NATIONAL INSTITUTES OF HEALTH

REPORT OF THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

October 2000

FOREWORD

Autoimmune diseases result from a dysfunction of the immune system in which the body attacks its own organs, tissues and cells. Physicians and scientists have identified more than 70 clinically distinct autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, immune-mediated diabetes, and systemic lupus erythematosus. While many autoimmune diseases are rare - affecting fewer than 200,000 individuals - collectively, these diseases afflict millions of Americans, an estimated five percent of the population. The social and financial burden of these chronic, debilitating diseases is immense, and includes poor quality of life, high health care costs, and substantial loss of productivity.

The past two decades of intensive and highly productive research on the immune system have resulted in a wealth of new information and extraordinary growth in conceptual understanding. These accomplishments now provide promising opportunities for major advances in the diagnosis, treatment, and prevention of autoimmune diseases. The National Institutes of Health (NIH) stands at the forefront of many of these accomplishments. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH institutes, offices, and centers support research in this area in collaboration with a wide range of professional and patient advocacy organizations. NIH has placed a high priority on coordination to ensure the effective participation of public and private organizations and the efficient use of research resources.

To facilitate collaboration among those NIH components, other Federal agencies, and private organizations with an interest in autoimmune diseases, the NIH established the Autoimmune Diseases Coordinating Committee in 1998, under the direction of the National Institute of Allergy and Infectious Diseases. Since its inception, the Committee has analyzed a wide range of ongoing and planned research programs and has developed cross-cutting initiatives to address key aspects of autoimmunity. In addition, the Committee has established workgroups to foster scientific collaborations and to develop research initiatives in a variety of promising areas, including new therapeutic approaches such as the induction of immune tolerance, disease prevention, and the role of gender, genetics, infectious agents, and environmental factors in disease susceptibility, onset, and progression.

In the 2lst century there will be unprecedented opportunities to understand autoimmune diseases at the molecular and genetic levels. A major goal of the Autoimmune Diseases Coordinating Committee is to forge a conceptual and mechanism-based understanding that emphasizes features shared among these disorders. This will enable scientists and clinicians to more rapidly translate new knowledge into more effective treatments. The following report highlights the importance of collaborative efforts in achieving these goals.

Ruth Kirschstein, M.D.
Principal Deputy Director
National Institutes of Health

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The National Institutes of Health (NIH) supports a wide range of research projects and programs in autoimmune diseases. Autoimmune diseases result from a disordered attack of the immune system on the body's own tissues, and they disproportionately affect women. These chronic and disabling diseases include insulin dependent diabetes mellitus (type 1 diabetes), multiple sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel disease, psoriasis, uveitis, and autoimmune thyroid disease.

This document, *Report of the NIH Autoimmune Diseases Coordinating Committee*, summarizes recent basic and clinical research programs supported by the NIH and non-Federal organizations, highlighting coordination and collaborative activities in 10 thematic areas, recent and ongoing activities of the Autoimmune Diseases Coordinating Committee, and emerging opportunities to improve treatment and develop preventive approaches for autoimmune diseases. Twenty-two NIH Institutes, Centers, and Offices; the U.S. Food and Drug Administration; the Centers for Disease Control and Prevention; the U.S. Department of Veterans Affairs; and 10 private organizations with an interest in autoimmune diseases are represented on the Committee. The research programs supported by these groups comprise a broad range of basic, pre-clinical, and clinical endeavors addressing many different diseases, organ systems, and aspects of autoimmune disease. This report is organized in four major sections:

1. Introduction, outlining the medical impact of autoimmune diseases, the establishment and activities of the Autoimmune Diseases Coordinating Committee, and collaborative planning and implementation of the FY 1999 Congressional Appropriation for Research in Autoimmunity;
2. NIH programs and activities in autoimmune diseases organized by thematic area;
3. Opportunities, emphasizing emerging areas of science that offer exciting possibilities for improving the lives of patients and others at risk for development of autoimmune diseases; and
4. Conclusions.

I. INTRODUCTION

Impact of Autoimmune Diseases. Autoimmune diseases include more than 70 different disorders affecting approximately 5 percent of the U.S. population. Women are disproportionately affected by most diseases, and minorities are at increased risk for certain diseases; for example, African Americans are at higher risk for development of SLE. The chronic nature of these diseases leads to increased health care costs, including hospitalizations and physician visits.

Establishment of the Autoimmune Diseases Coordinating Committee. Both House and Senate Appropriations Committee reports in 1998 encouraged the establishment of an NIH Autoimmune Diseases Coordinating Committee. The NIH established the committee under the direction of the National Institute of Allergy and Infectious Diseases (NIAID) in June 1998. In addition to NIH Institutes, Centers, and Offices, other Federal agencies with an interest in

autoimmune diseases were invited to participate, along with private organizations that support research in this area. This allows maximum coordination among groups working in areas of complementary and shared interests. The Committee has collected information on current research activities and funding levels, collaborated in developing and implementing scientific initiatives that address the intent of the FY 1999 Congressional Appropriation for Research in Autoimmunity, and recently established working groups to prospectively develop collaborative research programs.

Planning and Implementation of FY 1999 Congressional Appropriation for Research in Autoimmunity. In FY 1999, Congress included $30 million in the appropriation of NIAID for support of autoimmunity research. NIH staff developed seven new trans-NIH initiatives and approved an additional nine planned or ongoing programs to receive additional funding.

II. THE NIH INVESTMENT IN RESEARCH ON AUTOIMMUNE DISEASES

Overview. The majority of NIH support in autoimmune disease research is through unsolicited investigator-initiated research grants awarded by the Institutes, Centers, and Offices. The Autoimmune Diseases Coordinating Committee has enhanced trans-NIH exchange of information in these areas; facilitated coordination of solicited research among NIH Institutes, Centers, and Offices and private organizations; and promoted prospective planning and collaboration in new areas of research.

Major Research Programs by Thematic Areas. The Committee has collected data from its members concerning their support of autoimmunity research. This report summarizes the goals and achievements of funded NIH research programs organized in thematic areas.

- Programs in ***therapeutics*** include the Immune Tolerance Network, which will support clinical trials of promising new tolerance induction agents and development of novel assays or biomarkers of the tolerant state; Clinical Trials of Stem Cell Transplantation for Treatment of Autoimmune Diseases, which will perform safety and efficacy trials of this emerging but expensive approach; Autoimmunity Centers of Excellence, a network of basic and clinical research Centers focused on multiple autoimmune diseases, which will encourage interaction of basic scientists with clinical specialists, e.g., gastroenterologists, neurologists, and endocrinologists; Pilot Trials on Innovative Therapies for Rheumatic and Skin Diseases, which will support six clinical trials in rheumatic and skin diseases; and Human Islet Transplantation into Humans, which will perform clinical studies using new methods to induce immune tolerance to prevent recurrence of the autoimmune destruction of the beta cells in the islet and prevent transplant rejection.

- Research in ***prevention*** includes the nationwide Diabetes Prevention Trial—Type 1 and new Basic Immunology Vaccine Research Center, which will support fundamental research relevant to the design and development of improved vaccines for immunologic and infectious diseases.

- ***Genetics*** research includes the Multiple Autoimmune Diseases Genetics Consortium to collect clinical data and samples from families in which two or more individuals are affected

by two or more autoimmune diseases; the North American Rheumatoid Arthritis Consortium, a collaborative group dedicated to the collection and distribution of DNA and clinical information from families with rheumatoid arthritis; the International Histocompatibility Working Group, which develops, standardizes, and distributes highly sensitive reagents for tissue typing for disease risk assessment and transplantation matching; the National Ankylosing Spondylitis Consortium, a collaborative group dedicated to the collection, distribution, and analysis of DNA and genetic information from families with ankylosing spondylitis; and the Genetics of Juvenile Rheumatoid Arthritis (JRA) Study to collect and analyze clinical and genetic data on children with JRA.

- The role of ***infectious agents and environmental factors*** in the induction of autoimmune diseases was addressed in a recent solicitation of innovative research projects involving environmental toxins, infectious agents, and their interaction with genetic background in autoimmune diseases.

- Research into the ***pathogenesis and immune dysfunction*** in autoimmune diseases represents the largest area of research because studies in basic immunology, self-tolerance, mucosal immunity, and adaptive/innate immunity are the foundation of new approaches to treatment.

- Studies in ***epidemiology and risk factors*** are particularly important because autoimmune diseases disproportionately affect women and certain minority/ethnic groups. DAISY (Diabetes Autoimmunity Study in the Young) is a unique approach to this area in type 1 diabetes. Other natural history studies could facilitate discovery of immune surrogate markers, which are a critical need for clinical trials.

- Studies in ***organ specificity*** explore why the pancreas is targeted in type 1 diabetes, the joint in rheumatoid arthritis, and the central nervous system in multiple sclerosis. The NIH supported innovative approaches to this important question under a recent research solicitation.

- Development of improved ***animal models*** will enhance studies in all areas of autoimmunity research. In particular, models that more accurately reflect human autoimmune diseases are needed. The NIH Rat Autoimmune Model Repository and Development Center will facilitate the development and availability of genetically characterized, disease-free laboratory rats for autoimmune disease research.

- Quality of life is severely compromised for many patients with chronic diseases. Studies supported under ***nursing, behavioral, and health services research*** include new approaches to pain and disability management, training of professionals to help patients live with their disease, and the effect of stress, mood, and pain on the clinical manifestations and progression of disease.

- ***Research resources*** include development of new technologies in both basic and clinical research and establishment of clinical registries, animal repositories, and databases to support research in the nine other thematic areas.

