Progress in Autoimmune Diseases Research

National Institutes of Health

THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

Report to Congress

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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National Institute of Allergy and Infectious Diseases

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Foreword

Autoimmune diseases are a family of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. While many of these diseases are rare, collectively they affect 14.7 to 23.5 million people in this country, and – for reasons unknown – their prevalence is rising. Since cures are not yet available for most autoimmune diseases, patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, reduced productivity at work, and high medical expenses. And, because most of these diseases disproportionately afflict women, and are among the leading causes of death for young and middle-aged women, they impose a heavy burden on patients' families and on society.

For these reasons, Congress commissioned the Autoimmune Diseases Coordinating Committee (ADCC) to develop a comprehensive strategic Research Plan for National Institutes of Health (NIH)-funded autoimmune research with the goal of reducing the impact of autoimmune disease. Published in January 2002, the Autoimmune Diseases Research Plan was developed by ADCC members, other Federal and non-Federal experts in the field, and lay leaders in the autoimmune disease communities. It sets forth an ambitious and comprehensive research agenda aimed at generating more accurate epidemiologic profiles of autoimmune diseases; developing a greater understanding of the fundamental biologic principles underlying disease onset and progression; devising improved diagnostic tools; creating more effective interventions; and producing public and professional education and training programs.

Although it has been a short time since the Research Plan was established, we have seen significant progress in all of these areas – progress that has resulted from the combined efforts of NIH Institutes and Centers, other Federal agencies, nonprofit and patient advocacy groups, and partners in the private sector. This report details the progress made in NIH-funded autoimmune research since publication of the 2002 ADCC Autoimmune Diseases Research Plan.

It also identifies overarching priority areas that promise to accelerate autoimmune disease research. These areas include biomarker development, bioinformatics, and application of new technologies. The development of biomarkers can enable earlier diagnosis as well as aid physicians in selecting and monitoring treatment. New technologies, such as genomics and proteomics, provide scientists with the tools to study gene and protein patterns in tissue samples, providing vital insights into the onset and progression of disease.

Bioinformatics tools, which help scientists to assemble and analyze large amounts of data, will be particularly important in these endeavors. In many of these areas, the NIH Roadmap, which fosters trans-Institute and multidisciplinary collaboration as a way to address complex challenges in biomedical research, will synergize with the ADCC Autoimmune Diseases Research Plan.

Despite our progress, we recognize that more needs to be done so that we may close the gaps in our knowledge and achieve our overall goal of reducing the rising toll of autoimmune disease. For example, we need to gain a better understanding of the distribution of these diseases through epidemiologic studies, and of the environmental triggers that contribute to their onset. We must work to apply the knowledge provided by the Human Genome Project toward elucidating the hereditary risks of autoimmune diseases. As we learn more about the genetic and environmental factors contributing to these diseases, we will be able to develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body. In tandem, we must advance the training of scientists and health care workers so that we can effectively translate the advances in biomedical research to clinical practice.

NIH is deeply committed to supporting research and promoting progress toward conquering autoimmune diseases. The 2002 ADCC Autoimmune Diseases Research Plan provides a valuable guide to those goals. Reporting on our advances, as we do in this Progress Report, offers an opportunity to evaluate our progress, assess our path, and determine our direction for the future. Ultimately, basic and clinical research in this area will yield more effective prevention and treatment strategies for the millions who are at risk for or struggle with autoimmune diseases.

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Executive Summary

More than 80 human diseases are due at least in part to an inappropriate immune system response that results in damage to an individual's organs, tissues, or cells. Autoimmune diseases can affect any part of the body, and have myriad clinical manifestations that can be difficult to diagnose. At the same time, autoimmune diseases share many features related to their onset and progression. In addition, overlapping genetic traits enhance susceptibility to many of the diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family. While treatments are available for many autoimmune diseases, cures have yet to be discovered. For these and other reasons, the autoimmune diseases are best recognized as a family of related disorders that must be studied collectively as well as individually.

Though each of the autoimmune diseases is relatively rare, as a group they are among the most prevalent in the United States, affecting between 14.7 and 23.5 million people – up to eight percent of the population. They also are a leading cause of death among young and middle-aged women. For reasons that are poorly understood, the incidence and prevalence of autoimmune diseases is rising. The chronic and often debilitating nature of many autoimmune diseases increases the burden on patients, their families, and society in terms of medical costs, reduced quality of life, and lost productivity.

The Autoimmune Diseases Coordinating Committee

Responding to the need for a concerted national effort to reduce the burden of autoimmune diseases, the Autoimmune Diseases Coordinating Committee (ADCC) was established by the National Institutes of Health (NIH) in 1998 and placed under the direction of the National Institute of Allergy and Infectious Diseases (NIAID). The Children's Health Act of 2000 further defined the Committee's charge to expand, intensify, and coordinate research and related NIH activities with respect to autoimmune diseases. The Committee is composed of the directors, or their designees, of each of the Institutes and Centers involved in autoimmune disease research; representatives of other Federal agencies, including the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), whose programs include health functions or responsibilities relevant to these diseases; and representatives from a number of private organizations concerned with autoimmune diseases.

Since its inception, the ADCC has analyzed ongoing and proposed research programs in the autoimmune diseases and identified cross-cutting and collaborative initiatives to address key aspects of autoimmunity. In 2002, the ADCC prepared and presented to Congress the Autoimmune Diseases Research Plan, a comprehensive research agenda to quantify and monitor the burden of autoimmune diseases, determine the causes underlying their growing prevalence, and encourage research on their etiology and natural history. The Research Plan also is designed to promote the development of improved diagnostic and screening procedures and to inform the development and implementation of targeted clinical trials to evaluate new treatments, including the newest biologic agents. Finally, the ADCC is committed to improving training, education, and the dissemination of information about the autoimmune diseases to health care professionals and the public. Through the ADCC, NIH is coordinating and expanding its programs to reduce the burden of autoimmune diseases on the American people.

The NIH Commitment

The NIH has committed significant resources to reduce the burden of autoimmune diseases. Expenditures for autoimmune diseases by all NIH Institutes and Centers in 2003 reached $591.2 million, an increase of 36 percent over FY 2000. These figures do not include expenditures by other Federal agencies, such as the CDC and the Department of Veterans Affairs. In 2003, basic immunologic studies of the etiology of the autoimmune diseases received the largest share of support (45.5 percent) followed by investigations of the genetic (14.6 percent) and environmental (5.4 percent) factors underlying these disorders. Major expenditures were made to improve disease diagnosis and prognosis (13.9 percent) and for clinical trials and clinical research infrastructure (13.0 percent). Education, training, and information dissemination accounted for 1.7 percent of expenditures, and epidemiologic studies, including disease registries, totaled 3.3 percent. It is important to note that many projects focus on a variety of scientific questions, and therefore can be difficult to place into a single category. Because projects were categorized according to their primary area of emphasis, expenditures in some of the categories above may be understated.

Since its inception, the ADCC has analyzed ongoing and proposed research programs in the autoimmune diseases and identified cross-cutting and collaborative initiatives to address key aspects of autoimmunity.

NIH provides extramural support through grants and contracts awarded to medical schools, academic institutions, and other research organizations throughout the United States.

Sixty percent of funded autoimmune research in 2003 was conducted through unsolicited (investigator-initiated) grants. In addition, NIH capitalizes on promising opportunities to improve patient outcomes and promotes promising investigative areas by encouraging targeted research programs carried out under solicited research initiatives with dedicated funding, which amounted to 26 percent of the funds committed in 2003. These funds have supported interdisciplinary initiatives to develop new animal models to study the safety and efficacy of promising therapeutic approaches; establish multi-institutional clinical research programs to evaluate these promising therapies in humans; develop biomarkers of disease stage, activity, and therapeutic effects; and evaluate new technologies for identifying high-risk populations and improving patient screening, diagnosis, and management. A vigorous intramural research program in autoimmunity is carried out in many NIH Institutes, comprising 14 percent of the total expenditures.

The Research Agenda

The 2002 ADCC Autoimmune Diseases Research Plan outlined four major areas of emphasis: reducing the burden of disease; enhancing understanding of disease etiology; improving diagnosis, treatment, and prevention; and increasing training, education, and information dissemination activities. The following paragraphs highlight the significant progress made in each of these areas since publication of the Research Plan.

Progress in Epidemiology and Burden of Disease

Recent epidemiologic studies have focused on determining which specific groups and individuals are at greatest risk for various autoimmune diseases. Some such studies have shown marked differences in the incidence of systemic lupus erythematosus related to race and ethnicity. Specifically, both African American and Hispanic lupus patients tend to develop lupus earlier in life and experience more severe disease than Caucasian patients. Some of the observed disparities, however, may be associated with differences in access to health care, patient perceptions of disease, and assessments of disease activity by health care providers. Other studies have emphasized the importance of controlling pain in children with juvenile arthritis by showing that increased pain and fatigue can reduce participation in school and social activities.

Disease registries provide an important epidemiologic tool for tracing the natural history of disease, for assessing the burden of disease in various populations, and for identifying and tracking trends in incidence and prevalence of autoimmune diseases. The number

of disease-specific registries is increasing; such registries now exist for minority populations with lupus erythematosus, autoimmune diseases in the young, neonatal lupus, antiphospholipid syndrome, epidermolysis bullosa, Sjögren's syndrome, childhood diabetes, islet cell transplants for treatment of diabetes, and other diseases.

Progress in Etiology

As called for in the 2002 ADCC Autoimmune Diseases Research Plan, recent research on the etiology of autoimmune diseases has emphasized genetic factors contributing to the autoimmune diseases, environmental influences, and basic studies of immunologic mechanisms underlying autoimmunity.

Genetics

Researchers are identifying the genes that predispose individuals to develop autoimmune diseases, and studying how these genes initiate the disease process or exacerbate symptoms. Findings in these areas may lead to new interventions to minimize or reverse disease effects. To discover factors that may be common to more than one autoimmune disease, a Multiple Autoimmune Disease Genetics Consortium now serves as a repository for biologic samples and clinical data from families in which at least two family members are afflicted by two or more autoimmune diseases. Since most autoimmune diseases seem to be associated with multiple genetic traits, a new collaborative program was announced by several NIH Institutes to hasten gene discovery for complex disorders, including confirmed or suspected autoimmune disease. To address the genetics of multiple sclerosis, an international consortium brings together experts in genetics, genomic analysis, and bioinformatics, as well as in the diagnosis and treatment of this disease. An Inflammatory Bowel Disease Genetics Research Consortium helped to identify genes associated with Crohn's disease.

To discover factors that may be common to more than one autoimmune disease, a Multiple Autoimmune Disease Genetics Consortium now serves as a repository for biologic samples and clinical data from families in which at least two family members are afflicted by two or more autoimmune diseases.

In the past two years, NIH-supported researchers have identified the genetic basis of predisposition to vitiligo, a skin pigmentation disorder that tends to cluster in families and may foreshadow the onset of other autoimmune diseases. In addition, a genetic "signature" for lupus was identified in some patients with this disease who develop life-threatening

complications. Two gene variants also were found that are related to an increased risk of lupus among African American women. All of these discoveries are important steps toward better autoimmune disease treatment and prevention.

Environmental Factors

A program cosponsored by more than a dozen NIH Institutes and Centers supports basic and population-based research on the role that environmental, infectious, and genetic factors play in initiating or exacerbating autoimmune diseases. Infectious agents have received particular attention. For example, the product of a human gene that confers susceptibility to Crohn's disease recognizes components of certain bacteria. Viral infections have long been suspected as triggers of type 1 diabetes. Other recent research suggests that the numbers of regulatory T cells that normally hold potentially destructive immune responses in check are reduced by viral infection. New data have also emerged that link dietary exposure to certain foods, particularly the timing of introduction of cereals in infant diets, as a possible etiologic factor in type 1 diabetes. Another NIH program investigates whether *in utero* exposures cause increased susceptibility to autoimmune or other diseases later in life.

Immunologic Studies

Most investigations of the etiology of autoimmune diseases are carried out through individual investigator-initiated projects on such fundamental issues as the role of sex hormones and regulatory T cells in disease initiation. For example, recent studies have provided better understanding of the complex interaction between certain female hormones and the immune response, and may therefore help to explain the predominance of autoimmune diseases like lupus in women. Specifically, estradiol (an estrogen-like compound) was shown to induce a lupus-like disease in highly susceptible mice, but had no effect on normal mice. Researchers found that estradiol makes the B cells that produce autoantibodies resistant to the signals governing programmed cell death (apoptosis) that normally eliminate them. When lupus-susceptible mice were treated with prolactin, a hormone that stimulates milk production in the mammary glands, autoantibody-producing cells that are usually eliminated by the immune system survived and the mice developed lupus symptoms.

A number of NIH-supported studies have shown that regulatory T cells are crucial in controlling diseases such as type 1 diabetes, Crohn's disease, and ulcerative colitis. The recent finding that regulatory T cells are capable of terminating autoimmune responses suggests that they may have potential for treating a number of autoimmune disorders.

NIH has recently launched several large-scale initiatives to address multidisciplinary, cross-specialty issues that are beyond the capabilities of a single investigator. In the past two years, the Autoimmunity Centers of Excellence program has expanded from four to nine sites, and a cooperative study group on non-human primate immune tolerance has supported studies on promising methods of tolerance induction. A new multispecialty initiative examining how the immune system modifies behavior has shown that immune system regulatory molecules can affect brain function. Research has demonstrated that behavior can modify the course of some autoimmune diseases. Often the immune system responds differently in different organ systems. An NIH initiative on cardiovascular and respiratory health and disease supports efforts to map pathways of immune control in these systems, which often suffer inflammatory and immune-mediated damage. Other studies have clarified distinctions between inflammatory and genetic forms of muscle disease and elucidated mechanisms of cell injury in autoimmune disorders, focusing particularly on the role of immune system mediators called cytokines.

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Progress in Diagnosis, Treatment, and Prevention

The 2002 ADCC Autoimmune Diseases Research Plan identified three priorities for research related to diagnosis, treatment, and prevention of autoimmune diseases: expand initiatives and studies related to diagnosis and progression, enhance clinical trials infrastructure to facilitate clinical studies, and conduct clinical trials for a range of autoimmune disease treatments. Important progress has been made in each of these areas.

Diagnosis and Progression

Biomarkers are clinical signs or laboratory test results that correlate with the onset or progression of an autoimmune disease. As such, biomarkers hold great promise for earlier and more accurate autoimmune disease diagnosis, better prediction of disease flare-ups, and improved monitoring of disease progression and response to treatment.

Several biomarker initiatives are now underway. An autoimmune biomarkers collaborative network has been established to develop biomarkers for major rheumatic diseases, such as rheumatoid arthritis and lupus; the knowledge obtained through the network will

assist physicians in diagnosing and managing these diseases and facilitating clinical trials of new remedies. Another NIH initiative has promoted research to identify mechanisms involved in organ damage, and has stimulated innovative multidisciplinary translational and clinical studies to develop better ways of assessing immune and nonimmune mechanisms of tissue injury. These studies will help to provide a more comprehensive picture of autoimmune disease pathogenesis. Another project, aimed at hastening and improving the diagnosis of type 1 diabetes, uses noninvasive imaging techniques to detect islet damage to insulin-producing cells *in vivo* and to monitor engraftment of transplanted pancreatic islets. Researchers also are collaborating on improved methods of glucose monitoring that will be of value in improving control of blood sugar levels in children.

A major goal of autoimmune disease research is to identify people at risk before irreversible organ damage occurs. Investigators have recently applied tests to detect lupus-related autoantibodies in serum that often are present years before the patient displays disease symptoms. In addition, serum samples from patients with lupus were found to have antibodies that reacted with the Epstein-Barr virus, adding to the evidence that a virus may be an initiating agent in lupus. In another study of rheumatoid arthritis, high concentrations of autoantibodies and T cells in the blood were found to be predictive of rapid disease progression.

Clinical Trials Infrastructure

In the past two years, NIH has placed increasing emphasis on strengthening the clinical trials infrastructure to improve and accelerate the conduct of trials, and to enable scientists to derive the maximum information from them. These efforts have included developing and expanding specialized research centers, increasing the number of studies that utilize materials and data from clinical trials to elucidate underlying mechanisms of drug activity and immune response, and further developing research resources that can be shared by autoimmunity researchers across the disease and research continuum. For instance, NIH is supporting five multidisciplinary prevention centers devoted to developing interventions to prevent human autoimmune disease; these centers are now conducting preclinical and pilot studies on numerous autoimmune diseases. Another network facilitates clinical research in rare diseases, including those due to aberrant immune responses. NIH also sponsors several clinical trials networks. Research resource development has included database development to support autoimmunity research, development of immune-monitoring reagents, support of islet cell resource centers, and support of type 1 diabetes mouse model repositories.

Recent research has resulted in clarification of the utility of a biomarker as an outcome measure in type 1 diabetes clinical trials that focus on preserving beta cell function. Another study identified a genetic factor that dramatically reduces the risk of graft-versus-host disease following bone marrow transplant. In a study using non-human primates, researchers have determined that the portal vein is superior to the celiac artery for injecting islet cells during transplantation.

Clinical Trials

Clinical trials to assess treatment efficacy and patient safety are a crucial step in drug or device development. In accord with the 2002 ADCC Autoimmune Diseases Research Plan, NIH sponsors a broad range of clinical trials and clinical trial networks for autoimmune diseases. For example, 15 autoimmune disease clinical trials in nine centers are ongoing or in development through the recently expanded Immune Tolerance Network (ITN), which now involves investigators in the United States, Canada, Western Europe, and Australia. Other clinical trials consortia or individual trials are focused on preventing atherosclerosis in children with lupus, preventing type 1 diabetes in people at risk and preserving beta cell function in people newly diagnosed, assessing the utility of devices for continuous glucose monitoring in children with type 1 diabetes, improving stem cell transplantation for autoimmune disease patients, and developing innovative therapies for scleroderma and other rheumatic and skin diseases. In addition, through carefully selected studies NIH is bringing previously lacking scientific rigor to investigations of the possible benefit of complementary and alternative therapies in multiple sclerosis, rheumatoid arthritis, and diabetic neuropathy.

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Clinical trials launched or ongoing over the past two years have begun to provide important results. One trial showed that the drug etanercept eases the stiffness, spinal pain, and joint swelling of ankylosing spondylitis, a chronic inflammatory arthritis that typically strikes adolescent and young adult males. Another clinical trial of etanercept sponsored by multiple NIH institutes showed that children and teenagers with juvenile rheumatoid arthritis experience dramatic reductions in symptoms and markedly improved function. Many multiple sclerosis patients do not respond to currently-licensed therapies. A clinical trial of combined beta interferon and daclizumab therapy, however, showed that this treatment reduced numbers of inflammatory brain lesions in multiple sclerosis patients and led to improvements in measures of disease activity and disability.

Progress in Training, Education, and Information Dissemination

For the results of research to become integrated into clinical practice, information must be transferred to health care providers, patients, patients' families, and the general public. New programs have been initiated to facilitate training and education of health care professionals, and some of these have been launched through partnerships with key nonprofit organizations. For example, a multidisciplinary program that organized biobehavioral rheumatic disease workshops fostered collaboration among behavioral scientists, clinicians, and basic scientists in order to share information, improve communication, and overcome obstacles to collaboration among specialists in these diseases. Another workshop brought diabetes and angiogenesis researchers together to consider how recent advances in angiogenesis research can be applied to the creation of new therapies for type 1 diabetes and its complications. Research training grants are being made to new, midcareer, and established scientists and clinicians to attract them to careers in autoimmune disease research, and to increase their productivity.

A number of workshops have served as springboards for the development of new research collaborations and for fostering improved research coordination. For example, two recent workshops focused on issues related to multiple sclerosis. One focused on biomarkers, and brought together a wide range of experts to evaluate current knowledge about biomarkers in multiple sclerosis; another cosponsored workshop explored genetic factors in multiple sclerosis susceptibility and helped to create a collaborative network that will accelerate the discovery of susceptibility genes for this disease. Similarly, a Lupus Biomarkers Working Group was established recently to hasten the development of useful biomarkers for all aspects of this disease. Major collaborative efforts are underway to develop reagents for study of the pancreatic beta cell and to facilitate beta cell replacement therapy for type 1 diabetes.

Other recent training and education activities have centered on disseminating the latest research findings on myasthenia gravis, celiac disease, and inflammatory bowel disease, among others. In addition, NIH collaborates each year with numerous nonprofit and advocacy organizations to conduct training and education activities for researchers and clinicians on diverse autoimmune diseases. NIH also continues to maintain and expand its print and online information resources for patients, the general public, and health care providers.

Looking to the Future

Since publication of the 2002 ADCC Autoimmune Diseases Research Plan, substantial progress has been made to quantify and better understand the burden of autoimmune diseases; to define the factors that lead to their development; to improve the diagnosis, treatment, and prevention of autoimmune disorders; and to strengthen the autoimmunity research workforce and disseminate research findings to patients, clinicians, and the community. Numerous specific initiatives are underway in many of the areas highlighted in the Research Plan. These solicited research programs are producing a wealth of new knowledge and enhancing collaboration among basic scientists, clinical investigators, and individuals from a host of other technological disciplines ranging from bioinformatics to imaging approaches.

Over the next several years, NIH will exploit every opportunity to build upon its progress in autoimmune disease research, and looks forward eagerly to continuing successes that will yield new knowledge and interventions to improve the lives of all Americans affected by autoimmune diseases.

Introduction

The Nature and Magnitude of Autoimmune Diseases

One hundred years ago, renowned clinician William Osler observed that while some patients died when their bodies were unable to fight off an infection, other patients appeared to die from an excessive reaction by the body. Little was known about the human immune system at that time, and it was not until 50 years later that scientists demonstrated convincingly that disease could result not only from infection but from the body's misguided attack on itself, even in the absence of infection or other apparent cause. Today, we refer to this misguided attack as autoimmune disease and understand that a delicate balance determines the difference between a beneficial and injurious immune response.

We now recognize more than 80 clinically distinct human diseases that result at least in part from an autoimmune response. The cause of autoimmune disease remains unknown, although genetic factors play a major role in susceptibility. Some of these diseases may be triggered by an infectious agent or an environmental exposure, especially in individuals who have inherited a heightened susceptibility. Autoimmune diseases can affect any tissue or organ of the body. Because of this variability, they can cause a wide range of symptoms and organ injuries, depending upon the site of autoimmune attack.

Yet researchers have learned that autoimmune diseases also have many common features, particularly those related to disease initiation and progression. For this and many other reasons, autoimmune diseases are increasingly recognized as a family of related disorders that must be studied both individually and collectively in order to rapidly advance our ability to diagnose, treat, and prevent them.

Autoimmune diseases as a group impose a major burden on our Nation's health. While most of these diseases are individually rare, in the aggregate they affect between five and eight percent of Americans. Some autoimmune diseases are life-threatening. Virtually all are debilitating, and require lifelong medical care. Although treatments exist for many autoimmune diseases, we do not yet have definitive cures for any of them. As a result, autoimmune diseases impose a heavy financial and emotional burden on patients and their families, and contribute significantly to our rising national health care costs.

Autoimmune diseases likewise impose burdens on society as well as the individual patient and family. For example, because some autoimmune diseases disproportionately affect women during their reproductive years, these disorders can limit their ability to have children and to care for their families, both physically and financially. In addition, some autoimmune diseases disproportionately affect the minority groups that are often underserved by our medical system, exacerbating both the personal difficulties caused by their illnesses and the loss of their contributions to society.

Responding to a Critical Need through Research

Decades of immunology research have provided valuable insights into the intricacies of the immune system and the cellular, molecular, and genetic basis of autoimmunity. More recently, we have learned a great deal about the genes that contribute to disease, and the knowledge gained from the Human Genome Project is rapidly advancing research efforts in this area.

In the future, large-scale, population-based studies will play an increasingly important role in identifying precisely the genetic traits associated with autoimmune disease. As we are better able to identify individuals at greatest risk, we may ultimately find safe, practical, and affordable ways to intervene before the onset of irreversible injury. Yet genetic factors are only part of the story; elements in the environment are usually needed to trigger an autoimmune response, even in genetically-predisposed individuals. NIH-sponsored research has characterized many such factors, but others remain to be identified.

Today, autoimmune disease is commonly managed with immunosuppressive agents. These agents broadly reduce the immune response, placing patients at increased risk for infection. Fortunately, expanding knowledge of disease mechanisms has led to the development of novel interventions that selectively target harmful autoimmune responses. Several of these new targeted approaches are already in clinical use and are greatly improving treatment outcomes.

Well-organized, well-controlled clinical trials are a vital part of effective drug development. Because many autoimmune diseases are relatively uncommon, collaboration among different clinical centers is essential to ensure that a sufficient number of patients can enroll. Disease registries also play an important role as potential sources of patient referrals for clinical trials.

Given the diversity of autoimmune diseases, it is not surprising that they span the interests of multiple public and private organizations and that multiple NIH Institutes, Offices, and Centers support autoimmune diseases research. Several Federal agencies are partners with NIH in these endeavors. The U.S. Food and Drug Administration (FDA) is responsible for ensuring the safety and efficacy of new treatments and medical devices as well as of previously-licensed drugs that are being used to treat autoimmune disorders for the first time. Two other Federal agencies, the Centers for Disease Control and Prevention (CDC) and the Department of Veterans Affairs (VA) also make significant investments in autoimmune disease research. In addition, a wide-range of professional and patient advocacy organizations fund complementary studies and develop information resources and educational materials for clinicians and patients.

The pharmaceutical industry also plays a critical role in discovery of new treatments for these diseases, often in partnership with NIH. NIH and industry bring unique, but complementary assets to such partnerships. For example, NIH-funded studies often provide the fundamental knowledge base that facilitates industry's efforts. Such knowledge is invaluable in the earliest stages of product development, especially in the design of targeted interventions that take aim at specific mechanisms of disease. NIH also contributes to the training of scientists in the field of autoimmune research – many of whom eventually enter industry. While a number of promising drug candidates are in the industry "pipeline," there remains an ongoing need for basic research that fuels drug development. For more information about potential treatments currently being tested in clinical trials, see www.clinicaltrials.gov and http://www.fda.gov/default.htm.

The NIH Autoimmune Diseases Coordinating Committee

In 1998, recognizing the importance of information exchange and increased coordination across Federal agencies, Congress called for the establishment of the NIH Autoimmune Diseases Coordinating Committee (ADCC). ADCC members include designees of the more than a dozen NIH Institutes, Offices, and Centers that support autoimmune disease research, the FDA, VA, and CDC; additionally, representatives of many private organizations attend certain ADCC meetings. From its inception, the ADCC has worked to expand, intensify, and coordinate the activities of Federal agencies by: (1) information sharing; (2) developing research collaborations among funding agencies; (3) developing partnerships between Federal and private sector organizations; and (4) compiling and disseminating data about funding for autoimmune diseases research.

The Children's Health Act of 2000 (P.L. 106-310), Title XIX - NIH Initiative on Autoimmune Diseases, required the expansion, intensification, and coordination of Federal activities related to autoimmune diseases. It called on the ADCC to develop a forward-looking, comprehensive, and coordinated strategic plan for conducting and supporting research and education on autoimmune diseases across agencies and to solicit input from a broad range of scientists, patients, and advocacy groups. In 2002, the ADCC published the comprehensive Autoimmune Diseases Research Plan, which identified major areas of research in autoimmune diseases and designated specific activities in each major area that would accelerate efforts to understand and treat autoimmune diseases. The law further stipulated that every two years, the Department of Health and Human Services shall provide a report of progress in meeting the research needs identified in the Research Plan. This document is the first of these biennial progress reports.

Key Themes of the 2002 ADCC Autoimmune Diseases Research Plan

This progress report is organized around the four major themes identified in the 2002 ADCC Autoimmune Diseases Research Plan: (1) Epidemiology and Burden of Autoimmune Diseases; (2) Etiology of Autoimmune Diseases; (3) Diagnosis, Treatment, and Prevention; and (4) Training, Education, and Information Dissemination.

Epidemiology and Burden of Autoimmune Disease

Accurate and up-to-date information on the incidence, prevalence, and health care costs of autoimmune diseases is generally not available, and much of the existing information is outdated or derived from flawed case definitions and small samples. Yet the clustering of multiple autoimmune diseases in families, the predominance of many diseases in women and ethnic or racial groups, and the finding of multiple autoimmune diseases within a single individual underscore the need for comprehensive and well-coordinated epidemiologic studies. Only through such studies will we determine the true incidence and prevalence of individual autoimmune diseases. Such studies await the development of better and more accurate diagnostic tools.

