

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

Significant Items in House and Senate Appropriations Committee Report

FY 2007 House Appropriations Committee Report Language (H. Rpt. 109-515)

Item

***Burden of skin diseases.*** - The Committee notes the relationship between the recent Burden of Skin Diseases report and the September 2002 workshop on the burden of skin diseases sponsored by NIAMS. The committee continues to encourage NIAMS to expand the research portfolio on skin disease and develop partnerships with the skin disease research community to address the recognized challenges and future research endeavors. (p. 109)

Action taken or to be taken

NIAMS awarded a contract in May 2004 to examine existing data sets containing information on the burden of skin disease, including available epidemiological data, quality-of-life measures, and economic data. The researchers were also asked to identify available instruments used for the collection of data relating to disease in general, skin disease as a whole, and specific skin diseases. The final report from this contract was recently submitted to NIAMS for review and consideration. Results included in the report will be shared with the relevant research communities, as appropriate. Additionally, NIAMS will continue to work with researchers to make the most of existing databases, including new information from the Center for Disease Control and Prevention's National Health and Nutrition Examination Survey.

NIAMS-supported researchers have recently reported improvements to an established measure of skin disease. By paring down an existing measurement tool, researchers have been able to create a shorter instrument that may be easier to administer in large-scale data collection exercises. Additional work needs to be completed to further validate these findings; however, this study indicates the progress being made in addressing the concerns related to gathering information from both adult and pediatric patients, particularly in younger children where the parents will have to provide the data.

Other researchers have identified a gene called PSORS1 that plays a role in determining who gets psoriasis, and autoimmune skin disease. The researchers, along with colleagues from around the country and in Germany, looked closely at genetic samples from 678 families in which some of the family members had early-onset psoriasis, and they identified a specific alternate form of a gene as the one that confers susceptibility to this form of the disease. Support for this work was provided by the NIAMS, the National Center for Research Resources, the National Psoriasis Foundation, and others.

Additionally, NIAMS has signed a memorandum of understanding with the American Skin Association to support fellows funded by NIAMS under the Individual Postdoctoral National Research Service Awards (NRSA) program in epidemiology, clinical trials research, and outcomes research in skin diseases. NIAMS is committed to offering training support for current and future basic and clinical researchers focused on core components of its mission. The NRSA

mechanisms help to ensure the development of a diverse and highly trained workforce that is available to assume leadership roles related to the Nation's biomedical and behavioral research agenda.

#### Item

***Congenetic and genetic disease of bone.*** - The Committee is aware that thousands of children and adolescents nationwide suffer from musculoskeletal disorders and malformations. Diseases such as osteogenesis imperfecta, fibrous dysplasia, osteopetrosis, and Paget's disease are caused by poorly understood genetic mutations. In Paget's disease, underlying genetic defects can also be exacerbated by environmental factors. The Committee encourages NIAMS and NICHD to support research focusing on mechanisms of preventing fractures and improving bone quality and correcting malformations, on innovations in surgical and non-surgical approaches to treatment, on physical factors that affect growth, and on genetic defects that cause bone disease. (p. 109)

#### Action taken or to be taken

Bones are living tissues, which are regularly broken down by cells called osteoclasts and rebuilt by cells called osteoblasts. Normally, this process is kept in balance; however, several different genetic diseases can affect this process, leading to disease. For example, osteogenesis imperfecta (OI), a disorder characterized by bones that break easily, results from a genetic defect that affects the body's production of collagen, the major protein of the body's connective tissue. A person with OI has either less collagen or a poorer quality of collagen than normal, leading to weak bones that fracture easily. Fibrous dysplasia of bone is a developmental disorder characterized by expanding fibrous lesions of bone-forming tissue that result in pain, fracture, and/or deformity. Osteopetrosis is a group of genetic bone diseases that are characterized by an increase in skeletal mass resulting from inadequate bone breakdown. In osteopetrosis, osteoclasts usually are either fewer in number or are ineffective in breaking down bone, leading to dense but fragile bones. Finally, Paget's disease of bone is characterized by bones that grow too large and weak, also raising the risk of fracture due to poor bone quality.