Scientific Symposia, Workshops, and Publications. Support for scientific workshops in emerging areas of research, e.g., infectious etiologies of chronic diseases, discovery of human immune response genes, linking environmental agents and autoimmune diseases, neuropsychiatric manifestations of systemic lupus erythematosus, and accelerated atherosclerosis in systemic lupus erythematosus, is crucial in bringing new investigators and fresh approaches to important areas. A unique meeting called new Immunotherapies for Autoimmune Diseases included lay and scientific sessions. This format encouraged informal exchange and increased understanding between laypersons and scientists.

III. OPPORTUNITIES

In the 21st century, there will be unprecedented opportunities to understand autoimmune diseases at the molecular and genetic levels. A major goal of NIH research in this area is to forge a conceptual and mechanism-based understanding that emphasizes features shared among these disorders and facilitates discovery of new approaches that can be applied to autoimmune diseases affecting different organ systems. This will enable scientists and clinicians to more rapidly translate new knowledge into more effective treatments for a wide range of autoimmune diseases. Specific areas of particular opportunity include the following:

- ***Immune Tolerance—***Several novel biologics are in early clinical testing in patients with autoimmune diseases.

- ***Improved Diagnosis and Patient Management—***New technologies will allow improved diagnosis, staging, and risk assessment.

- ***Genetics—***Emerging information technologies will allow incorporation of new data from the Human Genome Project to increase understanding of the genetic component of autoimmune diseases.

- ***Gender and Autoimmunity—***Why women are affected disproportionately by these diseases is not known; new insights into differences in immune responses of men and women are emerging.

- ***Vaccines for Autoimmune Diseases—***Although no vaccine for any autoimmune disease exists at the present time, feasibility is clear from animal studies. Vaccines for autoimmune diseases will be distinct from vaccines given to prevent infectious diseases; vaccines for autoimmune diseases will turn off a destructive immune response directed at the body's own tissues. Vaccine development is a long and collaborative process involving many Federal agencies in partnership with academia and industry. The Institute of Medicine recently placed a high priority on development of vaccines for autoimmune diseases.

- ***Infectious Agents and Environmental Factors—***Infectious agents and environmental factors are postulated to play a role in the etiology of autoimmune diseases. Recently, several possible mechanisms in animal models have been identified. Further clarification of the role of these agents in the pathogenesis of disease is needed.

IV. CONCLUSIONS

The U.S. investment in biomedical research has yielded major advances in health and quality of life for Americans. However, with each advance comes a new set of challenges. The major challenges facing research in autoimmune diseases today are (1) development of a mechanism-based, conceptual understanding of autoimmune disease; (2) translation of this knowledge into new, broadly applicable strategies for treatment and prevention of multiple diseases; and (3) development of sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals. Through a wealth of collaborative programs outlined in this report, NIH-supported scientists are vigorously pursuing these goals.

I. INTRODUCTION

Scientific advances over the past several decades have revolutionized our understanding of the human immune system and have contributed substantially to improvements in the treatment of many immune-mediated diseases. The NIH has been at the forefront of many of these advances, including the awareness that a number of chronic diseases of previously unknown origin, including autoimmune disorders, arise from dysregulation of immune responses. As we enter the 21st century, these advances provide a solid foundation for translating basic research into clinical applications. Because autoimmune diseases affect multiple organ systems, many NIH Institutes, Centers, and Offices support research in this area. Therefore, NIH has placed a high priority on trans-Institute coordination to ensure the most effective use of research resources.

SCOPE OF THIS REPORT

This report focuses on (1) recent basic and clinical research programs on autoimmune diseases supported by the NIH and non-Federal organizations; (2) NIH activities to coordinate scientific planning and sponsorship of research programs, including collaborative efforts that address recent congressional interest in this area; and (3) future scientific opportunities and plans for trans-NIH initiatives and public-private research partnerships.

THE IMPACT OF AUTOIMMUNE DISEASES

Autoimmune diseases are a group of more than 70 chronic disorders resulting from dysregulation of immune responses, leading the body to attack its own cells and tissues. Organ-specific autoimmune diseases are characterized by immune-mediated injury localized to a single organ or tissue, e.g., the pancreas in type 1 diabetes and the central nervous system in multiple sclerosis (MS). In contrast, non-organ-specific diseases, such as systemic lupus erythematosus (SLE), are characterized by immune reactions against many different organs and tissues, resulting in widespread injury.

Collectively, autoimmune diseases affect at least 5 percent of the U.S. population. Statistics on the medical impact of selected autoimmune diseases include the following:

- **Rheumatoid Arthritis (RA):** 2.1 million cases in the United States, including 30,000 to 50,000 children; 80 percent with limitations in function; afflicts twice as many women as men; on an annual basis, results in 25,000 hospitalizations, 2.1 million lost workdays, and 12 physician visits per patient.

- **Type 1 diabetes:** 300,000 to 500,000 cases in the United States, including 123,000 younger than 20 years of age.

- **Multiple Sclerosis (MS):** 250,000 to 350,000 cases in the United States, resulting in 25,000 hospitalizations per year.

- **Systemic Lupus Erythematosus (SLE):** Approximately 240,000 cases in the United States; disproportionately affects women and minorities.

- **Inflammatory Bowel Disease (IBD):** More than 800,000 cases in the United States; more than two-thirds due to ulcerative colitis and approximately one-third due to Crohn's disease; 2.3 million outpatient visits per year and more than 31,000 restricted-activity days annually.

- **Autoimmune Thyroid Disease (ATD):** The mean incidence of Hashimoto's disease is 3.5 cases per 1,000 women per year (0.8 cases per 1,000 men); the prevalence of Graves' disease in England is 10 times higher in women than men, or 27 per 1,000 women.

ESTABLISHMENT OF THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

In FY 1998, the reports of both the Senate and the House Appropriations Committee addressed the importance of coordination of NIH-supported research activities relating to autoimmune diseases.

> **House Report Language—"***Autoimmunity is at the root of a family of over 80 interrelated major diseases affecting some 50 million Americans. The Committee suggests that the Director convene some type of coordinating body for autoimmune disease research at NIH, comprised of the various Institutes supporting research in this area, for the purpose of synergizing research among the Institutes on autoimmune related disorders. The resulting coordinated and improved use of existing research funds will facilitate and accelerate the application of important findings among the many research programs dealing with autoimmune diseases.*"
>
> **Senate Report Language—"***Autoimmunity is the root of a family of over 80 interrelated diseases that cut across the Institutes at the NIH. The Committee is aware of a recommendation to establish a coordinating council on autoimmune disease research to improve the use of existing research funds and facilitate the application of important findings among the many research programs dealing with autoimmune diseases at the NIH. The Committee requests that the Director give careful consideration to the creation of such a committee."*

The NIH established the Autoimmune Diseases Coordinating Committee (ADCC) in 1998 under the direction of the National Institute of Allergy and Infectious Diseases (NIAID). Committee members include 22 NIH Institutes, Offices, and Centers that support research on autoimmune diseases; the U.S. Food and Drug Administration (FDA); the U.S. Department of Veterans Affairs (VA); the Centers for Disease Control and Prevention (CDC); and private organizations that sponsor research in this area (Appendixes A and B). Since its initial meeting in June 1998, the Committee has (1) collected and analyzed information on current research activities and funding levels and (2) established multi-Institute collaborative working groups in areas of common interest and relevance to multiple autoimmune diseases. In addition, the Committee's efforts have facilitated a variety of other activities to further enhance coordination of research and increase partnerships between public and private organizations. Examples include the following:

- Extensive collaboration among many NIH Institutes, Centers, and Offices in planning and cosponsoring new research initiatives resulting from the additional FY 1999 congressional appropriation for autoimmunity research (as detailed below).

- Facilitation of new and continuation of established public-private research partnerships, e.g., linking the NIH with the Juvenile Diabetes Foundation International (JDFI), the Arthritis Foundation, the National Multiple Sclerosis Society, and the Crohn's and Colitis Foundation of America (CCFA).

- Cosponsorship of workshops and scientific symposia, e.g., linking the NIH and JDFl, Arthritis Foundation, American College of Rheumatology, and American Autoimmune Related Diseases Association (AARDA).

- Participation of NIH staff in scientific planning activities of non-Federal organizations, e.g., the National Multiple Sclerosis Society, Alliance for Lupus Research, and JDFI.

II. THE NIH INVESTMENT IN RESEARCH ON AUTOIMMUNE DISEASES

OVERVIEW

Major mechanisms of NIH support include individual research project grants, program project grants, contracts, and cooperative agreements. Investigator-initiated, unsolicited research projects make up the largest share of the NIH investment in this area. The Autoimmune Diseases Coordinating Committee serves as an important forum for trans-Institute exchange of information pertaining to the unsolicited research portfolios of individual Institutes, Centers, and Offices. The activities of the Autoimmune Diseases Coordinating Committee also include inter-Institute collaboration and coordination in the development, review, award, and postaward monitoring of solicited research programs. To enhance trans-NIH scientific planning, the Autoimmune Diseases Coordinating Committee has categorized autoimmune disease-related research activities in 10 thematic areas highlighted below.

In FY 1999, NIH Institutes committed more than $393 million in support of basic, preclinical, and clinical research on autoimmune diseases (Figure 1).