Etiology of Autoimmune Diseases

All autoimmune diseases result from malfunctions of the mechanisms that regulate immune system function, and scientists are exploring how the natural processes of

immune homeostasis are maintained or disrupted. In most cases, disease results from interactions between inherited and environmental factors. Scientists now have new tools to more fully characterize the genes involved in autoimmune diseases, including information from the Human Genome Project. In addition, various consortia are collecting data from individuals and families with autoimmune disease (for example, the Multiple Autoimmune Diseases Genetics Consortium, the North American Rheumatoid Arthritis Consortium, and the International Multiple Sclerosis Genetics Consortium). In contrast, the tools to decipher the environmental factors involved are less advanced, and progress in this area is more limited. However, several promising leads suggest that infectious agents play a larger role than previously thought as triggers of autoimmune disease. As with burden of disease studies, large-scale, longitudinal, population-based studies will be needed to more fully identify environmental and infectious triggers.

Diagnosis, Treatment, and Prevention of Autoimmune Diseases

Despite the diversity in their natural history and presentation, autoimmune diseases share a number of underlying mechanisms, and thus have the potential to respond to treatment with the same or related therapies. More selective and less toxic immunosuppressive and immunomodulatory agents are being used to treat these disorders, and promising immune tolerance approaches are emerging.

However, several factors limit our ability to conduct the most efficient clinical trials. For example, we lack standardized classification, diagnostic, and response criteria for most autoimmune diseases. NIH is working to meet the needs in this research area with programs such as the Autoimmunity Centers of Excellence, the Immune Tolerance Network, Type 1 Diabetes TrialNet, Planning Grants for Clinical Trials in Rheumatic and Skin Diseases, the Multidisciplinary Clinical Research Centers, and the Autoimmune Diseases Prevention Centers.

Training, Education, and Information Dissemination

Training, education, and information dissemination are instrumental to our efforts to translate biomedical research advances into clinical practice. For example, training and education for scientists and health care workers allow them to more effectively advance research and patient care. Information dissemination offers patients, their families, and the community critical information about their diseases and treatment options, including information about

access to clinical trials. Nonprofit organizations can play a crucial role in information dissemination, by providing support services to patients and their families, as well as distributing information about ongoing research efforts. Because of their unique role in the research process, open communication between the scientific community and these voluntary health organizations is important. Opportunities should be pursued for these groups to work together to develop and disseminate educational material for patients, their families and health care providers.

Overarching Priority Areas

As noted in the 2002 ADCC Autoimmune Diseases Research Plan, a number of overarching priority areas broadly influence progress in each of the above themes. These priorities include: (1) identification of biomarkers of disease, disease stage, therapy response, dietary components, and environmental or occupational agent exposure; (2) application of new technologies; and (3) integration of bioinformatics and advanced computational tools.

Biomarker Development

Discovering and validating biomarkers of the disease process is an overarching need in most clinical research areas. Biomarkers are clinical signs or routine laboratory studies that have been shown to correlate with clinical status. As such, they can contribute to patient management decisions and facilitate the conduct of clinical trials. Biomarkers can also include specific gene expression patterns and genetic polymorphisms, or immunologic assays of an investigational nature.

The discovery of biomarkers depends on an understanding of the genetic, infectious, environmental, and immunologic factors contributing to the pathogenesis of the disease; the natural history of the disease as seen in large epidemiology studies; novel high-throughput assays; and clearly defined clinical phenotypes of autoimmune diseases. Discovery requires multidisciplinary and creative teamwork; validation of candidate biomarkers entails rigorous clinical evaluation.

An expanded set of validated biomarkers for autoimmune diseases will allow: (1) earlier and more rapid diagnosis of disease resulting in earlier treatment; (2) intervention with the most effective therapies for particular stages of the disease process or for patients with a particular genetic background or immunologic background; (3) shorter, smaller, and less

costly clinical trials; and (4) more informative monitoring of drug efficacy leading to earlier discontinuation of ineffective therapies. Biomarkers could also be used to detect exposures to environmental factors that might increase the risk or severity of autoimmune disease.

Developing biomarkers of disease risk will enable scientists to both identify those who are at heightened risk for autoimmune disorders and design clinical trials of preventive approaches. For example, the discovery that relatives of diabetics who also carry certain human leukocyte antigen (HLA) genes and autoantibodies are at high risk for disease development has allowed prevention trials in this population to proceed.

Bioinformatics and New Technologies

Various new technologies are being applied to research on autoimmune diseases. For example, disease processes can now be characterized at a molecular level through the use of microarray technologies that reveal patterns of gene expression in tissue samples. Proteomics – the study of protein shape, function, and patterns of expression – can enable scientists to characterize the status of proteins in tissues and antibodies in serum. High-throughput technologies allow investigators to acquire large amounts of genomic and proteomic data and record the biological responses and activities of systems under study. Constructs called MHC-tetramers now allow scientists to sort and analyze T lymphocytes based on their recognition of specific antigens. These powerful tools are increasingly being applied not only at the laboratory bench but also within clinical research. Finally, mining and analysis of data derived from such studies depends on a variety of advanced computational tools.

These approaches are beginning to show results in the area of cancer diagnosis and management. A dedicated effort to apply these technologies to the family of autoimmune diseases is only beginning, but holds great promise.

The availability of the reference human genome sequence will greatly accelerate the identification of disease susceptibility and resistance genes. In addition, ongoing efforts to fully sequence the genomes of animal models, including mouse and rat, will be enormously important in understanding the genetics of autoimmune diseases. Similarly, clinical databases, disease registries, and repositories will greatly accelerate such efforts.

The NIH Roadmap

In the spring of 2002, the NIH Director initiated a wide-ranging effort to chart a clear course for biomedical research in the 21st century. The process involved consultation with more than 300 experts in academia, industry, and the public. Designated as the NIH Roadmap, the resulting series of initiatives will enable NIH as a whole to tackle complex challenges in biomedical research that are beyond the grasp of any single institute.

Three major themes that emerged in this planning process are now being addressed in a series of initiatives issued in FY 2004: (1) *New Pathways to Discovery*; (2) *Research Teams of the Future*; and (3) *Re-engineering the Clinical Research Enterprise*. The *New Pathways to Discovery* initiative includes support for resources such as libraries of molecules used to probe biological networks and identify potential targets for new therapies; imaging probes for molecular and cellular events; improved computational infrastructure for biomedical research; and nanotechnology devices capable of viewing and interacting with basic life processes. *Research Teams of the Future* addresses challenges posed by the increasing scale and complexity of contemporary biomedical research. This initiative will support interdisciplinary teams of investigators in the biological and physical sciences, and will encourage high-risk research and public-private partnerships. *Re-engineering the Clinical Research Enterprise* will foster new partnerships among academic researchers, organized patient communities, and community-based health care providers. Individual initiatives will support new standards for exchanging clinical information; harmonizing clinical research regulatory processes; improving technologies for assessment of clinical outcomes; developing new paradigms for interactions between NIH-funded investigators and patient advocates; and formulating new strategies for educating and training the current and future clinical research workforce. A major goal of this initiative is to engage and empower the public in the research process.

The family of autoimmune diseases is remarkable for its complexity and similar underlying mechanisms despite the involvement of multiple organ systems.

The family of autoimmune diseases is remarkable for its complexity and similar underlying mechanisms despite the involvement of multiple organ systems. Patients with autoimmune diseases fall under the care of physicians in a wide range of medical and surgical specialties. As such, autoimmune diseases research stands to benefit tremendously from the resources and knowledge generated through the NIH Roadmap. Patients with autoimmune diseases are fortunate to be represented by a large number of advocacy groups that will be welcome partners in many of the NIH Roadmap activities. For more information on the NIH Roadmap, see www.nihroadmap.nih.gov.

Current NIH Investment in Autoimmune Diseases Research

NIH expenditures for autoimmunity and autoimmune diseases research totaled $591.2 million in FY 2003, an increase of 36 percent over the FY 2000 total of $435.3 million. Table 1 lists FY 2003 NIH expenditures for autoimmune diseases research by Institute and Center. Because the majority of NIH awards are for multi-year projects (with an average duration of about four years), a relatively small fraction of the funds available in any year are devoted to new research endeavors. (The tables and figures in this section do not include funding from the Special Appropriation for Research on Type 1 Diabetes. The narrative in this report, however, describes initiatives funded in part by this appropriation, but not initiatives for which it is the sole funding source. A number of reports describing research funded by the Special Appropriation for Research on Type 1 Diabetes appear at http://www.niddk.nih.gov/federal/planning.htm#b).

TABLE 1: **FY 2003 NIH Expenditures for Autoimmune Diseases Research**

NIAMS	$	129,237,860
NIAID	$	107,293,900
NIDDK	$	105,044,824
NINDS	$	75,428,077
NEI	$	54,756,860
NHLBI	$	30,295,152
NCRR	$	19,521,075
NIDCR	$	16,562,521
NICHD	$	13,353,608
NIMH	$	9,210,875
NCI	$	8,686,585
NIEHS	$	6,640,615
OD	$	3,750,000
NINR	$	3,279,168
NCCAM	$	3,246,270
NHGRI	$	3,224,900
NIA	$	763,392
NIAAA	$	313,750
NIDCD	$	292,640
NIBIB	$	220,795
NCMHD	$	101,863
NIH TOTAL	**$**	**591,224,730**

FIGURE 1: **Comparison of Total NIH and NIH Autoimmune Research Funding (FY 1998-2003)**

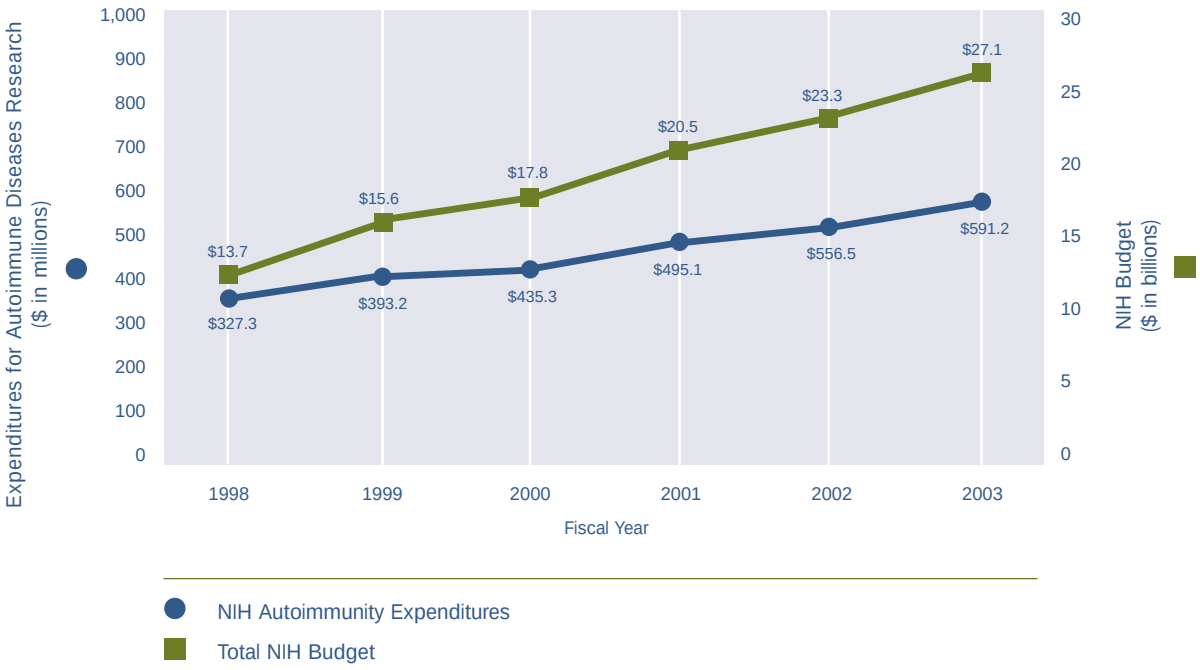

Figure 1 shows both NIH funding for autoimmune disease research and total NIH funding for the period FY 1998 to FY 2003. NIH funding of autoimmune diseases research increased approximately 80 percent over this time. The pace of this increase roughly paralleled the doubling of the NIH budget over the same interval. In 2003, however, biodefense research received unusually large funding increases, which contributed to the divergence of the funding curves.

FIGURE 2: **FY 2003 NIH Autoimmune Diseases Funding by Scientific Category (dollars in millions)**

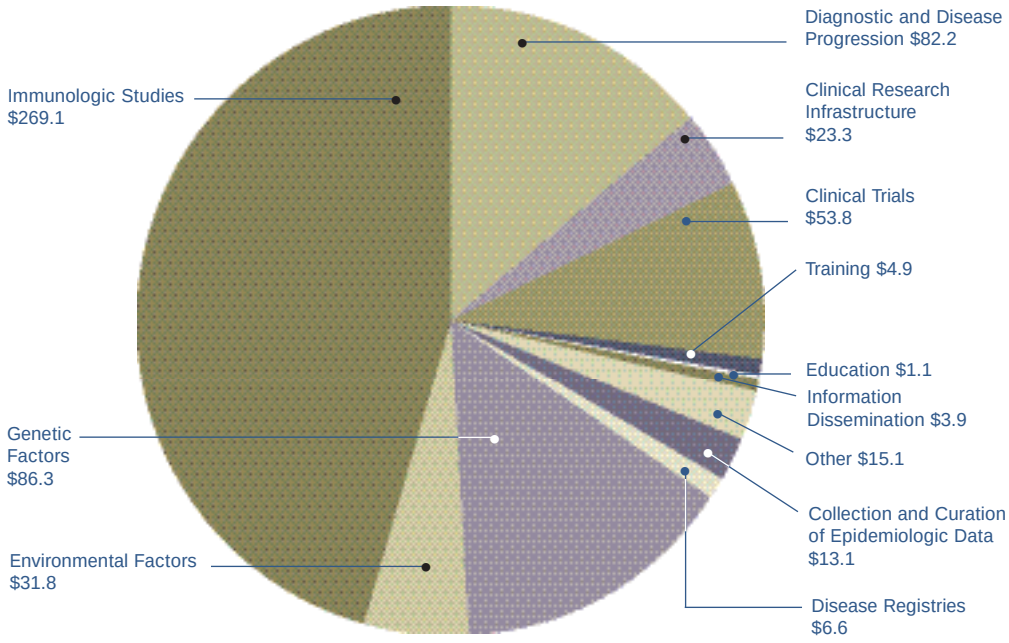

Figure 2 displays FY 2003 NIH funding by scientific category. As in past years, the largest expenditures were for fundamental studies of the genetic, environmental, and immunologic factors underlying autoimmune diseases. Substantial investments were made for studies related to diagnosis and disease progression, clinical research infrastructure, and conduct of clinical trials. It is important to note that many projects focus on several scientific questions and are thus difficult to place into a single category. For example, a training grant that focuses on training scientists in epidemiology could be classified in two areas that are relevant to this figure. Because projects were categorized according to their primary area of emphasis, Figure 2 may underreport data for certain research categories.

FIGURE 3: **NIH FY 2003 Autoimmune Diseases Research Funding by Disease or Organ Involvement**

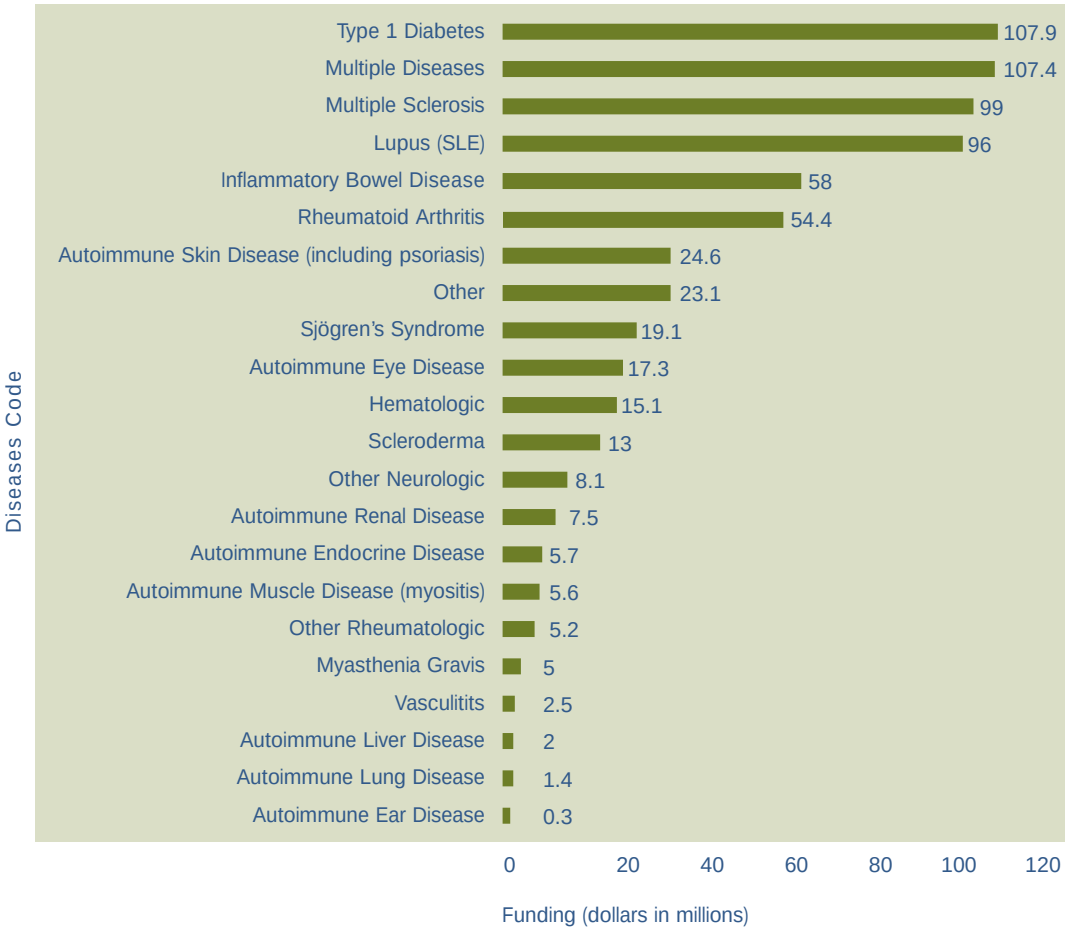

Figure 3 shows FY 2003 expenditures by autoimmune disease. NIH annually reports expenditures for autoimmune diseases research, as well as expenditures for systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), scleroderma, and myasthenia gravis (MG) (http://www.nih.gov/news/fundingresearchareas.htm). The expenditures listed for these five diseases are total NIH expenditures, which include research not coded to autoimmunity. The figure above lists expenditures for these five diseases in addition to expenditures for the autoimmune component of other autoimmune diseases. Projects focusing on factors common to multiple autoimmune diseases are included in the "multiple diseases" category. Because the figures for SLE, MS, IBD, scleroderma, and MG include more than just the autoimmune research component, the table is not additive to the total NIH autoimmune figure of $591.2.

NIH Funding Mechanisms

NIH supports both extramural research, largely through grants and contracts awarded to medical schools, academic institutions, and other research organizations, and intramural research, conducted in NIH-operated laboratories, most of which are located on the NIH campus in Bethesda, Maryland. The largest share of extramural research is funded through investigator-initiated, unsolicited grants that are judged to be of high scientific merit and technical feasibility by the NIH review system. This review system is two-tiered: it includes initial peer review by panels of scientific experts and secondary review by the National Advisory Councils of the NIH Institutes and Centers.

While continued support of unsolicited research is critical to the NIH mission in basic science, capitalizing on the most promising opportunities requires targeted research programs supported by funding dedicated to solicited research initiatives. Such initiatives are underway in multiple areas, including animal model studies to assess the safety and efficacy of promising therapies; the establishment of clinical research networks; the development and validation of biomarkers through clinical research; and the use of new and emerging technologies to identify high-risk populations, and for patient screening, diagnosis, and management. These solicited programs are also vital to foster collaboration among basic immunologists, clinicians, and scientists from disciplines such as bioinformatics and the chemical and physical sciences.

Because autoimmune diseases can affect virtually every organ of the body, research on these disorders spans multiple NIH Institutes. Despite their variability, however, these disorders are considered to be a family of diseases with many common features. Accordingly, research collaboration among Institutes is essential to progress. Collaboration allows NIH to leverage funding, pool resources, optimize scientific expertise, build synergy across the autoimmune research community, and facilitate communication among researchers and clinicians studying different diseases. NIH's emphasis on collaboration in autoimmune research is reflected in the number of cosponsored initiatives: as many as 45 of 77 ongoing solicited research programs are sponsored by more than one Institute.

FIGURE 4: **Solicited and Unsolicited Research Funding for Autoimmune Research in FY 2003 (dollars in millions)**

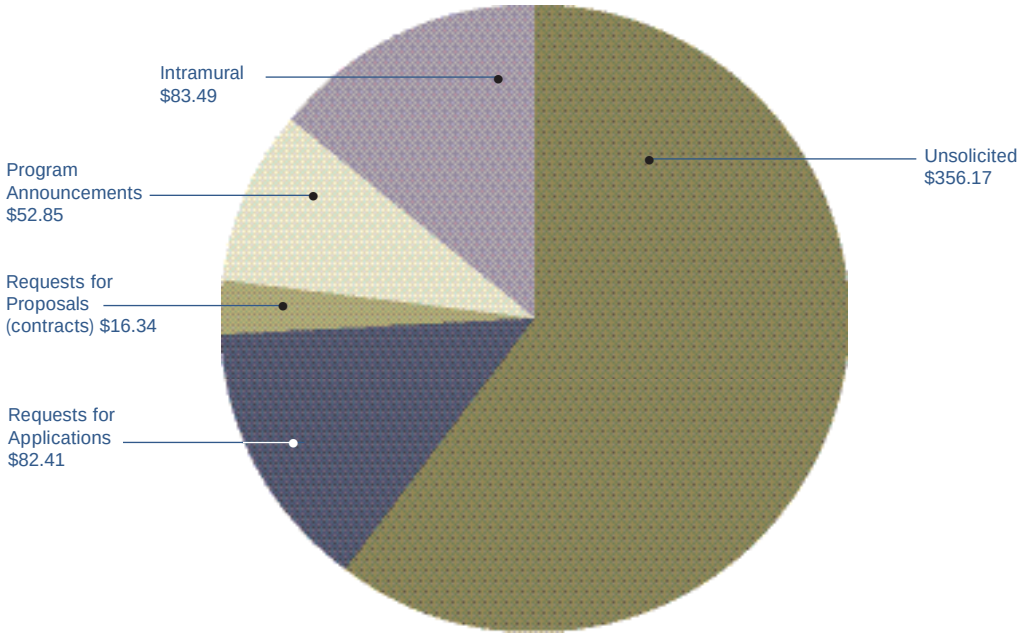

Figure 4 shows FY 2003 solicited and unsolicited funding for projects in autoimmune disease research. As illustrated, 14.1 percent of autoimmune disease research funding is devoted to projects conducted in NIH intramural laboratories. The balance is used for extramural research, of which 70.2 percent goes to investigator-initiated, unsolicited research project grants and 29.8 percent is targeted to specific research emphasis areas and solicited through initiatives published in the NIH Guide to Grants and Contracts.

Organization of the Report

The remaining chapters of this report provide relevant background and progress related to the four thematic areas and the major components of the 2002 ADCC Autoimmune Diseases Research Plan:

- The Burden of Autoimmune Diseases
- The Etiology of Autoimmune Diseases
- Diagnosis, Treatment, and Prevention
- Training, Education, and Information Dissemination

To provide context for those readers unfamiliar with the Research Plan submitted to Congress in December 2002, each chapter begins with a condensed background section. Each chapter then describes the major NIH research initiatives that address the objectives of the Research Plan. Each chapter also highlights a representative sample of NIH-funded scientific activities and achievements. The report concludes with a synopsis of soon-to-be-funded initiatives (not yet awarded at the time this report went to press), as well as others in development or planned for FY 2005 and 2006. Although two years is a relatively short time over which to assess scientific progress, taken together, these initiatives highlight NIH progress in meeting many objectives of the 2002 Research Plan. Appendices include: the 2002 ADCC Autoimmune Diseases Research Plan (Appendix A), NIH initiatives related to autoimmune disease (Appendix B), Autoimmune Diseases Coordinating Committee Roster (Appendix C), relevant excerpts from the Children's Health Act of 2000 (Appendix D), a list of acronyms used in this report (Appendix E), and a glossary of scientific and medical terms (Appendix F).

CHAPTER 1

The Burden of Autoimmune Diseases

Introduction

The burden of a human disease should be counted not only in terms of dollars spent on health care for people directly affected, but as the total cost to society. It must take into account the number of individuals who are ill and the direct and indirect effects of the illness on patients, their families, their associates, and the public. Patient and family burden may include economic losses (potentially including lost wages, loss of health insurance, out-of-pocket health care costs, and reduced ability to secure life, health, or disability insurance, mortgages, or loans), altered or abandoned career or educational goals, and stress, suffering, and uncertainty. Burden includes both the loss of work productivity and diminished contributions to the community at large. While the direct costs are difficult to quantify, the indirect effects may be virtually immeasurable in dollar terms. However, a more complete understanding of the true burden of autoimmune diseases is essential in order to mobilize the resources to minimize it.

Estimates of disease burden usually begin with epidemiologic studies of disease distribution in populations. These studies gather data on the number of affected individuals, the duration and severity of disease, and disease outcomes. Quantitative measures of the incidence, prevalence, morbidity, and mortality associated with the disease can be derived from these data. These estimates then can be used to identify factors associated with disease occurrence and provide clues to the causes of the disease.

Incidence, Prevalence, Morbidity, and Mortality of Autoimmune Diseases

Incidence is the rate at which new cases of a disease occur relative to population size and the passage of time. At present, few data exist that can be used to estimate the incidence of autoimmune diseases on a national scale. While some studies provide estimates for individual autoimmune diseases, these studies have been relatively small and geographically limited. Because of these limitations, scientists cannot extrapolate from these studies to generate national incidence data.

Prevalence is the ratio of the number of existing cases of a disease (active and in remission) in a population at a specific point in time to the total number of persons in the population.

Prevalence estimates take into account both the occurrence of new cases and duration of the disease, and therefore reflect both the natural history of the disease and the availability of treatments. Because autoimmune diseases are chronic, prevalence rates are usually high despite relatively low annual incidence rates.

Household survey data have been used to estimate prevalence for a number of more common autoimmune diseases. Many of these surveys, however, are limited because of the relatively small sample size, particularly in the case of the less common autoimmune diseases. In addition, because most household surveys rely on self-reporting of disease, they can lead to over-reporting or under-reporting.

The lack of reliable figures on the incidence and prevalence of autoimmune diseases significantly hampers research on these disorders. It is important to know the populations and individuals that are most susceptible to autoimmune diseases in order to understand the genetic and environmental factors that contribute to their onset. Moreover, without better disease surveillance studies, progress in treatment and prevention will be constrained.

Morbidity refers to the severity and complications of illness. Commonly used measures of morbidity include the number of days of hospitalization due to a specific disease, days lost from work or school, physician visits associated with a disease, and days of restricted activity. These measures can be used to estimate the impact of a disease in both monetary and non-monetary terms.

Unfortunately, we currently lack rigorous quantitative estimates of morbidity for most autoimmune diseases. The National Hospital Discharge Survey provides data on primary and secondary diagnoses, as well as reasons for hospitalization. These data, however, may not reflect the true morbidity associated with autoimmune disease because most patients are seen in an outpatient setting. Due to the scarcity of data sources, most of our understanding of the morbidity associated with autoimmune disease is based upon the impressions of physicians and patients.

Mortality is the number of deaths caused by a specific disease, including any deaths that result from treatment of the disease. This information is typically assembled from death certificates. Information is often lacking, however, about underlying factors that led to a person's death but are not listed as the immediate cause. It is likely, therefore, that estimates of autoimmune disease mortality based on death certificates alone understate the true magnitude of the problem.

Generating Incidence and Prevalence Estimates for Autoimmune Diseases

The most recent, large-scale study to determine *incidence* rates for autoimmune diseases was published in 1997 by Jacobsen and colleagues (*Clinical Immunology and Immunopathology,* 84:223-243, 1997). The investigators conducted an extensive review of more than 140 studies published between 1965 and 1995 that provided incidence estimates for autoimmune diseases. Controlled studies were available for only 24 of the estimated 80 autoimmune diseases. Based on data from these studies, Jacobsen et al. estimated an annual incidence of 1.3 new cases for every 1,000 females and 0.5 new cases for every 1,000 males in the United States in 1996. Although this study has stimulated additional epidemiological research on autoimmune diseases, it has several important limitations. Many of the source studies were conducted more than two decades earlier and other evidence now suggests that the incidence of many autoimmune diseases is increasing. The source studies focused on small populations in geographically localized areas, and contained only limited information on different populations. Further, diagnostic criteria used to identify and confirm cases varied substantially among different studies of the same autoimmune disease, hindering cross-study analyses.

