VII.
National Institute of Arthritis and Musculoskeletal and Skin Diseases

INTRODUCTION

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) conducts and supports basic and clinical research on many of the most debilitating diseases affecting the Nation's health, including the many forms of arthritis, osteoporosis, and other diseases of the musculoskeletal system and the skin. The normal structure and function of joints, muscles, bones, and skin are addressed as well. Basic research involves a wide variety of scientific disciplines, including immunology, genetics, molecular biology, structural biology, biochemistry, physiology, virology, and pharmacology. Clinical research, including epidemiologic studies and clinical trials, is conducted in the fields of rheumatology, orthopedics, bone endocrinology, sports medicine, and dermatology.

The Extramural Program of NIAMS supports research and research training at universities and medical centers through research grants and contracts. The four program branches deal with rheumatic diseases, muscle biology, musculoskeletal diseases, and skin diseases. The Intramural Research Program conducts research on the campus of the National Institutes of Health (NIH), Bethesda, Maryland. The Program consists of the Arthritis and Rheumatism Branch, the Bone and Connective Tissue Biology Branch, the Laboratory of Physical Biology, the Protein Expression Laboratory, the Laboratory of Skin Biology, and the Laboratory of Structural Biology Research.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

NIAMS researchers together with researchers at nine institutions have discovered gene mutations that define a new group of inflammatory diseases. The collaborating institutions are The New Children's Hospital, Westmead, New South Wales, Australia; Women's and Children's Hospital, North Adelaide, South Australia; St. Bartholomew's and the Royal London Hospital, Whitechapel, London, and the University of Nottingham, England; Helsinki University Central Hospital, Finland; National University of Ireland, Cork; Harvard Medical School, Boston, Massachusetts; the University of Texas, Houston; and the University of Vermont College of Medicine, Burlington. This discovery marks the first time that mutant tumor necrosis factor (TNF) receptor has been tied to an inherited disease.

The NIAMS researchers and their colleagues discovered genetic mutations on chromosome 12 that underlie a newly recognized group of inherited inflammatory disorders, including familial Hibernian fever. The disorders, collectively known as TNF receptor–associated periodic syndrome (TRAPS), are characterized by long, dramatic episodes of high fever, severe pain in the abdomen, chest, or joints; skin rash; and inflammation in or around the eyes. Some patients also develop amyloidosis, a potentially fatal disease in which a blood protein is deposited in vital organs.

The mutations, reported in *Cell* (April 2, 1999), involved a cell-surface receptor for the inflammatory protein TNF. Patients from seven families with TRAPS symptoms exhibited the mutations. Normally, the TNF receptor plays a role in the body's defenses against infectious and foreign agents. The mutant receptors are thought to predispose individuals to severe inflammation, which can be triggered by emotional stress or minor trauma or which can occur for no apparent reason.

These results are a very important contribution to better understanding of the role of the TNF pathway in disease. The findings may lead to additional therapies, targeted at the cellular level, for many immunologic and inflammatory disorders.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Activities With International and Multinational Organizations

International League of Dermatological Societies

The Director, NIAMS, chaired the International Meeting on Clinical Dermatology, Clinical Dermatology Update, in Florence, Italy, on March 4–7, 1999. He also gave a lecture on Bullous Diseases—News in Pathogenesis. The Director serves as president of the International Committee of Dermatology, and he chaired a meeting of that organization in fiscal year 1999.

Extramural Programs

Skin Diseases Branch

The Skin Diseases Branch has several European joint studies that generate sufficient patients for a variety of research questions. The three collaborating U.S. grantees are as follows:

1. University of Colorado Health Sciences Center, Denver—Researchers are exploring the genetic basis of vitiligo, by using cohorts in the United Kingdom and the United States to locate the gene(s) for this disease.

2. University of Michigan, Ann Arbor—Researchers are testing the genetic basis of psoriasis with European and U.S. cohorts, to localize the susceptibility gene(s).

3. University of Pennsylvania, Philadelphia—Researchers are conducting an epidemiologic study of risk factors for susceptibility to chronic lower-leg ulcers in cohorts in the United Kingdom and the United States.