NIAMS supports a broad portfolio of research in genetic diseases of bone including novel gene- and cell-based therapeutic approaches; the molecular and cellular mechanisms of disease; and the genetic and environmental risk factors that cause disease. For example, NIAMS-supported researchers recently discovered a potential approach to treating OI. The most common cause of OI is a defect in the gene that controls the production of Type 1 collagen proteins. In severe cases, this results in both the production of insufficient amounts of collagen and the production of defective collagen. The defective collagen interacts with other proteins, magnifying the defect's harmful effects. The challenge is to find a way to reduce or eliminate the production of the defective protein without affecting the same cells' production of normal collagen. In this study, specially designed ribozymes, acting as molecular scissors, were used to break the chemical links that held together the carriers of genetic information, thus cutting off communication between the defective gene and collagen-producing cells. The findings thus far have been limited to cultured cells and mice; much work remains to be done before ribozymes can be tested in people. But the success in targeting collagen production in bone clearly shows that the ribozyme approach has significant potential for treating not only OI, but many other genetic conditions involving atypical proteins.

NIAMS actively works with the bone research community at the NIH and beyond to develop a multi-faceted, collaborative approach in order to address both common and rare diseases of bone. For example, NIAMS – in conjunction with other NIH components, the Food and Drug Administration, and industry partners – is exploring a public-private collaboration on bone strength. The main goals of the initiative are to provide data supporting the use of new bone strength markers as surrogate endpoints for fractures in clinical trials, and to find measurements that predict risk of fracture more accurately than does bone density. This would facilitate the continued development and approval of new treatment alternatives to prevent fractures through the support of clinical trials that are smaller, shorter, and less expensive than current studies. This initiative has the potential to provide valuable information to researchers studying a variety of bone diseases.

#### Item

***Lupus.*** - The Committee is aware that despite numerous important research advances, few new therapies are available to patients with Lupus. Treatment with steroids, anti-inflammatory agents and immunosuppressive medications may be palliative but these medications have numerous side effects and may become less effective over time. Advances in the identification of lupus susceptibility genes and biomarkers make it imperative that a sustained effort be made to translate these research advances into clinically relevant treatments. The Committee encourages the Institute to develop focused programs designed to move research advances beyond the laboratory. (p. 109)

#### Action taken or to be taken

NIAMS has recently developed a new funding mechanism specifically designed to bring together basic and clinical research in a way that helps translate basic discoveries into new drugs, treatments and diagnostics. The Centers of Research Translation (CORT) program requires participating centers to encompass at least three projects, including one clinical and one basic research study. Lupus is the focus of one of the first CORT awards. Researchers will study the role of different cell types in lupus pathogenesis, develop markers of disease activity and severity, and look for new targets for treatment. The multifaceted approach promoted through the CORT mechanism will likely yield some of the most significant advances in understanding and treating lupus.

People with lupus often develop renal (kidney) disease, which may sometimes lead to end-stage renal disease (ESRD). Currently, the only way to tell if a patient has renal disease is by taking a biopsy of the kidney. Frequently, repeated biopsies are needed to determine the exact kind of disease and the most effective treatment. NIAMS-supported researchers have recently identified a potential new method to obtaining this information that does not involve using an invasive procedure such as a biopsy.

Researchers studied urine samples collected from 20 patients immediately before they underwent kidney biopsy. Using a process known as two-dimensional gel electrophoresis, they looked for proteins in the urine samples that could be biomarkers for lupus-related kidney disease. These results were then compared with the findings from the kidney biopsies. The researchers were able to identify a list of proteins in the urine of people with renal disease caused by lupus. These

biomarkers can be used to indicate the type and severity of renal disease in these patients, as well as the extent of damage to the kidney. Such biomarkers could form the basis of clinical tests that could help doctors to establish an effective treatment plan for these patients without putting them through repeated kidney biopsies. Further studies are needed to determine whether urine protein analysis could replace the use of biopsies to assess kidney damage in lupus.