Jacobsen et al. also reviewed more than 130 published studies in an effort to estimate the *prevalence* of autoimmune diseases. From this analysis, the investigators estimated that in 1996, 8.5 million people in the United States – 3.2 percent of the population – had at least one of the 24 autoimmune diseases evaluated in their studies. Current estimates of the prevalence of all autoimmune diseases range from 5 to 8 percent of the U.S. population; this corresponds to between 14.7 and 23.5 million people, based on August 2004 Census Bureau figures.

More recently, Cooper and Stroehla (*Autoimmunity Reviews*, 2:119-128, 2003) extended the Jacobsen analysis by examining incidence and prevalence data on autoimmune diseases that were not included in the 1997 study. In this study, the investigators confirmed the disproportionate occurrence of these diseases among women, and noted that the temporal pattern of incidence differs among the autoimmune diseases that have been studied most extensively. For example, incidence of type 1 diabetes has increased worldwide over the past 40 years, while incidence of rheumatoid arthritis seemingly has declined during this time period.

Only one study has estimated total mortality from autoimmune disease in the United States. Using data for 1995 from the CDC's National Center for Health Statistics, Walsh and Rau (*American Journal of Public Health*, 90:1463-1466, 2000) found that well-defined autoimmune diseases collectively were among the top ten leading causes of death for women in every age group up to 64 years of age.

The Disparate Impact of Autoimmune Diseases

Most autoimmune diseases disproportionately affect women. For some diseases, such as thyroiditis, scleroderma, lupus, and Sjögren's syndrome, more than 85 percent of patients are female. This gender disparity is smaller, though still substantial, in other autoimmune diseases, such as multiple sclerosis, myasthenia gravis, and inflammatory bowel disease. A few diseases, such as type 1 diabetes, affect men and women almost equally, whereas others, such as ankylosing spondylitis, occur more frequently in men. The reasons for these gender-based differences are not well understood, but the production of sex hormones is probably one important factor, since the disparities generally do not appear until puberty and tend to diminish after menopause.

Some reports suggest that autoimmune disease rates differ among racial groups, although the epidemiologic evidence is not always firm. Some research suggests that an objective definition of race does not exist among humans; in fact, data from the Human Genome Project has indicated that distinct races do not exist biologically. The racial and ethnic classifications typically used in research conform to those defined by the U.S. Census Bureau, and these have changed over time. Moreover, individual racial identifications are either self-reported or assigned by a census taker.

These classification problems notwithstanding, however, some generalizations can be made. Americans of African origin seem to be at higher risk than Americans of European origin for lupus and scleroderma, but are at lower risk for type 1 diabetes, thyroiditis, and multiple sclerosis. High rates of certain autoimmune diseases have been reported in specific Native American groups. Asian Americans living in Hawaii have among the lowest rates of some autoimmune diseases, such as multiple sclerosis and type 1 diabetes, but these rates seem to increase in Asian Americans who move to the United States mainland. Observations such as these illustrate the difficulty of separating relevant genetic factors from environmental influences such as diet, infectious agents, occupational and residential exposures, and lifestyle factors such as stress. (See also Chapter 3, Etiology of Autoimmune Diseases.)

The Role of Disease Registries in Autoimmune Disease Research

There are two types of disease registries, each of which has advantages and disadvantages. *Active registries* include all people with a particular disease (and often include matched controls) in a defined population. Full recruitment depends upon methods such as a careful survey of the population to ensure that all affected patients in the population are identified. The registry population may or may not reflect national demographics. Active registries can provide information not obtainable in any other way. They can be used to estimate disease prevalence in particular populations, compare rates among ethnic and racial groups or between genders, and provide information about family history, diet, environmental exposures, and the co-occurrence of other autoimmune diseases. Registries in which sampling is repeated periodically offer additional opportunities to better understand the natural history of a disease and identify warning signs that appear before the onset of clinical symptoms.

Passive registries are established when patients with a disease come forward voluntarily. The diagnosis for these individuals may be established with varying degrees of certainty and the composition of the patient cohort may not be representative of the population in general. Passive registries are sometimes established by patient advocacy groups. They have proven to be of great value in identifying populations suitable for studies of disease biomarkers and for conducting clinical trials.

Progress

The 2002 ADCC Autoimmune Diseases Research Plan identified opportunities in the following broad areas: (1) support of population-based epidemiological studies; (2) support of new and existing disease registries; and (3) development of improved methods to identify and track patients in clinical and epidemiologic studies. Since publication of the Research Plan, NIH has established new disease registries, launched new collections of epidemiologic data, and maintained support for more than a dozen existing autoimmune disease registries. Specific achievements and highlights of the new and ongoing disease registry efforts are provided in the narratives that follow. Highlights of research to identify and track patients in clinical and epidemiologic studies are provided in the chapters on etiology of autoimmune diseases and clinical research.

Collection and Curation of Epidemiologic Data

- **Diabetes Autoimmunity Study in the Young (DAISY)** is a prospective epidemiologic study of newborns that documents early childhood diet, infections, and vaccinations in an effort to understand the complex mechanisms that underlie the development of type 1 diabetes. The study group has established two unique cohorts that have as much as a 20-fold increased risk of type 1 diabetes: a cohort of newborns related to persons with type 1 diabetes and a cohort of newborns with type 1 diabetes associated HLA DR-DQ alleles identified from the general population. Onset of autoimmunity is monitored by measurement of islet autoantibodies in study participants at regular intervals. Children in the DAISY cohort are followed until the clinical diagnosis of type 1 diabetes or until they reach 15 years of age.

- In partnership with a private organization, NIH is conducting the **Prospective Assessment in Newborns for Diabetes Autoimmunity (PANDA)**. This is an ongoing epidemiologic study of 23,000 infants at genetic risk for diabetes through which researchers hope to detect the earliest changes in gene expression that occur as type 1 diabetes develops. The study has already identified an important immunologic basis for the autoimmune attack on the insulin-producing beta cells of the pancreas – a finding that now may be used as a target for therapy. Investigators are also initiating studies of evanescent proteins present during the earliest autoimmune attack on the beta cell. This high technology research should reveal new targets and pathways for the development of rational molecular interventions.

- A major initiative, called **Health Disparities in Rheumatic, Musculoskeletal, and Skin Diseases,** promotes the design, development, and testing of hypothesis-driven, innovative approaches to eliminating health disparities in these disorders. The initiative particularly encourages study of potentially modifiable environmental, social, and behavioral factors and of the gene-environment interactions that may underlie ethnic/racial disparities in disease prevalence and outcome. This initiative also encourages the development of descriptive and analytic epidemiologic studies needed to further characterize health disparities in autoimmune rheumatic, musculoskeletal, and skin diseases.

- The **Agricultural Health Study** is a longitudinal examination of the relationship between exposures related to farming (primarily pesticides) and diseases, including autoimmune diseases, in a large cohort of farm families. Although the study involves populations in rural settings, the exposures being studied – pesticides, solvents, nitrates, metals,

mycotoxins, and silica – are present in other environments, so the results will be applicable to broader populations.

- The **Carolina Lupus Study** is a population-based, case-control study in eastern North Carolina and South Carolina designed to examine hormonal and environmental influences on the etiology of systemic lupus erythematosus. Systemic lupus erythematosus disproportionately affects women, and in particular African American women, although the reasons for this excess risk are not known. This study offers the opportunity to examine hormonal, occupational, and environmental risk factors in a previously understudied population. These efforts may help to illuminate etiologic pathways and develop prevention strategies for susceptible populations. Environmental exposures under study include silica dust, solvents, heavy metals, and pesticides. The influence of genetic susceptibility to diseases is also being explored.

  Investigators have used data collected in this study to determine whether glutathione S-transferase (GST) polymorphisms and/or environmental exposures affect lupus risk. GST is an enzyme involved in the elimination of reactive oxygen species that may be generated by cellular oxidative stress induced by sunlight. Although the researchers did not find an association between systemic lupus erythematosus and either occupational sun exposure or GST polymorphisms alone, they noted that Caucasians with a specific GST polymorphism and a high degree of sun exposure also had an elevated risk of systemic lupus erythematosus.

- The ability to manage the often disabling symptoms of autoimmune disorders can have a considerable effect on the burden of disease. One project funded through the **Symptom Management for Chronic Neurological Conditions** initiative has examined health promotion and quality of life in individuals with multiple sclerosis. Through a longitudinal study of multiple sclerosis patients in urban and rural settings, investigators have studied barriers to health promotion among people with post-polio syndrome and those with multiple sclerosis. Fatigue and impairment are the most common barriers among both groups. A variety of publications from this analysis also have reported on marital stress and the use of complementary and alternative therapies for these patients.

Key Advances—Collection and Curation of Epidemiologic Data

Ethnicity and Systemic Lupus Erythematosus. Findings from the ongoing LUMINA (Lupus in Minorities: Nature versus Nurture) study of more than 300 African American, Hispanic, and Caucasian lupus patients aged 20 to 50 years indicate that ethnicity, which includes race, cultural values, beliefs, and practices, may affect patients with lupus. Both African American and Hispanic lupus patients tend to develop lupus earlier in life, experience greater disease symptoms at the time of diagnosis (including kidney problems), and have more severe disease overall than Caucasian patients. Further, African American patients have a higher frequency of neurologic problems such as seizures, hemorrhage, and stroke, while Hispanic patients experience cardiac disease more frequently. Although LUMINA results to date do not indicate that genetic influences are usually responsible for differences in the early course of lupus among these ethnic groups, researchers believe relevant genetic factors will eventually be identified.

Patient and Physician Assessments of Lupus in Minority Populations. Other data from the LUMINA study highlight different perceptions in the burden of disease that may influence health disparities. Researchers compared patients' and physicians' assessments of disease activity and found that these ratings differed in more than half of the cases. Physicians appeared to place more emphasis on laboratory data, while patients placed more emphasis on function. Ethnicity, however, did not account for the discrepancies in perceived disease activity.

Pain and Social Activity in Children with Juvenile Arthritis. Arthritis pain has been the focus of much research in adults, but there is an increasing awareness of the need to focus on pain in children with arthritis. In a recent study, researchers showed that increased anxiety, rather than depressed mood, was significantly associated with increased fatigue and pain frequency and intensity. Increased pain and fatigue were linked to reduced participation in school and social activities. In addition to treating pain aggressively with traditional pharmacologic therapies, the researchers also recommend including behavior-altering medication and cognitive-behavioral therapy to treat anxiety in children with juvenile arthritis.

Helping Mothers Deal with a Young Child's Diabetes. The incidence of type 1 diabetes among children under five years of age has been increasing. For parents, dealing with a young child with this chronic disease presents many challenges related to diet, meal planning, symptom recognition, and blood glucose monitoring. Investigators examining the experiences of mothers of young children with diabetes found that over half had stopped working due to the increased demands of caring for their child. Several stated that the care needs were "constant". Primary concerns included hypoglycemic reactions, worry about their child's future, time demands, and disease management. Many reported that assistance from health care providers and from family and friends helped them cope with the daily demands of diabetic care.

Disease Registries

New and ongoing autoimmune disease registries include:

- The **Collaborative Islet Transplant Registry (CITR)**, established in 2001, expedites progress and promotes safety in islet/beta cell transplantation through the collection, analysis, and communication of data from all islet/beta cell transplants performed in North America. This registry will permit investigators from participating transplant centers in the United States, Canada, and Europe to compile and analyze islet/beta cell transplantation data in an effort to identify critical risk factors and key determinants of success. Such information can be used to guide transplant centers in developing and refining islet/beta cell transplant protocols. In the 2004 annual report of the CITR, researchers from 12 participating medical centers in the United States and Canada detailed the experiences of 86 type 1 diabetes patients who had received at least one islet transplant between 1999 and 2003. The investigators reported that 61 percent of the patients no longer had to inject insulin six months after transplantation. One year after the procedure, 58 percent were still insulin independent. Researchers will continue to monitor patients to see how long they remain insulin independent.

- The **Multiple Autoimmune Diseases Genetics Consortium (MADGC)** is a collaborative effort to establish a repository of genetic material and clinical data collected from 400 multiplex families (three or more affected individuals) affected by two or more of the following autoimmune diseases: rheumatoid arthritis, juvenile rheumatoid arthritis, type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, autoimmune thyroid disease, psoriasis, and inflammatory bowel disease. One site manages the central repository of families, and two additional sites participate in the data collection effort. Data and samples from these families are available to researchers for studies intended to identify and characterize genes involved in susceptibility or resistance to autoimmune diseases.

- The **International Research Registry Network for Sjögren's Syndrome** has three overall objectives: (1) develop standardized diagnostic criteria for Sjögren's syndrome for use in disease research, prevention, diagnosis, and treatment, (2) collect, process, and store patients' clinical data and specimens, and (3) provide these resources to researchers interested in Sjögren's syndrome research. The registry was established in 2003 and began patient enrollment in November 2004. Participating countries include Argentina, China, Denmark, and Japan. Each participating site is gathering patients' medical and family histories and performing oral and ocular examinations. Blood, tear,

and saliva samples also are being collected and biopsies of labial salivary glands are being obtained. Follow-up visits will be scheduled during the second year of the study. The registry is currently enrolling patients with primary Sjögren's syndrome, although patients with secondary Sjögren's syndrome may be included at a later time. The availability of well-characterized biological materials from patients will help investigators design studies to increase understanding of Sjögren's syndrome prevalence and uncover the precise etiology, pathogenesis, and impact of this disease on oral and general health.

- **Search for Diabetes in Youth (SEARCH)**, a five-year, multicenter study, is developing a uniform, population-based approach to estimating type 1, type 2, and other forms of diabetes in a population of approximately five million children. SEARCH consists of six clinical centers, a laboratory center, and a data coordinating center. These centers are expected to have access to about 7,000 prevalent cases and 800 incident cases of diabetes per year over a five-year period. The majority of cases are expected to be type 1 diabetes. The study has three operational phases. The first phase, focused on developing an organizational framework, study objectives and protocol, and communications and management systems, has been completed. The goal of the second phase is to conduct complete ascertainment, recruitment, in-person visits, and laboratory analyses of all prevalent cases of diabetes in 2001. As of April 2004, 6,059 cases had been registered, and in-person visits had been initiated. The goal of phase three, which began in summer 2002, is to conduct ascertainment, recruitment, baseline and follow-up visits, and laboratory analyses of incident cases of diabetes for years 2002 to 2005. For the years 2002 and 2003, 1,238 and 1,029 incident cases of diabetes, respectively, were identified and registered. SEARCH is led by the CDC and cosponsored by NIH.

- The **Consortium for the Longitudinal Evaluations of African Americans with Early Rheumatoid Arthritis (CLEAR)** collects clinical and x-ray data and DNA to help scientists analyze genetic and nongenetic factors that might predict disease course and outcomes of rheumatoid arthritis. Academic centers in the southeastern United States have enrolled and are following more than 200 African American patients with early rheumatoid arthritis. In addition, biological samples and clinical data have been provided to four other research projects investigating markers of disease progression and bone changes associated with this disease.

- The **Research Registry for Neonatal Lupus** provides material for basic research on the causes of this disease, tracks important epidemiological data such as incidence, and facilitates

family counseling. Registry data will facilitate development of improved methods of diagnosis, prevention, and treatment.

- The **National Alopecia Areata Registry** classifies medical and family history data for patients with three major forms of alopecia: alopecia areata, alopecia totalis, and alopecia universalis.

- The **National Registry on Antiphospholipid Syndrome** collects and updates clinical, demographic, and laboratory information from patients with antiphospholipid syndrome (APS) and makes it available to researchers and medical practitioners. Registry scientists collect data on patients with clinical signs of APS and on asymptomatic individuals who have antibodies but have not yet developed any clinical signs of the disease.

- The **National Epidermolysis Bullosa Registry** focuses on clarifying the underlying causes of this disease, improving methods of diagnosis, and developing effective methods of treatment and prevention. More than 3,000 individuals with all forms of epidermolysis bullosa have been enrolled to date. Where indicated, selected diagnostic procedures, such as immunomapping and electron microscopy, are available.

- The **Scleroderma Registry** identifies cases of systemic sclerosis; verifies all diagnoses; provides a continuous update of scleroderma prevalence, incidence, and mortality; and establishes prospectively average rates of annual mortality. A major focus of the registry is to establish a cohort of incident cases for early intervention trials and genetic studies, as well as for basic science and other clinical and epidemiologic studies. More than 200 individuals have been enrolled to date. Using data from this registry, scientists have made significant progress in identifying DNA regions that may be linked to disease. Registry samples and research data have also been instrumental in advancing new projects examining the expression of immune system genes and antibodies to nuclear components.

- The **Research Registry for Juvenile Rheumatoid Arthritis** collects data on multicase families with affected sibling pairs and is developing a related genomics program to identify susceptibility genes for this disease. Scientists have hypothesized that juvenile rheumatic disease is a complex genetic trait. The Juvenile Rheumatoid Arthritis (JRA) Affected Sibling Pair Registry has been expanded to explore this hypothesis and serve as a national resource for genetic research. The discovery phase of this effort is exploring the genome using high-throughput technology to identify chromosome regions and

genes involved in JRA susceptibility. This goal will be accomplished by: (1) expanding both multiplex (families with two or more affected members) and simplex (families with one affected member) family DNA collections by maintaining DNA sample collections for distribution to researchers, (2) performing single nucleotide polymorphism (SNP) typing of chromosomal regions of interest as well as identifying candidate genes, (3) organizing a consensus conference to facilitate collaboration, and (4) promoting exploratory projects, such as exploratory proteomics analyses. Through this effort, scientists hope to apply knowledge gained from the Human Genome Project to benefit children with chronic autoimmune arthropathies.

- The **Lupus Registry and Repository** supports a core facility dedicated to collecting and characterizing multiplex lupus pedigrees. The registry currently includes 624 pedigrees; 287 of these include multiple cases that are especially useful for genetic linkage analyses. DNA, plasma, and serum samples are provided to more than 28 other projects across the country. The registry also distributes its annual Lupus Linkage Newsletter to all study participants, referring physicians, and patient advocacy organizations.

- The **North American Rheumatoid Arthritis Consortium** operates a national registry dedicated to identifying and characterizing sibling pairs with rheumatoid arthritis. The goals of the registry are: (1) to collect data from at least 1,000 families in which two or more siblings are afflicted with rheumatoid arthritis and (2) to search for genes that predispose to rheumatoid arthritis, with the ultimate goals of understanding the cause of this disease and improving diagnosis and treatment. This project will provide resources to enable the discovery of the specific genes involved in the susceptibility and outcome of rheumatoid arthritis. Such resources generally consist of clinical information and biological material from well-defined patient populations, and databases containing data on clinical phenotype, genotypes, and other biomarkers. These databases and biological repositories are designed to allow for the addition over time of new information, such as clinical follow-up, genotyping, and other biomarkers. More than 1,000 sibling pairs with rheumatoid arthritis are currently enrolled; the collection is currently being enhanced with the recruitment of trios and a case control cohort of 1,000 control individuals.

- The **Human Specimens Bank** is a registry for patients with multiple sclerosis and other neurological disorders who wish to donate their brains posthumously for use in research. The repository has been a valuable resource for multiple sclerosis researchers.

CHAPTER 2

The Etiology of Autoimmune Diseases

Introduction

Fundamentally, all autoimmune diseases are a consequence of impaired immune function that results from interactions of genetic and environmental factors. Despite important progress, much remains to be learned about these factors and their interactions. Advances in this area are providing a foundation for more effective therapies and prevention strategies.

Immune Dysfunction

A principal function of the immune system is to eliminate infectious agents, while not attacking the body's own tissues. Whereas autoimmunity – an immune response to self – occurs to some degree in all normal individuals, autoimmune disease – the pathologic consequence of an autoimmune response – is relatively infrequent. To limit autoimmune responses and minimize the chances of harm, the body employs a number of mechanisms referred to collectively as *self-tolerance*.

Self-reactive B and T lymphocytes are eliminated during their development in the bone marrow or thymus by *negative selection*. This process, referred to as *central tolerance*, is somewhat "leaky" and a few self-reactive B and T cells escape into the blood of all individuals. *Peripheral tolerance* is the process by which autoreactive cells are controlled so as not to damage cells and tissues. *Anergy*, *immunologic ignorance*, and active *regulation* are three major mechanisms involved in peripheral tolerance.

Anergy occurs when self-reactive lymphocytes encounter their particular antigen without the help of the secondary co-stimulatory signals needed to initiate an immune response. Under these conditions, the lymphocytes may remain in a state of prolonged unresponsiveness until the co-stimulatory signals are provided. The missing co-stimulatory signals may be provided by tissue inflammation due to infection, which would then trigger a destructive autoimmune response.

Immunologic ignorance occurs when self-reactive lymphocytes encounter very low levels of their corresponding antigen or fail to detect antigen, perhaps because they do not localize in the appropriate site. Under these conditions, lymphocytes remain in an unresponsive state, but retain the ability to respond if appropriately stimulated. Localization of lymphocytes is influenced by production of attraction molecules and adhesion molecules

on the lining of blood vessels; together, these determine the pattern of lymphocyte migration through the body. Local injury or infection may stimulate the production of these molecules, causing self-reactive lymphocytes to migrate to the site where they will encounter their antigen and initiate an autoimmune response.

Regulatory mechanisms include specialized populations of T cells and antigen-presenting cells that control immune responses. These cells secrete cytokines and other factors that directly or indirectly reduce the activity of any potentially autoreactive T and B cells nearby or block the migration of pathogenic T cells into target organs. Other regulatory cells release substances that counteract tissue injury or promote healing. The importance of regulatory T cells is exemplified in humans by the IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X* linked) syndrome, in which a defective gene interferes with T regulatory cell production.

In-depth knowledge of these mechanisms has enabled the development of many new drug candidates and is stimulating translational research to bring the most promising of these to clinical testing. Moreover, some previously licensed drugs that target particular mediators of inflammation, such as tumor necrosis factor alpha (TNF-α), are now being used in an expanding range of autoimmune diseases with shared inflammatory pathways.

Genetic Factors

The tendency to develop an autoimmune disease is in part hereditary. Initially, clinicians observed that a single patient may develop more than one autoimmune disease and that related members of the same family may share an autoimmune disease. These observations led to rigorously controlled epidemiologic studies comparing the occurrence of autoimmune diseases in genetically identical twins to the occurrence of these diseases in nonidentical twins. Several such studies reported a concurrence rate between identical twins of 15 percent to 50 percent, with a mean of approximately 30 percent. In contrast, nonidentical twins have about the same risk of developing an autoimmune disease as any other sibling, about two to five percent. Therefore, heredity is estimated to account for about one-third of the risk of developing an autoimmune disease. In contrast to other inherited diseases (such as cystic fibrosis, Tay-Sachs disease, or sickle cell disease) that result from disease-causing mutations in a single gene, most autoimmune diseases result from the combined effects of several genes that must act in concert to determine disease susceptibility. The disease-related versions of these genes may be relatively common in the population, but unless present in combination they are not associated with disease.

Some genes affect the immune response itself, whereas others increase the vulnerability of the target organ to autoimmune attack. Of all such genes identified to date, the most completely characterized are members of the family of genes of the major histocompatibility complex, or MHC. These genes are determinants of tissue compatibility and are thus responsible for tissue graft rejection. This group of genes – in humans referred to as HLA (human leukocyte antigens) – also controls key steps in the immune response, especially those related to recognition by T cells of specific antigens presented to them by antigen-presenting cells.

Another prominent group of genes associated with the incidence of autoimmune diseases encode components of co-stimulatory pathways such as cytotoxic T lymphocyte antigen 4 (CTLA-4). This surface molecule on T cells initiates a series of events that limit lymphocyte proliferation, so that blocking CTLA-4, or deleting it genetically, enhances autoimmune disease in experimental animals. Other genetic traits that determine inherited susceptibility to autoimmune disease act through particular cytokines, which are molecules immune system cells use to communicate among themselves.

Environmental Factors

Approximately one-third of the risk of developing an autoimmune disease can be attributed to heritable factors; the remainder is thought to be associated with non-inherited events. Some of these events arise from the randomness that characterizes human exposures and others from the diversity of the immune system itself – a diversity that enables the immune system to recognize a broad range of bacteria and viruses. These environmental factors account for the occurrence of autoimmune disease in only one member of a pair of genetically identical animals or identical twins.

Certain environmental agents play a clear role in instigating autoimmune processes. For example, drugs such as procainamide and hydrolyzine can induce a lupus-like syndrome in genetically-susceptible individuals that remits when the drug is discontinued. Other drug-induced autoimmune diseases have been described, including some of the hemolytic anemias, thrombocytopenias, and leukopenias.

The possible role of exposure to various metals in autoimmune disease has been explored, primarily through laboratory and animal studies. Generally, metals inhibit immune cell proliferation and activation, with notable exceptions. Mercury, gold, and silver, for example, can induce lymphocyte proliferation and subsequent autoimmunity. Genetically-susceptible

mice develop a lupus-like condition when dosed with mercury, silver, or gold. It is likely, however, that the autoimmune disorders that result from exposure to various metals occur through distinct mechanisms.

Abnormal immune responses may also be due to a deficiency of a specific substance. For example, selenium deficiency has been linked with autoimmune thyroiditis and cardiomyopathy in humans; some people with these disorders improve when given selenium supplements. As with studies of the role of metals, the mechanism of action remains unclear.

Other environmental exposures have been studied, but associating such exposures with specific disorders is difficult. Some epidemiologic information suggests an association between dietary iodine and iodine-thyroiditis, and between silica and both scleroderma and lupus in certain industrial settings. Additional research has explored possible relationships between autoimmune disease and exposures to organic compounds, principally the halogenated hydrocarbon trichloroethylene (TCE) and polychlorinated biphenyls (PCBs). TCE metabolites have been associated with systemic lupus erythematosus, systemic sclerosis, and other autoimmune disorders. The evidence for PCB effects is sparse. Similarly, a few epidemiologic studies have examined occupational exposures to dioxins; however, firm epidemiologic evidence of a cause and effect association has yet to be shown. Similarly, investigations of exposure to pesticides and estrogenic compounds are areas of considerable research interest, but require additional exploration.

Ultraviolet radiation from sun exposure can exacerbate disease in patients with systemic lupus erythematosus. Other epidemiologic studies suggest that ultraviolet exposure may be protective in multiple sclerosis and rheumatoid arthritis; however, conflicting animal studies indicate that ultraviolet exposure may increase autoimmune disease risk in genetically-predisposed individuals.

Infectious agents are the most often cited environmental factors implicated as triggers of autoimmune diseases. A classic example is the central role of the Group A beta-hemolytic streptococcus in the development of rheumatic heart disease. Acute Guillain-Barré syndrome has been associated with a number of bacterial and viral infections, and reactive arthritis has been linked to a variety of intestinal infections. Indirect evidence has implicated a number of infections in type 1 diabetes mellitus (see inset on page 43) and multiple sclerosis, and has focused renewed attention on the possible role of Epstein-Barr virus (EBV) in lupus and rheumatoid arthritis.

Despite these leads, the exact mechanisms by which infection induces a particular autoimmune disease are unknown. In the case of streptococcus, it is believed that an antigen of the microorganism resembles an antigen present in the heart, and that a cross-reactive immune response to the infecting microorganism causes immune-mediated damage to the heart. This phenomenon is referred to as molecular mimicry. In other instances, microorganisms or local inflammation may alter antigens of the host so that the immune system sees them as foreign. Infections may also increase immune cell expression of co-stimulatory molecules and thus promote autoimmune responses.

Lifestyle Factors

Lifestyle factors may also contribute to the development or progression of autoimmune diseases. For example, nutritional factors that affect immune function and interactions between dietary factors and other exposures are important areas of research. Antioxidants may play a role in immune function, particularly with respect to autoimmunity. Lupus-prone mice show delayed symptom onset or prolonged survival when given antioxidant supplements, as well as when total fat and caloric intake are reduced or dietary fatty acid (e.g., omega-3 fatty acids) content is manipulated. The potential role of diet in autoimmune disease remains an important issue for patients and clinicians.

Smoking has been associated with an increased risk of rheumatoid arthritis in several studies, but inconsistent results were found in studies of smoking and lupus. Smoking may be associated with a reduced risk of ulcerative colitis, an inflammatory bowel disease. It is important to understand the mechanisms through which smoking may affect autoimmune disorders and why different effects are seen across the spectrum of diseases.