In an ongoing study, an NIAMS grantee at the Medical College of Wisconsin, Milwaukee, is collaborating, under a subcontract, with investigators at the University of São Paulo, Brazil. This joint research team has focused on the blackfly species that are present in the areas of endemic pemphigus foliaceus in Brazil as the likely trigger of autoimmune

events in susceptible populations. They have compared the subspecies present in villages where there is high prevalence of disease with genetically similar subspecies in nearby villages where there is little disease. The scientists discovered a wider variation in subspecies than had been suspected. They are now characterizing the antigens from these blackfly subspecies, to identify the antigen(s) most likely to be the environmental trigger(s) for the disease.

International Meetings

On April 14–18, 1999, the Director, NIAMS, was invited to give a special lecture on Dermatology and the Immune System, at the VIIIth International Congress of Dermatology Meeting, in Cairo, Egypt. In May 1999, the Director was invited to be a special lecturer at Hokkaido University School of Medicine, Sapporo, Japan, where he spoke on The Skin as a Target and Effector Organ for Immune-Mediated Diseases, and at Ajou University, Seoul, Korea, where he made a presentation on Immune Reactivity of Skin. In addition, the Director was an invited guest speaker at the 40th Annual Meeting of the North American Clinical Dermatological Society, in Alberta, on July 3–10, 1999. He gave two lectures: (1) The Skin Immune System—Why Study It? (2) From the Bench to the Bedside—How Do We Get There? In October 1999, the Director presented the Heinrich Irenäus Quincke Memorial Lecture, in Kiel, Germany, and participated at the 20th World Congress of Dermatology, in Paris, France.

Arthritis and Rheumatism Branch

The Chief of the Chemical Immunology Section, Arthritis and Rheumatism Branch, was a plenary speaker at the 3rd Membrane Forum on the Biophysics and Structure of Biomembranes, in Nagoya, Japan, on March 26–31, 1999. He also participated in a meeting of the International Council for Science, Committee on Membership and Statutes, in Paris, France, on April 13, 1999, and in the General Assembly of the council, as a member of the U.S. delegation from the National Academy of Sciences and as a member of the Committee on Membership and Statutes, in Cairo, Egypt, on September 25–October 2, 1999.

The Chief of the Connective Tissue Diseases Section was the Kovacs Visiting Lecturer at the Royal Society of Medicine, in Birmingham, London, and Sheffield, England, and Glasgow, Scotland, where he delivered several lectures in March 1999.

The Chief of the Genetics Section chaired a session and gave an invited lecture at the 2nd International Symposium in Memory of Richard M. Goodman, Genomic Views of Jewish History, in Ma'ale Hachamisha, Israel, on May 30–June 2, 1999. He also gave an invited lecture at the Weizmann Institute of Science, Rehovot, Israel, in June.

The Chief of the Inflammatory Joint Diseases Section presented a plenary lecture on Neuroendocrine–Immune Interactions and Autoimmunity, at a European Research Conference on Cytokines, Hormones, and Immunity. The conference was held in Castelvecchio Pascoli, Italy, in September 1999. Also in September, the Chief chaired a session and presented a seminar on Neuroendocrine Mechanisms in the Autoimmune Diseases, at the 4th International Congress of the International Society for Neuroimmunomodulation, in Lugano, Switzerland. A Visiting Fellow from Bulgaria was also invited to give a lecture on hormonal regulation of balance of cytokines from type 1 and type 2 helper T cells (TH1 and TH2 cells).

The Chief of the Lymphocyte Cell Biology Section was an invited speaker at the meeting on systemic lupus erythematosus, SLE '99, in Vienna, Austria, on January 25, 1999. In March 1999, he also gave lectures in Japan, at Kobe University Medical School; Osaka University Medical School; Tohoku University Medical School, Sendai; Chiba University Medical School; Keio University Medical School, Tokyo; and the University of Tokyo. In addition, the Chief made presentations at the International Symposium on Proinflammatory Cytokines and Immunoregulation, in Tokyo, on March 16, 1999, and at the 24th European Symposium on Hormones and Cell Regulation, at Mt. Ste. Odile, in Alsace, France, on September 24, 1999.