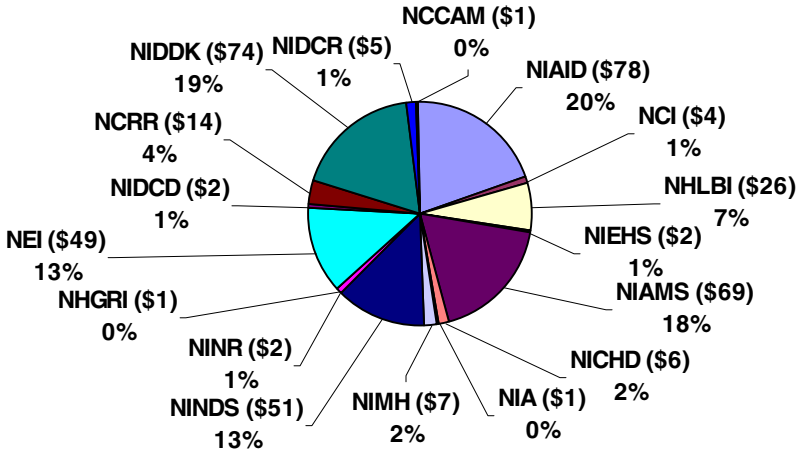

Figure 1. Total NIH Funding for Autoimmune Diseases in FY 1999 by Institute ($ in Millions)

PLANNING AND IMPLEMENTATION OF FY 1999 CONGRESSIONAL APPROPRIATION FOR RESEARCH IN AUTOIMMUNITY

The Conference Report accompanying H.R. 4329, the Omnibus Consolidated and Emergency Supplemental Appropriation for FY 1999, contained the following language:

> *"The conference agreement includes $1,570,102,000 for the NIAID instead of $1,540,102,000 as proposed by the Senate and $1,470,460,000 as proposed by the House.*
>
> *Autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, diabetes, and lupus affect millions of Americans and disproportionately affect women and minorities. It is believed that enhanced research in this area holds the potential to cure and prevent many diseases. In addition, more needs to be known about the specific environmental agents that are causing the onset of the diseases, genetic susceptibility, and how the body regulates the autoimmune response. Therefore, NIAID is strongly urged to expand its research efforts to capitalize on recent discoveries of autoimmune reactions and newly developed treatments that can suppress immune responses without toxic side effects. It is understood that the NIH Autoimmune Diseases Coordinating Committee should provide greater coordination and renewed focus for autoimmunity research on the NIH campus."*

The prior establishment of the trans-NIH Autoimmune Diseases Coordinating Committee facilitated a coordinated scientific planning process to design and implement new research programs in response to congressional intent. The guiding principles of this planning process included an emphasis on (1) cross-disciplinary research addressing multiple autoimmune diseases; (2) support for a mechanism-based approach, encompassing fundamental investigations of disease pathogenesis and clinical trials involving new diagnostic and therapeutic approaches; and (3) selected research programs focusing on specific diseases and/or extraordinary scientific opportunities.

Seven new trans-NIH initiatives emerged from this process, and nine previously planned or ongoing initiatives received increased support (Appendix C). The majority of the new and previously planned initiatives involved joint sponsorship by multiple NIH components. Figure 2 shows the distribution of dollars among the NIH Institutes and Centers and major project areas.

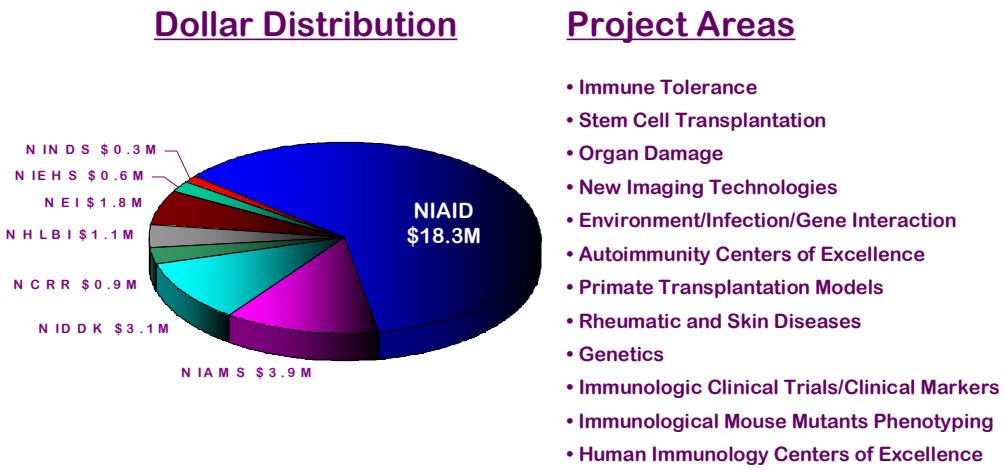

Figure 2. Distribution of FY 1999 Autoimmunity Funds: NIH Institutes and Centers and Major Project Areas

MAJOR RESEARCH PROGRAMS BY THEMATIC AREAS

The development of autoimmune diseases reflects complex interactions between the immune system, genetic background, and environmental factors. Therefore, NIH-supported research is broad in scope, ranging from understanding the determinants of disease to developing effective therapies and strategies for preventing disease. The members of the NIH Autoimmune Diseases Coordinating Committee code the research that they support according to thematic areas. The latest figures available are for FY 1998 (Figure 3). Within this framework, NIH Institutes, Centers, and Offices and non-Federal partners coordinate efforts through research partnerships, sponsorship of workshops, and establishment of databases and other research resources accessible to the research community (Appendix D).

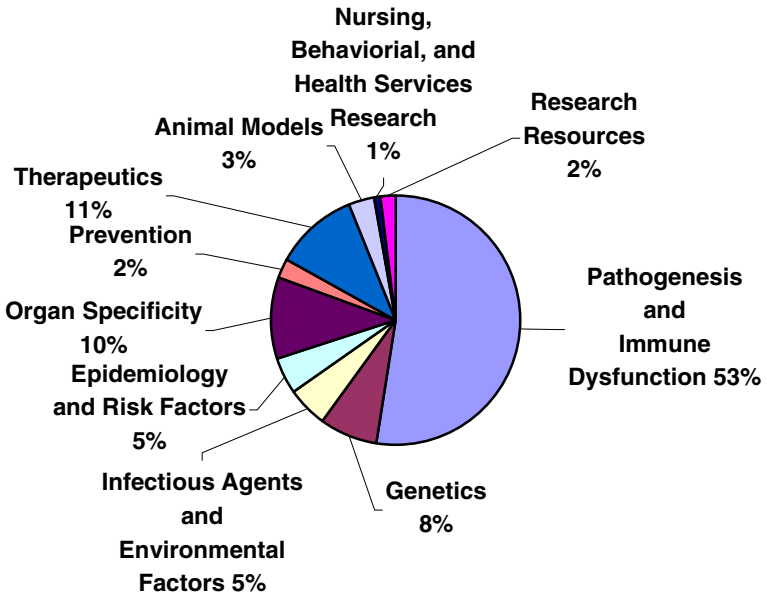

Figure 3. FY 1998 NIH Autoimmune Diseases Funding by Thematic Area

THERAPEUTICS—The NIH investment in basic research has yielded the knowledge necessary to develop new therapeutic strategies for the treatment of immune-mediated diseases. These preclinical research advances have provided an impetus for established pharmaceutical and emerging biotechnology companies to develop novel agents that may more selectively inhibit the deleterious immune responses in autoimmune diseases. The NIH is capitalizing on these advances through increased sponsorship of clinical trials, often in partnership with industry. Major ongoing and new clinical research programs include the following:

- **Immune Tolerance Network.** The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases. Tolerogenic approaches seek to modulate or block deleterious immune responses critical in the development and progression of disease and in the rejection of transplanted organs, tissues, and cells. In 1998, NIAID published a long-term research plan to accelerate the study of immune tolerance, particularly in the clinical setting (http://www.niaid.nih.gov/publications/immune/contents.htm). A major new clinical research program emanating from this research plan was established in September 1999, under the joint sponsorship of NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the JDFI. This unique consortium of more than 40 institutions in the United States, Canada, Western Europe, and Australia is dedicated to the clinical evaluation of promising tolerance induction therapies in four areas: kidney transplantation, islet transplantation for type 1 diabetes, autoimmune disorders, and asthma and allergic diseases (http://www.immunetolerance.org). The network will also develop assays and biomarkers to measure the induction, maintenance, and loss of immune tolerance in humans. Various clinical studies are in development for many autoimmune diseases, including MS, RA, type 1 diabetes, and SLE.

- **Stem Cell Transplantation for the Treatment of Autoimmune Diseases.** Stem cell transplantation is currently under evaluation for treatment of multiple autoimmune diseases. Several studies of safety have been completed; however, case-controlled studies of efficacy have not yet been conducted. In FY 1999, NIH initiated a coordinated research effort to study the safety and effectiveness of these treatment regimens for several autoimmune disorders.

- **Pilot Clinical Trials on Innovative Therapies for Rheumatic and Skin Diseases.** This research initiative was implemented in FY 1999, under the leadership of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), with several NIH Institutes, to develop innovative therapies for the treatment of rheumatic and skin diseases. Awards were made for research on the following diseases: Wegener's granulomatosis, RA, scleroderma, SLE, and ankylosing spondylitis (AS).

- **Autoimmunity Centers of Excellence.** Four research centers were established in FY 1999 to support collaborative basic and clinical research on autoimmune diseases, including single-site or multisite clinical trials of immunomodulatory therapies. The Centers bring together many different subspecialists (e.g., neurologists, gastroenterologists, and rheumatologists), as well as basic scientists, increasing clinical and research collaborations in autoimmunity.