Gender Differences

Differences in the immune response of men and women may be related to sex hormones such as androgens and estrogens. Estrogens can stimulate B cell growth, antibody production, and cytokine release, and may be important stimulators of B cell immunity and increased susceptibility to autoimmune disease. In multiple sclerosis – the incidence of which is twice as high in women as in men – a protective effect of pregnancy has been observed, suggesting that reproductive hormones may help reduce symptoms of autoimmunity. Estrogen treatments have been found to be beneficial for both sexes in animal models of this disease. These effects may be mediated via the expansion of regulatory T cells, which

maintain tolerance in normal individuals. Understanding these effects is particularly important in light of the increasing number of people exposed to a wide range of synthetic chemicals with estrogenic or anti-estrogenic activity. These include hormone supplementation, hormone blockers, pesticides, insecticides, fungicides, and food and herbal products.

The sexually dimorphic pituitary hormones, prolactin and growth hormone, as well as liver-derived insulin-like growth factor-1, also affect autoimmune disease. Women have higher levels of these hormones than men. Prolactin and growth hormone enhance autoimmunity, whereas insulin-like growth factor-1 promotes the recovery and repair of injured neural tissue. These hormones may act directly on immune cells or they may mediate their effects through modulation of the hypothalamic-pituitary-adrenal/gonadal axis.

Additional research is needed to determine more conclusively whether fetal cells have a causal role in autoimmune disease, or if they might serve as a predictive biomarker.

In type 1 diabetes the gender ratio is close to even; however, females predominate in many other juvenile autoimmune diseases and in those with onset after menopause. These observations suggest that changes in hormone levels may be an overly simplistic explanation for the observed gender differences.

Microchimerism refers to the presence of a population of cells in one individual derived from another. Microchimerism can result when cells pass between mother and fetus during pregnancy. After pregnancy, some of these foreign cells may remain in both mother and child. These cells (usually male cells) have been detected in mothers up to 20 years following the birth of a child. Some studies have reported the presence of fetal progenitor cells in women with scleroderma, Hashimoto's thyroiditis, and primary biliary cirrhosis, suggesting that persistent microchimerism may allow the development of autoimmune disease. Other studies suggest that microchimerism may occur more commonly than previously thought, including among women who do not develop autoimmune disease. Additional research is needed to determine more conclusively whether fetal cells have a causal role in autoimmune disease, or if they might serve as a predictive biomarker.

Progress

The 2002 ADCC Autoimmune Diseases Research Plan identified opportunities in the following broad areas: (1) identification of genetic, environmental, and immunologic factors that contribute to autoimmune diseases; (2) characterization of the mechanisms by which these factors influence

autoimmunity; (3) development of resources to facilitate genetics research; and (4) development and characterization of animal models of autoimmune diseases. Since publication of the Research Plan, NIH has addressed all of these areas through unsolicited research grants and through a large number of solicited research initiatives. Specific achievements and highlights of the new and ongoing programs are provided in the narratives and insets that follow.

Genetic Factors

In the past two years, important progress has been made in identifying key genes that predispose individuals and families to autoimmune diseases. The research has focused both on how these genes may work to initiate the disease process or exacerbate symptoms and on the potential of these discoveries to lead to new interventions that minimize or reverse the negative effects of genetic influences. In the future, research in this area may provide the basis for gene repair strategies.

- To support this crucial research, NIH administers several programs designed to explore genetic aspects of individual autoimmune disorders, as well as genetic factors that may be common to a group of autoimmune diseases. One of these programs, the **Multiple Autoimmune Disease Genetics Consortium (MAGDC)**, is a repository for biological samples and clinical data from families in which at least two individuals are affected by two or more different autoimmune diseases. The database currently includes samples and accompanying data from 263 families, with an additional 94 near completion. This resource recently was evaluated by a panel of experts in disease gene mapping who provided recommendations for further strengthening it.

- Genetic factors are known to contribute to a broad spectrum of neurological and neurobehavioral diseases. Many single-gene neurological disorders and their familial inheritance patterns have been well characterized. Other disorders, especially the autoimmune neurological disorders, however, have much more complicated inheritance patterns, influenced by multiple genes or by a combination of genetic and environmental factors. A Program Announcement supported by several NIH Institutes, **Gene Discovery for Complex Neurological and Neurobehavioral Disorders**, promotes research aimed at identifying susceptibility genes for numerous complex neurological and neurobehavioral disorders, including those with a confirmed or suspected autoimmune basis. This program began in 2003 and has funded nine research projects, including one investigating the genetic epidemiology of multiple sclerosis.

- The **Inflammatory Bowel Disease (IBD) Genetics Research Consortium** was established to promote participation of multiple IBD Genetic Research Centers in studies to identify genes associated with Crohn's disease and ulcerative colitis. Six genetic research centers, a coordinating center, and a patient sample repository are being funded to identify genes or genomic regions that are associated with increased risk of IBD and with specific phenotypic manifestations, such as early age of onset, location, complications, rate of progression, response to therapy, or susceptibility to environmental risk factors. This detailed characterization of the genetic susceptibility and resistance loci for IBD may lead to a better understanding of disease pathogenesis and environmental modifying factors, rational design of specific pharmaceutical or biological therapies, accurate diagnostic testing for IBD risk, and better rationale for selecting available therapies and assessing prognosis.

- Recently developed techniques such as high-density arrays of hybridization probes and high-throughput sequencing of concatenated DNA fragments now allow assessment of messenger RNA levels for very large numbers of genes with a single procedure. However, widespread adoption of these techniques presents both technical and conceptual challenges. Technical problems include the skill and experience of technical staff, the availability of standardized probes, and the bioinformatic challenges of analyzing very large data sets. Conceptually, it has been difficult to frame rigorous hypotheses and models that integrate the enormous amount of detail obtained in these experiments with broader questions in biology and medicine. The primary objectives of the NIH initiative, **Gene Expression Studies in Arthritis and Musculoskeletal and Skin Diseases,** are to focus resources on specific biological and medical problems for which the immediate application of comprehensive gene expression analysis technology might yield significant new insights, and to direct support to groups that currently are in the best position to make use of these technologies. In FY 2003, 12 new projects were funded in response to this initiative. These projects are examining a variety of disease areas including the pathogenic pathways involved in spontaneous arthritis, regulation of inflammatory genes in rheumatoid arthritis, and genomic studies in juvenile rheumatoid arthritis.

- Another effort that focuses on genetic resources and technologies is the **International Histocompatibility Working Group (IHWG).** The IHWG, which includes some 200 laboratories in more than 70 countries, is developing a catalog of the genes constituting the Major Histocompatibility Complex (known as HLA), and is identifying differences among these genes in populations worldwide. The HLA gene complex contains over 220 identified genes, and 40 apparently novel genes. These genes are estimated to

have over 1,000 allelic forms. Such diversity in the HLA complex can lead to variability in: responses to infection or immunization; susceptibility to autoimmune diseases; and acceptance and graft-associated disease of organ, tissue, or cell transplants. The IHWG currently has four autoimmune disease components: type 1 diabetes, rheumatoid arthritis, ankylosing spondylitis, and narcolepsy. For each of these diseases, participating groups are recruiting patients and normal controls matched for the primary disease-associated HLA allele(s), and recruiting families to identify a parent who is homozygous for the primary disease-associated allele(s). Researchers are using these data to identify and characterize additional genes in the HLA complex that may influence susceptibility or resistance to these diseases. The dbMHC database, developed through the IHWG, provides an open, publicly accessible and searchable platform for DNA and clinical data related to the HLA genes. This database is a unique source of high-resolution HLA data. In early 2004, the first portion of the dbMHC data was released on the Internet. The data – results from clinical blood and marrow stem cell transplants involving more than 1,300 unrelated donors and recipients from around the world – will enable researchers to generate and test hypotheses on the role of donor matching in blood and marrow stem cell transplants and the occurrence of graft-versus-host disease.

- The **Specialized Centers of Clinically Oriented Research (SCCOR) in Hemostatic and Thrombotic Diseases** initiative brings together multidisciplinary groups of investigators in basic, applied, and clinical arenas to address relevant clinical issues in hemostatic and thrombotic diseases, including polygeneic analyses of thrombotic disorders; diagnosis, assays, and treatment of venous thrombosis; thrombosis in special populations; inflammation and thrombosis; immune disorders; von Willebrand factor; protease-activated receptors; and vascular diversity. SCCOR emphasizes innovative ideas that have the potential to be translated to clinical applications. Research funded through this initiative is exploring how differential expression of membrane phospholipids influence procoagulant and anticoagulant activity. Scientists have developed a monoclonal antibody to b2 glycoprotein, a membrane phospholipid, which inhibits an anticoagulant pathway activated in lupus.

- Intramural researchers have investigated the genetic underpinnings of Autoimmune Lymphoproliferative Syndrome (ALPS), a disorder of defective lymphocyte programmed cell death characterized by lymphadenopathy, splenomegaly, and autoimmunity. This research has revealed that patients with two novel mutations in the *Fas* gene (involved in initiating programmed cell death) have lymphocytes that are effectively inactive. Symptoms of autoimmunity in these patients are probably caused by the inability of their lymphocytes to signal other cells. Additional studies have suggested an association between this genetic mutation and lymphocyte tumors in ALPS patients.

Key Advances—Genetic Factors

Genetic Basis of Predisposition for Vitiligo and Other Autoimmune Diseases. Vitiligo, a common autoimmune disorder characterized by patchy loss of pigment in the skin and hair can be a socially devastating disease, particularly in more darkly pigmented individuals. Vitiligo often clusters in families, and frequently is seen in individuals who have multiple autoimmune diseases. Studies of families from the United States and the United Kingdom affected by vitiligo identified a specific location on chromosome 1 as the major susceptibility site for the disorder. These studies also documented that within the same family, there were likely to be multiple members with vitiligo and other individuals with autoimmune thyroid disease, pernicious anemia, Addison's disease, lupus, and inflammatory bowel disease. This new information marks an important step in research into vitiligo prevention and treatment.

Genetic Site Suggests Psoriasis Susceptibility. Researchers have identified two genes associated with psoriasis on chromosome 17. The region between these two genes acts as a binding site for the protein RUNX1, which normally regulates genes involved in immune reactions. The researchers found that when this region is altered, susceptibility to psoriasis occurs. This defective regulation may cause an increased activation of T cells, triggering the inflammation and rapid turnover of skin cells characteristic of the disease, and may cause skin cells known as keratinocytes to develop abnormally and divide much faster. This study, involving 242 European families with 572 individuals diagnosed with psoriasis, advances progress toward understanding the cause of psoriasis in patients with a family history of the disease, and will inform studies of other psoriasis populations and other inflammatory diseases.

Genetic Risk Factor Found for Lupus in African American Women. Two variant forms of a gene that promotes the formation of nitric oxide, a molecule involved in blood vessel dynamics and nerve transmission, may be a risk factor for lupus in African American women. Lupus is three times more common, and is frequently more severe, in African American women than in Caucasian women. The variant gene forms occurred much more frequently among the female African American lupus patients studied than among controls matched for age, sex, and race. These same gene forms are associated with improved outcomes in some African patients with malaria.

Researchers Uncover a Genetic "Signature" for Lupus. Scientists have discovered a genetic "signature" present in some patients with lupus who develop life-threatening complications such as blood disorders, central nervous system damage, and kidney failure. Of the

thousands of genes analyzed in the blood cells of lupus patients and healthy controls, 14 were linked to a subset of lupus patients with severe disease. Referred to collectively as the IFN expression signature, these genes are activated by interferons, a complex family of signaling proteins involved in immune response regulation. Patients with severe lupus consistently showed higher expression of the IFN signature genes. These findings should help to identify lupus patients who are at high risk for severe disease before serious complications arise, and they provide evidence for possible new therapies to block IFN pathways in patients with severe lupus. Gene expression patterns in blood cells may be useful in identifying patients most likely to benefit from these new therapies, and may help identify disease pathways in other autoimmune and inflammatory disorders.

Mapping Multiple Sclerosis Susceptibility in African Americans. Certain histocompatibility antigen genes (HLA types) are associated with a slightly higher risk of multiple sclerosis, although it has been difficult to determine precisely which alleles are involved. African Americans are at lower risk for multiple sclerosis compared with northern European or Caucasian Americans, and also show greater rates of recombination between the HLA gene regions thought to be involved in multiple sclerosis. Genetic studies of HLA types in this low-risk population have identified a candidate gene that can now be used to investigate how an HLA subtype may contribute to multiple sclerosis susceptibility.

Genetic Factors in Rheumatoid Arthritis. Two recent studies have yielded important information about genetic changes that influence rheumatoid arthritis. In the first of these, collaborating public and private international researchers found that variations in the *interleukin-6 (IL-6)* gene increase susceptibility to systemic juvenile rheumatoid arthritis (JRA). DNA samples from 222 American, British, and French families that have children with JRA revealed that these children are more likely to inherit a specific variant in the *IL-6* gene. Children who developed JRA at age five or older showed significantly higher levels of this variant compared with those who developed the disease before age five. The findings suggest that distinct genetic profiles may exist that affect the age of onset and disease severity. Continued discovery of such disease-associated genes may lead to clinically useful subgroupings of systemic JRA.

The second study found that gene expression may be at least partly responsible for the inflammation of cells that line the joints (synovial fibroblasts) and for cartilage and bone destruction in rheumatoid arthritis. Investigators hypothesized that in JRA patients the synovial membrane is gradually re-populated by immature bone marrow cells that express embryonic growth factors. When cultured in the laboratory, these cells expressed as many

as eight embryonic growth factors, as well as inflammatory cytokines (substances involved in cell-to-cell communication). The embryonic growth factor expression appears to precede the production of inflammatory cytokines, since introducing genes encoding these products into normal fibroblasts also induced cytokine production. The findings indicate that intrinsic properties of the synovial cells, independent of the immune response, may contribute to changes observed in the joints of rheumatoid arthritis patients, and suggest the possibility of new therapies that will modify the activities of synovial cells.

Fine Tuning Tissue Typing for Successful Bone Marrow Transplantation. Class I and II human leukocyte antigen (HLA) molecules are essential for immune recognition of pathogens. Class I HLA molecules are also the primary trigger of immune recognition of donor bone marrow and subsequent graft rejection by the recipient. The probability of finding an HLA-identical, unrelated bone marrow donor is very low, due to the tremendous genetic diversity in the six Class I genes. Therefore, most patients receive partially mismatched grafts. HLA matching is determined either by DNA sequence analysis of HLA genes or, more conventionally, by antibody recognition of the HLA molecules, termed HLA allele or antigen typing, respectively. The assumption is that antigen mismatches have a higher risk of graft failure than allele mismatches. In a large, continuing study on the role of HLA mismatching in bone marrow transplant outcome, including a comparison of the two typing methods, investigators made several important discoveries about the risk of graft rejection for allele and/or antigen mismatches. Only the five alleles considered to be the most critical in determining transplant outcome were studied. The risk of graft versus host disease, graft rejection, and mortality was increased by a single allele mismatch. This risk was further compounded if there were mismatches for multiple alleles. In addition, some allelic mismatches confer more risk than others, and the risk associated with mismatching a given allele differs for individuals of Caucasian versus Asian descent. The investigators found that allele versus antigen mismatching confers different risk for graft rejection, demonstrating that qualitative differences in tissue typing contribute to risk determination. Together, these results are leading to new strategies for the selection of bone marrow donors that could significantly improve the odds of engraftment.

New Gene Linked to Autoimmune Polyglandular Syndrome. Autoimmune polyglandular syndrome is a rare autoimmune disease marked by lymphocyte infiltration and antibody deposits in multiple organs. Researchers have determined that this disorder occurs in people who carry a defective form of the *AIRE* (autoimmune regulator) gene. The AIRE protein is a transcription factor that increases “out of place” expression of a large number of genes in the

thymus, thereby promoting T cell tolerance. If T cells do not encounter these proteins – as might happen when mutations are present in the gene – autoimmune T cells survive and mature, leading to autoimmunity. These findings underscore the importance of thymically imposed "central" tolerance in the control of autoimmunity.

Card 15 Mediates Host Recognition of Bacterial Components: Implications for Crohn's Disease. Important clues to the pathogenesis of Crohn's disease have recently emerged from genetic research. Familial Crohn's disease has been linked to several parts of the human genome, including a locus on chromosome 16 (IBD1) now identified as the CARD15 gene. As many as 50 percent of patients with Crohn's disease have mutations in this gene, which appears to play a role in innate immunity, and specifically in signaling mediated by bacterial peptidoglycans. The CARD15 gene encodes the CARD15 protein, which recognizes bacterial components and activates immune response through a nuclear transcription factor called NF-kB. NF-kB is a master regulator of stress and immune responses in many cell types. Bacterial components can also activate NF-kB through the cell-surface Toll-like receptor 2 (TLR2). Mutations in the CARD15 gene cause loss of function of NF-kB in *in vitro* assays. However, these *in vitro* observations are discordant with findings in the disease, which is characterized by increased NF-kB activation and a marked increase in proinflammatory cytokines produced by T helper 1 cells in the mucosa. Recent studies of lymphoid cells from mice bred to be homozygous for the mutant *card15* gene demonstrate an increase in TLR-2 mediated activation of NF-kB and Th1 cytokines. These mouse and human studies suggest that mutations in the CARD15 gene lead to the heightened inflammatory response of patients with Crohn's disease.

Environmental Factors

- NIH supports a number of major initiatives on environmental influences in autoimmune disease, such as its program on **Environment/Infection/Gene Interactions in Autoimmune Diseases.** Cosponsored by more than a dozen NIH Institutes and Centers, this initiative supports innovative basic or population-based research on the role of environmental and infectious agents in the initiation and/or exacerbation of autoimmune diseases, including the role of specific environmental exposures and the interaction of genetic, hormonal, and environmental factors. Projects funded through this initiative are investigating the effect of mercury exposure on the CD95 apoptotic cell death pathway, the role of environmental factors in the development of primary biliary cirrhosis, and the effects of environmental contaminants with estrogenic effects – such as chlordecone, methoxychlor, and DDT – on the development of systemic lupus erythematosus in animal models.

- Another important NIH program is the **Fetal Basis of Adult Disease: Role of the Environment** initiative, designed to stimulate research on the effects of *in utero* exposures that cause permanent functional changes. Such changes, while not overtly or grossly teratogenic, nonetheless result in increased susceptibility to disease/dysfunction later in life, including autoimmune disease. Approximately 40 percent of major developmental defects, which afflict two to five percent of live-born infants, are thought to result from the adverse exposure of a genetically-predisposed fetus to intrauterine environmental factors. In many cases, a fetus is more sensitive than an adult to the same environmental insults, which may cause altered gene expression, cell production, and differentiation that affect the structure and function of tissues, organs, and systems. This program encourages applications of new high-throughput functional-genomic, metabolomic, proteomic, and bioinformatic technologies to study the latent effects of *in utero* environmental exposures. This initiative funded 22 grants during its first three years. A final solicitation for exploratory grants was released in 2004.

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- In another area of immune-related disease, NIH is conducting an initiative focused on **Glial Cell Inflammatory Mechanisms of HIV-1 Induced Cell Injury in the Nervous System.** The program, launched in 2003, promotes research on the role of neuro-inflammation in initiating and exacerbating cellular injury and death in the context of HIV-1 infection of the central nervous system (CNS). Neurologic dysfunction, including cognitive deficits, motor impairment, and behavioral problems, is a devastating complication of HIV-1 infection that affects about 25 percent of infected individuals. The mechanisms that cause these neurological symptoms are not yet clear, but may include neuro-inflammatory responses to HIV-1 infection. The number of HIV-1 cells in the brain that are typically infected is low, and does not explain the extent of the neuropathology observed. Susceptibility to CNS complications could result from either individual genetic differences or variations in viral strains. Emerging evidence from this initiative indicates that HIV-1 proteins exhibit toxicity to nerve cells only when non-neuronal, immunocompetent cells such as macrophages, microglia, or astrocytes are present. To date, six grants have been funded through this program. Findings from these studies may also be applicable to understanding and controlling inflammation in other neurological disorders, such as multiple sclerosis.

- The **Environmental Autoimmunity Group**, an intramural program at NIH, is conducting studies on adult and childhood rheumatic diseases in an effort to understand genetic and environmental risk factors and underlying mechanisms for these disorders. Scientists are pursuing studies of twins; studies of the role of maternal-fetal and fetal-maternal cellular exchange in the development and maintenance of rheumatic diseases; international studies of myositis, using the naturally-occurring variations in genes to understand variations in clinical expression and risk factors; assessment of possible genetic risk factors for the development of myositis following silicone implants and vaccines; and assessment of new biologic therapies in myositis.

Key Advances—Environmental Factors

Activation of Autoimmune T Cells by Bacterial Products. Susceptibility and resistance to experimental autoimmune encephalomyelitis (EAE), an animal model for MS, are both strongly affected by genetic background. Even transgenic generation of a high frequency of self-reactive T cells – which usually renders an animal highly susceptible to EAE – rarely induced spontaneous EAE in a resistant strain called B10.S. This relative resistance was controlled by antigen-presenting cells (APC) rather than by T cell defect; however, treatment of mice with bacterial products such as lipopolysaccaride that activate so-called "Toll-like receptors" induced disease. These results demonstrated that activation of APCs via innate immune receptors can break self-tolerance and trigger autoimmunity even in a genetically resistant mouse strain.

Infections That Induce Diabetes in Rats Modulate T Cell Populations. Viral infections and other environmental factors are thought to play a role in type 1 diabetes among genetically-susceptible individuals. Spontaneous type 1 diabetes does not normally occur in viral antibody-free BB rats (a well-characterized animal model that resembles many features of human insulin-dependent type 1 diabetes), but can be induced in about one-third of these animals by infecting them with the RV parvovirus. The virus infects lymphoid organs and endothelial cells but not insulin-producing beta cells. Scientists recently analyzed the immune responses of both BB and normal rats to infection with either RV or a related virus called H-1, which does not cause diabetes. RV infection caused a significant decrease in regulatory CD4+CD25+ T cells in the spleens of both the BB and normal rat. RV infection also increased levels of these cells in the pancreatic lymph nodes of BB rats but had no effect on this population of cells in normal rats. These findings suggest that RV but not H-1 infection alters T cell regulation in the BB rat, and suggests a mechanism by which an underlying genetic predisposition and an environmental factor can work together to transform a mere predisposition toward autoimmune diabetes into actual disease.

Environmental Triggers for Autoimmune Thyroiditis. The incidence of autoimmune thyroiditis has risen steadily over the past several decades. Some scientists have speculated that the increase is due to the widespread use of iodized salt. Investigators looking for possible environmental triggers for this disease conducted a study using a mouse strain bred to spontaneously develop autoimmune thyroiditis. They found that: (1) increased dietary iodine led to earlier and more severe disease; (2) the disease occurred only in a subset of genetically-predisposed subjects; (3) a high iodine diet increased the immune response to thyroglobulin (Tg), an antigen associated with thyroiditis; and (4) iodine restriction reduced lymphocytic infiltration, a marker of disease progression and severity. Although the exact mechanism underlying this autoimmune response to iodine remains unclear, the investigators identified several possibilities linked with Tg. The study suggests that autoimmune thyroiditis is associated with a gene-environment interaction.

The Autoimmunity Centers of Excellence

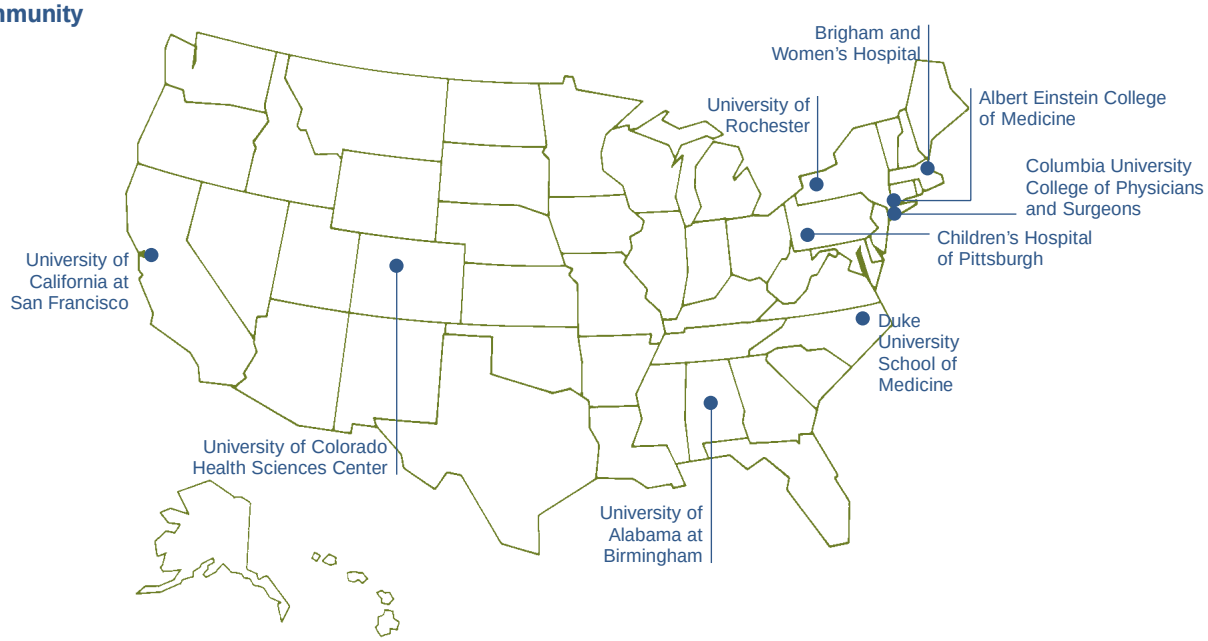
In major academic medical centers across the Nation, NIH supports the cooperative Autoimmunity Centers of Excellence (ACE) program, designed to accelerate the translation of scientific research findings into effective therapies for autoimmune diseases. The ACE program was recently expanded from five centers to nine (see map on p. 45 for locations) and renewed for an additional five years beginning in 2003.

The ACE program brings together basic, preclinical, and clinical researchers to increase understanding of self-tolerance, immune modulation, and other immune mechanisms that may provide new therapeutic targets; test these discoveries in animal models; and conduct clinical trials of promising treatment interventions. The basic and clinical components of the centers work cooperatively to select, design, and perform the laboratory and animal studies, clinical trials, and trial-associated mechanistic studies. Many of the clinical trials are multisite collaborations among institutions in several geographic areas. Diseases currently under study in the ACE include systemic lupus erythematosus, lupus nephritis, multiple sclerosis, type 1 diabetes mellitus, rheumatoid arthritis, psoriatic arthritis, psoriasis, biliary cirrhosis, scleroderma, pemphigus vulgaris, ulcerative colitis, Sjögren's syndrome, and multiple autoimmune disease syndrome.

Among the basic and preclinical studies conducted by the ACE are investigations of the mechanisms by which T regulatory cells control potentially pathogenic effector cells; mapping, identifying, and cloning the genes of diabetes-resistant mice; and investigating whether inflammatory stimuli, such as tumor necrosis factor alpha (TNF-α), influence the migration of immature B cells and autoimmune B cell responses. Other research conducted by the ACE is testing the hypothesis that four critical events lead to autoimmune diseases: (1) predisposing genes influence T cell function, (2) tolerant autoreactive T cell clones are activated, (3) regulatory mechanisms fail, and (4) pathogenic autoantibodies and T cells damage tissues. Studies seeking to develop new therapeutic targets include investigations of the effect of statins on the peripheral mononuclear cells of lupus patients, and possible strategies for inducing antigen non-specific immunomodulation and long-term tolerance by inhibiting T cell activation.

Numerous clinical trials are underway or planned. For example, one ongoing trial is testing the clinical and immune effects of Sirolimus and another is testing copaxone and albuteral in multiple sclerosis patients. Another trial is testing a B cell-specific monoclonal antibody for treatment of systemic lupus. A completed study demonstrated that treatment with a T cell-specific monoclonal antibody benefits patients with recently diagnosed type 1 diabetes. Among the trials under development or recently launched are a statin treatment for rheumatoid arthritis, DNase I treatment for systemic lupus, a TNF-specific monoclonal antibody for treating lupus nephritis, and a B cell-specific monoclonal antibody for treating early rheumatoid arthritis.