Bone and Connective Tissue Biology Branch

The Chief of the Craniofacial Development Section, Bone and Connective Tissue Biology Branch, gave a keynote address entitled A New Face for a New Millennium, at the European Craniofacial Meeting, in Manchester, England, on June 15, 1999. He was also an invited speaker at the XIIth Congress for the International Confederation for Plastic, Reconstructive, and Aesthetic Surgery, in San Francisco, California, on June 30, 1999, where he also gave a seminar entitled Human Faces, DNA Chips, and the Human Genome. A Senior Staff Fellow in the Craniofacial Development Section was an invited speaker at the International Symposium on Craniofacial Morphology, Universität Witten/Herdecke, Witten, Germany, on May 12, 1999, and gave a seminar on Animal Modeling of Apert Syndrome.

Laboratory of Physical Biology

The Chief of the Laboratory of Physical Biology was an invited speaker at the Institute of Atomic and Molecular Sciences, in Taipei, Taiwan, in May 1999, where he presented a lecture entitled Single Molecule Biomechanics. He was also the keynote speaker at the 5th Symposium on Recent Advances in Biophysics, Taiwan Biophysical Society Annual Symposium, at the National Chung-Hsien University, in Taichung, on May 12, 1999. He gave a lecture on Titin and Nebulin: Giant Protein Rulers of Muscle Structure and Function. On May 17, 1999, the Chief was an invited symposium speaker at the Veterans General Hospital, Taipei; his presentation was entitled Sex, Sound, and Muscle.

Laboratory of Skin Biology

The Chief of the Molecular Biology of Keratinization Section, Laboratory of Skin Biology, was an invited participant at the meeting of the Korean Society for Investigative Dermatology, in Seoul, on January 25–29, 1999, and at the Gordon Research Conference on Barrier Function, in Ciocco, Italy, on April 11–16, 1999.

Laboratory of Structural Biology Research

The Chief of the Laboratory of Structural Biology Research was an invited speaker at the EMBO (European Molecular Biology Organ) Workshop, in Prague, Czech Republic, on August 9–13, 1999, and the at the Protein Society Symposium, in Garmisch, Germany, on September 18–23, 1999.

Intramural Programs and Activities
Arthritis and Rheumatism Branch

Connective Tissue Diseases Section

The Connective Tissue Diseases Section, Arthritis and Rheumatism Branch, continued an active collaboration on glycogen storage disease type II (acid maltase deficiency) with colleagues at the Hospital Debrousse, Lyon, France, and Erasmus University, Rotterdam, the Netherlands.

In an ongoing investigation, a Visiting Fellow from China is studying the gene for acid α-glucosidase (acid maltase). Another Visiting Fellow, from India, continued to work on the pathogenesis of myositis.

Genetics Section

The Genetics Section collaborated with research groups in Australia, Finland, Ireland, and the United Kingdom to study the genetic basis of dominantly inherited periodic fevers. An Exchange Scientist from London, England, participated in these studies. This work was reported in the article "Germline mutations in the extracellular domains of the 55-kilodalton TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes" (*Cell*, April 2, 1999). Additional findings were reported at the Arthritis Research Conference, in Alexandria, Virginia, on August 6–8, 1999, and the 49th Annual Meeting of the American Society of Human Genetics, in San Francisco, California, on October 19–23, 1999.

The Genetics Section continued joint research with groups in Israel and Italy, to study the genetics of familial Mediterranean fever (FMF). A Visiting Fellow from Armenia also participated in these studies. Some of this work was reported in the article "Mutation and haplotype studies of FMF reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population" (*American Journal of Human Genetics*, April 1999). Additional findings were presented at the Arthritis Research Conference and at the 49th Annual Meeting of the American Society of Human Genetics.

An Exchange Scientist from Israel studied mutations of the gene for FMF (MEFV) in patients and families manifesting both FMF and Behçet's disease.

Another Exchange Scientist from Israel performed studies that led to the identification of a second gene underlying cystinuria, a hereditary cause of kidney stones. This work was published in September 1999, in the article "Refined mapping of the CSNU3 gene to a 1.8-Mb region on chromosome 19q13.1 using historical recombinants in Libyan Jewish cystinuria patients," in *Genomics*, and in the article "Non–type I cystinuria caused by mutations in *SLC7A9*, encoding a subunit ($b^{o,+}$ AT) of rBAT," in *Nature Genetics*.