- **Clinical Trials and Clinical Markers in Immunologic Diseases.** In FY 2000, NIAID with several NIH components will begin a new research program focused on orphan clinical trials of immunomodulatory treatments for immune-mediated diseases, including autoimmune disorders, and the development of biological markers to measure disease activity, risk, and therapeutic effect.

- **Hyperaccelerated Awards for Mechanistic Studies of Immune Disease Trials.** This existing research program supports mechanistic studies in conjunction with clinical trials of immunomodulatory interventions for immune-mediated diseases. Multiple NIH Institutes, Centers, and Offices are cosponsoring this program, which incorporates expedited procedures for review and award of meritorious grant applications within 13 weeks of submission.

- **Cyclophosphamide in Scleroderma Pulmonary Disease.** In FY 1999, the National Heart, Lung, and Blood Institute (NHLBI) began an investigator-initiated clinical trial of cyclophosphamide in the treatment of the pulmonary fibrosis associated with systemic sclerosis. In systemic sclerosis, interstitial pulmonary fibrosis is frequent (80 percent) and is now the leading cause of death. The mortality rate of patients with impaired pulmonary function is 40 to 45 percent within 10 years of onset. Uncontrolled studies suggest that cyclophosphamide may stabilize or improve lung function in systemic sclerosis patients. The study is a 5-year, 13-center, parallel-group, double-blind, randomized, controlled, phase III clinical trial of oral cyclophosphamide versus placebo to assess the efficacy of cyclophosphamide in stabilizing or improving the course of pulmonary disease in scleroderma. NIAMS also contributes to the support of this study.

- **Human Islet Transplantation Into Humans.** This program will support clinical studies using new methods to induce immune tolerance to prevent recurrence of the autoimmune destruction of beta cells in the islet and to prevent transplant rejection. The NIDDK, NIAID, and JDFI support this program.

- **New Strategies for the Treatment of Type 1 Diabetes.** In FY 2000, the NIDDK, NIAID, and National Institute of Child Health and Development (NICHD) will begin a new program supporting clinical studies to test new approaches to treat type 1 diabetes, including studies of immunomodulation.

PREVENTION—Knowledge of the genetic and environmental determinants of disease, coupled with a better understanding of human immunology, will provide the basis for the development of preventive approaches. Prevention or delay of disease onset for certain autoimmune diseases has been demonstrated in animal models.

- **Diabetes Prevention Trial—Type 1.** Under the sponsorship of the NIDDK, NIAID, NICHD, CDC, JDFI, and the American Diabetes Association (ADA), this national multisite cooperative clinical trial is evaluating the use of parenteral and oral insulin for prevention of type 1 diabetes in high-risk and intermediate-risk relatives of patients with type 1 diabetes. The first results from this study are expected in FY 2002.

- **Basic Immunology Vaccine Research Centers.** In FY 2000, NIAID will establish a new research program to support fundamental research relevant to the design and development of

improved vaccines for immunologic and infectious diseases. This effort will enable the application of basic immunologic principles to the rational design of prevention strategies.

GENETICS—Certain autoimmune diseases have been linked to a particular set of genes called the major histocompatibility complex (MHC), known to be important in controlling immune responses. Recent findings suggest that other families of genes that regulate immune responses may be involved in the pathogenesis of autoimmune diseases.

- **North American Rheumatoid Arthritis Consortium.** In FY 1997, the North American Rheumatoid Arthritis Consortium was established as part of a collaborative effort among NIAID, NIAMS, and the Arthritis Foundation (AF). Through this consortium, a registry and repository of clinical and genetic data has been developed as a research resource for the discovery of RA susceptibility genes.

- **Multiple Autoimmune Diseases Genetics Consortium.** Under this FY 1999 research initiative, a repository of genetic and clinical data and samples is being developed from families in which two or more individuals are affected by two or more autoimmune diseases. This resource will promote research to advance the discovery of human immune response genes involved in autoimmunity.

- **Functional Genomics of the Developing Pancreas.** This NIDDK research initiative will support the production, sequencing, and distribution of cDNA libraries for discovery and functional studies of genes regulating development of the normal and diabetic pancreas.

- **International Histocompatibility Working Group (IHWG).** The National Cancer Institute (NCI), NHLBI, NIDDK, and NIAID support the IHWG to develop, standardize, and distribute highly sensitive reagents for tissue typing worldwide. These efforts enhance identification of healthy individuals at risk for development of autoimmune disorders and ensure that transplant recipients will receive optimally matched donor organs and tissues.

- **North American Spondylitis Consortium.** NIAMS established this consortium in FY 1999 to identify susceptibility genes for AS, a rare but painful disease of the spine primarily affecting men. Ten research centers and the Spondylitis Association of America are participating in this activity.

- **Juvenile Rheumatoid Arthritis Study.** NIAMS expanded this registry in FY 1999 to collect DNA and to identify susceptibility genes for juvenile rheumatoid arthritis.

- **Lupus Registries and Repository.** NIAMS established a registry and repository to collect clinical data and samples from patients with SLE and their families. This resource should assist investigators in identifying genes that determine susceptibility to lupus. A separate Registry for Neonatal Lupus will enhance the search for basic defects in neonatal lupus and may lead to improved diagnosis, treatment, and prevention methods. This registry is also supported by NIAMS.

- **Vitiligo Genetic Linkage Project.** Vitiligo is an autoimmune disease resulting in patchy depigmentation of the skin, which is particularly disfiguring in dark-skinned individuals. The

aggregation of the disease in families is being utilized by Dr. Richard Spritz at the University of Colorado to map the vitiligo gene(s) in a U.S. and a United Kingdom cohort of vitiligo families. This project is supported by NIAMS.

INFECTIOUS AGENTS AND ENVIRONMENTAL FACTORS—A growing body of research concerns the role of infectious agents in triggering certain chronic diseases, including autoimmune disorders. Recently, several mechanisms have been proposed for this association and have proven to be operative in animal models.

- **Environmental/Infectious/Genetic Interactions in Autoimmune Disease.** In FY 1999, under the leadership of the National Institute of Environmental Health Sciences (NIEHS) with multiple collaborating NIH Institutes, Centers, and Offices, a research program was established to support innovative studies to elucidate the role of environmental and infectious agents in autoimmune diseases and to clarify their interaction with genes in modulating immune responses. Enhanced knowledge in this area will contribute to the discovery of new therapeutic and preventive strategies.

- **Carolina Lupus Study.** The NIEHS Division of Intramural Research supports the Carolina Lupus Study to identify the role of infectious agents and environmental exposures in the development of lupus, with a particular focus on African American women, who are disproportionately affected by this disease.

PATHOGENESIS AND IMMUNE DYSFUNCTION—Research in this area focuses on understanding the disease process, particularly the defects in the immune response that cause the body to attack its own tissues and cells.

- **Diabetes Centers of Excellence.** This continuation of a longstanding basic research program is supported jointly by the NIDDK, NIAID, and JDFI and focuses on increasing understanding of the fundamental disease processes and mechanisms involved in diabetes. A majority of the projects supported under this program address type 1 diabetes.

- **NIAID-JDFI Interdisciplinary Programs in Autoimmunity.** Five multidisciplinary projects are supported under this program to investigate the molecular, immunologic, and genetic mechanisms in the pathogenesis of autoimmunity.

- **Human Immunology Centers of Excellence.** In FY 1999, NIAID established four new research centers focused on multidisciplinary approaches to define the mechanisms responsible for normal and pathologic human immune responses.

- **Innovative Research on Human Mucosal Immunity.** The CCFA joined NIAID and the National Institute of Dental and Craniofacial Research (NIDCR) in sponsoring this FY 2000 research initiative to promote innovative investigations of the human mucosal immune system and its role in the pathogenesis of autoimmune diseases, including IBD.

- **Innovative Research on Immune Tolerance.** NIAID and NIDDK will cosponsor this initiative to support innovative research on mechanisms underlying long-term immune

tolerance and to identify novel targets for future drug development. These projects will begin in FY 2001.

- **Diabetes and Endrocrinology Research Centers and Diabetes Research Training Centers.** A portion of these Centers supports basic and clinical research on type 1 diabetes and other autoimmune diseases.

- **Veterans Administration (VA) Medical Centers.** Basic and clinical research on autoimmune diseases is supported by the VA Medical Research Service through merit review grants. A distinctive feature of VA-sponsored research is the high proportion of medical doctorate investigators supported at VA Medical Centers across the United States.

EPIDEMIOLOGY AND RISK FACTORS—The incidence and prevalence of some autoimmune diseases appear to be increased in certain ethnic groups; for example, SLE, RA, and MS are increased in African American, certain Native American, and Caucasian populations, respectively. For many autoimmune diseases, relatively little is known about natural history preceding the onset of overt disease or about the genetic, behavioral, and environmental factors that contribute to disease progression. An expanded knowledge base in these areas would facilitate the design, implementation, and evaluation of prevention efforts.

- **DAISY (Diabetes Autoimmunity Study in the Young).** This long-term study, supported by NIDDK and NIAID, includes collection and followup of two cohorts: (1) healthy siblings and offspring of people with type 1 diabetes and (2) healthy newborns with type 1 diabetes-associated MHC genes but without a family history of diabetes. The study is collecting and analyzing data on infections, vaccination, diet, MHC genes, and autoantibodies to beta cell antigens in these cohorts.

ORGAN SPECIFICITY—Research in this area seeks to explain why the immune attack is limited to a specific organ in some autoimmune diseases (e.g., the central nervous system in MS), whereas in others, the tissue injury is widespread (e.g., SLE). Recent findings suggest that the target organ may play a more active role than previously thought in molding the tissue-specific immune responses.