The Autoimmunity Centers of Excellence



Immunologic Studies

- Many of the immunologic studies sponsored by NIH over the past two years have explored the role of male and female hormones on autoimmune disease etiology, the role of regulatory T cells in these disorders, and other areas of inquiry into the etiology of the many autoimmune diseases. Most of these studies have been conducted through new and ongoing initiatives, many of them supported by multiple Institutes and Centers. The **Autoimmunity Centers of Excellence** program is one of the broadest umbrellas for such work, bringing together basic scientists and diverse clinical sub-specialists to conduct cross-disciplinary autoimmune disease research. The **Non-Human Primate Cooperative Study Group (NHPCSG)** is another initiative that targets priority areas identified by the 2002 ADCC Autoimmune Diseases Research Plan. This program supports studies to evaluate the safety and efficacy of promising tolerance induction treatment regimens in non-human primate models of kidney and islet transplantation. The knowledge gained from this research effort is critical to the translation of successful tolerance induction strategies from small animal models to clinical trials. Begun in 1999, this program was expanded in 2002. Researchers supported through this program have made significant progress with tolerogenic regimens, including costimulation blockade and T cell depletion to induce long-term kidney and islet allograft survival. In 2000, specific-pathogen free Rhesus macaque and Cynomolgus macaque breeding colonies were

established to ensure a ready source of high-quality monkeys for these tolerance studies. This program will be renewed in FY 2005. In 2004, an opportunities pool of funds was provided to the NHPCSG Steering Committee to allow rapid support of pilot projects, shared resources and collaborations, and new or emerging tolerogenic regimen opportunities. All projects funded through the opportunities pool will be directed to preclinical type 1 diabetes-related transplantation tolerance research.

- An initiative entitled **Identifying Functional Links between the Immune System and Brain Function Including Behavior** focuses NIH support on studies that examine how the immune system modifies brain function and behavior. Over the past two years, new data published by researchers supported by this program have shown significant effects of cytokines and immune cells in brain regions regulating cognition and emotion. Additional work is focused on identifying the pathways mediating bidirectional communication between the brain and peripheral circulation. Newly developed tools are enabling the localization and measurement of cytokine levels in the intact brain, as well as helping to identify novel roles in normal brain development and function for proteins that were previously believed to function only in immune-activated states. Basic studies such as these are essential for uncovering the machinery regulating the long-term impact of illness and antibody activation on brain function. Ten projects have been funded through this program.

- The **Neuropsychiatric Systemic Lupus Erythematosus** initiative, launched in 2002, includes basic and clinical studies on the neuropsychiatric aspects of lupus. The five projects funded through this initiative are applying new tools and approaches to discovering the underlying causes of this disease.

- To increase fundamental knowledge of the molecular mechanisms and signaling processes that regulate the immune system in the heart, vasculature, lungs, and blood, NIH supports an initiative on **Cardiovascular, Lung, and Blood Immunobiology in Health and Disease.** This program studies the unique immunologic demands faced by the cardiovascular, respiratory, and blood systems; the novel pathways of immune control developed by each system to process foreign antigens in a manner that does not interfere with the system's primary biological functions; and the mechanisms that keep the immune system and associated inflammatory responses in check, yet prepared to respond quickly to potentially deadly or disease-causing materials. Research supported through this initiative has advanced our knowledge of the inflammatory mechanisms

underlying atherosclerosis and cardiovascular diseases. Given that the incidence of atherosclerosis is higher among people with lupus, this information can be vital to understanding and managing various health complications associated with lupus. Scientists have noted that recruitment of dendritic cells at sites of injury in blood vessels contributes to inflammation. Immune cell-lipid interactions, which decreases in immune cell types (such as B cells) and increases in factors such as serum amyloid A, all seem to contribute to cardiovascular complications.

- In addition, NIH recognizes that the biomedical sciences require a constant infusion of new ideas, techniques, and points of view. These may differ substantially from current thinking or practice and may not yet be supported by substantial preliminary data. For this reason, NIH supports a number of initiatives designed to promote innovative research. For example, the initiative in **High Risk Rheumatic and Musculoskeletal and Skin Diseases Research** aims to broaden fundamental biomedical, biobehavioral, and biomedical technology research by encouraging applications for high-risk research projects that require a preliminary test of feasibility. The goal is to support research with the potential for developing ground-breaking technology or methodologies that may lead to significant expansion of biomedical research horizons, precipitate a paradigm shift in research, or lead to substantial improvements in human health. Under this initiative, established autoimmune disease researchers are encouraged to propose testing of a novel idea, resource, or technology, and experienced investigators with no previous work in rheumatic, musculoskeletal, or skin diseases are encouraged to apply their expertise to research relevant to these disorders.

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- Likewise, the **NIH Exploratory/Developmental Research Grant Award** fosters the introduction of novel scientific ideas, model systems, tools, agents, targets, and technologies that have the potential to substantially advance biomedical research. This award is intended to support exploratory and developmental research projects in their earliest stages. Such studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models or applications that could have major impact on a field of biomedical, behavioral, or clinical research.

Key Advances—Immunologic Studies

Estrogen and Autoimmunity. Compared with men, women are at greater risk for autoimmune diseases, including lupus, rheumatoid arthritis, and multiple sclerosis. Scientists have long suspected that sex hormones such as estradiol may account for the increased risk, but the mechanisms underlying this effect are poorly understood. Working with mice genetically manipulated to produce autoantibodies when given the appropriate biochemical signals, researchers studied estradiol effects on the induction and improper regulation of autoimmune responses. In these mice, estradiol induced lupus-like disease. In contrast, estradiol had no effect on cells from normal mice. The research team also discovered that estradiol makes immune cells that produce autoantibodies (B cells) more resistant to signals that turn them off. In contrast, women with multiple sclerosis often see improvement in their symptoms during pregnancy and estrogen treatment has been found to be beneficial for both sexes in animal models for multiple sclerosis. These estrogen effects may be mediated via the expansion of regulatory T cells, which maintain tolerance in normal individuals. These studies highlight the complex roles that sex hormones may play in autoimmunity and enhance our understanding of mechanisms of autoimmune disease.

The Female Hormone Prolactin Affects Development of Cells Involved in Systemic Lupus Erythematosus. In another study to elucidate the role of female hormones in autoimmune disease, NIH-supported researchers showed that the female hormone prolactin can influence the development of cells that produce antibodies responsible for systemic lupus erythematosus symptoms. When systemic lupus erythematosus-susceptible mice were treated with prolactin, antibody-producing cells that are normally eliminated by the immune system survived and the mice developed systemic lupus erythematosus symptoms. Understanding how prolactin and related hormones influence the survival and function of these cells and other components of the immune system may lead to new treatments for systemic lupus erythematosus and other autoimmune diseases.

The Role of Regulatory T Cells in Type 1 Diabetes Onset and Progression. Three recent NIH-supported studies have added markedly to our understanding of the role of regulatory T cells in type 1 diabetes. The first of these investigated possible early steps in diabetes onset. The prelude to type 1 diabetes is leukocyte infiltration into the pancreatic islets. Activation of T cells occurs in the pancreatic lymph nodes when T lymphocytes that can attack islet beta cells encounter antigen-presenting cells (APCs) displaying peptides from beta cell proteins. The immune system contains three types of antigen-presenting cells (macrophages, dendritic cells, and B cells). A wave of beta cell death occurs at two weeks of age in the mouse. At the same time, a specific dendritic cell population engulfs the dying beta cell fragments and migrates to the pancreatic lymph nodes. These findings suggest that naïve T cell activation occurs in the pancreatic lymph nodes when these cells encounter dendritic cells that present beta cell proteins on their surface.

The second of these studies explored possible interactions of genetic elements and environmental factors in type 1 diabetes. The cluster of genes encoding the major histocompatibility complex (MHC) has consistently shown strong association with the etiology of type 1 diabetes. MHC proteins expressed on cell surfaces are responsible for the compatibility (or lack of compatibility) of the tissues of genetically different individuals. T cells constantly monitor the cells of the body, searching for any that express foreign antigen fragments not belonging to class I or II MHC. CD8+ T cells and CD4+ T cells recognize class I and class II MHC molecules, respectively. Although a significant proportion of patients with type 1 diabetes express specific class II MHC molecules, the roles these molecules play in disease initiation are not clear. In a mouse model of diabetes, however, mice that express both class I and class II molecules were less likely to develop disease than mice that could only express class I.

A third study found that a transcription factor called T-bet controls CD8+ T lymphocyte autoimmune responses. Aggressive type 1 diabetes progression is partially supported by the cytokine interferon-gamma (IFN-γ), and T-bet has been shown to control IFN-γ production in CD4+ lymphocytes. Mice engineered to develop diabetes and deficient in T-bet protein were significantly resistant to diabetes onset. This finding is supported by the fact that islets from diabetic mice were heavily infiltrated with CD8+ T cells, whereas islets from mice deficient in T-bet had less CD8+ T cell infiltration. In addition, CD8+ T lymphocyte populations deficient in T-bet but still capable of producing IFN-γ were reduced. This study identifies T-bet as a potential target for therapeutic prevention of type 1 diabetes and other autoimmune diseases.

Regulatory T Cells Grown *In Vitro* Suppress Autoimmune Diabetes. Induction of immune tolerance – the lack of harmful immune responses without ongoing immunosuppressive therapy – is the goal of research to prevent or treat immune-mediated diseases. Research in animal models suggests that successful tolerance induction requires both the elimination of tissue-damaging cells and the activation of regulatory T cells, which modulate pathogenic immune responses. Studies further suggest that the regulatory T cell population is diminished or functionally impaired in patients and animals with autoimmune disease. It has been difficult to assess the therapeutic potential of regulatory T cells because they respond poorly to *in vitro* stimuli and do not proliferate well outside the body. An NIH-funded investigator has now developed an *in vitro* method for eliciting robust regulatory T cell proliferation, however, and confirmed that small numbers of these cells can reverse new onset and chronic diabetes in a type 1 diabetes mouse model and prevent islet graft rejection in diabetic mice. This advance will allow further study of regulatory T cell characteristics, mechanisms of action, and application to other models of immune-mediated diseases, such as graft rejection and graft-versus-host disease (GVHD). Ultimately, regulatory T cells grown *in vitro* and reinfused into patients may be used to treat a variety of immune-mediated diseases.

Regulatory T Cells Can Inhibit Disease-Causing Immune Responses in the Gut. The chronic inflammatory bowel diseases Crohn's disease and ulcerative colitis result from a complex interplay of genetic predisposition and environmental, bacterial, and immune factors. They are thought to arise in part due to an inappropriate reaction by the body's immune system against the normally harmless bacteria present in the digestive tract. In healthy people, signals that promote an immune response against these bacteria are held in check by countervailing inhibitory signals; when this balance is upset, the gut becomes chronically inflamed. Researchers have recently found evidence that a specific subpopulation of regulatory T cells with anti-inflammatory activity – Tr1 cells – can inhibit the activity of another kind of T cell with pro-inflammatory activity – Th1 cells. In culture, Tr1 cells inhibit the ability of Th1 cells to proliferate and release interferon gamma, an important pro-inflammatory signal. This inhibition seems to be mediated both by factors secreted by the Tr1 cells and by direct cell-cell contact between the two cell types. In a mouse model of bowel inflammation, inoculation of the animals with Th1 cells alone caused colitis, but co-inoculation with both Th1 and Tr1 cells did not. These findings suggest that regulatory T cells may play an important role in controlling the immune response to bacteria in the gut.

Molecular Mechanisms of Brain Changes in Lupus Revealed. The manifestations of lupus are diverse; it can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Researchers have now described some of the molecular mechanisms that lead to injury of the central nervous system in people with lupus. The antibodies that bind DNA in individuals with lupus also target receptors for the neurotransmitter glutamate and are present in the cerebrospinal fluid. These antibodies cause the cognitive impairment that occurs in some patients with lupus. This finding helps to explain nervous system complications in lupus, and may lead to new therapeutic strategies.

Defective Regulatory T Cell Function in Multiple Sclerosis. Multiple sclerosis is a chronic inflammatory disease in which activated T cells migrate into the central nervous system and attack the myelin sheath surrounding neurons. Under normal conditions, regulatory T cells help to suppress proliferation and activity of the T cells that conduct the attack. Recent experiments showed that regulatory T cells isolated from patients newly diagnosed with multiple sclerosis were less able to suppress the effects of activated T cells. This study is the first to demonstrate that dysfunction of regulatory T cells may contribute to autoimmunity in patients with multiple sclerosis.

Genetic Insufficiency of T Cell Transcription Factor Derails Immune Control. Naturally occurring regulatory T cells represent five to ten percent of CD4+ T cells and possess potent immunoregulatory functions essential to peripheral self-tolerance. Regulatory T cells express Foxp3, a member of the forkhead-winged helix family of transcription factors. *Foxp3* is a master control gene for regulatory T cells and identifies these cells as a distinct subset of T cells. In scurfy mice, genetic insufficiency of *Foxp3* causes

autoimmune and inflammatory disease. In humans, defects in the *Foxp3* gene underlie loss of tolerance and immune dysregulation. These results raise the prospect of novel approaches to controlling autoimmunity.

Anti-Peptide Autoantibodies and Fatal Anaphylaxis in NOD Mice. Scientists have observed the presence of specific anti-insulin autoantibodies in studies of animals with diabetes, and research suggests that amino acids 9-23 of the insulin B chain are a target for autoimmunity in this disease. When the insulin B:9-23 peptide is administered to NOD mice (a particularly well-studied animal model for type 1 diabetes), it prevents diabetes. Yet, recent experience has demonstrated the potential dangers of disease exacerbation or anaphylaxis with peptide immunotherapy. In light of this evidence, scientists examined whether long-term administration of the B:9-23 peptide *without adjuvant* (agents that increase the potency of vaccines) might be an effective treatment without producing harmful side effects. Surprisingly, they found that peptide administration consistently induced fatal anaphylaxis in NOD mice after 6 weeks of dosing. Anaphylaxis, however, could be blocked with combined treatment of antihistamine and platelet-activating factor antagonist, or with combined anti-IgG receptor and anti-IgE antibodies. Three to four weeks of peptide treatment induced high amounts of anti-B:9-23 antibodies. Further, the scientists noted that the insulin B:13-23 peptide induced anaphylaxis and was more potent than the B:9-23 peptide. They concluded that administration of the insulin peptides B:9-23 and B:13-23, even in the absence of adjuvant, can induce a dramatic immune response leading to anaphylaxis in NOD mice.

Expression of Immunomodulatory Molecules in Salivary Glands. A gene therapy protocol was developed to express two immunomodulatory molecules (human vasoactive intestinal peptide and a soluble form of the tumor necrosis factor alpha receptor) in a mouse model of Sjögren's syndrome. Initial results suggest that expression of each gene locally can modify disease.

CHAPTER 3

Diagnosis, Treatment, and Prevention

Introduction

Autoimmune diseases vary greatly in natural history and presentation. At the same time, however, they seem to share many underlying immunologic mechanisms, and thus might respond to similar treatment strategies. Over the past decade, more selective and less toxic immunosuppressive and immunomodulatory agents have been developed to treat many of the more than 80 autoimmune disorders so far identified. Now, scientists are using the growing knowledge of the mechanisms of autoimmunity to develop promising approaches for inducing immune tolerance, and are developing new and better strategies for early diagnosis, treatment, and eventually prevention. They also are striving to strengthen the clinical research infrastructure needed to test these new interventions.

Diagnosis of Autoimmune Diseases

The first step in managing patients with any disorder is proper diagnosis. Diagnosing autoimmune diseases can be particularly difficult, however, because these disorders can affect any organ or tissue in the body, and produce highly diverse clinical manifestations, depending on the site of autoimmune attack. Moreover, disease symptoms are often not apparent until the disease has reached a relatively advanced stage.

Diagnosis of an autoimmune disease typically begins with a careful health history, including assessment of possible occupational and environmental exposures. Many of the early symptoms of these disorders, such as fatigue, joint and muscle pain, fever, or weight change, are nonspecific. While these symptoms alone may not point to a particular autoimmune disease, when considered in retrospect they can help to pinpoint when the disease process began. Added diagnostic clues may be revealed through family history, as the presence of autoimmune disease in a patient's family further suggests that an autoimmune disease should be considered among the diagnostic possibilities. Similarly, a social and occupational history may identify exposures associated with a particular autoimmune disorder.

Laboratory testing helps to establish the location and extent of disease. Such testing can reveal the presence of specific autoantibodies, which can be a strong indicator of an autoimmune disorder. Although laboratory testing has limitations, it is currently the cornerstone of diagnosis. Some immunologic tests are difficult to interpret, however, and must always be considered along with clinical findings.

Recent studies suggest that autoantibody detection may be valuable in earlier diagnosis of autoimmune diseases, thereby allowing treatment to be initiated sooner. Research has shown that individuals who go on to develop clinical manifestations of type 1 diabetes, for example, often have had multiple antibodies to the insulin-producing islet cells for some time before disease is evident. The presence of such antibodies, especially if coupled with a family history and genetic factors associated with the disease, increases the likelihood that symptoms will appear in the future. In some instances it may be possible to use antibodies to monitor response to treatment or to forecast an exacerbation of a disease in remission. However, because some autoimmune diseases are caused by infiltrating cells rather than autoantibodies, practical tests for cell-mediated autoimmune reactions are a high priority need.

Imaging technology can also be a valuable diagnostic tool. For example, imaging tests that reveal areas of demyelinization in the brain (plaques) have been useful for diagnosing and staging multiple sclerosis and for monitoring responses to therapy. Other specialized imaging technologies are of increasing value in following the course of several autoimmune disorders.

The absence of generally accepted diagnostic standards has hampered efforts of researchers and clinicians to identify autoimmune diseases at early stages. For a few diseases, including lupus, multiple sclerosis, and rheumatoid arthritis, professional groups have developed diagnostic criteria. These criteria are essential for epidemiologic studies, but may not always be valid for clinical diagnosis in individual cases. Because so many early symptoms of autoimmune disease are relatively non-specific, years may go by before a definitive diagnosis can be reached and treatment initiated. These long delays represent a particular hardship for patients, who too often go from one physician to another seeking a cause of their illness. These problems have stimulated recent investigations seeking better objective indicators of disease called biomarkers. Often based on a particular pattern of biochemical and immunologic data linked to a specific disease or disease risk, biomarkers have the potential to considerably improve our ability to diagnose autoimmune disorders earlier in the disease process.

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The Promise of Biomarkers

Biomarkers are physiologic characteristics that indicate the presence of either specific biologic processes or specific responses to pharmacologic agents. To be useful, a biomarker must be objectively and reliably measurable. Researchers and clinicians in autoimmune disease prevention and treatment are investing great effort to identify and validate biomarkers that can reveal increased disease risk, disease initiation and progression, response to treatment, environmental influences, and other important information.

Autoimmune disease biomarkers have the potential to enable diagnosis before the onset of symptoms, predict specific organ involvement and disease flares, identify clinically meaningful disease subsets, predict and monitor response to therapy, and describe organ or tissue damage. Biomarkers might also be very useful in preclinical studies to identify genetic predisposition to disease or environmental triggers, and they may provide early information about the potential efficacy of experimental agents or mechanisms underlying drug activity. Biomarkers will also enhance the conduct of clinical trials, because they can serve as surrogate endpoints that substitute for traditional clinical endpoints and therefore help predict the effect of a therapeutic intervention. With an adequate arsenal of biomarkers, it will likely become possible to conduct shorter clinical trials involving fewer patients. Prevention trials in particular, which tend to be lengthy and expensive, may benefit from the availability of validated surrogate endpoints.

Biomarker development and validation is complex and many biomarkers are needed, since those that are useful at one stage of disease may not be useful at other stages. Research to date suggests that some biomarkers may be common to a variety of autoimmune diseases, although others are disease-specific. Currently, many biomarker candidates have been identified, but few, if any have been confirmed conclusively enough to enable their routine use in clinical and epidemiologic studies or patient care. Achieving this goal, however, is a high NIH priority. Consistent with the direction provided by the Roadmap, NIH is continuing to build on the research infrastructure needed to accelerate biomarker development, such as shared biorepositories, microarrays, and proteomics centers; statistical core services; bioinformatics; validation laboratories; and scientific collaborations.

Treatment of Autoimmune Diseases

Treatments to reduce the symptoms of most autoimmune diseases are available, but definitive cures have yet to be developed. In general, two approaches to treatment are currently available. The first involves replacing or repairing impaired function. For example, patients with type 1 diabetes mellitus can take insulin to replace the hormone that is not produced by their damaged pancreatic islet cells. Similarly, patients with autoimmune thyroiditis can be treated with thyroid hormones. These methods do not arrest the autoimmune process, although the patient may undergo remission while receiving symptom-based treatment. In most cases, however, the patient must depend on replacement therapy throughout his or her lifetime.

Sometimes a damaged organ can be replaced by transplantation. For example, scientists are now testing the effectiveness of islet cell transplant as a treatment for diabetes. Patients with end-stage renal disease or dilated cardiomyopathy may be candidates for a kidney or heart transplant. In the future, stem cell therapies might allow replacement or repair of damaged organs. Replacement therapy is most likely to be successful if the impaired function is localized to a single organ system.

The second treatment approach centers on suppressing the destructive autoimmune response. Systemic autoimmune diseases often require general suppression of the immune response. Immunosuppressive drugs reduce the overall immune response and thereby ameliorate the manifestations of the disease. However, because these drugs also reduce the individual's resistance to infection, they must be used with great caution. In addition, they often have adverse side effects. Such treatments are most often used in debilitating diseases such as lupus and rheumatoid arthritis.

Much effort has been devoted in recent years to developing more focused therapies than global immunosuppression, most of which target a specific step in the tissue-damaging inflammatory response. A number of promising new biologic agents that produce more targeted immunosuppression are already in advanced clinical trials. They include monoclonal antibodies that decrease T cells or B cells specifically, act on only activated T cells, inhibit particular cytokine mediators of inflammation, or block the recruitment and localization of lymphocytes to the target organ. Although these targeted approaches usually have fewer side effects, they may increase the patient's vulnerability to infection, and therefore also must be used with caution. Moreover, a therapy that benefits one autoimmune disease will sometimes make another disorder worse.

An even more refined treatment approach is to arrest the harmful autoimmune response – usually at the point of lymphocyte recognition – without dampening the immune response overall. This approach usually involves identifying the precise antigen responsible for initiating the pathogenic autoimmune response, and blocking it at the point of lymphocyte recognition. While successful in animal studies, this approach has thus far been problematic in humans. By the time most patients are treated, their disease has usually advanced to a point where the immune response has encompassed multiple epitopes on the same antigen or even other molecules of the affected organ. Blocking a single epitope at this stage is unlikely to be effective. Earlier diagnosis, however, would make this treatment approach more feasible in humans.

By the time most patients are treated, their disease has usually advanced to a point where the immune response has encompassed multiple epitopes on the same antigen or even other molecules of the affected organ.

Researchers are using our growing knowledge of the biology of immune response to develop innovative new intervention strategies. These include bone marrow transplantation and strategies to enhance a naturally-occurring regulatory mechanism (e.g., shifting immune response from a damaging T cell subpopulation to a less injurious one, or increasing the number of regulatory cells produced by the thymus). Other interventions may include new therapies and counseling about avoiding exacerbating factors (e.g., certain infections, environmental agents).

Prevention of Autoimmune Diseases

Prevention – arresting the autoimmune process at its outset before irreversible tissue injury occurs – remains the long-range goal of much autoimmune disease research. Yet to effectively develop and implement prevention strategies, scientists must first be able to identify individuals or populations at risk for developing an autoimmune disorder. Since about one-third of autoimmune disease risk is inherited, it will be important to define the genetic make-up of the most susceptible individuals in order to target prevention efforts. This effort has been aided by our increasing knowledge of the human genome and the genes that contribute to autoimmune susceptibility (see also p. 56, Genetic Factors). As with prevention research in other diseases such as cancer, efforts to learn about a disease in highly affected families often lead to the design of prevention strategies that are effective in populations with no known genetic vulnerability.

Many autoimmune disorders involve environmental factors, and identifying these is a major focus of prevention research. Environmental triggers may include infectious agents, normal dietary components (e.g., celiac disease symptoms can be avoided by eliminating gluten in the diet), supplements and food contaminants such as mercury, or occupational or other environmental exposures. As we learn more about environmental influences in autoimmune disease, it may be possible to prevent the onset of disease even in the most vulnerable individuals. For example, identifying those at high risk for type 1 diabetes depends on a combination of genetic factors and the appearance of islet autoantibodies. The presence of these autoantibodies precedes clinical symptoms, but is a strong indicator of relatively rapid progression to frank diabetes.

The third essential step in a prevention program is to develop preventive interventions that can be safely and ethically implemented before disease is evident. Such measures, when they become available, can be coupled with public screening programs designed to identify individuals at risk.

Progress

The 2002 ADCC Autoimmune Diseases Research Plan identified several research opportunities in basic and clinical research, and ultimately patient care. These include: (1) improving diagnosis and disease monitoring through expanded research on biomarkers and bioimaging; (2) strengthening the clinical research infrastructure through centralized, broad-based clinical research centers, and the development of better classification and response criteria; and (3) creating public-private partnerships for clinical trials. Since publication of the 2002 Research Plan, NIH has continued support for a number of productive programs in clinical research and has launched several new initiatives. For example, numerous initiatives supporting clinical trials are underway, including strengthening clinical research infrastructure. Selected examples of new and continuing programs – and of scientific advances achieved over the past two years – are described below. We describe these programs according to the four broad categories noted above, but in most cases they address more than a single objective.

Diagnosis and Disease Progression

Established and new initiatives in this area support studies to improve diagnosis and to better understand the mechanisms underlying disease progression. Biomarkers of disease and disease progression continue to be a major focus of studies in this area. For example, the goal of the **Autoimmune Biomarkers Collaborative Network** is to develop biomarkers for two major rheumatic diseases – rheumatoid arthritis and lupus – that can be used reliably in a clinical setting to define disease subsets or to follow disease activity and progression. The new tools developed through the network will assist physicians in diagnosis, selection and management of therapy, and collection of predictive information about disease flares and long-term outcome.

Multiple NIH Institutes cosponsor the initiative, **Microcirculation and Target Organ Damage in Rheumatic and Skin Diseases,** which addresses the mechanisms of organ damage and microcirculation alterations in rheumatic and autoimmune skin diseases. In FY 2003, nine grants were awarded in response to this initiative. These studies focus on the immune and non-immune mechanisms governing injury induction and development, and relevant genetics of microcirculation and organ involvement in rheumatic diseases. Knowledge gained from research in this area will help to construct a more comprehensive picture of autoimmune disease pathogenesis. Defining the pathogenic processes involving specific target organs may provide the scientific rationale for new types of interventions.

The **Beta Cell Imaging Initiative** funds efforts to develop techniques or reagents to image or otherwise noninvasively detect pancreatic islet beta cells *in vivo* in order to measure their mass, function, or evidence of inflammation, or to monitor engraftment of transplanted isolated pancreatic islets. These measurements can be used to monitor individuals at high risk for type 1 diabetes and assess their response to preventive therapy. Six projects have been funded through the program. Researchers funded through this initiative recently developed a novel magnetic label to selectively target a population of T cells that contribute to diabetes development in non-obese diabetic (NOD) mice. The researchers were then able to noninvasively visualize the recruitment of autoreactive T cells to the pancreas in real time using magnetic resonance imaging (MRI). This novel technique will provide new insights into the autoimmune process that causes type 1 diabetes, which should ultimately lead to new prevention strategies.

The **Beta Cell Biology Consortium** seeks to understand basic mechanisms underlying pancreatic development and function; generate a renewable source of pancreatic beta cells to facilitate the development of cell-based therapies for diabetes; understand the requirements for survival and engraftment of transplanted cells or tissue; and generate novel resources for research, such as "PancChips" containing all known genes expressed in both the human and mouse pancreas. Identifying beta cell proteins and generating well-characterized antibodies that bind both human and mouse islet cell antigens will facilitate studies of pathogenesis.

Pulmonary fibrosis is an autoimmune disease of unknown cause that is characterized by inflammation and scarring of the lungs. The scarring can progress to the point that the lungs are unable to provide sufficient oxygen to the body. The **Pulmonary Fibrosis: Molecular Targets and Interventions** initiative supports research to discover and validate molecular targets for interfering with the fibrogenesis associated with this disease. Research on drugs that act on previously or newly identified targets to attenuate, halt, or reverse fibrogenesis is also encouraged. Five projects funded through this program are searching for new molecular targets for treating idiopathic pulmonary fibrosis (IPF). Within these projects, scientists are conducting gene array analyses in IPF lung tissue samples for collagen and for Interleukin-4 and Interleukin-13 cytokines – which are over-expressed in IPF – and exploring whether these exaggerated responses can be suppressed in animal models using a drug based on the pseudomonas exotoxin. Another study is examining the effectiveness in mice of a molecule called survivin that enhances programmed cell death in fibroblasts. This initiative underscores the need for alternative approaches to current treatments (usually anti-inflammatory drugs such as steroids) that will reduce treatment costs, increase specificity, and produce fewer side effects.

