowledge and data-collection instruments, and how to access the data more effectively; and future data needs and instruments for facilitating the collection of the data. In response to this workshop, a solicitation designed to encourage research in the area of burden of skin disease is currently under development and is set for release in early 2004.

Additionally, the NIAMS sponsored a workshop in September 2003 on immune modulation in the treatment of skin diseases. The workshop examined immune regulation as it relates to various skin diseases and their therapies. Recommendations from this meeting will facilitate the development of future research initiatives focused on treatment strategies for a range of skin diseases, including vitiligo.

Item

Marfan syndrome - The Committee commends NIAMS for its vital support of research on heritable disorders of connective tissue (HDCT), which includes Marfan syndrome. Marfan syndrome is a life-threatening, progressive and degenerative genetic disorder affecting several organ systems. The Committee encourages NIAMS to collaborate with other Institutes and ~~patient foundations to develop~~ a comprehensive analysis of research opportunities including a

multi-institute research plan for Marfan syndrome and related disorders through all available mechanisms, as appropriate. (p. 80)

Action taken or to be taken

Marfan syndrome is a heritable condition that affects the connective tissue. Marfan syndrome is caused by a defect (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, Marfan syndrome can affect many body systems, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs. It is estimated that at least 1 in 5,000 people in the United States have the disorder.

In November 2000, the NIAMS joined the NIH Office of Rare Diseases, the National Institute of Child Health and Human Development (NICHD) and several nonprofit organizations outside NIH, in sponsoring the Third Workshop on Heritable Disorders of Connective Tissue. This Workshop focused on multidisciplinary approaches to the question of pathogenesis of connective tissue diseases, such as Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos. All levels of investigation (genetic approaches, biochemical approaches, developmental approaches, and cell-matrix interactions) were discussed. By focusing on multidisciplinary approaches and common themes important in matrix biology, the goal was to stimulate new collaborations between researchers interested in different diseases and facilitate more rapid progress in this area. As a result of this Workshop, NIAMS and the National Heart, Lung, and Blood Institute (NHLBI) released a request for applications focused on research on heritable disorders of connective tissue. The NIAMS funded eight new grants in response to this solicitation and the NHLBI awarded several grants as well. These projects have complemented other NIH-sponsored research being conducted around the country which is examining areas of research such as the development of mouse models that carry mutations in the fibrillin gene and the evaluation of treatment options for individuals with Marfan syndrome.

In addition to these collaborations, the NIAMS continues to work closely with other NIH components such as the National Institute on Aging and the NICHD in exploring research in other heritable disorders of connective tissue such as osteogenesis imperfecta. In 2001, the NIAMS announced the award of four new projects, which will add information to the body of knowledge for other heritable disorders of connective tissue.

Item

Pemphigus registry - The Committee encourages NIAMS to consider establishing a national pemphigus registry, which would be important to the scientific community and patients in identifying the epidemiology, improving the understanding of the potential causes, and assessing the value of therapies for this chronic and life-threatening autoimmune disease. (p. 80)

Action taken or to be taken

Pemphigus is an umbrella term for a group of rare, autoimmune blistering diseases of the skin and mucous membranes. Normally, our immune system produces antibodies that attack viruses and bacteria in an effort to keep us healthy. In a person with pemphigus, however, the immune system mistakenly perceives the cells in skin and mucous membranes as foreign, and attacks them. The part of the cells that are attacked in pemphigus are proteins called desmogleins. These proteins form the glue that attaches adjacent skin cells, keeping the skin intact. When desmogleins are attacked, the cells become separated from each other. This causes burn-like lesions or blisters that do not heal. In some cases, these blisters can cover a significant area of the skin.

The NIAMS supports a broad range of research on pemphigus, to better understand what causes the various forms of this disease and to help develop more effective therapies. This includes projects using mouse models to explore the biological function of desmogleins in cell adhesion in the skin, and efforts to elucidate the environmental and genetic risk factors associated with pemphigus in certain populations. Other scientists are working to clarify the causes of blister formation in both mouse models and human patients with pemphigus and bullous impetigo, a common skin disease. A better grasp of the mechanisms of blister formation could shed light on new treatment strategies. The Institute also supports the training of investigators engaged in patient-oriented research on autoimmune skin diseases such as pemphigus. This includes funding for scientists who are studying therapeutic interventions to minimize steroid-induced osteoporosis in patients with the disease. Although the Institute does not currently support a research registry for pemphigus, we would welcome meritorious applications to develop such a resource the next time the NIAMS announces an open competition to establish new research registries.