- **Target Organ Damage in Autoimmune Diseases.** Under the leadership of NIAMS, multiple NIH components, including NIAID, NIDCR, NIDDK, NHLBI, National Eye Institute (NEI), National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Deafness and Communication Disorders (NIDCD), National Institute of Mental Health (NIMH), and Office of Research on Women's Health (ORWH), developed a FY 1999 research initiative to stimulate innovative and multidisciplinary studies of the involvement of target organs in autoimmune diseases. Knowledge gained in this area will make it possible to construct a more comprehensive picture of disease pathogenesis and will provide a scientific basis for new therapeutic interventions.

ANIMAL MODELS—The development of improved animal models will enhance studies in all of the above areas. In particular, models that more faithfully mimic human disease are essential in the preclinical evaluation of new therapeutic approaches and the application of such approaches in the clinical setting.

- **Nonhuman Primate Transplant Tolerance Cooperative Study Group.** In FY 1998 and FY 1999, NIAID and NIDDK established this cooperative research program to evaluate the safety and efficacy of promising tolerance induction treatment regimens in nonhuman primate models of kidney and islet transplantation. The knowledge gained from this research effort will be critical to moving tolerance induction strategies into clinical trials.

- **Immunological Phenotyping of Mouse Mutants.** In FY 1999, the National Center for Research Resources (NCRR) joined NIAID, NEI, NIEHS, NHLBI, NIDDK, and ORWH to cosponsor the development of new technologies for rapid immunologic screening of normal and mutagenized mice. These efforts will enable the detection and characterization of abnormal immune responses, with an emphasis on immune dysfunction associated with autoimmune diseases.

- **NIH Autoimmune Rat Model Repository and Development Center.** This collaborative effort of multiple NIH Institutes organized by NIAMS and the NIH Office of Research Services' Veterinary Resources Program will develop and make available to researchers genetically characterized and disease-free laboratory rats for autoimmune disease research.

NURSING, BEHAVIORAL, AND HEALTH SERVICES RESEARCH—Quality of life can be severely compromised for those suffering from autoimmune diseases. The NIH supports a variety of unsolicited research, intervention, and education programs aimed at improving disease management and quality of life for patients with chronic illness, their families, and their caregivers. To promote the recruitment and development of health care professionals who treat patients with chronic illnesses, the NIH supports training programs and scientific and professional meetings in this area.

- **General Clinical Research Centers.** The GCRCs, a NCRR-supported resource for clinical research, study the effect of stress, mood, and pain on disease pathology and develop new strategies to monitor disease activity and novel approaches for management of disease. Programs include Intensive Therapy for Youth with IDDM (insulin dependent diabetes mellitus) at Washington University, St. Louis, MO; Biobehavioral Model of Stress and Multiple Sclerosis at the University of Pittsburgh, PA; and Psychosocial Aspects of Scleroderma at the University of California, San Diego.

- **Adolescent Diabetes Control and Quality of Life Improved by Combining Intensive Diabetes Therapy With Coping Skills Training.** Interventions to improve metabolic control and quality of life in children with diabetes are of critical importance to reduce or prevent the onset of a number of long-term complications, e.g., blindness, heart disease, stroke, kidney failure, amputations, and nerve damage. National Institute of Nursing Research (NINR)-funded research is determining whether a coping skills training program, in conjunction with intensive therapy, will enhance quality of life, increase metabolic control (which is extremely difficult to control in diabetic children), and reduce adverse diabetes events in adolescents. An NIH clinical trial has shown that intensive diabetes therapy can reduce the number and severity of diabetes complications in adolescents and young adults.

RESEARCH RESOURCES—Research resources include support for the training of basic and clinical researchers and a broad range of equipment and infrastructure needs.

- **JDFI Islet Production Network.** The JDFI supports seven institutions in the United States and Western Europe to produce islet cells for research. As part of the Foundation's cosponsorship of the Immune Tolerance Network, islets for clinical trials in transplantation for type 1 diabetes are being provided to qualified Network investigators.

- **NIAID Repository of Transgenic and Gene-Targeted Mutant Mice.** NIAID supports a repository of genetically manipulated mice and provides for the importation, verification, cryopreservation, breeding, and distribution of novel strains of transgenic or gene knockout mice for use by the extramural research community. This resource includes mouse models relevant for preclinical studies of autoimmunity.

- **NIAID MHC Tetramer Core Facility.** In FY 1998, NIAID established a national facility to provide researchers with peptide-MHC tetrameric molecules for analyzing antigen-specific T cell responses. This methodology replaces and greatly improves upon cumbersome, insensitive, and time-consuming assays. Furthermore, by centralizing the production of these tetramers, reagents can be produced economically and can be made available to investigators at greatly reduced costs. Because T cells are central to virtually all adaptive immune responses, this technology is applicable to studies in many areas, including autoimmune disorders.

- **New Imaging Technologies for Autoimmune Diseases.** Under the leadership of NIAID, with cosponsorship of multiple NIH Institutes, a FY 1999 research initiative was started to develop new methods of in vivo imaging of the immune system in small animal models of human autoimmune diseases. The development of high-resolution imaging technologies will provide new, powerful, noninvasive methods to visualize ongoing normal and deleterious immune responses. Further adaptation of high-resolution imaging for use in humans holds promise for noninvasive detection, diagnosis, and monitoring of immunologic diseases and a new approach for evaluating the efficacy of therapies and vaccines.

- **Imaging Pancreatic Beta Cell Mass, Function, or Inflammation.** The NIDDK is sponsoring an initiative in FY 2000 to stimulate the development of techniques or reagents leading to the ability to image or otherwise noninvasively detect pancreatic beta cells in vivo and measure their function, mass, or evidence of inflammation.

- **Transplant Registries.** NIAID, NCI, and NHLBI support the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (AMBTR). The IBMTR/ABMTR have collected data on blood cell and bone marrow transplantation for more than 20 years from more than 290 institutions worldwide. Studies address questions regarding short- and long-term outcomes in defined patient groups, relevant prognostic factors, the efficacy of different transplant approaches, and the economic impact of bone marrow transplantation. Both registries serve as a national resource for patients and patient advocacy groups, physicians, researchers, and the NIH. These registries have been collecting data on stem cell transplants performed for autoimmune diseases since early 1998.

- **Pancreas Transplant Registry.** Supported by the NIDDK, this registry at the University of Minnesota has collected data on nearly 10,000 pancreas transplants from more than 200 institutions. Based on analysis of data from the registry, the Health Care Financing Administration and some third-party payors now cover the costs of pancreas transplants for individuals who are also undergoing kidney transplant as a result of diabetes.

- **Specialized Centers of Research (SCOR).** Currently, NIAMS SCORs are targeted for RA, SLE, and scleroderma, among other diseases. A SCOR brings together basic and clinical researchers to provide mutually supportive research interactions to (1) advance basic research on disease causation and (2) expedite transfer of these advances into clinical applications and improved patient care. Present studies at the SCORs include a focus on the genetics of SLE and scleroderma.

SCIENTIFIC SYMPOSIA, WORKSHOPS, AND PUBLICATIONS

NIH Institutes, Centers, and Offices cosponsor a variety of scientific, programmatic, educational, and informational activities, often in collaboration with non-Federal partners. Recent (FY 1999 and FY 2000) examples include:

- **Infectious Etiologies of Chronic Diseases.** This workshop focused on causative roles for infectious agents in chronic disease, e.g., herpes and human papilloma viruses in Kaposi's sarcoma and cervical cancer, respectively. Workshop participants evaluated preliminary data implicating additional agents in chronic disease, including autoimmune diseases, and identified key components and resource needs of a targeted research effort for future discovery of such agents. (NCI, NIAID)

- **Discovery of Human Immune Response Genes.** This workshop focused on resource needs (e.g., patient and normal control cohorts, registries, DNA repositories, cDNA, sequencing and bioinformatics capabilities) to identify, characterize, and determine the functions of novel genes involved in autoimmune disorders. [NIAID, NIH Office of Rare Diseases (ORD)]

- **Linking Environmental Agents and Autoimmune Diseases.** This workshop defined the state of the art, future directions, and research needs to understand the mechanistic links between environmental agents and development or exacerbation of autoimmune diseases. [NIEHS, NIAMS, NIAID, NIDDK, ORD, ORWH, Environmental Protection Agency, JDFI, American Autoimmune Related Diseases Association (AARDA)]

- **Basic Research Conference of the American College of Rheumatology.** For the second year, this meeting has been cosponsored by NIAMS and NIAID. The focus of the 1999 conference, which had a record attendance of approximately 600 participants, was the basic biology of B cells and their role in autoimmune diseases.