Pulmonary fibrosis is an autoimmune disease of unknown cause that is characterized by inflammation and scarring of the lungs.

An initiative on **Neuroprotective CNS Barriers in Neurological Diseases** emphasizes studies of the blood-brain barrier in health and disease. In multiple sclerosis patients, the blood-brain barrier breaks down and allows the infiltration of immune cells into the brain. An understanding of this cell migration promises to be useful in developing novel multiple sclerosis therapies. This initiative also encourages studies to enhance the effectiveness

of drug and gene delivery strategies for treating neurological diseases such as multiple sclerosis. The program, launched in 2003, has funded three grants to date.

Multiple sclerosis is characterized by chronic inflammation and demyelination of the central nervous system that over time leads to neurodegeneration. While axonal damage and neuronal cell death are likely to be the major causes of disability in the later, progressive phase of multiple sclerosis, new evidence suggests that even in early stages severance of nerve axons may occur and lead to irreparable nerve damage. The current FDA-approved therapies focus on the inflammatory autoimmune components of the disease, and do not appear to significantly impact this neural tissue loss. **Axonal Damage in Multiple Sclerosis: Strategies for Protection and Repair** is a new initiative for clinical and translational research that targets neurodegeneration in multiple sclerosis and explores neuroprotective and regenerative therapies. It is hoped that the combination of approved immunomodulatory therapies and future neuroprotective and regenerative treatment regimens will lead to improved outcomes for patients.

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Mechanistic Studies

The mechanisms underlying treatments for immune disorders are often poorly understood, even in cases where efficacy has been shown (e.g., allergen immunotherapy, multiple sclerosis treatments such as interferons, copolymer-I, and other immunomodulatory regimens under development). In addition, clinical trials supported by industry, NIH, and other organizations often do not include studies to determine a drug's mechanism of action. The **Hyperaccelerated Awards/Mechanisms in Immunomodulation Trials** program supports mechanistic studies in conjunction with clinical trials of: (1) immunomodulatory interventions for immune-mediated diseases, including asthma and allergy; (2) chronic inflammatory and autoimmune disorders; (3) transplant rejection; and (4) primary immunodeficiency diseases. Patient samples from these clinical trials are used for studies exploring the basic underlying mechanisms of therapeutic effect, immunologic function, disease pathogenesis, and surrogate markers of disease activity and therapeutic effect. Since its inception as a pilot program in 1998, this program has been renewed annually. Of the 40 studies funded overall, 18 focus on autoimmune diseases. In most cases, the clinical trial is sponsored by industry and the mechanistic studies are

supported by NIH. Multiple NIH Institutes, Centers, and Offices cosponsor this program, which incorporates procedures for expedited grant application review that allows funding within as few as 13 weeks of submission of the grant application.

A similar program, **Ancillary Studies in Heart, Lung, and Blood Disease Trials** uses patients and patient materials from ongoing clinical trials related to heart, lung, and blood diseases to address mechanisms of disease pathogenesis, surrogate markers or biomarkers of disease risk or activity and therapeutic effect, mechanisms underlying human cardiopulmonary and hematologic function in general, or mechanisms underlying interventions. For example, an ongoing clinical trial is comparing two plasma treatment methods as a therapy for thrombotic thrombocytopenic purpura (TTP). An ancillary study accompanying this trial has analyzed 105 plasma samples taken from 36 patients. Studies to accelerate the development of new technologies within the context of such mechanistic investigations are also encouraged. Information derived from these studies may help to design treatments, or the timing of treatments, that can be targeted to patients with specific responses or characteristics. Mechanistic studies in clinical trials supported by any source (industry, public, and private) are eligible. Under an expedited peer review process, awards are issued to successful applicants approximately 15 weeks following application receipt.

Key Advances—Diagnosis and Disease Progression

Identifying People at Risk for Lupus Years Before Clinical Onset of Disease. The immune systems of people with lupus form antibodies that attack normal tissues and organs, including the kidneys, brain, central nervous system, blood and blood vessels, skin, lungs, heart, and joints. Lupus is marked by periods of illness (flares), and periods of wellness (remission), and is a leading cause of kidney disease, stroke, and premature cardiovascular disease in women of childbearing age. It is difficult to diagnose because its variable symptoms mimic those of other diseases, and it cannot be diagnosed definitively with laboratory tests. Lupus has no known cause or cure, but a combination of genetic, environmental, and hormonal factors are believed to work together to cause the disease. Early detection and treatment can usually lessen lupus progression and severity, but even with treatment it can be fatal. Researchers have recently developed a blood serum test that can identify the autoantibodies associated with lupus years before a person displays disease symptoms. It was observed that these antibodies recognize certain epitopes of the Epstein-Barr virus that may cross-react with autoantigens. If so, this may be an example of molecular mimicry. In addition, specific chromosomal segments have been associated with lupus in specific populations – 11p13 in African Americans with lupus; 12q24 in Hispanic and European Americans – and a number of other genes have been associated with specific lupus symptoms in an ethnically mixed population. The ability to identify people at risk of lupus before symptoms appear will significantly improve their health care management, and may lead to novel treatments for lupus and other immune diseases.

Scientists Find Markers for Rapid Progression of Rheumatoid Arthritis (RA). Researchers have identified markers that are early indicators of progressive disease in rheumatoid arthritis (RA). The following factors, when present at disease onset predict x-ray evidence of rapid progression: older age, bone erosions, presence and amount of rheumatoid factor (an antibody in the blood), variations in specific genes related to immune function and to the protein uteroglobin, and T cells (CD4+, CD28null) associated with an aging immune system. Other possible biologic markers, including initial joint pain and swelling, were determined not to be predictive of rapid progression. Because RA progression can vary substantially, early aggressive treatment with disease-modifying antirheumatic drugs is frequently recommended despite some toxicity risks. The study's findings suggest that more appropriate treatment strategies could be based on likely disease course, and underscore the need for further investigation.

Predictive Markers for Type 1 Diabetes. Researchers have identified the genes for human IA-2 and IA-2 beta, both of which have been found to be major autoantigens in type 1 diabetes. To determine if these autoantigens could serve as predictive biomarkers for the disease, researchers conducted a clinical study in which they followed approximately 10,000 school children for up to ten years to check for the presence of autoantibodies. Eleven of these children went on to develop diabetes and ten were found to have autoantibodies to IA-2 years before they developed type 1 diabetes. An important outcome from this and similar studies is that autoantibodies to IA-2 and IA-2 beta appear years before the development of clinically apparent type 1 diabetes and, therefore, can serve as predictive markers for this disease.

Clinical Research Infrastructure

New and ongoing NIH activities designed to strengthen the clinical trials infrastructure are improving clinical trials, hastening the trials themselves, and enabling scientists to derive the maximum information from them. Specialized research centers, for example, are enabling scientists to test potential therapeutic agents on a larger scale and at a more rapid pace than in the past. Initiatives designed to improve the clinical trials infrastructure are described below.

Centers and Networks

The multidisciplinary **Cooperative Study Group for Autoimmune Diseases Prevention (Prevention Centers)** is a five-year program supporting an interactive and collaborative network of investigators devoted to understanding immune homeostasis in both health and autoimmune disease, and to developing interventions to prevent human autoimmune disease. The five participating centers in this program support preclinical research, innovative pilot projects, and clinical studies. Funded projects, which focus on type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and celiac disease, are exploring regulatory T cells, familial relationships in autoimmunity, genomic and proteomic analysis in autoimmune disease, and CD40/CD154 blockade. During the first three years of the program, grantees have produced 55 original research publications and three of 25 pilot projects have matured into investigator-initiated grants.

The **Specialized Centers of Clinically Oriented Research (SCCOR) in Transfusion Biology and Medicine** program aims to improve the safety and efficacy of transfused blood and blood components, determine the indications for their use, and evaluate immunologic responses following their administration. This initiative encourages the use of innovative technologies to conduct basic research and facilitate the transfer of the basic knowledge to the clinical arena. NIH also supports Specialized Centers of Research (SCORs) in systemic lupus erythematosus, rheumatoid arthritis, and scleroderma. In FY 2002, two new SCOR centers focused on systemic lupus erythematosus were established. These centers are investigating the role of antibodies in systemic lupus erythematosus and the immunologic and genetic factors important to this disease.

In several areas of inquiry in skin disease research, including autoimmune skin diseases, scientists have reached the stage at which broad advances can be fostered by research core centers. The **Skin Diseases Research Core Centers** provide the resources to

enable a number of established, currently-funded investigators – often from different disciplines – to adopt a multidisciplinary approach to common research problems in skin diseases in order to increase research productivity. This approach ensures greater productivity than from each of the separate projects. Resources most often provided through these research core centers include automated support for repetitive tasks and those amenable to automation or preparation in large batches (e.g., histology or tissue culture), access to complex instrumentation, animal preparation and care, and other services and training (e.g., molecular biology, biostatistics).

The **Cooperative Multicenter Research Network to Test Glucose Sensors in Children with Type 1 Diabetes Mellitus** supports a collaborative research consortium that will use continuous glucose monitoring devices to evaluate the incidence, magnitude, and duration of hypoglycemia in children with type 1 diabetes mellitus. The devices will also be used to evaluate blood sugar control in children without diabetes. The consortium may also investigate the value of providing data from these devices to health care professionals so that they can better help their pediatric patients achieve good blood sugar control.

The goals of the NIH **Multidisciplinary Clinical Research Centers (MCRC) for Arthritis and Musculoskeletal and Skin Diseases** are to prevent disease and improve outcomes for patients with arthritis and other rheumatic diseases, musculoskeletal and orthopedic disorders, bone and muscle diseases, and skin diseases. Each center is organized around a methodology core that includes a minimum of three highly meritorious multidisciplinary projects. Each MCRC provides key support for developing and implementing clinical projects that address a critical issue directly involving prevention, assessment, and/or outcomes for patients with one or more chronic diseases. In FY 2003, three new centers were funded, two of which are focused primarily on rheumatic disease. One will study scleroderma and systemic lupus erythematosus, two rheumatic diseases that disproportionately affect the African American community. Another will examine environmental influences on the development of osteoarthritis, social determinants of arthritis outcomes, as well as social support, perceived control, and psychological adjustment in vasculitis patients and their families.

Resources most often provided through these research core centers include automated support for repetitive tasks and those amenable to automation or preparation in large batches.

The **Rare Diseases Clinical Research Network** facilitates clinical research on rare diseases through support for: (1) collaborative research, longitudinal studies, clinical studies and trials, and pilot and demonstration projects; (2) clinical investigator training in rare diseases research; (3) distributed clinical data management incorporating novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms; and (4) access to information on rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the lay public. Each network includes a government/academic/industry/advocacy consortium focusing on a subgroup of rare diseases. One of these consortia is the **Vasculitis Clinical Research Consortium** (see also p.90). **The Data and Technology Coordinating Center**, a collaboration between database and computational/computer science innovators, provides a scalable coordinated clinical data management system, a portal and tools for integrating publicly available datasets for data mining, Web-based recruitment and referral, and a user-friendly Web site with resources for the public, research scientists, and clinicians. This cooperative program facilitates identification of biomarkers for disease risk, disease severity/activity, and clinical outcome and encourages development of new approaches to diagnosis, prevention, and treatment of rare diseases.

Research Resource Development

The **International Histocompatibility Working Group (IHWG)** is a multidisciplinary network of more than 200 laboratories in over 70 countries. The collective goal of this large group is to catalog the human leukocyte antigen (HLA) gene complex, and to characterize the relationship between certain HLA genes and immune-mediated diseases, including autoimmunity and transplant-related diseases. In 2004, the IHWG created a searchable HLA database that integrates gene sequences with clinical information as a platform for future research in immune-mediated diseases.

The **NIH Tetramer Facility** provides custom synthesis and distribution of soluble major histocompatibility complex (MHC)-peptide tetramer reagents that can be used to detect antigen-specific T cells. MHC molecules come in two basic forms: MHC class I and class II. These MHC molecules can present fragments (i.e., peptides) of pathogen or self proteins to different subsets of T cells. MHC class I/peptide complexes activate cytotoxic T cells to eliminate diseased or infected cells, whereas MHC class II/peptide complexes activate T helper cells to produce growth factors that regulate the immune response. Since opening in 1999, the NIH Tetramer Facility has provided 1,912 tetramer reagents to 486 investigators in 20 countries throughout the world. While 90 percent of the tetramer

reagents are distributed to scientists in the United States, tetramer reagents also have been shipped internationally. Since 2002, a small number of preassembled MHC class II tetramers also have been available to the research community. These reagents include a tetramer that will detect human T cells involved in the pathogenesis of type 1 diabetes. The NIH Tetramer Facility currently is developing novel technologies to expand production of MHC class II tetramers and development of CD1 tetramers. The CD1 family of MHC-like molecules activates T cells that play crucial roles in both pathogen-specific responses and in regulation of the immune system. The Tetramer Facility currently supplies CD1 monomers to the research community and its next priority will be to produce and distribute human CD1 tetramers. These reagents can also be applied to studies ranging from protection against microbial pathogens, including potential bioweapons, to control of autoimmune diseases and tumor metastases.

The NIH Tetramer Facility currently is developing novel technologies to expand production of MHC class II tetramers and development of CD1 tetramers.

The **Development of Immune Monitoring Reagents and MHC Typing Technologies for Non-Human Primates** initiative embodies NIH's continuing commitment to advance preclinical, non-human primate (NHP) research in the fields of infectious disease vaccine development, transplantation, and autoimmune diseases. The goal of one contract funded through this initiative is to develop, produce, and distribute NHP immune monitoring and immune modulating reagents that are needed to: (1) evaluate NHP immune responses in vaccine and adjuvant development for infectious diseases, transplantation research, and autoimmune and infectious disease models; and (2) develop novel immune-based therapeutics, vaccines, and adjuvants. In addition, this initiative supports two contracts for the development of rapid, high-throughput, medium- to high-resolution technologies for major histocompatibility complex (MHC) typing of various NHP species. A high degree of NHP MHC gene/allele discovery is required to develop and validate the typing technologies.

Recent publications have reported that some patients with type 1 diabetes have achieved long-term insulin independence after receiving human pancreatic islet cell transplants. To expand these observations and bring such therapies into practice, NIH has partnered with a nonprofit organization to establish **Islet Cell Resource (ICR)** centers that promote the isolation, purification, and characterization of human pancreatic islet cells for transplantation into diabetic patients. The initiative also established a separate Administrative and

Bioinformatics Coordinating Center (ABCC) to coordinate the ICRs' activities. Six ICRs widely distributed across the United States are responsible for procuring whole pancreata, utilizing state-of-the-art techniques for isolation and quality control of islet cell preparations, and distributing islets for approved research or clinical protocols. They also perform research and development to improve isolation techniques, cellular viability and function, and shipping procedures.

Animal models are invaluable tools for exploring disease pathogenesis and for testing the safety and efficacy of promising interventions in preclinical studies. Through the **Type 1 Diabetes Mouse Animal Models,** investigators can gain access to two animal repositories that maintain and distribute up to 52 mouse strains important to research on the pathogenesis of type 1 diabetes. The repository aims to maintain at least 150 mouse strains. In addition, all congenic non-obese diabetic (NOD) mouse strains, many of which have proven useful in studies of several autoimmune diseases in addition to type 1 diabetes, are now available to investigators. Through the NOD mouse sequencing project, investigators have also sequenced the complete bacterial artificial chromosome (BAC) library of the NOD mouse and used this resource to complete a physical map of the BAC clones. The library, which contains 240,000 clones, was recently released to the scientific community. As a next step, investigators are planning to identify the single nucleotide differences between NOD mouse clone end sequences and the B6 mouse genome (a nondiabetic mouse strain) and to use this sequencing information to identify and map candidate genes. Such information will guide efforts to isolate genes that contribute to type 1 diabetes development in humans.

Other Clinical Research Infrastructure Initiatives

The **NIH Clinical Trial Planning Grant Program** supports the development of Phase III clinical trials, including establishing the research team, developing data management and research oversight tools, defining recruitment strategies, and finalizing the protocol and other essential elements of the study, including an operations/procedures manual. This grant is not designed for preliminary data collection or for conducting pilot studies to support the rationale for a clinical trial. Instead, it is designed to: (1) allow early peer review of the proposed trial rationale, (2) permit assessment of the design/protocol in its early form, (3) support development of a detailed operating procedures manual, and (4) support development of other essential clinical trial elements as defined by the participating NIH Institutes and Centers.

The **National Electronic Clinical Trials and Research (NECTAR) Network** is a component of the NIH Roadmap thematic area, *Re-engineering the Clinical Research Enterprise*. NECTAR is a national network of new and existing clinical research sites, programs, and systems. Its purpose is to link clinical research networks in order to expand their utility, maximize connectivity among the sites, and provide scientists with increased analytic capacity. The network will establish data standards (e.g., common exchange vocabularies), provide software applications to support clinical research tasks, and institute a network infrastructure to integrate available data resources. Launched in 2004, NECTAR has a projected completion date of 2006.

As more investigators study cancer treatment vaccines, it has become apparent that a fine line exists between inducing immunity to tumor antigens, many of which are expressed on normal cells, and causing a harmful autoimmune response.

Chronic Graft-Versus-Host Disease (GVHD) Consensus Criteria in Clinical Trials. Graft-versus-host disease (GVHD) is difficult to diagnose because no agreed-upon objective definitions of signs and symptoms currently exist. Recently, a diverse group of NIH intramural, NIH extramural and non-NIH scientists began a project to develop consensus criteria for chronic GVHD in clinical trials. This effort is modeled after similar international efforts to assess polymyositis and lupus. In 2005, the group intends to develop standard diagnostic criteria, response criteria, pathologic criteria, and biomarkers characteristic of this disease.

As more investigators study cancer treatment vaccines, it has become apparent that a fine line exists between inducing immunity to tumor antigens, many of which are expressed on normal cells, and causing a harmful autoimmune response. For this reason, patients with prior autoimmune disease may be ineligible for cancer vaccine trials. In addition, before receiving a vaccine, patients are carefully monitored for any signs of autoimmunity, such as antibodies to double-stranded DNA or histones, vasculitis, thyroiditis, cardiomyopathy, vitiligo, retinal pigmentation, or other clinical signs of immune pathology. By studying the timing of autoimmune responses compared to therapeutic responses, it may be possible to optimize the safety of dendritic cell vaccines.

Key Advances—Clinical Research Infrastructure

C-peptide is the Appropriate Outcome Measure for Type 1 Diabetes Clinical Trials to Preserve Beta Cell Function. The underlying cause of type 1 diabetes, loss of beta cell function, has become the therapeutic target for a number of interventions in patients with the disease. Even though insulin therapies continue to improve, it remains difficult to achieve normal glycemic control in type 1 diabetes, especially long term. Retaining beta cell function in patients with type 1 diabetes, however, is known to result in reduced hypoglycemia and improved glycemic control. This improved control reduces complications including retinopathy, nephropathy, neuropathy and atherosclerosis. In addition to insulin, the beta cells secrete C-peptide, a by-product of insulin production derived from a precursor (proinsulin) in the insulin production process. C-peptide is produced on a 1:1 basis with insulin and allows monitoring of endogenous pancreatic insulin secretion in individuals receiving insulin therapy; therapy for type 1 diabetes utilizes insulin, not proinsulin, so any C-peptide present is endogenously produced. At a non-profit-sponsored conference, a professional consensus was reached that monitoring C-peptide secretion is the most suitable primary outcome variable for trials of therapies intended to slow beta cell destruction in patients with new-onset type 1 diabetes. Available data demonstrate that even a relatively modest increase in C-peptide levels is a reliable marker for clinically meaningful benefits. Thus, the development of therapies for preventing or delaying progression of type 1 diabetes will be facilitated by trials in patients with new-onset type 1 diabetes that use C-peptide concentration to monitor beta cell function.

Pancreatic Islet Transplantation Using the Non-human Primate (Rhesus) Model Indicates the Portal Vein is Superior to the Celiac Artery as the Islet Infusion Site. NIH-funded researchers established a non-human primate islet allotransplant model to assess whether transplanting islets into the gut arterial system would more safely, and as effectively, support long-term islet allograft survival as the traditional portal vein approach. Because islets make up less than two percent of pancreatic cell mass but consume an estimated 20 percent of arterial blood flow, the researchers hypothesized that the arterial site might be better. Access to the arterial system is also easier and safer than the portal system. Rhesus macaques from which the pancreas was removed were transplanted with allogeneic islets infused into either the portal vein or the celiac artery. To prevent rejection, the animals were given daclizumab, tacrolimus, and rapamycin. Five of the six animals receiving a portal vein infusion achieved normal glycemic levels without insulin supplementation. In contrast, none of the animals given intra-arterial islets showed even transient insulin independence. Two of the latter animals received a second islet transplant, this time to the portal system, and both achieved insulin independence. Thus, intraportal islet transplantation under conventional immunosuppression is feasible in primates and can result in long-term insulin independence when adequate immunosuppression is maintained. Arterial islet injection, however, does not appear to be a viable islet transplantation technique.

KEY ADVANCES

A Protective Gene for Graft-Versus-Host Disease Following Bone Marrow Transplantation. Hematopoietic cell transplantation (HCT) is an effective therapy for a number of life-threatening diseases, including various forms of leukemia. The primary complication of HCT is graft-versus-host disease (GVHD), in which donor T cells that accompany the transplanted blood progenitor cells produce an immune response against host organs and tissues, often with fatal consequences. In a study of nearly 1,000 recipients of HCT from unrelated donors, researchers discovered that a genetic variant of the *interleukin 10* (*IL-I0*) gene decreases the risk of acute GVHD and death after HCT by close to 50 percent. This protective variant is associated with increased production of IL-10, a cytokine that suppresses the production of inflammatory cytokines and promotes the development of tolerance (the lack of a deleterious immune response to the host organs and tissues). These important findings provide new avenues for developing novel IL-10-based therapies for decreasing GVHD and mortality in patients undergoing HCT. In addition, knowledge of patient *IL-I0* genotype may help clinicians better inform their patients about relative risks of HCT.

Clinical Trials

Many agents that show promising results in preclinical studies do not advance to clinical trials. Clinical trials represent a lengthy and expensive aspect of drug or device development, and entail considerable financial risk for pharmaceutical or biotechnology companies. As in other diseases, new treatments for autoimmune diseases are sometimes discovered when practitioners identify new uses for medications originally approved for other conditions. Nonetheless, new and ongoing trials are paving the way for new treatments for patients with diverse autoimmune disorders. In addition, early stage trials in particular are crucial to understanding the mechanisms that underlie drug activity or the lack thereof.

In accordance with the areas of emphasis outlined in the 2002 ADCC Autoimmune Diseases Research Plan, NIH continues to sponsor a broad range of clinical trials and clinical trial networks. One of these, the **Immune Tolerance Network** (ITN, see inset p. 71), is a consortium of more than 80 investigators in the United States, Canada, Western Europe, and Australia dedicated to the clinical evaluation of promising therapies that can induce immune tolerance in kidney, liver, and islet cell transplantation, as well as medical treatments for all autoimmune disorders, asthma, and allergic diseases. Currently, 15 of the 30 ITN clinical trials that are ongoing or in development focus on autoimmune disorders.

The **Autoimmunity Centers of Excellence** initiative (see also inset, p. 44) was expanded in FY 2003 from four to nine centers. These centers are devoted to collaborative basic and clinical research on autoimmune diseases, including single site and multisite clinical trials of immunomodulatory therapies. The centers bring together many different clinical sub-specialists (e.g., neurologists, gastroenterologists, rheumatologists), as well as basic scientists, to facilitate autoimmunity research collaboration. This group is currently conducting clinical trials testing immune-modulating therapies in lupus and multiple sclerosis, with trials in type 1 diabetes planned. Multiple NIH Institutes and Offices support this program.

The Immune Tolerance Network: An Innovative Model for Clinical Tolerance Research

The Immune Tolerance Network (ITN) is an international consortium of more than 80 scientists and physicians dedicated to identifying and evaluating new ways to induce stable, long-term immune tolerance for immune-mediated diseases, including autoimmune disorders. These novel treatment strategies center on reprogramming immune cells so that they no longer attack the patient's own tissues (known as self-tolerance) but still effectively guard the body against bacteria, viruses, and other pathogens. Because tolerance-inducing therapies would eliminate the need for lifelong immunosuppressive drug regimens – which themselves have common and serious side effects – they have the potential to revolutionize the management of many autoimmune diseases.

The ITN partners with the biotechnology and pharmaceutical industries to examine potential tolerance-inducing therapies and conduct clinical trials of those that are most promising. All of the clinical trials also include integrated studies on the underlying mechanisms of these approaches, as well as on markers and assays to measure the induction, maintenance, or loss of tolerance. These mechanistic and biomarker studies are supported by a wide range of scientific and technical expertise and more than a dozen core facilities, including high-throughput genomics and proteomics cores. Many ITN activities address emphasis areas of the NIH Roadmap for re-engineering the clinical research enterprise. For example, the ITN has developed a robust specimen and clinical assay tracking system and bioinformatics tools for integrating complex clinical and mechanistic data across trials in multiple immune-mediated diseases.

Currently, the ITN supports 15 trials for a variety of autoimmune diseases, including multiple sclerosis, rheumatologic disorders, and type 1 diabetes. Additional clinical trials focus on kidney, bone marrow, liver, stem cell, or islet transplantation, and immune tolerance strategies in asthma and allergic disorders. For more information, visit http://www.immunetolerance.org.

The **Atherosclerosis Prevention in Pediatric Lupus Erythematosus** (APPLE) trial, initiated in 2003, is a new effort to test the effects of statins – drugs currently used to lower low-density lipoprotein levels – to protect the blood vessels of children with lupus. Scientists hope that these agents will prevent the arterial fat build-up that can develop in young lupus patients. Over 12 months, 20 centers in the Pediatric Rheumatology Research Network will enroll 250 children with recent-onset lupus who will be treated with the drug atorvastatin for 36 months. This effort will establish the largest cohort of pediatric lupus patients enrolled in a prospective study.

The FDA has approved both interferon-beta (IFN-β) and glatiramer acetate (GA) for the treatment of relapsing forms of multiple sclerosis. It is not known, however, whether one of these therapies is more effective than the other or whether the combination of both therapies would produce even greater benefit than either treatment alone. The **CombiRx trial** is a randomized, controlled Phase III clinical trial comparing the efficacy of combining IFN-β and GA. The CombiRX trial involves nearly 70 investigational sites in North America and will recruit approximately 1,000 patients. As an ancillary study to the trial, NIH intramural investigators will conduct a large biomarker study that will incorporate genetic mapping, gene expression studies, histocompatibility typing, and proteomics technology.

In August 2001, the Diabetes Prevention Trial 1 was reconfigured as the **Diabetes TrialNet Consortium**. TrialNet provides infrastructure and support for multiple clinical trials aimed at preserving insulin-producing cells in individuals at risk for type 1 diabetes and in those with new-onset type 1 diabetes. The study group consists of 18 clinical centers worldwide – in the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia, and New Zealand – with approximately 100 additional affiliates that recruit and study patients. An additional network involving hundreds of remote locations connected via satellites participates in screening subjects for eligibility to enroll in TrialNet studies. Research under TrialNet is supported by a compounding pharmacy, an insulin autoantibody laboratory, an islet cell antibody laboratory, a class II major histocompatibility protein and DNA extraction lab, and a beta cell function laboratory. Studies will include natural history studies and diabetes intervention studies. Currently, several studies are enrolling patients. A clinical trial of mycophenolate mofetil (MMF) and daclizumab (DZB) is underway in individuals with new-onset type 1 diabetes. The Natural History Study is examining events leading to type 1 diabetes onset and will facilitate enrollment of eligible individuals into planned studies of interventions to arrest the disease process. Another study is comparing methods of assessing beta cell function in new-onset type 1 diabetes

to aid in measuring trial outcomes. A trial to determine whether nutritional supplements containing an omega-3 fatty acid will prevent onset of type 1 diabetes among infants at high risk will begin in 2005. Several other protocols are under development.

NIH's **Trial to Reduce the Incidence of Type 1 Diabetes Mellitus in the Genetically At-Risk (TRIGR)** study is a multisite, randomized, controlled clinical trial designed to determine whether the onset of type 1 diabetes can be delayed or prevented by weaning genetically-susceptible infants to a diet containing a hydrosylate of cow milk protein (experimental group), instead of to a standard cow's milk-based infant formula (control group). TRIGR is in the process of enrolling 2,000 genetically-susceptible infants at 73 sites in 15 countries. Enrollment and follow-up will continue for eight years. The primary outcome will be the determination of the prevalence of type 1 diabetes in each of the two groups in 2011. Interim analyses of the development of autoantibodies directed against islet cell antigens in the two groups are planned for 2005 and 2008. If TRIGR confirms the benefit of this simple nutritional intervention, the public health implications will be great.