#### Item

**Marfan syndrome.** - The Committee commends NIAMS and its collaborative efforts with other institutes to provide vital research on Marfan syndrome, a life-threatening, progressive and degenerative genetic disorder which is characterized by aortic aneurysms, orthopedic disabilities and ocular manifestations. Management of the syndrome by complicated aortic surgery is extending the life span of many. However, it has introduced a new generation of people with debilitating painful orthopedic issues such as early-onset arthritis, back pain and headaches due to dural ectasia and joint, leg and foot pain. Basic, translational and clinical research including the natural history of skeletal problems in this area is needed to investigate the underlying causes of these manifestations and to investigate therapeutic choices. This research is essential to improve the quality of life of those suffering from Marfan syndrome. The Committee encourages NIAMS to support research in this area through all available mechanisms, as appropriate. (p. 109)

#### Action taken or to be taken

Caused by a mutation in the gene that encodes for fibrillin-1 (a protein component of connective tissue), Marfan syndrome can affect the bones, skin, eyes, heart and blood vessels, nervous system and lungs. The syndrome can prove fatal if it weakens the aorta (the largest artery of the body) to the point of rupture. Traditionally, scientists have believed that fibrillin-1 played primarily a structural role in connective tissue disease, and that the only way to prevent aortic aneurysm or rupture in Marfan patients was to surgically replace the aorta. But, recent findings about the role of fibrillin have not only offered new insight into the cause of aortic rupture in Marfan syndrome, but also have offered clues to simpler, less invasive ways to prevent it. Previous research has indicated that fibrillin-1 regulates the growth factor, transforming growth factor-beta (TGF- $\beta$ ), and that this growth factor is in excess in Marfan syndrome patients. Looking for an easier way to slow down the activity of TGF- $\beta$ , NIAMS-supported researchers decided to try the drug losartan, which is known to suppress TGF- $\beta$  in animal models of other conditions. Researchers found that when animals with established aortic aneurysm were treated with losartan, the architecture of the aortic wall was restored and aortic rupture was prevented. In follow-up to this study, the National Heart, Lung, and Blood Institute now supports a natural drug therapy clinical trial in this area as part of the Pediatric Heart Network. The results of both studies have exciting implications for treating the serious complications of Marfan syndrome with a drug already in widespread clinical use.

Additionally, NIAMS-supported researchers are investigating the contribution of fibrillin to bone physiology in order to uncover the pathological underpinning of the skeletal manifestations of Marfan syndrome. Preliminary research has suggested that fibrillin-1 deficiencies affect bone formation and resorption by altering the signals that control the maintenance of bone mass. The current investigation aims to advance the understanding of fibrillin function in the skeleton and shed new light on the relationship between bone formation, growth and turnover, and the role of

the architectural matrix that contributes to bone strength. Results from this study will broaden the base of scientific knowledge which could lead to the design of new therapies for bone mineral replacement in patients affected with Marfan syndrome.

#### Item

***Mucopolysaccharidosis (MPS)***. - The Committee encourages the NIAMS to support and work collaboratively with NIDDK in an effort to achieve a greater understanding of bone and joint lesions in MPS disorders. The committee supports meaningful NIAMS involvement with other institutes in research and specifically addresses the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored, and potential therapeutic approaches to treating these debilitating aspects of MPS and related disorders. The Committee encourages NIAMS to work with participating NIH institutes and the MPS academic and patient advocate community to support and focus efforts in this area of study that can be particularly beneficial to patients. (p. 110)

#### Action taken or to be taken

The mucopolysaccharidoses (MPS) are caused by genetic defects in certain metabolic processes. The genetic defect is present in all cells in an affected individual, but the severity of the consequences varies from one cell type to another. In addition, different genetic defects yield different combinations of effects. The most serious problems usually occur in the central nervous system, heart, and airways. In some types of MPS, cells of the skeleton are significantly affected, most often resulting in deformed bones and swollen joints with limited movement.

The greatest potential for benefit to individuals with MPS lies in efforts to correct the underlying metabolic defect, which typically arises from deficiency of a specific enzyme. One approach to this goal is infusion of the missing enzyme directly into the blood. Alternatively, therapy can provide cells able to make the enzyme, either by transplantation of marrow cells from a normal donor, or by transferring the normal gene into cells of the affected individual. These therapeutic approaches are being pursued by the appropriate NIH components.

Because cells throughout the body can take up enzymes from the blood, approaches that provide enzymes only in the blood or only in cells of the marrow or liver can improve the skeletal outcomes for individuals with MPS. However, the cells of the skeleton are not efficiently replaced by marrow transplantation, and the cells of cartilage have little exposure to circulating blood. These difficulties also limit therapy of other skeletal disorders, including arthritis, osteogenesis imperfecta, and various chondrodystrophies.