- **New Immunotherapies for Autoimmune Diseases.** This unique, dual-track symposium highlighted research advances and opportunities in autoimmune diseases for a combined audience of lay and scientific participants. [NIAID, NIEHS, NIAMS, NIDDK, NINDS,

ORWH, ORD, AARDA, JDFI, Arthritis Foundation (AF), Crohn's & Colitis Foundation of America (CCFA), Myositis Foundation, Sjogren's Syndrome Foundation, National Pemphigus Foundation]

- **Institute of Medicine (IOM) Study on Safety of Silicone Breast Implants.** In 1997, Congress expressed concerns about fragmentation of research on the safety and health effects of silicone and instructed the Department of Health and Human Services (DHHS) to commission an IOM expert review of research on the association of silicone implants with "autoimmune-like" syndromes (http://www.nap.edu/books/0309065321/html/). (NIAMS, NCI, NIAID, ORWH, FDA Office of Women's Health, CDC, DHHS Office of Public Health and Science, DHHS Office of the Assistant Secretary for Science Policy and Evaluation)

- **Second Annual Arthritis Research Conference.** This conference brings together the NIH and privately supported trainees and their mentors to highlight ongoing research in rheumatologic diseases. (NIAMS, NIAID, AF, American College of Rheumatology)

- **Workshop on Accelerated Atherosclerosis in Systemic Lupus Erythematosus.** The goals of the conference were to (1) identify and establish potential interventions aimed at reducing mortality and morbidity from accelerated atherosclerosis in SLE and (2) identify research opportunities to establish the pathogenesis of accelerated atherosclerosis in SLE. (NIAMS, NHLBI)

- **Neuropsychiatric Manifestations of Systemic Lupus Erythematosus.** The goals of the meeting were to (1) address current conceptual and evaluative tools in rheumatology, neurology, psychiatry, and psychology and their applications to the problem of nervous system involvement in SLE and (2) identify research opportunities using the approaches and tools described for the purpose of facilitating diagnosis and treatment of patients with neuropsychiatric manifestations of SLE. (NIAMS)

- **Gene Therapy Approaches for Diabetes and Its Complications.** This workshop assessed the current understanding of the pathogenesis of diabetes and its complications and identified strategies that use gene therapy to intervene in the induction and progression of diabetes. Investigators described their results using gene therapy approaches to treat diabetes in both animal models and patients. (NIDDK, NCRR, NIAID, NHLBI, JDFI, ADA)

- **Stem Cells and Pancreatic Development.** The objective of this workshop is to bring together investigators from multiple disciplines doing state-of-the-art research in stem cell biology and developmental biology of the pancreas to develop methods for stimulating growth or regeneration of beta cells. (NIDDK, ADA, JDFI)

III. OPPORTUNITIES

In the 21st century, there will be unprecedented opportunities to understand autoimmune diseases at the molecular and genetic levels. A major goal of NIH research in this area is to forge a conceptual and mechanism-based understanding that emphasizes features shared among these disorders. This will enable scientists and clinicians to more rapidly translate new knowledge into more effective treatments for a wide range of autoimmune diseases. Many of

these opportunities are outlined in detail in the strategic plans of the individual NIH Institutes located on the World Wide Web (http://www.nih.gov). Individually, these plans pave the way for significant scientific and clinical advances in selected areas, many of which are outlined below. Taken together, the continued success of these efforts will require leadership at the Federal level and a high degree of coordination at the NIH.

To begin to address these needs, in November 1999, members of the Autoimmune Diseases Coordinating Committee established nine workgroups to foster scientific collaborations and to develop research initiatives in the following areas: (1) vaccines for autoimmune diseases, (2) functional genomics of autoimmunity, (3) gender and autoimmunity, (4) autoimmunity across the lifespan, (5) environment's role in autoimmunity, (6) neuropsychiatric manifestations of SLE, (7) clinical registries for autoimmune diseases, (8) basic and clinical research in scleroderma, and 9) ankylosing spondyloarthropathies. Opportunities in several of these and other highly promising areas are outlined in the sections that follow.

IMMUNE TOLERANCE

Tolerance induction is a major therapeutic goal for the three major disease-related areas of modern immunology: autoimmunity, transplantation, and allergy/asthma. Furthermore, understanding the basic processes that control immune recognition will facilitate new approaches to augment protective immunity, including the design of improved vaccines. Thus, findings generated from this research will be highly relevant to many NIH components. In autoimmunity, efforts to induce tolerance have focused largely on oral administration of antigen. To date, it has not been possible to duplicate in humans several very encouraging studies of oral tolerance in animal models. Through the research programs described above, and in collaboration with industry, NIH-supported scientists are now poised to explore a variety of other promising approaches, including (1) costimulatory blockade, (2) T cell depleting recombinant immunotoxins, (3) small peptide inhibitors of T cell activation, (4) stem cell transplantation, and (5) gene transfer-based approaches for cytokine modulation. The development of improved animal models, including nonhuman primate models of autoimmune diseases, will be key to the success of these efforts.

IMPROVED DIAGNOSIS AND PATIENT MANAGEMENT

Autoimmune diseases present many complex challenges to the clinician. Prominent among these are the difficulties in establishing a diagnosis early in the course of disease and the lack of surrogate markers to monitor therapy and predict clinical outcomes. Thus, new tools are needed to ensure that the most promising experimental approaches will lead to better clinical outcomes. Examples include technologies for (1) whole body imaging and imaging immune activation at the cellular level in vivo; (2) tracking numbers and functional activation of antigen-specific immune cells; (3) staging disease, measuring responses to therapy, and predicting clinical outcomes; and (4) profiling disease susceptibility through low-cost, high-throughput, sensitive, and specific screening measures suitable for large-scale prevention trials. The NIH is providing the research infrastructures to support these endeavors through repositories, reagent facilities, and a wealth of recently initiated cooperative clinical programs. Examples of the latter include the Autoimmunity Centers of Excellence, the Immune Tolerance Network, Pilot Trials on Innovative Therapies for Rheumatic and Skin Diseases, Clinical Trials and Clinical Markers in

Immunologic Diseases, the Immunohistocompatibility Working Group, the Diabetes Prevention Trial—Type 1; and the proposed Diabetes TrialNet.

GENETICS

As the sequencing of the human genome approaches completion, it will be possible to define autoimmune diseases by focusing on individual genes and the proteins they encode. For example, it will be possible to rapidly, systematically, and at low cost determine the functional state of activation of immune cells and target tissues through a variety of DNA-based technologies, such as DNA microarrays. Similarly, advances in these technologies will enable rapid, low-cost profiling to measure the risks of developing disease in healthy individuals. A major challenge for the NIH will be to establish the bioinformatics capacity to link a variety of disease- and organ-specific databases for hypothesis generation and clinical profiling in a cross-disciplinary manner. A number of NIH Institutes are currently collaborating in this area. In particular, the Genetics Working Group of the Autoimmune Diseases Coordinating Committee is exploring options for a common autoimmune disease genetics database to facilitate data mining and identification of overlapping genetic regions controlling autoimmunity. The NIH currently supports the collection of clinical data and samples from families with various autoimmune diseases for use in research studies. Examples include the Multiple Autoimmune Disease Genetics Consortium, North American Rheumatoid Arthritis Consortium, Lupus Registry and Repository, and Juvenile Rheumatoid Arthritis Study.

GENDER AND AUTOIMMUNITY

Autoimmune diseases disproportionately affect women. For certain autoimmune diseases, incidence rates in females are 2 to 9 times higher than in matched male populations. Many of these diseases increase in frequency after puberty or flare during pregnancy, suggesting a role for sex hormones in their pathogenesis. Recent findings of increased numbers of long-lived cells of fetal origin in patients with certain autoimmune diseases, however, suggest the increased female incidence may be related to factors other than hormones. Thus, both hormonal and nonhormonal factors may contribute to gender-based differences in immune responses.

NIAID sponsored a meeting on gender and autoimmunity and recently participated in a task force on sexual dimorphism in autoimmune disease organized by the National Multiple Sclerosis Society, the latter of which resulted in a major review article titled “A Gender Gap in Autoimmunity,” published in *Science* in 1999. The ORWH report titled “Agenda for Research on Women’s Health for the 21st Century: A Report of the Task Force on NIH Women’s Health Research Agenda for the 21st Century” highlighted the importance of determining the differences in the immune responses of men and women. Each of the groups recommended increased support for basic and clinical research on sex-based differences in the immune response. Recently, NIAID and the National Multiple Sclerosis Society have begun discussion of approaches to collaboratively target this important gap in our knowledge, to provide wider visibility of the problem and the opportunities, and to allow increased support for high-quality and relevant gender-based research. Other NIH Institutes, Centers, and Offices have expressed interest in this effort by joining the Autoimmune Diseases Coordinating Committee workgroup on gender and autoimmunity.

VACCINES FOR AUTOIMMUNE DISEASES

The 1999 IOM report titled "Vaccines for the 21st Century" identified vaccines for autoimmune diseases as level-one priorities based on potential medical, social, and economic benefits to society. Vaccines for autoimmune diseases will be distinct from vaccines given to generate immunity to infectious agents. Instead, vaccines for autoimmunity will turn off a destructive immune response directed at the body's own tissues. Although there are currently no vaccines against any autoimmune disease, successes in animal models and increased understanding of autoimmunity indicate the feasibility of developing preventive vaccines for these diseases. Distinct vaccines for each disease will likely be required. Whether general population vaccination or targeted vaccines based on genetic risk will be necessary, however, is not clear. NIAID, with its long history of vaccine development for infectious diseases, is aware of the extensive collaboration of academia, government, industry, and the public required for success. Through the Autoimmune Diseases Coordinating Committee, several Institutes and organizations are beginning to work toward this goal.

INFECTIOUS AGENTS AND ENVIRONMENTAL FACTORS

Because identical twins are not concordant for development of autoimmune disease, an environmental or infectious factor, in addition to genetic background, may be necessary. Multiple infectious agents have been suggested, but a definitive mechanism or association has been elusive. Recently, animal studies have elucidated several possible mechanisms, and human studies have focused on several particular agents. It is not likely that a single agent will be involved in each disease, but these new leads might elucidate the role of foreign organisms or compounds in the triggering of these diseases. This knowledge should lead to new approaches to treatment and prevention.