The **Stem Cell Transplantation for Autoimmune Disease Treatment Consortium** will conduct clinical trials designed to study the safety and efficacy of high-dose immunosuppressive or immunoablative therapy followed by autologous stem cell transplantation as a treatment for severe progressive autoimmune disease. In particular, these studies focus on severe systemic sclerosis (SSc), refractory systemic lupus erythematosus, and multiple sclerosis. The trials differ in the details of the immunosuppressive preparative regimens. They are, however, based on the common theory that destroying the autoreactive lymphocyte population with high-dose chemotherapy (with or without radiation) followed by autologous transplant with hematopoietic cell transplantation, will permit resetting of the immune system and the re-induction of self-tolerance. Phase I studies have demonstrated the safety of the procedure in patients with autoimmune diseases. Phase II/III studies will identify patients most likely to benefit from this therapy, determine optimal conditioning regimens, and provide a more rigorous assessment of therapeutic efficacy. In addition, integrated studies of the immunologic mechanisms underlying this therapeutic approach will be performed. It is anticipated that protocols for autologous hematopoietic cell transplantation in SSc, systemic lupus erythematosus, and multiple sclerosis will be opening in late 2004 and early 2005.

In its life-threatening forms, lupus is extremely resistant to treatment. Because no cure exists for severe systemic lupus erythematosus, and as a complementary effort to NIH

initiatives in chronic graft-versus-host disease, two Institutes collaborated to bring together expertise in transplantation and in systemic lupus erythematosus to develop a **research program of hematopoietic stem cell transplantation and cellular immunotherapy for systemic lupus erythematosus**. The goal of the program is to cure patients of the disease, and also to use the basic science research expertise at both Institutes to gain a better understanding of the processes that cause systemic lupus erythematosus. Knowledge of these abnormal immunologic processes might then be used to develop better targeted (auto) immune therapies for cancer. The first result of this collaboration is the Phase II protocol, "Intensified Lymphodepletion Followed by Autologous Hematopoietic Stem Cell Transplantation in Patients with severe systemic lupus erythematosus." The unique aspects of this study are: (1) the first use of a less intensive, less toxic, lymphoablative regimen for transplantation in systemic lupus erythematosus; (2) precisely defined eligibility and disease response criteria; and (3) a comprehensive battery of laboratory research studies designed to investigate the biology of systemic lupus erythematosus and post-transplant responses. The primary endpoint is a relapse-free clinical response at 24 months post-transplantation. The study is actively enrolling subjects. This protocol should serve as a foundation for future studies of cellular immunotherapy intended to re-establish a disease-free immune system and lasting remissions or cures for lupus and cancer.

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Other clinical trial activities include NIH's longstanding **Innovative Therapies for Rheumatic and Skin Diseases** initiative, which supports evaluations of therapies for rheumatic and skin diseases such as Wegener's granulomatosis, rheumatoid arthritis, scleroderma, lupus, ankylosing spondylitis, and inflammatory, autoimmune, and genetic skin diseases. **Clinical Trials and Clinical Markers in Immunologic Diseases** focuses on orphan clinical trials of immunomodulatory treatments for immune-mediated diseases, including autoimmune disorders, and the development of biologic markers to measure disease activity, risk, and therapeutic effect. **Cyclophosphamide in Scleroderma Pulmonary Disease** is an initiative supporting an investigator-initiated five-year, 13-center, parallel-group, double-blinded, randomized, Phase III clinical trial of cyclophosphamide for the treatment of pulmonary fibrosis associated with systemic sclerosis. The study began enrolling patients from 15 U.S. medical centers in September 2002. The current study population consists primarily of women (71 percent). To date, 162 patients have been enrolled, and study findings are

anticipated in 2005. Two clinical trials, **Evaluation and Treatment of Salivary Gland Dysfunction** and **Natural History of Salivary Gland Dysfunction and Sjögren's Syndrome,** focus on patients with complaints of dry mouth or Sjögren's syndrome.

The NIH **Intramural Hematology Program** is one of the largest research programs in aplastic anemia in the United States. Under this program, scientists have established that aplastic anemia is characterized by immune-mediated destruction of bone marrow stem cells, resulting in often fatal anemia, thrombocytopenia, and neutropenia. Investigators also have shown that treatment with a combination of anti-thymocyte globulin and cyclosporine improves blood count in the majority of aplastic anemia patients. For some types of aplastic anemia, more modest immunosuppressive therapy also appears to be effective. Studies suggest that some molecular and genetic features of aplastic anemia are similar to those seen in clonal hematologic diseases such as paroxysmal nocturnal hemoglobinuria and myelodysplasia (a common syndrome in older persons). Moreover, myelodysplasia appears to respond to the same immunosuppressive therapies that are used to treat aplastic anemia.

Therapies based on **Complementary and Alternative Medicine** are widely used but largely unproven as treatments for autoimmune disease. NIH is supporting selected studies of clinical and basic science approaches using complementary and alternative medicine in multiple sclerosis, rheumatoid arthritis, fibromyalgia, and diabetic neuropathy. Some of these studies are randomized, controlled clinical trials of complementary and alternative medicine products, and will provide the scientific rigor that has previously been lacking in most studies of these therapies. For example, intramural researchers at the NIH have recently published data on the effectiveness on an extract from the plant Thunder God Vine (*Tryptergium wilfordii)* in a small group of people with treatment-resistant rheumatoid arthritis. The drug, which slows down the overactive immune system, reduces inflammation by turning off inflammatory genes such as tumor necrosis factor alpha, and reduces the activity of B and T cells, was shown to safely and effectively reduce pain and inflammation. A larger clinical trial to confirm the drug's benefit and safety is ongoing.

Key Advances—Clinical Trials

Type 1 Diabetes Treatment with Anti-CD3 Antibody Shows Promise as Immune Therapy. At the onset of type 1 diabetes, the pancreas continues to produce low levels of insulin. NIH-supported researchers have recently shown that treatment within six weeks of disease onset using a novel immunotherapy that targets T cells slowed the loss of insulin production in nine of 12 treated patients. Although the treatment was given over a two-week course, the effects were still evident one year later. Treatment may directly affect the disease-causing T cells, induce populations of T cells that down-regulate these cells, or both. These preliminary results indicate that the immune processes leading to destruction of target organs in autoimmune diseases can be interrupted with novel immune therapies that have long-lasting effects. NIH is supporting Phase II studies of this treatment through a collaboration with the Immune Tolerance Network and the Autoimmunity Centers of Excellence.

Treating Diabetes with Islet Cell Transplants. The Edmonton Protocol is the first international multicenter trial in islet cell transplantation. Enrollment of 36 participants at nine centers was complete in January 2003. The primary endpoint for this study is insulin independence at one year after the final transplant with adequate glycemic control. Currently, 53 percent of the patients are insulin independent. Of these, five achieved insulin independence after a single transplant, seven became insulin independent after two transplants, and another seven achieved independence after three transplants. Six patients were withdrawn from the study due to transplant failure. Though the treatment was generally well tolerated, a small number of patients withdrew from the study due to mouth ulcers, headaches, or by choice. The most serious transplant complications included hemorrhage, portal vein thrombosis, and a biliary leak. Other complications have included mouth ulcers, leukopenia, abnormal liver function tests, anemia, and diarrhea. There have been no deaths, instances of post-transplant lymphoproliferative disorder, malignancies, or opportunistic infections. The benefits of this treatment protocol are evidenced by excellent glucose control in the insulin independent group as well as improved glucose control in the insulin dependent group. Following a similar protocol, NIH Clinical Center researchers achieved comparable success and complication rates in another, smaller study of nine transplant patients.

Novel Combination Therapy Inhibits Disease Activity in Multiple Sclerosis. Multiple sclerosis, which affects approximately 250,000 to 400,000 people in the United States, is an autoimmune disease characterized by inflammation in the brain and spinal

cord. This inflammation results in symptoms such as muscle weakness and disturbances in vision and coordination, making multiple sclerosis a leading cause of disability. Current therapies for multiple sclerosis, such as beta-interferon, are not effective in some cases. A small preliminary study led by an NIH research team has shown that supplementing beta-interferon therapy with the monoclonal antibody daclizumab, which blocks the action of the key immune system signaling molecule IL-2, results in decreased numbers of inflammatory lesions in the brain and improvements in some measures of disease activity and disability. These findings may pave the way for more specific and effective therapies for multiple sclerosis.

Survival after Pancreas Transplantation in Patients with Diabetes and Preserved Kidney Function. Solitary pancreas transplantation (i.e., pancreas alone or pancreas-after-kidney) for diabetes mellitus remains controversial due to procedure-associated morbidity/mortality, toxicity of immunosuppression, expense, and unproven effects on the secondary complications of diabetes. Whether transplantation offers a survival advantage over conventional therapies for diabetes remains unknown. A retrospective, observational cohort study of 11,572 patients with diabetes mellitus who were on the waiting list for pancreas transplantation (pancreas alone, pancreas-after-kidney, or simultaneous pancreas-kidney) from 1995 to 2000 was conducted at 124 transplant centers in the United States. The primary outcome measure was all-cause mortality within four years of transplant. The study showed that survival for those with diabetes and preserved kidney function and receiving a solitary pancreas transplant was significantly worse compared with the survival of waiting-list patients receiving conventional therapy.

Relief for Patients with Ankylosing Spondylitis. This disease, a chronic inflammatory arthritis characterized by joint stiffness, pain, and extra bone growth that can result in partial or complete fusion of the spine, typically strikes adolescent and young adult males. No cure currently exists, and available treatments have not been shown to reduce spinal symptoms. NIH-supported researchers determined that the drug etanercept alleviates the pain and stiffness associated with ankylosing spondylitis. Etanercept is a tumor necrosis factor (TNF) antagonist, i.e., a substance that blocks the action of TNF, a naturally occurring protein that contributes to the inflammation found in ankylosing spondylitis. In a small clinical trial, some patients received twice-weekly injections of etanercept and other patients received a placebo for four months. At the end of the trial, 80 percent of the patients taking the drug reported less morning stiffness, spinal pain, and joint swelling, compared to 30 percent in the placebo group. All patients continued to take their pretrial medications for ankylosing spondylitis, including nonsteroidal anti-inflammatory drugs

(NSAIDs), oral corticosteroids, and disease-modifying antirheumatic drugs, during the trial. Results from the trial suggest that etanercept can be used safely in combination with other anti-inflammatory and immunosuppressive drugs.

Treatment of Sjögren's Syndrome. Etanercept was also tested in a placebo-controlled, randomized clinical trial of Sjögren's syndrome. While the drug was safe to use in these patients, it did not improve objective or subjective measures of oral and ocular symptoms after 12 weeks. These results suggest that therapeutic concentrations of etanercept were unable to reach salivary tissue after systemic administration, that the role of TNF-alpha in the pathogenesis of this disease may be less important than previously thought, or that a role for this cytokine is critical at an earlier time in the pathogenic mechanism. Etanercept may prove useful in determining biological differences between various autoimmune diseases, of particular importance to patients who present with multiple autoimmune disorders.

Treatment for Juvenile Rheumatoid Arthritis. Another clinical trial of etanercept showed it to be a safe and effective drug for treatment of children and teenagers with juvenile rheumatoid arthritis (JRA). The children given etanercept all showed dramatic improvement in all measures of arthritis impact – symptoms, joint abnormalities, ability to perform daily functions, and laboratory tests – and the drug was well tolerated. These findings offer the hope of active lives for children with JRA. This successful clinical trial is the culmination of many years of basic research supported by numerous NIH components.

CHAPTER 4

Training, Education, and Information Dissemination

Introduction

To fully capitalize on scientific advances in autoimmune disease, the advances must be translated into clinical practice. Successful translation to the clinic requires the training of current and future scientists and health care workers, continuing education of health care providers, and effective information dissemination to patients, their families, and the public. Because of the number and diversity of autoimmune diseases, and because the care of patients with these disorders involves so many different specialties, achieving these goals is difficult.

Training

One of the most important challenges in autoimmune disease research today is to provide training and career development for both established scientists and new researchers. Multidisciplinary training is a key part of this effort. Such training, which is essential for basic and clinical investigators at all stages of their careers, will enable scientists to move beyond traditional educational and research cultures to explore autoimmune disease in new and innovative ways. Further, support for multidisciplinary research teams will provide the expertise needed to more effectively address these diverse disorders. Investigators with expertise in epidemiology and bioinformatics are particularly needed. Collaborative training programs between professional and nonprofit health organizations and the NIH clinical programs for research in autoimmune disease can go a long way toward meeting these critical training needs.

Education

Physician training begins in medical schools. Medical school curricula, however, are structured around diagnosis and treatment related to specific organ systems, so it is not surprising that medical practice in the United States is based largely on organ-related specialties. As a result, medical students and practicing physicians alike rarely gain an in-depth understanding of the autoimmune diseases, or appreciate the commonalities and complexities of these diseases.

Today, many medical treatments are based on a growing understanding of disease etiology. This shift in treatment paradigms has led to the development of specialties that are focused on specific causative factors, such as infection or allergy. As new, biologically-based autoimmune disease treatments emerge, it will be necessary to train autoimmunity

specialists who have the requisite experience and skills needed to employ these therapies effectively. At this time, we must work to heighten awareness and understanding of autoimmune diseases among practicing physicians, nurses, dentists, optometrists, and other health care workers, so that all providers will be aware of the non-specific nature of many autoimmune disease symptoms and consider these diseases in patient diagnosis. Toward this end, continuing education initiatives focused on earlier diagnosis and awareness of available treatments and clinical trials are a high priority for reaching health care professionals through clinics, conferences, workshops, publications, and other communication channels.

Information Dissemination

In the area of autoimmune diseases, it can truly be said that the patient is often the best advocate. But effective self-advocacy requires knowledge. Therefore, it is important that the general public gain a better understanding of specific autoimmune diseases and elements common to these diseases. Patients and family members need to know more about the risk factors, signs and symptoms, diagnostic tools, and available treatments for autoimmune diseases. Moreover, people should be aware that some families may be predisposed to these disorders, and that one or more autoimmune diseases may occur either in a single individual or in members of that person's immediate or extended family. The presence of an autoimmune disease is thus an important part of an individual's family medical history.

Progress

Since the ADCC Autoimmune Diseases Research Plan was developed in 2002, the NIH and its public and private sector partners have launched or maintained several programs to: (1) provide training and career development for new and established investigators, with an emphasis on expanding opportunities in epidemiology and bioinformatics and creating a multidisciplinary research environment; (2) develop and promote a wide range of educational materials for health care professionals; and (3) develop multiple approaches and materials to increase patient and public awareness of autoimmune diseases and available treatments.

Training

Over the past two years, several important initiatives have advanced our efforts to strengthen the cadre of established scientists and clinicians working in autoimmunity, and to attract new investigators to autoimmune disease research. The **Mentored Research Scientist Development Awards** are designed to provide scientists with additional experience in order to gain expertise in a research area new to the applicant or in an area that would demonstrably enhance the applicant's scientific career. These awards are generally reserved for individuals interested in switching to a new research field, for individuals who have interrupted their career because of illness or pressing family care responsibilities, or for faculty at minority institutions who want to enhance their capacity for independent research. The **Independent Research Scientist Development Award** provides support for recently independent scientists with outstanding potential to become future leaders in biomedical, behavioral, or clinical sciences. The **Mentored Clinical Scientist Development Award** provides support for clinicians who need an intensive period of mentored research experience. The **Midcareer Investigator Award in Patient-Oriented Research** allows clinicians to conduct patient-oriented research and to act as mentors for beginning clinical investigators. Candidates must be working in a research environment, conducting patient-oriented research, and have independent research support.

NIH also provides **Mentored Patient-Oriented Research Career Development Awards** that support investigators who have made a commitment to focus their research endeavors on patient-oriented research. The initiative offers a nonrenewable three- to five-year period of supervised study and research for clinically-trained professionals; grantees may focus on mechanisms of disease, therapeutic interventions, new technology development, or clinical trials. Likewise, the Small Grant Program for New Investigators facilitates the entry of promising new investigators into research on arthritis and musculoskeletal and skin diseases and injuries. Both programs prepare investigators to compete successfully for independent research support. Further, NIH launched the Training and Career Development in Biopsychosocial Rheumatic, Musculoskeletal, and Skin Diseases Research initiative to attract promising behavioral researchers to the study of these disease areas, and to encourage biomedical

Over the past two years, several important initiatives have advanced our efforts to strengthen the cadre of established scientists and clinicians working in autoimmunity, and to attract new investigators to autoimmune disease research.

researchers to adopt a biopsychosocial approach to research, with the ultimate goal of enhancing the quality of interdisciplinary research in these diseases. Three such career awards were funded in FY 2004.

The **Multidisciplinary Biobehavioral Rheumatic Diseases Workshops** initiative was developed to foster interdisciplinary communication and collaboration among behavioral scientists, physicians, and basic scientists with shared interests or expertise in rheumatic diseases. Limited communication between disparate professional cultures has been an obstacle to developing a robust biopsychosocial research agenda in this area. The workshops are designed to promote new collaborations, attract new investigators to rheumatic disease research, and define scientific needs and opportunities.

Training programs for rheumatology research fellows have added a significant community-based component through a Community Health Center (CHC) in Washington, D.C. The CHC augments training opportunities at the NIH Clinical Center for NIH fellows as well as visiting fellows, residents, and medical and other health professional students, and provides a focus on minority health and health disparities in rheumatic diseases. Additionally, a public-private partnership was developed to provide research training to pediatric rheumatology fellows.

Education

Conferences, workshops, clinics, grand rounds, and other communication channels are invaluable tools for disseminating new research findings and providing opportunities for investigators and health care professionals from diverse disciplines to discuss the implications and applications of new knowledge, treatments, and autoimmune disease treatment clinical trials. Such meetings bring together basic and clinical investigators from around the world to discuss research and research infrastructure needs, and options for meeting those needs. Workshops frequently serve as a springboard for developing new research collaborations and networks, and for improving research coordination. The following paragraphs describe a few of the many such communication activities sponsored each year by NIH Institutes and Centers.

The new **Federal Working Group on Lupus** (FWGL) is designed to coordinate Federal efforts in lupus research and education. The working group comprises representatives from all relevant Department of Health and Human Services (DHHS) agencies and other

Federal departments with an interest in lupus. The second meeting of the FWGL was held in the summer of 2004. A new **Lupus Biomarkers Working Group** was created to bring together the entire lupus community to hasten the development of lupus biomarkers; at the 2004 meeting of this group, the status and future plans of the Biomarkers Working Group, as well as future opportunities in lupus stem cell trials, were discussed.

Two recent workshops focused on multiple sclerosis. **Biomarkers in Multiple Sclerosis**, convened in April 2004, included a wide range of experts from fields such as immunology, neuro-imaging, cell biology, and clinical research. The purpose of the workshop was to discuss and evaluate biomarkers for diagnosing multiple sclerosis, monitoring specific disease processes, assessing therapies, and predicting disease course. The participants discussed biomarkers for immune activation, blood-brain barrier disruption, axonal damage, and de- and remyelination, as well as sample collection, assay methods, and evaluation criteria. The September 2003 international workshop called **Genetics and Multiple Sclerosis: Future Prospects** explored the genetic underpinnings of multiple sclerosis, which have thus far eluded definitive identification. The goal of the workshop was to create a collaborative multiple sclerosis genetics network to share strategies, reagents, methods, data, and samples in an effort to accelerate the discovery of multiple sclerosis susceptibility genes. Following the meeting, which was cosponsored by NIH and the National Multiple Sclerosis Society, genetics researchers from the United States and the United Kingdom have come together to form the International Multiple Sclerosis Genetics Consortium.

The September 2003 international workshop called Genetics and Multiple Sclerosis: Future Prospects explored the genetic underpinnings of multiple sclerosis, which have thus far eluded definitive identification.

Another public-private collaboration produced the June 2002 **Tenth International Conference on Myasthenia Gravis and Related Disorders: Biochemical Basis for Diseases of the Neuromuscular Junction.** This conference highlighted the large number of pre- and post-synaptic molecules at the neuromuscular junction that, when rendered dysfunctional due to genetic, toxic, or immunologic insults, give rise to clinical disease. Conference participants explored autoimmunity issues in neuromuscular diseases including myasthenia gravis, stiff person syndrome (SPS), and myositis. The conference also showcased experimental models of autoimmune disorders, advances in epidemiology and measurement in myasthenia gravis, current diagnostics and treatments, and future therapies.

In November 2003, an NIH-sponsored workshop, **Glutamic Acid Decarboxylase (GAD) Autoimmunity in Batten Disease,** brought together experts in Batten disease, a rare and little understood hereditary nervous system disorder leading to neurologic impairment. The workshop also addressed related issues in type I diabetes, SPS, Rasmussen's encephalitis, and central nervous system autoimmunity. **A Multidisciplinary Biobehavioral Rheumatic Diseases Workshop** brought together behavioral scientists, physicians, and basic scientists to explore the etiology, course, and outcomes of rheumatic diseases.

In 2004, NIH sponsored a two-day working group meeting of behavioral, biological, and immunological scientists entitled Increasing Opportunities in Biobehavioral Research, which was designed to produce recommendations for the advancement of biobehavioral research.

Considerable scientific progress has been made recently in understanding celiac disease, but questions remain about how this new information should be integrated into diagnosis and treatment strategies. NIH convened a **Celiac Disease Consensus Conference** in June 2004 to assess current scientific knowledge on celiac disease and provide recommendations for its appropriate diagnosis and management. The latest research findings were presented to an independent panel charged with weighing all of the scientific evidence and preparing a consensus statement addressing key questions about the disease. The panel reported that celiac disease, once believed to be a rare condition, affects up to one percent of the U.S. population, and that the most important step in diagnosing celiac disease is to recognize its myriad clinical features. The panel also provided recommendations on who should be tested for celiac disease, disease management, and directions for future research.

In 2004, NIH sponsored a two-day working group meeting of behavioral, biological, and immunological scientists entitled **Increasing Opportunities in Biobehavioral Research,** which was designed to produce recommendations for the advancement of biobehavioral research. Discussions at the meeting focused on future scientific directions and on the need to educate researchers in biobehavioral measurement and analytic methods; the use of interdisciplinary biobehavioral approaches was emphasized. Also in 2004, a meeting on **Promoting Research on Focal Cognitive Deficits in Non-Dementing Disorders** reviewed current knowledge on these deficits in non-dementing central nervous system disorders, such as multiple sclerosis, and their effects on quality of life, health behaviors/decision-making, and health outcomes. The meeting identified research challenges, gaps, emerging methods, and clinical research opportunities.

Each year, NIH collaborates with many nonprofit and advocacy organizations to conduct training and education activities for researchers and clinicians on diverse autoimmune diseases. These cosponsoring organizations have included the Sjögren's Syndrome Foundation, the Myasthenia Gravis Foundation of America, the National Multiple Sclerosis Society, the Juvenile Diabetes Research Foundation, the American Association of Immunologists, the Federation of Clinical Immunology Societies, the American College of Rheumatology, the American Autoimmune Related Diseases Association, and the American Academy of Allergy, Asthma, and Immunology.

Information Dissemination

Among the many information dissemination activities sponsored by NIH, the conference, **Lupus Today: Research into Action,** provides an excellent example of how resources from diverse organizations and constituencies can be leveraged to great effect. This September 2003 scientific meeting drew together nearly two dozen public and private sponsors and cosponsors to discuss the current status and future directions of lupus research and treatment. The primary goals of the conference were to inform, energize, and share the excitement about the future of lupus research with patients and their families, physicians, health care workers, scientists, and organizations involved in lupus research and outreach. The meeting brought together national leaders in lupus research to describe key research accomplishments, and to discuss implications for managing the disease now and in the future. The conference also included panel discussions on the impact of lupus on patients and their families, the role of advocacy groups, patient participation in clinical studies, and the future of lupus clinical trials.

NIH is currently collaborating with a nonprofit partner to develop a pediatric rheumatic diseases CD-ROM designed to give health professionals and the general public easy access to the latest information on pediatric rheumatic diseases. In addition, the comprehensive, professional manual, *LUPUS: A Patient Care Guide for Nurses and Other Health Professionals*, is being updated. It provides practical information on a range of topics, including symptoms and diagnosis, advances in lupus research, lab tests for diagnosis and evaluation, medications, health care interventions for general and specific manifestations of lupus, and resources for more information.

NIH has expanded its culturally sensitive public awareness information materials to include numerous titles in bilingual, non-English, and easy-to-read formats, available in print as well

as electronic formats. These are designed to meet the needs of a wide range of audiences, including people with limited English proficiency. This material includes NIH's Spanish language Web site, brochures such as ¿Tengo Lupus? (Do I Have Lupus), and Fast Facts series.

NIH also continues to offer and strengthen a variety of online and other information sources for patients, their families, and health care providers. These include:

- **MEDLINEplus** (http://www.nlm.nih.gov/medlineplus), an easy-to-use resource for accessing the published literature on autoimmune diseases and other medical topics.

- **ClinicalTrials.gov** (http://clinicaltrials.gov), the NIH website that enables health providers and patients to search for clinical trials addressing specific diseases, including autoimmune diseases.

- **NIH Institutes and Centers Web pages**. These provide a wealth of information about the mission and activities of each organization, key contacts, links to relevant literature, and other information of use to the public and to health care providers.

- **NIH Institute Clearinghouses** stock and distribute, usually at no charge to the public and health care community, both print and audiovisual materials on various autoimmune and other medical conditions. Orders can be placed by telephone or written request, or online. The clearinghouses are a crucial information resource for the many people in the United States who still do not have Internet access.

- **The Genetic and Rare Diseases Information Center** (http://rarediseases.info.nih.gov/html/resources/info_cntr.html) provides personalized responses in English or Spanish to questions from the general public, including patients and their families, health care professionals, and biomedical researchers about rare and genetic diseases including the majority of autoimmune diseases.

CHAPTER 5

Looking to the Future

The preceding chapters summarize the NIH commitment to research on autoimmune diseases and chronicle progress in the two years since publication of the 2002 ADCC Autoimmune Diseases Research Plan. As noted, initiatives are underway in many of the areas highlighted in the ADCC Research Plan, including: developing animal model studies to assess the safety and efficacy of promising new therapeutic approaches; establishing multi-institutional clinical research programs to evaluate these promising therapies in humans; identifying and validating biomarkers of disease stage, activity, and therapeutic effects; and employing new and emerging technologies for identifying high-risk populations, and for patient screening, diagnosis, and management. These solicited research programs are yielding new knowledge and enhancing collaboration among basic scientists, clinical investigators, and individuals from many fields, including bioinformatics and imaging technology.

Burden of Disease

The supply of organs from deceased donors is insufficient to meet the needs of people with end-stage organ failure who require an organ transplant. Patients receiving transplants from living donors have better outcomes, but a better understanding is needed of the medical risks facing living donors, both on an immediate and long-term basis. The **Living Organ Donor Registry** will establish a consortium to strengthen the foundation for policy decisions regarding living organ donation.

Etiology

Initiatives targeting issues in the etiology of autoimmune disease include **HLA Region Genetics in Immune-Mediated Diseases**, a cooperative research group that will continue the work of the International Histocompatibility Working Group. The major focus of this initiative will be to define the association between human leukocyte antigen (HLA) region genes and immune-mediated diseases, including risk and severity of disease, and organ, tissue, and cell transplantation outcomes. Among the diseases specifically targeted are graft-versus-host disease, graft rejection, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, common variable immunodeficiency and IgA deficiency. The data and information gained from these projects will be essential to advance such diverse fields as vaccine development, immunotherapy, donor selection and outcome prediction in tissue and solid organ transplant, and population studies/health

disparities/minority health issues. One of the most useful products of this research will be high quality data about associations between HLA genes, genetic markers, and specific autoimmune diseases, which will be readily accessible to clinicians, scientists, and the public through the publicly accessible dbMHC website. This website will be continually updated to display HLA genetics data associated with clinical transplant, disease, and human population diversity.

Mechanistic studies in **Autoimmune Disease and Patient Genotype** are planned. These studies will use patient genotypes to identify correlations between different autoimmune diseases.

Elucidation of the mechanisms underlying Sjögren's syndrome is the focus of a planned initiative on **Sjögren's Syndrome: A Model Complex Disease.** This initiative is intended to stimulate multidisciplinary research to delineate the genetic, environmental, and immunological aspects of the disease. This information will help researchers to develop new therapies for this disorder.