A Visiting Fellow from Korea cloned the mouse and rat homologues to the FMF gene and has developed an FMF knockout mouse. Some of his work was presented at the Arthritis Research Conference and at the 49th Annual Meeting of the American Society of Human Genetics.

An Exchange Scientist from Portugal studied the genetics of familial amyloid polyneuropathy. Part of this work was reported in the article "Genetic anticipation in Portuguese kindreds with familial amyloidotic polyneuropathy is unlikely to be caused by triplet repeat expansions," in *Human Genetics*, in June 1999.

Inflammatory Joint Diseases Section

The Inflammatory Joint Diseases Section continued a research project with colleagues at Kyoto University, Japan, on synoviocyte biology relevant to rheumatoid arthritis. A report on results of this study was published in *Arthritis and Rheumatism*, in June 1999.

A Visiting Fellow from India presented a report at the 49th Annual Meeting of the American Society of Human Genetics. She also coauthored research reports on the development of a genetic-linkage map for the rat and the identification of quantitative trait loci regulating experimental arthritis that were published in 1999. The reports were published in *Transplantation Proceedings, Mammalian Genome, Molecular Medicine Today,* and *Current Rheumatology Reports*.

Lymphocyte Cell Biology Section

The Lymphocyte Cell Biology Section continued to work with scientists at the University of Brescia, Italy, and Tohoku University, Sendai, Japan, to study patients with immunodeficiencies.

A Visiting Fellow from Austria published review articles on cytokine signaling, in Life Sciences and Immunologist, in June 1999. A Visiting Fellow from France published a study on interferon regulatory factor 1, in the Journal of Immunology. A Visiting Associate from Italy published a research report on a new interleukin 2–dependent substrate, in the Journal of Immunology, in February 1999. The Visiting Fellows and Visiting Associate coauthored a report on TNF receptor mutations, in Cell, in April 1999.

Signal Transduction Group

The Head of the Signal Transduction Group and a scientist from Hôpital Cochin, Paris, France, are collaborating on studies involving the role of a hematopoietic cell–specific protein in regulating gene expression in T cells and mast cells. These studies have provided new insights on how proteins traffic from the cytosol to the nucleus in the cells under study.

In ongoing research, the Signal Transduction Group and a scientist at the National Institute of Medical Research, London, England, are exploring the role of a hematopoietic cell–specific protein in inflammation. This research is revealing new insights on how Fc receptors regulate cytokine genes.

A Visiting Fellow from Italy discovered that cytokine production in mast cells is tightly controlled by a feedback mechanism that involves the protein kinase C family. A Pan American Fellow from Mexico studied the relationship between Fc receptor engagement and induction of particular cytokine genes.

Bone and Connective Tissue Biology Branch

Craniofacial Development Section

The Craniofacial Development Section, Bone and Connective Tissue Biology Branch, continues to work with scientists at Tohoku University, Sendai, Japan, on the study of regulatory mechanisms of extracellular matrices on the phenotypic expression of chondroblasts and osteoblasts.

Collaboration among a Senior Staff Fellow and scientists at the University of Helsinki, Finland, the University of California, San Francisco, and the University of Southern California, Los Angeles, resulted in publication of the article "EGF (epidermal growth factor) receptor function is necessary for normal craniofacial development and palate closure," in *Nature Genetics*, in May 1999.

A Senior Staff Fellow received a Short-term Visiting Research Grant from the NIH and the Japanese Society for the Promotion of Sciences Joint Program, to perform research at Tohoku University.

Collaboration among a Senior Staff Fellow, two Visiting Fellows from Japan, and scientists from Kanazawa University, Japan, will result in publication of the article "Nerve growth factor (NGF) supports tooth morphogenesis in mouse first branchial arch explants," in *Developmental Dynamics,* in November 1999.