The NIAMS supports a wide range of research aimed at improving the treatment of skeletal disorders. Included are efforts to reduce inflammation and cartilage erosion in arthritic joints, replace genetically defective skeletal cells by transplantation, target gene transfer to cells of the skeleton, and rebuild damaged skeletal tissues by tissue engineering. Advances in these areas are expected to benefit individuals with MPS, just as they benefit those with skeletal disorders arising from other causes.

#### Item

***Osteoporosis.*** - The Committee is aware that osteoporosis is becoming widespread in all ages of our population. The Committee encourages NIAMS to collaborate with other institutes to support research into the pathophysiology of bone loss in varied populations and in targeted therapies to improve bone density and bone quality according to the etiology of osteoporosis. Furthermore, the Committee encourages research to identify patients at risk for fracture who do not meet current criteria for osteoporosis, as well as to study the effects of available and developing osteoporosis treatments on the reduction of fracture risk in these patients. (p. 110)

#### Action taken or to be taken

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures. NIAMS continues to build on the base of previous research in osteoporosis by supporting a broad range of research aimed at developing new diagnostics and treatments for this disease. For example, NIAMS-supported researchers are examining the genetic and cellular mechanisms involved in bone build-up and breakdown in order to develop novel drug and gene therapies for bone diseases. Additionally, NIAMS supports research on the natural history of osteoporosis to better understand the genetic and environmental risk factors contributing to bone disease in both men and women.

In conjunction with other NIH components, the FDA, and industry partners, the NIAMS is exploring a public-private collaboration on bone strength. The main goals of this initiative are to provide data supporting the use of new bone strength markers as surrogate endpoints for fractures in clinical trials, and to find measurements that predict risk of fracture more accurately than does bone density. This would facilitate the continued development and approval of new treatment alternatives to prevent fractures through the support of clinical trials that are smaller, shorter, and less expensive than current studies.

Identifying dietary factors in building and maintaining bone quality is another important approach in NIAMS research. In partnership with the American Society for Bone and Mineral Research, NIAMS co-sponsored the “Contemporary Diagnosis and Treatment of Vitamin D-Related Disorders” scientific conference on December 4-5, 2006. Vitamin D plays a crucial role in the absorption of calcium and the mineralization of bone. This meeting convened scientists and clinicians from a wide range of disciplines to clarify recent advances and prioritize the key questions that researchers must address to improve the future diagnosis and treatment of diseases such as osteoporosis.

Osteoporosis can strike at any age and affects both men and women. In 2000, NIAMS launched a multi-center study of osteoporosis and fractures in older men known as Mr. OS. Nearly 6,000 men over the age of 65 have been recruited and data are being evaluated. Recently, researchers have identified specific lifestyle, medical and demographic characteristics that are associated with low bone mass and potentially fracture risk in older men. This information could be used in the clinic to facilitate the identification of men at high risk of fracture, to target interventions to these individuals, and to help understand the etiology of fracture in men.

Additionally, it is important to build bone mass across the lifespan. The rapid increase in bone mass that takes place during puberty is being studied by researchers supported by NIAMS. This period of life is critical for reaching peak bone mineral density. NIAMS-supported researchers

are examining the hormonal, genetic, and dietary factors that can enhance maximum calcium absorption and bone development during puberty, with the goal of reducing the incidence of osteoporosis later in life.

FY 2007 Senate Appropriations Committee Report Language (S. Rpt. 109-287)

Item

***Burden of Skin Diseases.*** - The Committee notes the relationship between the recent Burden of Skin Diseases report and the September 2002 workshop on the burden of skin diseases sponsored by NIAMS. The Committee continues to urge NIAMS to expand the research portfolio on skin disease and develop partnerships with the skin disease research community to address the recognized challenges and future research endeavors. (p. 138)

Action taken or to be taken

Please refer to page 173 of this document for NIAMS' response to this significant item regarding the burden of skin diseases.

Item

***Congenital and Genetic Disease of Bone.*** - The Committee is aware that thousands of children and adolescents nationwide suffer from musculoskeletal disorders and malformations. Diseases such as osteogenesis imperfecta, fibrous dysplasia, osteopetrosis, and Paget's disease are caused by poorly understood genetic mutations. In Paget's disease, underlying genetic defects can also be exacerbated by environmental factors. The Committee urges NIAMS and NICHD to support research focusing on mechanisms of preventing fractures and improving bone quality and correcting malformations, on innovations in surgical and non-surgical approaches to treatment, on physical factors that affect growth, and on genetic defects that cause bone disease. (p. 139)

Action taken or to be taken

Please refer to page 174 of this document for NIAMS' response to this significant item regarding congenital and genetic disease of bone.