IV. CONCLUSIONS

The U.S. investment in biomedical research has yielded major advances in health and quality of life for Americans. However, each advance brings a new set of challenges. The major challenges facing research in autoimmune diseases today are (1) development of a mechanism-based, conceptual understanding of autoimmune disease; (2) translation of this knowledge into new, broadly applicable strategies for treatment and prevention of multiple diseases; and (3) development of sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals. Through a wealth of individual, coordinated, and collaborative programs outlined in this report, NIH-supported scientists are vigorously pursuing these goals.

Appendix A

AUTOIMMUNE DISEASES COORDINATING COMMITTEE ROSTER
February 2000

NIH Institutes, Centers, and Offices

Elaine Collier, M.D.
National Institute of Allergy and Infectious Diseases

Susana A. Serrate-Sztein, M.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Audrey Penn, M.D.
National Institute of Neurological Disorders and Stroke

Hilary Sigmon, Ph.D., R.N.
National Institute of Nursing Research

Barbara B. Mittleman, M.D.
National Institute on Aging

A. Julianna Gulya, M.D.
National Institute on Deafness and Other Communication Disorders

Ellen S. Liberman, Ph.D.
National Eye Institute

Barbara Linder, M.D., Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Karen Winer, M.D.
National Institute of Child Health and Human Development

Kenneth A. Gruber, Ph.D.
National Institute of Dental and Craniofacial Research

John F. Finerty, Ph.D.
National Cancer Institute

Robert Musson, Ph.D.
National Heart, Lung, and Blood Institute

Dianne Rausch, Ph.D.
National Institute of Mental Health

Jerry Robinson, Ph.D.
National Center for Research Resources

Jeffrey Trent, Ph.D.
National Human Genome Research Institute

Jagjitsingh H. Khalsa, Ph.D.
National Institute on Drug Abuse

Kathleen Michels, Ph.D.
Fogarty International Center

Pamela Marino, Ph.D.
National Institute of General Medical Sciences

Steven K. Akiyama, Ph.D.
National Institute of Environmental Health Sciences

Calbert A. Laing, Ph.D.
Center for Scientific Review

Vivian Pinn, M.D.
Office of Research on Women's Health

Stephen C. Groft, Pharm. D.
Office of Rare Diseases

Federal Agencies

Jeffrey N. Siegel, M.D.
FDA/Center for Biologics Evaluation and Research

Sahar M. Dawisha, M.D.
FDA/Center for Devices and Radiological Health

Kent Johnson, M.D.
FDA/Center for Drug Evaluation and Research

Robert F. Ashman, M.D.
Department of Veterans Affairs

Patricia W. Mueller, Ph.D.
Centers for Disease Control and Prevention

Private Organizations

Virginia Ladd/Stanley M. Finger, Ph.D.
American Autoimmune Related Diseases Association

Stephen C. Reingold, Ph.D.
National Multiple Sclerosis Society

John H. Klippel, M.D.
Arthritis Foundation

Robert A. Goldstein, M.D., Ph.D.
Juvenile Diabetes Foundation International

Lloyd Mayer, M.D.
Crohn's and Colitis Foundation of America

Margaret Dowd
The S.L.E. Foundation

Jane Salmon, M.D.
American College of Rheumatology

Janice Wherry, M.D., Ph.D.
Pharmaceutical Research and Manufacturers of America

Katherine Morland Hammitt
Arthur I. Grayzel, M.D., M.A.C.R.
Elaine Alexander, M.D., Ph.D.
Sjogren's Syndrome Foundation

Richard Kahn, Ph.D.
American Diabetes Association

Appendix B

AUTOIMMUNE DISEASES COORDINATING COMMITTEE MISSION STATEMENTS

NIH Institutes, Centers, and Offices

The **National Institute of Allergy and Infectious Diseases (NIAID)** conducts and supports research to elucidate the etiopathology of all autoimmune diseases and to develop new approaches to prevent and treat these immune-mediated diseases.

The **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)** conducts and supports research into the causes, treatment, and prevention of autoimmune components of rheumatic and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases.

The **National Cancer Institute (NCI)** conducts and supports autoimmunity research in paraneoplastic syndromes, in which autoimmune diseases are symptoms of an underlying malignancy, and in the deliberate induction of tumor-specific autoimmune responses for immunotherapeutic approaches to the treatment and cure of cancer.

The **National Institute of Child Health and Human Development (NICHD)** conducts and supports research in the prevention and treatment of type 1 diabetes and in the reproductive sciences including premature ovarian failure of autoimmune etiology and uterine changes that occur in women with autoimmunity.

The **National Institute on Deafness and Other Communication Disorders (NIDCD)** conducts and supports research in the impact of autoimmune diseases on hearing, balance, smell, taste, voice, speech, and language.

The **National Institute of Dental and Craniofacial Research (NIDCR)** conducts and supports research in autoimmune diseases of the oral cavity, such as Sjogren's syndrome.

The **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)** has broad interests in the area of autoimmunity and autoimmune diseases, including endocrine diseases, such as type 1 diabetes and thyroiditis; digestive track and nutritional diseases, such as inflammatory bowel disease, celiac disease, primary biliary cirrhosis, and other autoimmune liver diseases; and kidney and blood/bone diseases, such as glomerulonephritis. A new "joint" branch within NIDDK, the Navy/NIDDK Transplant and Autoimmunity Branch, will study autoimmune pathogenesis of type 1 diabetes and perform translational research leading to islet transplants for type 1 diabetics.

The **National Institute on Drug Abuse (NIDA)** supports more than 85 percent of the world's research on health aspects of drug abuse and addiction. It also supports research on infections, including HIV/AIDS, and associated medical and health consequences, including immunosuppression in drug users. Research areas within NIDA's mission include the effects of

drug abuse in patients with rheumatoid arthritis, diabetes-related metabolic disorders, lupus, and other autoimmune disorders.

The **National Institute of Environmental Health Sciences (NIEHS)** conducts and supports research to elucidate the role of environmental factors in the etiopathology of autoimmune diseases.

The **National Eye Institute (NEI)** conducts and supports autoimmunity research in immunosuppression, tolerance, anterior chamber associated immune deviation, ocular complications from autoimmune diseases, and autoimmune uveitis.

The **National Heart, Lung, and Blood Institute (NHLBI)** supports investigations of the contribution of autoimmunity to diseases under its purview and in transfusion medicine and the use of autoimmune reagents and responses in disease diagnosis, treatment, and prevention.

The **National Institute of Mental Health (NIMH)** conducts and supports research in the contribution of central nervous system autoimmunity to the development of neuropsychiatric and behavioral disorders, such as autism, bulimia nervosa, and pediatric autoimmune neuropsychiatric disorders (PANDAS).

The **National Institute of Neurological Disorders and Stroke (NINDS)** conducts and supports research in autoimmune disorders of nerve and muscle such as multiple sclerosis, acute and chronic neurodegenerative diseases involving inflammatory mechanisms, and the impact of autoimmunity on the blood-brain barrier.

The **National Institute of Nursing Research (NINR)** supports research to establish a scientific basis for the care of individuals across the lifespan—from management of patients during illness and recovery to the reduction of risks for disease and disability and the promotion of healthy lifestyles. Research extends to problems encountered by patients, families, and caregivers and emphasizes the special needs of at-risk and underserved populations. Autoimmunity research aims to develop strategies to promote self-management, cope with chronic illness, promote adherence to treatment, and prevent complications in conditions such as diabetes, rheumatoid arthritis, and irritable bowel syndrome.

The **Fogarty International Center (FIC)** promotes international cooperation in biomedical sciences by encouraging collaboration between U.S. and foreign scientists.

The **National Center for Research Resources (NCRR)** provides a comprehensive range of resources and technologies to support biomedical research. Scientists use these resources to better understand, prevent, and treat autoimmune diseases.

The **Office of Research on Women's Health (ORWH)** works with the NIH Institutes and Centers to ensure that NIH-supported research focuses on issues important to women's health, to ensure that women and minorities are included in NIH-supported clinical research, and to enhance career opportunities for women in biomedical research.

Federal Agencies

The **U.S. Food and Drug Administration (FDA)** regulates biological products, including blood, vaccines, therapeutics, and related drugs and devices, according to statutory authorities; assures that safe and effective drugs are available to Americans; ensures the safety and effectiveness of medical devices; and eliminates unnecessary human exposure to man-made radiation from medical, occupational, and consumer products.

The Office of Research and Development at the **U.S. Department of Veterans Affairs (VA)** National Headquarters improves the effectiveness, efficiency, and accessibility of health care services for veterans by supporting research on the pathology, diagnosis, and treatment of autoimmune diseases.

Private Organizations

The **American Autoimmune Related Diseases Association (AARDA)** is a nonprofit organization that fosters and facilitates collaboration in education, public awareness, research, patient services, information dissemination, and research in all autoimmune diseases.

The **American College of Rheumatology (ACR)**, a nonprofit organization of physicians, health professionals, and scientists, advances rheumatology through programs of education, research, and advocacy and fosters excellence in the care of people with rheumatic and musculoskeletal diseases.

The **Crohn's and Colitis Foundation of America (CCFA)** is a nonprofit research organization that seeks the cause of and cure for Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease.

The **National Multiple Sclerosis Society (NMSS)**, a nonprofit organization, researches the cause and impact of MS and seeks to identify effective preventions, treatments, and a cure for this disease by obtaining and applying scientifically gathered basic, clinical, and health services knowledge.