In addition, the NIAMS recently held two meetings that have important implications for those affected by pemphigus, as well as for scientists studying the disease. In September 2002, the Institute sponsored a meeting entitled, Workshop on the Burden of Skin Disease. The purpose of this meeting was to examine the current definition of burden of skin disease and to evaluate the existing tools used to measure disease burden. In follow-up to this meeting, the NIAMS is developing an initiative to identify and prioritize data sets and data collection instruments that may be useful in answering burden of skin disease research questions. This effort will also point to missing data and instruments that may need to be developed in the future. In September 2003, the NIAMS, in conjunction with the NIH Office of Rare Diseases, held a conference on immunomodulatory drugs in the treatment of skin diseases. The conference explored what we can learn about the pathophysiology of skin diseases by looking at how new, immunomodulatory drugs work. Pemphigus was one of the diseases discussed at this meeting. We anticipate that the recommendations from this conference will help identify scientific opportunities that may promote a better understanding of various skin diseases such as pemphigus and how best to treat them. Finally, the NIAMS is committed to developing and disseminating science-based health information for patients and providers who are affected by autoimmune diseases such as pemphigus. To this end, the Institute has developed an information packet on pemphigus and other blistering disorders of the skin, and a Questions and Answers booklet on autoimmunity.

Item

Burden of skin diseases - The Committee encourages NIAMS to consider supporting the development of new tools to measure the burden of skin diseases and training researchers in this area. (p. 80)

Action taken or to be taken

In September 2002, the NIAMS sponsored a meeting entitled, Workshop on the Burden of Skin Disease. The purpose of this meeting was to examine the current definition of burden of skin disease and to evaluate the existing tools used to measure burden. In follow up to the recommendations of the September 2002 meeting and on recommendation of the planning committee, NIAMS proposes to survey the existing data sets that could be mined to determine components of the burden of skin disease; survey available data collection instruments to collect such data as they relate to disease in general skin disease as a whole, and specific skin diseases; and array the available data in a matrix against personal, family and societal impact. The NIAMS is currently developing a request for proposals which will provide support for a contract to address these recommendations. Award of this contact is set for FY 2004. This contract will identify and prioritize missing data and data collection instruments to allow efficient development of the missing instruments and data in subsequent projects/initiatives.

In September 1999, the NIAMS co-sponsored a meeting entitled, Epidemiology/Health Services Research: Prospects for Developments in Skin Disease. Recommendations from this meeting were used to develop a request for applications which focused on bringing new researchers into the field of epidemiology, clinical trials research, and outcomes research in skin diseases. Through a public-private collaboration, several projects have been awarded in response to this solicitation. These projects are examining areas such as patient-oriented outcomes research, the identification of high risk populations, and surrogate marker identification.

FY 2004 Senate Appropriations Committee Report Language (S. Rpt. 108-10)

Item

Bone and Cartilage Diseases - The Committee urges NIAMS to explore new avenues for cell- and gene-based therapies for the treatment of bone and cartilage diseases, such as osteoporosis, Paget s disease, and osteogenesis imperfecta. Identifying new targets for enhancing bone formation and blocking bone destruction should be a major focus, with studies that integrate basic and clinical approaches regarding bone forming cell development. (p. 140)

Action taken or to be taken

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

Item

Lupus - The Committee encourages the Institute to provide the highest possible funding level for lupus research and explore all possible scientific opportunities for prevention, treatment and cure of this devastating disease. (p. 141)

Action taken or to be taken

Please refer to page NIAMS-28 of this document for NIAMS response of this significant item regarding Lupus.

Item

Neurofibromatosis - Neurofibromatosis [NF] is a common genetic disorder of the nervous system. Its symptoms vary in kind and degree and may be severely disabling, mildly disfiguring, or can even go undetected. Some individuals with NF have many skin neurofibromas (tumors on the nerves) on the face and body and light brown (café-au-lait) spots on the skin. A variety of skeletal abnormalities may also be present such as bowing of the legs, curvature of the spine (scoliosis), or thinning of the shin bone. The Committee requests that NIAMS work in partnership with the NF community to identify and explore research of mutual concern and to be prepared to discuss its progress at the fiscal year 2005 appropriations hearing. (p. 141)

Action taken or to be taken

The neurofibromatoses are genetic disorders of the nervous system that primarily affect the development and growth of neural (nerve) cell tissues. These disorders cause tumors to grow on nerves and produce other abnormalities such as skin changes and bone deformities. The neurofibromatoses occur in both sexes and in all races and ethnic groups. Neurofibromatosis type 1 (NF1) is the more common type of the neurofibromatoses, occurring in about 1 in 4,000 individuals in the United States. At the NIH, the National Institute of Neurological Disorders and Stroke (NINDS) is the lead component for research on the neurofibromatoses.

The NIAMS has a long and successful history of partnering with public and private organizations for the advancement of science. To this end, NIAMS welcomes the opportunity to work with other NIH components and private organizations to advance research in the area of neurofibromatosis, particularly when addressing the skin and bone manifestations associated with this disorder. Additionally, many of the outstanding projects currently funded in the areas of skin and bone research will contribute to the body of knowledge for neurofibromatosis. For example, current projects in skin pigmentation, skeletal development and bone growth, correction of skeletal deformities, nonunions (failure of a fractured bone to heal normally), and scoliosis (curvature of the spine) and other spinal deformities may have important implications for neurofibromatosis research.