Item

***Genetics of Rare Disorders.*** - The Committee urges NIAMS to collaborate with NICHD, NIDCR, and NIDDK to expand research on the genetics for the rare disorders fibrous dysplasia and osteopetrosis, and to expand research on mechanisms of these diseases in humans. (p. 139)

Action taken or to be taken

Genetic influences on the skeleton are complex, potentially reflecting the contributions of many different genes. For example, fibrous dysplasia is a developmental disorder characterized by expanding fibrous lesions of bone-forming tissue that results in pain, fracture, and/or deformity. While mutations leading to the activation of gene-regulating signaling pathways in bone have been identified in patients, the mechanism leading to fibrous dysplasia is not clear. In osteopetrosis, the cells that break down bone (osteoclasts) usually are either fewer in number or are ineffective in breaking down bone, leading to dense but fragile bones. To date, the precise genetic control of osteoclast function remains inadequately understood. Several NIAMS-

supported researchers are working to identify the gene-regulating signaling pathways in bone cells that control bone formation and break down. Advances in locating these pathways would provide researchers with additional clues to facilitate the development of potential therapeutic and prevention strategies for these and other diseases of bone.

In addition to ongoing research efforts in these areas, NIAMS has recently released a long-range plan that outlines scientific opportunities, research needs and gaps that we currently envision, including research in the developmental biology of bone, genetics of bone physiology, molecular and cellular biology of bone diseases, and gene therapies for bone diseases. The purpose of this long-range plan is to serve as a broad scientific outline for the NIAMS, and for the investigative and lay communities, by identifying compelling research opportunities. NIAMS has shared this plan with colleagues in the bone research community in order to identify potential areas for collaboration within the NIH and with relevant professional and patient advocacy organizations.

Additionally, the NIAMS leads the Federal Working Group on Bone Diseases, an interagency committee focusing on both common and rare bone disorders. The working group offers a forum for sharing information and facilitating the development, early in the planning stages, of collaborative research activities based on each agency's mission. Several other NIH components including the National Institute of Child Health and Human Development, the National Institute on Aging, the National Institute of Diabetes, Digestive, and Kidney Disorders, the National Institute of Dental and Craniofacial Research, the National Cancer Institute, and the National Center for Complementary and Alternative Medicine participate in working group activities. The most recent meeting of the working group was held in October 2006 and included an overview of opportunities available to bone researchers interested in genome-wide association studies, as well as research examining the influence of interactions between genes and the environment on disease development.

#### Item

***Lupus.*** - The Committee is aware that despite numerous important research advances, few new therapies are available to patients with lupus. Treatment with steroids, anti-inflammatory agents and immunosuppressive medications may be palliative but these medications have numerous side effects and may become less effective over time. Advances in the identification of lupus susceptibility genes and biomarkers make it imperative that a sustained effort be made to translate these research advances into clinically relevant treatments. The Committee urges the Institute to develop focused programs designed to move research advances from the laboratory to the patient's bedside so that the complications of lupus and the underlying disease can be treated more effectively. (p. 139)

#### Action taken or to be taken

Please refer to page 175 of this document for NIAMS' response to this significant item regarding lupus.

#### Item

***Marfan Syndrome.*** - The Committee commends NIAMS for supporting research on Marfan syndrome and for collaborating with other Institutes to study this disease. Better management of cardiovascular issues associated with Marfan syndrome has extended the lives of many but has

introduced an older generation of people who live with chronic pain because of orthopedic problems. Basic, translational and clinical research including the natural history of skeletal problems is required to understand the underlying early orthopedic deterioration in people with Marfan syndrome and to investigate possible therapeutic choices. The Committee urges NIAMS to support this effort through all available mechanisms, as deemed appropriate. (p. 139)

Action taken or to be taken

Please refer to page 176 of this document for NIAMS' response to this significant item regarding Marfan syndrome.