A Visiting Fellow from Japan investigated the molecular signals for differentiation of cranial neural crest cells in cartilage. His work, "Msx2 is a repressor of chondrogenic differentiation in migratory cranial neural crest cells," was submitted for publication and was awarded the Fellows Award for Research Excellence from the NIH.

Another Visiting Fellow from Japan examined a mutation of the FGFR2 gene for tyrosine kinase receptor in relation to craniofacial and skeletal malformations. His work, entitled "Transgenic mice expressing P253R mutant of FGFR2 exhibit craniofacial dysmorphogenesis with similarities to human Apert syndrome," was submitted for publication.

A Visiting Associate from Japan is studying the molecular regulation of cartilage formation by bone morphogenetic protein (BMP) and EGF. His article, "Convergence of the BMP and EGF signaling pathways on Smad1 in the regulation of chondrogenesis," will be published in the *International Journal of Developmental Biology,* in November 1999. Another article, "Positionally dependent chondrogenesis induced by BMP4 is co-regulated by Sox9 and Msx2," has been accepted for publication in *Developmental Dynamics,* in April 2000.

Collaboration between a Japanese Guest Researcher and another Japanese Visiting Fellow in the Functional Genomics Unit at the National Institute of Dental and Craniofacial Research resulted in publication of the article "Expression pattern of macrophage migration inhibitory factor during embryogenesis," in *Mechanisms of Development.*

A Senior Staff Fellow and an Intramural Research Training Award (IRTA) Fellow worked with scientists at the DNA/Cell Bank and Gene Research Laboratory, Hacettepe University, Ankara, Turkey, on the mapping of genetic mutations for the genetic disorder postaxial polydactyly type A2.

Laboratory of Physical Biology

Macromolecular Biophysics Section

The Macromolecular Biophysics Section, Laboratory of Physical Biology, collaborated with researchers at McGill University, Montreal, on a radiation inactivation study of reverse transcriptase and with researchers at McMaster University, Hamilton, Ontario, on a radiation inactivation study of glucose transporter.

Muscle Biophysics Section

A senior investigator from the Muscle Biophysics Section worked with researchers at the Institute of Cell Biology, Swiss Federal Institute of Technology, Zürich, to study interactions between muscle LIM protein (MLP) and N-RAP, as well as N-RAP expression and localization in an MLP-deficient mouse model of dilated cardiomyopathy. (N-RAP is a novel muscle protein with sequences homologous to those of nebulin.)

The Section collaborated with the European Molecular Biology Laboratory, Heidelberg, Germany, on the role of a capping protein in the structure and function of the Z line of striated muscles. The Section also worked with the Institute of Chemistry, Academia Scinica, Taipei, Taiwan, on a project to determine high-resolution structure of the elastic PEVK domains of the giant elastic protein, titin, by nuclear magnetic resonance (NMR) techniques.

A Visiting Scientist from China worked on x-ray diffraction from living skeletal muscle and successfully identified, for the first time, the structure of myosin that is weakly bound to actin in the biochemical state of actin myosin, in the process of converting chemical energy of adenosine triphosphate hydrolysis to mechanical energy for muscle contraction.

A Visiting Fellow from China pursued molecular modeling of skeletal muscle and analyzed the x-ray diffraction patterns to establish the three-dimensional motif of myosins binding to actin in rigor muscle. An IRTA Fellow from China studied the mechanism of regulation in skeletal muscle, particularly the structural role of troponin.

A Visiting Fellow from England worked on the application of molecular modeling of actomyosin interactions.

As a Guest Researcher in the Section, a senior scientist from Bristol University, England, pursued dynamic molecular modeling of the effects of binding various nucleotides in the active site of myosin molecule. This research will lead to a better understanding of why some nucleotides are hydrolyzed, but some others are not, and will give further insight on the energy transduction involved in muscle contraction.

Laboratory of Skin Biology

Genetic Studies Section

In ongoing research, the Genetics Studies Section, Laboratory of Skin Biology, continued its long-standing collaboration with investigators at Ain-Shams Medical Genetics Clinic, Cairo, Egypt, to study the genetic basis of hereditary skin disorders. The Section also worked with the University of Rostock, Germany, to investigate mutations of the PTCH gene in patients with odontogenic cysts.