Item

Pemphigus Registry - The Committee urges NIAMS to establish a National Pemphigus Registry to identify the epidemiology, improve the understanding of the potential causes, and assess the value of old and new therapies for the chronic, life-threatening autoimmune disease known as pemphigus.

Action taken or to be taken

Please refer to page NIAMS-36 of this document for NIAMS response to this significant item regarding the Pemphigus Registry.

Item

Scleroderma - The Committee is encouraged by NIAMS s growing interest in scleroderma, a chronic and progressive disease that predominantly strikes women. Scleroderma is a disfiguring and can be life-threatening and effective treatments are lacking. More research is critically needed in order to identify the genetic risk factors for scleroderma and to develop safe and effective treatments. The Committee urges NIAMS to collaborate with other Institutes, including NHLBI, NIDDK, and NIDCR, to generate additional research opportunities for scleroderma.

(p. 141)

Action taken or to be taken

Please refer to page NIAMS-32 of this document for NIAMS response to this significant item regarding Scleroderma.

Item

Skin Disease - The Committee was pleased to learn that NIAMS conducted a workshop on the Burden of Skin Diseases. The Committee encourages NIAMS to examine the findings from the workshop and encourages the development of new tools to better measure the burden of skin diseases, and the training of researchers in this important area. The Committee further encourages NIAMS to move forward expeditiously to generate the required data in collaboration with the Center for Disease Control and Prevention [CDC], Agency for Health Care Policy and Research [AHCPR], and Health Resources and Service Administration [HRSA], as well as other agencies and organizations that participated in the conference. (p. 141)

Action taken or to be taken

Please refer to pages NIAMS-37 of this document for NIAMS response to this significant item regarding Skin Disease.

FY 2004 Conference Committee Report Language (H. Rpt.108-401)

Item

Duchenne muscular dystrophy The conferees urge NIAMS, in collaboration with NINDS and NICHD, to accelerate clinical trials to improve treatment for patients with Duchenne muscular dystrophy. The conferees encourage NIAMS to actively seek and assess clinical trial proposals and to expedite the review process for clinical research in Duchenne muscular dystrophy. The conferees encourage the funding for three additional centers of excellence by the end of fiscal year 2004. (p. 773)

Action taken or to be taken

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), along with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Child Health and Human Development (NICHD), are committed to improving the treatment of patients with muscular dystrophy (MD). Clinical research is an important component of the recently established Muscular Dystrophy Cooperative Research Centers (MDCRCs). These centers - which are being funded by NIAMS, NINDS and NICHD - support an integrated basic and clinical research program focused on improving knowledge and treatment of MD. The centers are designed to accelerate the translation of fundamental scientific advances to the clinic through close interactions between basic researchers and clinicians. Two of the centers, at the University of Pittsburgh and the University of Washington, have a particular focus on the Duchenne form of MD.

The NIH has taken other proactive steps to advance clinical and translational research on muscular dystrophy. In January 2001, NIAMS and NINDS issued a program announcement with set-aside funds entitled Therapeutic and Pathogenic Approaches for the Muscular Dystrophies. This solicitation has resulted in a number of funded projects designed to advance treatment interventions for MD. One study, a clinical trial funded by NINDS, is testing whether the common antibiotic gentamicin has therapeutic potential for patients with both the Duchenne and limb-girdle forms of MD. This trial may provide new insights that will help shape the course of ~~future clinical studies in thi~~s area. Other projects funded as a result of this initiative focus on bridging the gap between basic research and clinical trials. This translational research is needed to determine the most promising clinical strategies to bring to trial. For example, studies funded by NIAMS and NINDS are aimed at improving gene therapy for Duchenne MD, including gene vector design and vector delivery methods. Other work supported by NIAMS is focused on special muscle-generating stem cells that can improve muscle regeneration and deliver the missing protein dystrophin to damaged muscles in a mouse model of DMD. Such studies of muscle cell transplantation in animal models could provide insights for developing new treatments for human patients. The NIH continues to welcome new proposals for translational and clinical research aimed at treating and delaying the progression of MD and related neuromuscular diseases.

The NIH will continue its efforts to further basic, translational, and clinical research in MD in the coming years. During fiscal year (FY) 2004, the NIH plans to re-issue the solicitation for the MDCRCs, and expects to fund up to two additional centers - one each by NIAMS and NINDS - in FY 2005. It is important to note that the MDCRC program is only one of the many ways that NIAMS, NINDS and NICHD are working together to further MD research. In recent years, the three institutes have co-sponsored initiatives and workshops on MD. All three institutes are represented on the Muscular Dystrophy Coordinating Committee (MDCC), which held its first meeting in July 2003. The MDCC is currently in the process of developing a research and education plan for MD. It is critical that NIH use its resources to continue to support a wide range of activities on MD. Such a multi-faceted approach will likely yield the most significant advances in understanding and treating the muscular dystrophies.