Item

***Musculoskeletal Trauma and Skeletal Pain.*** - The Committee recognizes that more than half of all Americans who are injured each year incur injuries to the musculoskeletal system. Back pain is a major reason for lost time from work, and, in our military, bone trauma is now accounting for over 50 percent of all combat injuries. The Committee urges NIAMS, NIA, NIDCR, and NCCAM to study ways to better understand the epidemiology of back pain, improve on existing diagnostic techniques for back pain, as well as to develop new ones. The Committee also encourages the expansion of research to improve diagnostic and therapeutic approaches to lower the impact of musculoskeletal trauma. (p. 139)

Action taken or to be taken

At some point, back pain affects an estimated 8 out of 10 people. It is one of our society's most common medical problems. Additionally, accidental injury and chronic disease cause musculoskeletal pain that can be difficult to diagnose and treat. NIAMS is committed to supporting research examining the causes of these conditions, as well as the development of new diagnostic and treatment options.

Most recently, NIAMS-supported researchers have published results from the Spine Patient Outcomes Research Trial (SPORT), the largest trial to date comparing surgical and non-surgical interventions for the treatment of low back and associated leg pain caused by lumbar intervertebral disk herniation. Patients receiving surgery underwent a lumbar discectomy, a procedure involving the removal, in part or whole, of an intervertebral disk. The non-surgical intervention consisted of physical therapy, education/counseling, home exercise instruction, and nonsteroidal anti-inflammatory drugs. After 2 years, improvements in levels of reported pain were seen in all patients regardless of their treatment protocol; however, patients receiving surgery reported having the highest level of improvement across both groups. The results of this study have broadened our understanding of the effectiveness of surgical versus non-surgical interventions for treating these common and often debilitating musculoskeletal conditions. Patients and their health care providers will be able to use the results of this study to help them select a treatment intervention based on their preferences.

The NIAMS, along with several other NIH components including the National Institute of Nursing Research, National Institute on Aging, National Institute of Dental and Craniofacial Research, and the National Center for Complementary and Alternative Medicine, recently released a Program Announcement entitled, "Mechanisms, Models, Measurement, and Management in Pain Research." Researchers were invited to submit proposals that sought to

improve the understanding of the causes, costs, and societal effects of both acute and chronic pain and the relationships between the two. Additionally, proposals that link such understandings to the development of better approaches to therapeutic interventions, including complementary and alternative medicine interventions, and management of acute and chronic pain were encouraged.

NIAMS has also developed a new funding mechanism for Centers of Research Translation (CORTs). One of the first funded CORTs will study the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, for healing of fragility fractures in the elderly. CORT grants require centers to be highly translational and encompass at least three projects, including one clinical and one basic research study. The research being conducted at this particular CORT has the potential to provide new therapies for the types of injuries that occur in combat, automobile accidents, and other types of trauma involving bone.

Lastly, along with the American Academy of Orthopaedic Surgeons, NIAMS co-sponsored Extremity War Injuries: State-of-the-Art and Future Directions, a scientific symposium that took place in Washington, DC, January 24-27, 2006. The three-day event addressed wound management, antibiotics and infection, long-bone stabilization, management of segmental bone defects, and amputee care. Techniques and treatments developed and employed for wartime injuries can be used in managing civilian trauma and medical complications. Advances in the management of extremity injuries will lead to quicker recovery times from blast injuries, better response rates to infection, and new advances in amputee care, benefiting both military and civilian patients.

#### Item

***Osteoporosis.*** - The Committee is aware that osteoporosis is becoming widespread in all ages of our population. NIAMS is urged to collaborate with other Institutes to support research into the pathophysiology of bone loss in varied populations and in targeted therapies to improve bone density and bone quality according to the etiology of osteoporosis. Furthermore, the Committee urges research to identify patients at risk for fracture who do not meet current criteria for osteoporosis, as well as to study the effects of available and developing osteoporosis treatments on the reduction of fracture risk in these patients. (p. 140)

#### Action taken or to be taken

Please refer to page 178 of this document for NIAMS' response to this significant item regarding osteoporosis.

#### Item

***Psoriasis.*** - The Committee is disappointed that funding for psoriasis research has not grown significantly over the past decade. The Committee strongly urges NIAMS to expand and coordinate genetic, clinical, and basic psoriasis and psoriatic arthritis research and related activities, with emphasis on the cellular and molecular mechanisms of disease; genetics that lead to psoriasis susceptibility; the natural course and history of psoriasis before, during and after treatment with conventional therapies; the role of inflammation in skin and joints and co-morbidities such as obesity, depression and hypertension; the development of diagnostic tests for

psoriatic arthritis; the unique challenges faced by children with psoriasis; and the use of certain types of antibodies to prevent relapse of psoriasis. (p. 140)

#### Action taken or to be taken

NIAMS funds a variety of research aimed at uncovering the cellular and molecular processes that contribute to the development of psoriasis and psoriatic arthritis, expanding our knowledge of genes that play a role in causing these diseases, and the creation of more effective treatments in order to help increase the quality of life for adults and children.