The Section Chief and staff scientist, in collaboration with an investigator at Brown University, Providence, Rhode Island, traveled to Cairo, in February 1999, to pursue research on hereditary skin disease in Egypt and to develop DNA-based genetic diagnostic capabilities at Ain-Shams Medical Genetics Clinic. This project is funded by a grant from the U.S.-Egypt Joint Science and Technology Fund.

An IRTA Fellow traveled to Cairo to establish diagnostic testing for fragile X syndrome, at Ain-Shams Medical Genetics Clinic. This project also receives funding from the U.S.-Egypt Joint Science and Technology Fund.

The Section hosted a Visiting Fellow from Ukraine who investigated new methods for detection of gene mutations in hereditary skin diseases and for development of a cDNA (complementary DNA) library for epidermal differentiation.

Molecular Biology of Keratinization Section

The Molecular Biology of Keratinization Section continues cooperative efforts in the following international research:

- studies of the function of transglutaminases on membrane surfaces, with the University of Debrecen, Hungary;
- studies of the expression and function of transglutaminases in epidermal differen-

tiation and apoptosis, with the University of Rome, Tor Vergata, and Istituto Dermopatico dell'Immacolata, Rome, Italy;

■ studies of the biophysical and solution structures of transglutaminase substrates, as visualized by NMR and x-ray crystallography, with the Institute of Fundamental Sciences, Massey University, Palmerston North, New Zealand;

■ studies of the structure of intermediate filaments, with the Institute of Fundamental Sciences, Massey University, Palmerston North; and

■ biophysical and solution structures of intermediate filament coiled coils, as visualized by NMR and x-ray crystallography, with the Maurice Müller Institute, University of Basel, Switzerland.

A Visiting Scientist and staff scientist from Bulgaria studied the postsynthetic modifications of several epidermal structural proteins. A Visiting Fellow from China investigated the structures of keratin intermediate filaments. Two Visiting Scientists and three Visiting Fellows from Korea studied the expression and function of transglutaminase substrates in normal and degenerative tissues, the regulation of epidermal gene expression, and genes encoding enzymes involved in postsynthetic modifications of skin proteins. A Visiting Fellow from Ukraine examined the structures of protein involved in barrier function and their interactions with membranes.

Laboratory of Structural Biology Research

The Laboratory of Structural Biology Research continues to collaborate in several international research efforts, including studies with the following institutions:

■ Commonwealth Scientific and Industrial Research Organization, Geelong, Australia, and Massey University, Palmerston North, New Zealand, to investigate the structure of "hard" α-keratin filaments;

■ University of Graz, Austria, in a joint structural study of the adenosine triphosphatase encoded by the gene for resistance to diazaborine, in yeast;

■ Max Planck Institute for Biochemistry, Martinsried, Germany, to implement the technology of electron tomography and prepare a review on energy-dependent proteases;

■ Medical Research Council, Institute of Virology, Glasgow, Scotland, to investigate the capsid structure of oyster herpesvirus, an evolutionarily remote herpesvirus; and

■ Centro Nacional de Biotecnologia, Madrid, Spain, to perform electron microscopy studies of human astrovirus.

A Visiting Fellow from Canada studied the interaction between the REV protein of human immunodeficiency virus and tubulin and is also working on assembly of hepatitis B virus.

A Visiting Associate from China successfully carried out numerous electron microscopy projects, including high-resolution work on iridium-labeled core antigen of hepatitis B virus, cytomegalovirus capsids, actomyosin filaments, and nucleoprotein filaments involved in mutagenesis and repair of DNA.

A Visiting Fellow from the Czech Republic completed studies of the assembly of the cornified cell envelopes of terminally differentiated keratinocytes, by electron microscopy and biochemical methods.

An IRTA Fellow from India investigated structural transitions of virus capsids in a time-resolved manner.

A Visiting Fellow from Japan analyzed the three-dimensional structure of the energy-dependent ClpAP protease of *Escherichia coli*. Another Visiting Fellow from Japan started work on a virus-engineering project. A Visiting Associate from New Zealand developed novel image-processing software and successfully applied it to determine the three-dimensional structures of viruses at unprecedented high resolution.