The **Sjogren's Syndrome Foundation** is a nonprofit organization that educates patients, their families, the public, and healthcare providers about Sjogren's syndrome and encourages research for new treatments and a cure for this disease.

The **Systemic Lupus Erythematosus Foundation**, a non-profit organization, seeks the cause, improved treatment, and a cure for lupus by funding medical research and providing services to assist patients, families, and friends.

Appendix C

FY 1999 AUTOIMMUNITY RESEARCH INITIATIVES

Initiative Title	Cosponsors
Autoimmunity Centers of Excellence	**NIAID***, NIDDK, ORWH, NIAMS
Clinical Trials and Clinical Markers for Immunologic Diseases	**NIAID**
Environment/Infection/Gene Interaction in Autoimmunity	**NIEHS**, NIAID, NIDDK, NIAMS, NICHD, NIDCD, NEI, NHLBI, NINDS, NIMH, NIDCR, ORWH
Human Immunology Centers of Excellence	**NIAID**
Human Islet Transplantation into Humans	**NIDDK**, NIAID, JDFI
Hyperaccelerated Award/Mechanisms in Immune Disease Trials	**NIAID**, NIAMS, NIDDK, NINDS, NHLBI, ORWH
Immune Tolerance Network: Autoimmune Disease	**NIAID**, NIDDK, JDFI
Immunological Phenotyping of Mouse Mutants	**NIAID**, NCRR, NEI, NHLBI, NIDDK, NIEHS, ORWH
Multiple Autoimmune Disease Genetics Consortium (MADGC)	**NIAID,** NIAMS, NHLBI, NIDDK, NICHD, NIDCR, ORWH
New Imaging Technologies for Autoimmune Disease	**NIAID**, NCI, NCRR, NEI, NHLBI, NIAMS, NIDCR, NIDDK, NIMH, NINDS, ORWH
Nonhuman Primate Models of Transplantation Tolerance	**NIAID**, NIDDK, NCRR
Pilot Trials on Innovative Therapies for Rheumatic and Skin Diseases	**NIAMS**, NIAID, NICHD, ORWH
Rat Autoimmune Disease Genetic Resource	**NIAMS**, NIAID, NHLBI, NIDCR, NIDDK, NCRR, NINDS
Stem Cell Transplantation for Treatment of Autoimmune Diseases	**NIAID,** NHLBI, NIDDK, NIDCR, NICHD, ORWH
Supplements to NIAMS Registries and Repositories	**NIAMS**
Target Organ Damage in Autoimmune Disease	**NIAMS**, NIAID, NIDCR, NIDDK, NICHD, NIEHS, NIDCD, NEI, NHLBI, NINDS, NIMH, ORWH

*Bold indicates the lead Institute.

Appendix D
NIH-Sponsored Initiatives in Autoimmune Diseases Research
FY 1996 to FY 2001

Initiative	Supporting Institute(s) and Organizations	FY
Innovative Grants on Immune Tolerance	NIAID, NIDDK	2001–2003
Specialized Centers of Research (SCORs) in Osteoporosis, Rheumatoid Arthritis, and Scleroderma	NIAMS	2001–2005
Multidisciplinary Clinical Research Centers for Arthritis and Musculoskeletal and Skin Diseases	NIAMS	2001–2005
Transitional Career Development Award in Women's Health Research	NIA, NIAID, NIAMS, NCI, NICHD, NIDCR, NIDA, NIEHS, NHLBI, NIMH, NINDS, NINR, ORWH, PFIZER	2001–2004
Skin Diseases Research Core Centers	NIAMS	2001–2005
Rheumatic Diseases Core Centers	NIAMS	2001–2005
Hyperaccelerated Award/Mechanisms in Immunomodulation Trials	NIAID, NIA, NIAMS, NIDDK, NHLBI, NINDS, ORWH	2000–2004
New Strategies for the Treatment of Type 1 Diabetes	NIDDK NIAID, NICHD	2000–2002
Innovative Research in Human Mucosal Immunity	NIAID, NIDCR, CCFA	2000–2001
High-Risk Arthritis and Musculoskeletal and Skin Diseases Research	NIAMS	2000–2001
Prevalence and Diagnosis of Celiac Disease	NIDDK	2000–2004
Mechanisms of Chondroprotection	NIAMS	2000–2004
Diabetes Centers of Excellence	NIDDK, NIAID, JDFI	2000–2004
Clinical Trials and Clinical Markers for Immunologic Diseases	NIAID	2000–20004
Immune Tolerance Network	NIAID, NIDDK, JDFI	1999–2006
Immunological Phenotyping of Mouse Mutants	NIAID, NCRR, NEI, NHLBI, NIDDK, NIEHS, ORWH	1999–2000
New Imaging Technologies for Autoimmune Diseases	NIAID, NCI, NCRR, NEI, NHLBI, NIAMS, NIDCR, NIDDK, NIMH, NINDS, ORWH	1999–2003
Multiple Autoimmune Diseases Genetics Consortium	NIAID	1999–2004
Clinical Trials in Stem Cell Transplantation for Autoimmune Diseases	NIAID	1999–2004
Rat Autoimmune Model Repository	NIAMS, NIAID	1999–2003
Pilot Trials on Innovative Therapies for Rheumatic and Skin Diseases	NIAMS, NIAID	1999–2003
Nonhuman Primate Transplant Tolerance Cooperative Study Group	NIAID, NIDDK, NCRR	1999–2003
Target Organ Damage in Autoimmune Diseases	NIAMS, NIAID, NIDCR, NIDDK, NICHD, NIEHS, NIDCD, NEI, NHLBI, NINDS, NIMH, ORWH	1999–2003
Human Rheumatic Disease Registries	NIAMS	1999
Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications	NIDDK, NIAID, NCRR, NHLBI, NIDCR, NICHD, NEI	1999–2000
Human Islet Transplantation Into Humans	NIDDK, NIAID, JDFI	1999–2003
Environment/Infection/Gene Interactions in Autoimmune Disease	NIEHS, NIAID, NIDDK, NIAMS, NICHD, NIDCD, NEI, NHLBI, NINDS, NIMH, NIDCR, ORWH	1999–2001
Autoimmunity Centers of Excellence	NIAID, NIDDK, NIAMS, ORWH	1999–2002
Hyperaccelerated Award/Mechanisms in Immune Disease Trials	NIAID, NIAMS, NIDDK, NINDS, NHLBI, ORWH	1999–2003
Human Immunology Centers of Excellence	NIAID	1999–2002

Appendix D
NIH-Sponsored Initiatives in Autoimmune Diseases Research
FY 1996 to FY 2001
(continued)

Initiative	Supporting Institute(s) and Organizations	FY
Specialized Centers of Research (SCORs) in Osteoporosis, Rheumatoid Arthritis, and Scleroderma	NIAMS	1998/1999–2002/2003
Immunopathogenesis of Type 1 Diabetes	NIDDK, NIAID, NICHD	1998–2000
Cellular and Molecular Approaches to Achieving Euglycemia	NIDDK, NCRR, NIAID, NICHD, NIA	1998–2000
Thrombocytopenia: Pathogenesis and Treatment	NHLBI	1998–2002
Transplantation Tolerance	NIAID, NIDDK	1998–2001
Specialized Centers of Research (SCORs) in Osteoarthritis and Systemic Lupus Erythematosus	NIAMS	1997/1998–2000/2001
Diabetes Interdisciplinary Research Programs	NIDDK, NIAID, JDFI	1997–2001
Autoimmunity: Genetics, Mechanisms, and Signaling	NIAID, NIAMS, NIDDK, NIA, ORWH	1997–2003
Mucosal Immunity in Pathogenesis/Prevention of Human Disease	NIAID, NIHLBI, NIA, NIAMS, NIDCD, NIDR, NIDDK, ORWH	1996–2003
Cellular and Molecular Mechanisms of Diabetic Cardiomyopathy	NHLBI, NIDDK, NIA	2000-2002
Role of Microbes in Autoimmune and Immune-Mediated Diseases	NIAID, NINDS, NIAMS	1996–2003
Gender in the Pathogenesis of Autoimmunity: Mechanisms	NIAID, NIAMS, NINDS, NIDDK, NIDR, ORWH	1996-2003
Mechanisms Underlying Immunotherapy Trials in Autoimmunity	NIAID, NIDDK, NIAMS, ORWH	1996–2000
Interdisciplinary Programs in Autoimmune Disease	NIAID, NIDDK, JDFI	1996–1999
Mucosal and Synovial Gene Transfer in Infection/Inflammation	NIAID, NIAMS	1996–2000

Appendix E

LIST OF ABBREVIATIONS AND ACRONYMS

AARDA	American Autoimmune Related Diseases Association
ADA	American Diabetes Association
AF	Arthritis Foundation
AMBTR	Autologous Blood and Marrow Transplant Registry
AS	Ankylosing spondylitis
ATD	Autoimmune thyroid disease
CCFA	Crohn's and Colitis Foundation of America
CDC	Centers for Disease Control and Prevention
FDA	U.S. Food and Drug Administration
GCRC	General Clinical Research Center
IBD	Inflammatory bowel disease
IBMTR	International Bone Marrow Transplant Registry
IHWG	International Histocompatibility Working Group
IOM	Institute of Medicine
JDFI	Juvenile Diabetes Foundation International
JRA	Juvenile rheumatoid arthritis
MHC	Major histocompatibility complex
MS	Multiple sclerosis
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
ORD	Office of Rare Diseases
ORWH	Office of Research on Women's Health
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
VA	U.S. Department of Veterans Affairs