Skin cells usually grow deep in the epidermis of the skin, pushing the maturing cells slowly toward the surface where they perform the barrier function of the skin. Eventually, the outermost layer of cells gets sloughed off and is replaced by the cells below. With psoriasis, it can happen in just a few days because the cells divide too fast and pile up on the surface. NIAMS-supported researchers have recently reported findings on how cells of the epidermis go through the process of growing and differentiating. By understanding the normal mechanisms that control how stratified tissues such as the epidermis are able to maintain a balance between growth and differentiation and also repair themselves in response to injury, the scientists have gained a better understanding of how different disorders of the skin – including psoriasis – arise when various aspects of these normal mechanisms become faulty. With this new understanding of the process, the scientists have also begun to use genetic studies in mice to try to identify which genes are necessary in the process.

Other genetic research supported by NIAMS has already led to the discovery of a gene called PSORS1 which plays a role in determining who gets psoriasis. Researchers looked closely at genetic samples from 678 families in which some of the family members had early-onset psoriasis, and they identified a specific gene allele (an alternate form of a gene) as the one that confers susceptibility to this form of the skin disease. Other researchers are continuing to build upon these discoveries to further understand how the PSORS1 and related genes increase susceptibility to psoriasis. The benefit to finding a gene that makes people susceptible to developing psoriasis is that scientists may be able to examine targeted therapies which could result in the prevention or improved treatment of the disease. Current treatments for psoriasis often suppress the entire immune system, leaving the person vulnerable to various infections. Ideally, treatments aimed at a particular gene would shut down only the process which causes the disease, providing relief, while still leaving a functioning immune system.

NIAMS-supported researchers have also demonstrated a connection between psoriasis and increased risk for other diseases, such as cardiovascular disease. The same inflammatory process that speeds up the growth cycle of skin cells in psoriasis is also involved in promoting blockages of arteries and ultimately causing ruptures of plaques, leading to heart attacks. The risk is nearly doubled in younger patients (30 to 40 years old) with severe psoriasis compared to those without the disease. This study demonstrates the importance for people with psoriasis to modify their cardiovascular risk factors as much as possible, by quitting smoking and controlling weight, blood pressure, cholesterol, and other factors that could increase the risk of heart disease.

#### Item

***Tuberous Sclerosis Complex [TSC].*** - The Committee urges NIAMS to explore new strategies for the treatment of skin manifestations of TSC utilizing knowledge of basic mechanisms, such as mTOR inhibitors and angiogenesis inhibitors. (p.140)

Action taken or to be taken

Tuberous sclerosis complex (TSC) is a rare and genetic, neurological disorder primarily characterized by seizures, mental retardation, and skin and eye lesions. Small benign tumors may grow on the face and eyes, as well as in the brain, kidneys, and other organs. Individuals with TSC may experience none or all of the associated symptoms with varying degrees or severity.

NIAMS-supported researchers are currently examining the mechanisms of the development of TSC and associated angiogenesis (blood vessel development). TSC is caused by mutations in genes TSC1 or TSC2 whose protein products, hamartin and tuberlin, respectively, normally function as a complex that regulates many cellular processes, including cell growth. NIAMS-supported researchers have created a mouse model with mutations in the tuberlin gene that develops unique skin and brain tumors similar to those in TSC patients. Investigators are exploring how molecular signals upstream and downstream of the hamartin/tuberlin complex affect tumor development and growth. Knowledge of how the upstream and downstream events impact the development of TSC may lead to therapies that can prevent or improve the skin manifestations of the disease in humans.

TSC1 and TSC2 are part of the mTOR signaling pathway which is involved in the regulation of protein translation and cell growth. Several NIAMS-funded researchers are working on signaling in the mTOR pathway and its involvement in normal cellular processes and abnormal conditions and diseases. A better understanding of the mTOR pathway will provide additional targets for drug intervention in TSC, as well as a better understanding of how mutations in TSC1 and TSC2 lead to abnormalities in multiple organ systems.