Biomarker identification will be promoted through the recent initiative to Catalog the Human Salivary Proteome.

Biomarker identification will be promoted through the recent initiative to **Catalog the Human Salivary Proteome.** The use of state-of-the-art proteomic technologies is expected to lead to the identification of proteins and their complexes in parotid, sub-mandibular, and sublingual glandular saliva. A comprehensive analysis of salivary proteins has not previously been attempted. In addition to identifying the salivary proteins, this initiative will identify variations in post-translational modifications of salivary proteins, which cannot be captured by genomic or transcriptional analysis.

The **Autoimmunity Centers of Excellence (ACEs)** will be expanded beyond the current nine centers, if resources allow. Three clinical trials of immunomodulatory agents are currently ongoing at these centers, and several others are in development. A great strength of this program is that it brings together diverse disease specialists, who design and conduct clinical trials, and basic scientists, who carry out mechanistic studies in association with the trials. In addition, the **Innovative Grants on Immune Tolerance** program will be renewed through a new solicitation.

The Role of Innate Immunity in Autoimmune Rheumatic Diseases is a new initiative designed to expand our understanding of autoimmune disease etiology. Its purpose is to stimulate and encourage innovative and multidisciplinary research to apply recent advances in innate immunity to the etiology and pathogenesis of autoimmune rheumatic disease. Studies supported by this initiative may be individual research projects or exploratory/developmental grants.

Several Institutes will sponsor a new initiative on the **Immunobiology of Xenotransplantation**. Two to five preclinical projects will be supported, focusing on key immunologic and physiologic issues in large animal models of xenotransplantation. One emphasis area for this program will be the transplantation of porcine pancreatic islets into non-human primates. If successful, xenotransplantation would reduce the need for human organs, tissues, and cells to treat patients with end-stage organ diseases.

NIH maintains **Pathogen-Free Breeding Colonies of Indian Rhesus Macaques and Cynomolgus Macaques** for preclinical research in kidney and islet transplantation to induce tolerance. A contract will be awarded to support the expansion of these colonies to meet growing research needs in this area.

Diagnosis, Treatment, and Prevention

Clinical trials will be conducted through a new consortium called **Clinical Trials in Organ Transplantation,** which will evaluate modified or new therapeutic regimens in kidney, liver, heart, and lung transplantation and conduct studies of the underlying immune mechanism of graft acceptance or rejection. This initiative will help to enhance our understanding of immune-mediated morbidity and mortality of solid organ transplantation.

Understanding how activated immune cells penetrate the blood-brain barrier is critical for developing therapies that can protect and repair the central nervous system injured by autoimmune disease or inflammation. The **Neuroprotective CNS Barriers in Neurological Diseases** initiative funds mechanistic studies of the neuroprotective blood-brain barrier in the pediatric, adult, and aged brain. This solicitation also encourages studies to improve drug and gene delivery strategies for treatment of neurological diseases, including autoimmune diseases that affect the nervous system.

The recently announced initiative, **Axonal Damage in Multiple Sclerosis: Strategies for Protection and Repair**, invites applications for clinical and translational research in multiple sclerosis that target the neurodegeneration associated with the disease and explore neuroprotective and regenerative therapies. It is hoped that the combination of approved immunomodulatory therapies with future neuroprotective and regenerative treatment regimens will lead to improved outcomes for patients with multiple sclerosis.

Non-Invasive Methods for Diagnosis and Progression of Diabetes, Kidney, Urological, Hematological, and Digestive Diseases is a new initiative to develop imaging and other non- or minimally-invasive technologies to detect, characterize, diagnose, and identify persons with a predisposition to autoimmune disease, as well as to monitor responses to treatment. To enhance ongoing disease management of people with autoimmune disorders, NIH is launching an initiative on **Chronic Disease Self-Management in Understudied Populations** that will promote self-management among individuals with chronic (including autoimmune) conditions who are not often targeted in intervention studies because of their location, age, ethnicity, or other demographic factors.

A number of new and reissued initiatives will address clinical trials infrastructure priorities identified in the Research Plan.

The new **Vasculitis Clinical Research Consortium (VCRC)**, one of the consortia of the **Rare Diseases Clinical Research Network**, will facilitate clinical investigation of various forms of inflammatory vasculitis. Four centers will combine their clinical and research expertise with the resources of the General Clinical Research Centers at each site to form the core of the consortium. Several domestic and foreign secondary centers will also be incorporated into the consortium. The VCRC will serve as a focal point for vasculitis research in the United States and internationally for both clinical investigators and patients.

A number of new and reissued initiatives will address clinical trials infrastructure priorities identified in the Research Plan. **High Risk Rheumatic and Musculoskeletal and Skin Diseases Research** will support research that may lead to significant expansion of biomedical research horizons, precipitate a paradigm shift in research, or lead to substantial improvements in human health in rheumatic or musculoskeletal or skin diseases. High-throughput small molecule screening for use in both research and drug delivery programs will be further encouraged through an initiative titled **Development of Assays for High-Throughput Drug Screening.** Projects that advance research to identify and define

protein expression patterns, post-translational modification of proteins, and protein-protein interaction in cells, tissues, and organ systems will be supported through the initiative, **Proteomics: Diabetes, Obesity, and Endocrine, Digestive, Kidney, Urologic, and Hematologic Diseases**. In addition, a new **Lung Tissue Resource** will be developed to facilitate studies of pulmonary diseases by establishing a program for standardized processing, storage, and distribution of lung tissues and their associated clinical data.

A number of new initiatives will support mechanistic studies associated with clinical trials to strengthen our understanding of the mechanisms underlying treatment responses in autoimmune diseases. One of these, **Ancillary Studies to Major Ongoing Clinical Research Studies**, supports investigator-initiated ancillary studies to ongoing large-scale clinical trials, epidemiological studies, and disease databases. These studies focus on a wide range of diseases and conditions including diabetes, obesity, acute and chronic liver disease, chronic kidney disease, and benign prostatic hyperplasia. In addition, NIH will continue to fund ancillary studies through its program of **Hyperaccelerated Award/ Mechanisms in Immunomodulation Trials**. This initiative is re-competed each year.

Other initiatives in support of the clinical trials infrastructure include **Identification of Novel Therapies for Autoimmune Hepatic and Gastrointestinal Diseases.** The goal of this initiative is to stimulate innovative research aimed at revealing novel targets for diagnosing, monitoring, or treating idiopathic autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune gastritis (pernicious anemia), celiac disease, and microscopic colitis, all of which are suspected of having an autoimmune basis. Details regarding pathogenesis, genetic susceptibility, and environmental modifiers are poorly understood for most of these diseases. The **Identification and Management of Symptom Clusters** initiative will support studies that seek to identify clusters of interrelated symptoms and pathogenic pathways, develop assessment tools, and design intervention studies. A **Clinical Trial Outcomes Instrument Development Grant Program** will solicit research applications to develop, apply, and evaluate new measures of clinical trial outcomes to better assess treatment safety, efficacy, and effectiveness for rheumatic, skin, bone, and muscle diseases.

Two very important initiatives that are slated for recompetition in the near future are the **Immune Tolerance Network** and the **Cooperative Study Group for Autoimmune Disease Prevention**.

Training, Education, and Information Dissemination

NIH will continue its **Small Grant Program for New Investigators** to stimulate and facilitate the entry of promising new investigators into many areas of research, including autoimmune disease research. To improve information dissemination to the public, multiple NIH Institutes and Centers and DHHS components will launch an initiative for **Understanding and Promoting Health Literacy**. Investigators will be invited to submit grant applications aimed at increasing scientific understanding of the nature of health literacy and its relationship to healthy behaviors, illness prevention and treatment, chronic disease management, health disparities, risk assessment of environmental factors, and health outcomes. This knowledge is needed to develop ways to strengthen health literacy, and improve communication between health professionals and diverse consumer or patient audiences. Such knowledge will help enable health care and public health systems to serve individuals and populations more effectively, and employ strategies that reduce health disparities in the population.

In the coming years, NIH will build upon its progress in autoimmune disease research. We look forward eagerly to continuing successes that will yield new knowledge and interventions to improve the lives of all Americans affected by autoimmune disease.

Appendices

Appendix A
2002 ADCC Autoimmune Diseases Research Plan

The Burden of Autoimmune Diseases

Collection and Curation of Epidemiologic Data

- Support research to optimize design and validate feasibility of methodologies appropriate for population-based epidemiology and surveillance studies in autoimmune diseases.

- Establish new and improve existing methods to identify and track patients with autoimmune disease.
  - Establish uniform case definitions and a process for updating case definitions.
  - Identify, validate, and incorporate biomarkers of disease in case definitions.
  - Increase the accuracy of hospital discharge and death certificate data and establish national surveillance and reporting mechanisms.
  - Develop and validate methods for confirming self-reported diagnoses of autoimmune diseases.
  - Establish partnerships between Federal agencies and large health maintenance organizations with stable participant pools for case finding and tracking natural history.

- Design and conduct multidisciplinary, population-based epidemiology and surveillance studies with sufficient racial, ethnic, socioeconomic, and geographic diversity to identify the incidence, prevalence, morbidity, and mortality of autoimmune disease in the United States.
  - Determine the extent to which differences in the distribution of genetic and nogenetic factors, such as infectious and non-infectious environmental exposures and lifestyle, contribute to observed difference in disease occurrence and distribution.
  - Identify differences in the incidence and prevalence of individual autoimmune disorders among racial, ethnic, socioeconomic, and geographically distinct subpopulations.

Disease Registries

- Expand support for a population-based multidisciplinary autoimmune diseases registry to enhance collection and analysis of data over time on causation, natural history, morbidity and mortality of autoimmune diseases.
  - Utilize a multidisciplinary, integrated approach with collection of data on multiple diseases.
  - Support research on the feasibility and optimal design of the registry to allow collation of data at the state and national levels.
  - Address ethical concerns in the collection of data and samples.
  - Provide epidemiology, statistical, clinical disease, and bioinformatics expertise.
  - Incorporate biomarker data in registries.

- Provide infrastructure for long-term support of registries and epidemiology studies.

The Etiology of Autoimmune Diseases

Genetic Factors

- Identify genetic factors that influence autoimmune diseases.
  - Identify disease susceptibility and protective loci and their interaction.
  - Determine genetic polymorphisms that correlate with disease phenotype.
  - Provide long-term support for existing genetic repositories; establish genetic repositories for additional autoimmune disorders; ensure adequate representation of disease phenotypes and races.
  - Support research on gene/environment interactions important in development and manifestation of autoimmune diseases.

- Provide resources for production, storage, and distribution of materials and probes for genetic research to the research community centrally.
  - Transgenic and knockout animals;
  - cDNA, EST,and BAC libraries;
  - Large collections of family, disease, and case control samples with clinical data including intermediate phenotypes;
  - Microarray facilities and reagents, including bioinformatics support;
  - Genetic and serologic reagents for high throughput analyses of human leukocyte antigens;
  - Access to genetic databases for multiple animal species.

Environmental Factors

- Identify environmental factors.
  - Support research to identify infectious and environmental agents in biologic samples.
  - Support research to develop novel assays to identify prior exposures to environmental agents, including chemicals, toxins, and infectious agents.
  - Develop high throughput, standardized, specific, and sensitive laboratory assays for infectious and noninfectious environmental factors that can be used in large epidemiologic studies.

- Establish mechanistic relationships between environmental factors and autoimmunity.
  - Support collection, banking, and distribution of patient materials from epidemiologic studies for basic research studies of the interaction between infectious and other environmental factors and genetic factors for development of autoimmune diseases.
  - Support basic and clinical research on mechanisms by which infectious agents or other environmental factors may trigger or modulate autoimmunity or autoimmune diseases.

Immunologic Studies

- Identify and characterize immune mechanisms underlying autoimmune diseases.
  - Support basic research on mechanisms and loss of self-tolerance, including mechanisms to control autoreactive cells.
  - Support basic research on tissue specificity, target organ recognition, and immune injury and pathogenesis among different autoimmune diseases.
  - Define the role of the innate immune system in regulation of self-tolerance and development of autoimmunity.
  - Determine the differences in immune responses of males and females and the role of sex in development of disease.
  - Investigate the role of geography and ethnicity in the immune response.
  - Determine the interactions of the immune, endocrine, and nervous systems in regulation of self-tolerance.
  - Support core facilities for production and distribution of specialized reagents for research, including MHC-tetramers, antibodies, and microarrays.
  - Establish and expand proteomics capabilities within NIH-sponsored research programs.

- Promote development and appropriate use of animal models.
  - Promote development and characterization of novel animal models for autoimmune diseases.
  - Ensure accessibility to investigators at reasonable cost of animal models, including transgenic and genetically engineered models.
  - Establish central support for bioinformatics for autoimmune disease researchers, including integration of international databases and collaborative analyses.

Diagnosis, Treatment, and Prevention

Diagnosis and Disease Progression

- Expand support for identification and validation of biomarkers.
  - Biomarkers of disease risk, stage, and activity;
  - Markers of immune activity prior to and during early stages of disease;
  - Discovery and validation of biomarkers specific for individual autoimmune diseases;
  - Biomarkers of response to therapy, drug availability, and metabolism.

- Expand support for bioengineering and bioimaging research and development and procurement of large instruments and shared facilities.
  - Support development of imaging instrumentation to assess immune function i*n vivo.*
  - Accelerate the development of high-resolution instruments for evaluation of structural damage in autoimmune diseases, e.g., joints, kidneys, brain.
  - Support basic research leading to development of probes to assess end-organ function, e.g., technologies for measurement of pancreatic islet and beta cell mass.
  - Support preclinical and clinical research on cell and tissue engineering, organ repair and regeneration, and advanced prosthetic devices.
  - Promote collaborations among engineers, chemists, physicists, and the immunology research community through workshops, symposia, and research solicitations.

Clinical Research Infrastructure

- Develop centralized, broad-based autoimmune diseases clinical research centers.
  - Collaborative clinical approach involving multiple disciplines and specialties addressing multiple autoimmune diseases;

- Research related to diagnosis, treatment, prevention, and rehabilitation of multiple autoimmune diseases;
- Centralized and integrated data collection and analysis;
- Core and reference laboratories;
- Distribution of drugs and shared reagents;
- Repositories for DNA and clinical samples;
- Physician and research support staff training;
- Expertise in bioethics, regulatory requirements, and human subjects' protections.

Clinical Trials

- Define disease classification and response criteria for multiple autoimmune diseases and promote their use in research studies and in clinical practice.
  - Convene workshops and expert panel meetings to define disease classification criteria and disease response criteria (outcomes criteria).
  - Establish Federal partnerships with professional societies and provide support to refine, validate, and update pilot criteria through research studies and in clinical practice settings.
  - Standardize clinical, behavioral, and psychometric evaluation instruments used in clinical trials of autoimmune diseases.
  - Convene international workshops to standardize laboratory assays, reporting units, and normal ranges for cellular and humoral assays of autoimmunity.

- Support screening for identification of individuals at risk for autoimmune diseases.
  - Identification of susceptibility genes, including MHC and non-MHC loci;
  - Identification and validation of assays for relevant autoantibodies and T cells;
  - Development of high throughput screening assays;
  - Shared facilities for large-scale screening efforts.

- Promote public-private partnerships for support of clinical trials.
  - Support clinical trials in autoimmune diseases.
  - Partner with industry to facilitate the development of agents for autoimmune diseases that are not orphan (i.e., affect <200,000 persons) but affect too small a population to be profitable.
  - Foster collaborations and research partnerships between NIH, industry, non-Federal sponsors, and regulatory agencies.

- Expand Federal support for clinical research and clinical trials on rare autoimmune diseases.
- Support studies of complementary and alternative medicine therapies.
- Support bioinformatics capabilities for cross-trial analyses, data mining, and hypothesis generation, including data from negative trials that are not published.
- Include studies of basic mechanisms in association with all clinical trials.

Training, Education, and Information Dissemination

Training

- Identify new opportunities and continue support for training and career development for new and established basic science and clinical investigators in autoimmune disease research. Include specialized training in epidemiology and bioinformatics.

- Support multidisciplinary training of specialists at all levels, including midcareer level.

- Provide increased training opportunities for health care professionals by establishing collaborative training programs between professional and nonprofit health organizations and NIH clinical programs for research in autoimmune disease.

Education

- Develop and promote the use of a wide range of educational programs and continuing medical education materials in autoimmune disease for health care professionals, incorporating the latest research advances on autoimmunity and autoimmune diseases.

Information Dissemination

- Develop communication and information dissemination strategies for health care providers, patients and their families, and the public using a broad range of formats and technologies to maximize access and incorporate current information resources.

- Develop a public awareness campaign for autoimmune diseases in collaboration with private organizations and public service agencies.

- Provide information about clinical trials to evaluate prevention and treatment regimens that will enable patients and their physicians to make informed choices.

- Develop culturally sensitive public awareness information materials aimed at patients, families, and health care providers of diverse races and ethnicities.

- Establish a centralized, consolidated autoimmunity/autoimmune disease information center accessible to professionals and the public via the Internet.

- Provide information on complementary and alternative therapies.

- Provide objective evaluation, in lay language, of available therapeutic agents.

Appendix B
NIH Initiatives Related to Autoimmune Disease Research

The following is a compendium of all NIH initiatives in the area of autoimmune diseases research. Additional information about many of these initiatives can be found at http://grants1.nih.gov/grants/guide/index.html.

I. The Burden of Autoimmune Diseases

Collection and Curation of Epidemiologic Data

Diabetes Autoimmunity Study in the Young (DAISY) – an epidemiologic study that prospectively follows newborns and documents early childhood diet, reported and measured infections, and vaccinations in an effort to understand the complex mechanisms that underlie the development of type 1 diabetes.

Prospective Assessment in Newborns for Diabetes Autoimmunity (PANDA) – an epidemiologic study following 23,000 infants at genetic risk for diabetes in an effort to detect the earliest changes in gene expression in the pathogenesis of type 1 diabetes.

Health Disparities in Rheumatic, Musculoskeletal and Skin Diseases – promotes the design, development, and testing of hypothesis-driven innovative approaches to eliminate health disparities in rheumatic, musculoskeletal, and skin diseases.

Agricultural Health Study – a longitudinal study examining the relationship between farming-related exposures (pesticides, solvents, nitrates, metals, mycotoxins, and silica) and diseases, including autoimmune diseases, in a large cohort of farm families.

Carolina Lupus Study – a population-based, case control study in eastern North Carolina and South Carolina designed to examine hormonal and environmental influences on the etiology of systemic lupus erythematosus.

Symptom Management for Chronic Neurological Conditions – supports studies on issues related to managing the symptoms of selected chronic neurological conditions, including multiple sclerosis.

Disease Registries

Collaborative Islet Transplant Registry (CITR) – expedites progress and promotes safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive, current data on all islet/beta cell transplants performed in North America. This registry will permit investigators from participating transplant centers in the United States, Canada, and Europe to compile and analyze islet/beta cell transplantation data in an effort to identify critical risk factors and key determinants of success.

The Multiple Autoimmune Diseases Genetics Consortium (MADGC) – a collaborative effort to establish a repository of genetic materials and clinical data collected from multiplex families affected by two or more selected autoimmune diseases with the goal of identifying and characterizing the genes that are common to these diseases.

International Research Registry Network for Sjögren's Syndrome – focuses on developing standardized diagnostic criteria for Sjögren's syndrome for use in research and clinical settings, and establishing a collection of well-characterized biological patient materials for use in basic and clinical studies of this syndrome.

Search for Diabetes in Youth (SEARCH) – a multicenter study focused on developing a uniform, population-based approach to generating incidence estimates of type 1, type 2, and other forms of diabetes in children.

Consortium for the Longitudinal Evaluations of African Americans with Early Rheumatoid Arthritis (CLEAR) – collects clinical and x-ray data and DNA to help scientists analyze genetic and nongenetic factors that might predict disease course and outcomes of rheumatoid arthritis. Academic centers in the southeast United States are recruiting African Americans to join the registry.

Research Registry for Neonatal Lupus – provides material for basic research on the causes of this disease, tracks important data such as incidence, and facilitates family counseling. Registry data will facilitate development of improved methods of diagnosis, prevention, and treatment.

National Alopecia Areata Registry – classifies medical and family history data for patients with three major forms of alopecia areata: alopecia areata, alopecia totalis, and alopecia universalis.

National Registry on Antiphospholipid Syndrome – collects and updates clinical, demographic, and laboratory information from patients with antiphospholipid syndrome and makes it available to researchers and medical practitioners concerned with diagnosis and treatment.

National Epidermolysis Bullosa Registry – focuses on identifying underlying causes of this disease, improving methods of diagnosis, and developing effective methods of treatment and prevention.

Scleroderma Registry – identifies cases of systemic sclerosis; verifies all diagnoses; provides a continuous update of the prevalence, incidence, and mortality due to scleroderma; and establishes prospectively rates of average annual mortality. A major focus of the registry is to establish a cohort of incident cases for early intervention trials and genetic studies, as well as for basic science and other clinical and epidemiologic studies.

Research Registry for Juvenile Rheumatoid Arthritis – collects data on multicase families with affected sibling pairs. The registry also is developing a related genomics program to identify the susceptibility genes for this disease.

Lupus Registry and Repository – supports a core facility dedicated to collecting and characterizing multiplex lupus pedigrees.

The North American Rheumatoid Arthritis Consortium – a national repository dedicated to identifying and characterizing sibling pairs with rheumatoid arthritis with the aim of identifying the genes that predispose individuals for rheumatoid arthritis.

The Human Specimens Bank – a registry for patients with multiple sclerosis (and patients with other neurological disorders) who wish to posthumously donate their brains for use in research.

II. The Etiology of Autoimmune Diseases

Genetic Factors

Multiple Autoimmune Disease Genetic Consortium (MADGC) – a repository of biological samples and clinical data from families in which at least two individuals are affected by two or more different autoimmune diseases. (Note: also under Burden of Autoimmune Diseases, page 101.)

Gene Discovery for Complex Neurological and Neurobehavioral Disorders – promotes research aimed at identifying susceptibility genes for numerous complex neurological and neurobehavioral disorders, including those with a confirmed or suspected autoimmune basis.

International Multiple Sclerosis Genetics Consortium – a multidisciplinary effort to identify the combinations of genes that underlie multiple sclerosis. The consortium has established a dataset for genetic analysis of 1,800 families affected by multiple sclerosis, along with clinical and demographic data for each DNA sample.

Inflammatory Bowel Disease Genetics Research Consortium – promotes participation of multiple inflammatory bowel disease Genetic Research Centers in studies to identify the genes associated with Crohn's disease and ulcerative colitis.

Gene Expression Studies in Arthritis and Musculoskeletal and Skin Diseases – focuses on applying resources needed to address specific biological and medical problems for which the immediate application of comprehensive gene expression analysis technology can yield new insights, and directing support to groups that are in the best position to make use of these technologies.

International Histocompatibility Working Group (IHWG) – supports efforts to develop a catalog of the genes constituting the Major Histocompatibility Complex (known as HLA), and to identify differences among these genes in populations worldwide.

Specialized Centers of Clinically Oriented Research in Hemostatic and Thrombotic Diseases – supports multidisciplinary efforts of innovative approaches to address relevant clinical issues in hemostatic and thrombotic diseases, including

polygeneic analyses of thrombotic disorders; diagnosis, assays, and treatment of venous thrombosis; thrombosis in special populations; inflammation and thrombosis; immune disorders; von Willebrand factor; protease-activated receptors; and vascular diversity.

Environmental Factors

Environment/Infection/Gene Interactions in Autoimmune Diseases – supports innovative basic or population-based research on the role of environmental and infectious agents in the initiation and/or exacerabation of autoimmune diseases.

Fetal Basis of Adult Disease: Role of the Environment – promotes research on the effects of *in utero* exposures that cause permanent functional changes that result in increased susceptibility to disease/dysfunction later in life, including autoimmune disease.

Glial Cell Inflammatory Mechanisms of HIV-1 Induced Cell Injury in the Nervous System – encourages studies on the role of neuroinflammation in initiating and exacerbating cellular injury and death in the context of HIV-1 infection of the central nervous system. Findings from these studies may be applicable to understanding and controlling inflammation of other neurological disorders, such as multiple sclerosis.

Immunologic Studies

Autoimmunity Centers of Excellence – an integrated and multidisciplinary program that promotes research to increase understanding of self tolerance, immune modulation, and other immune mechanisms that may provide new therapeutic targets; test these discoveries in animal models; and conduct clinical trials of promising treatment interventions.

Non-human Primate Cooperative Study Group (NHPCSG) – supports studies to evaluate the safety and efficacy of promising tolerance induction treatment regimens in non-human primate models of kidney and islet transplantation. The knowledge gained from this research effort is critical to the translation of successful tolerance induction strategies from small animal models to clinical trials.

Identifying Functional Links Between the Immune System and Brain Function Including Behavior – supports basic neuroimmunology research and studies examining how the immune system modifies brain function and behavior.

Neuropsychiatric Systemic Lupus Erythematosus – promotes basic and clinical studies on the neuropsychiatric aspects of lupus.

Cardiovascular, Lung, and Blood Immunobiology of Health and Disease – encourages studies of the fundamental cellular and molecular mechanisms and signaling processes that regulate the immune system in the heart, vasculature, lungs, and blood in both health and disease.

High Risk Rheumatic and Musculoskeletal and Skin Diseases Research – promotes highly innovative and novel studies with the potential for developing groundbreaking technology or methodologies that expand biomedical research horizons, precipitate a paradigm shift in research, or lead to a substantial improvement in human health.

NIH Exploratory/Developmental Research Grant Award – fosters the introduction of novel scientific ideas, model systems, tools, agents, targets, and technologies that potentially may advance biomedical research.

III. Diagnosis, Treatment, and Prevention

Diagnosis and Disease Progression

Autoimmune Biomarkers Collaborative Network – promotes the development of biomarkers for rheumatoid arthritis and lupus that can be used reliably in a clinical setting to define disease subsets or to monitor disease activity and progression.

Microcirculation and Target Organ Damage in Rheumatic and Skin Diseases – addresses the mechanisms of end organ damage and alterations in microcirculation in rheumatic and autoimmune skin diseases.

Beta Cell Imaging Initiative – supports efforts to develop techniques or reagents to image or otherwise noninvasively detect pancreatic islet beta cells *in vivo* in order to

measure their mass, function, or evidence of inflammation, or to monitor engraftment of transplanted isolated pancreatic islets.

Beta Cell Biology Consortium – promotes research to understand basic mechanisms underlying pancreatic development and function; generate a renewable source of pancreatic beta cells to facilitate the development of cell-based therapies for diabetes; understand the requirements for survival and engraftment of transplanted cells/tissue; and generate novel resources for research.

Pulmonary Fibrosis: Molecular Targets and Interventions – supports research to discover and validate molecular targets for interfering with the fibrogenesis associated with pulmonary fibrosis.

Neuroprotective CNS Barriers in Neurological Diseases – emphasizes studies of the neurobiological and cerebrovascular mechanisms through which the neuroprotective blood-brain barrier functions in the healthy and diseased pediatric, adult, and aged brain.

Axonal Damage in Multiple Sclerosis: Strategies for Protection and Repair – focuses on clinical and translational research in multiple sclerosis that targets the neurodegenerative aspect of this disease and explores neuroprotective and regenerative therapies for multiple sclerosis.

Hyperaccelerated Awards/Mechanisms in Immunomodulation Trials – supports mechanistic studies in conjunction with clinical trials of immunomodulatory interventions for immune-mediated diseases, including asthma and allergy, chronic inflammatory and autoimmune disorders, transplant rejection, and primary immunodeficiency diseases.

Ancillary Studies in Heart, Lung, and Blood Disease Trials – supports ancillary mechanistic studies using patients and patient materials from ongoing clinical trials related to heart, lung, and blood diseases to address mechanisms of disease pathogenesis, surrogate markers or biomarkers of disease activity and therapeutic effect, mechanisms underlying human cardiopulmonary and hematologic function in general, or mechanisms underlying interventions.

Clinical Research Infrastructure

Cooperative Study Group for Autoimmune Diseases Prevention (Prevention Centers) – supports an interactive and collaborative network of investigators devoted to advancing our understanding of immune homeostasis in health and in autoimmune states and to developing interventions to prevent human autoimmune disease.

Specialized Centers of Clinically Oriented Research (SCCOR) in Transfusion Biology and Medicine – aims to improve the safety and efficacy of blood and blood components, determine the indications for their use, evaluate and possibly modify immunologic responses following their administration. This initiative encourages the use of new and innovative technologies to conduct quality basic research and facilitate the transfer of the basic knowledge to the clinical arena.

Cooperative Multicenter Research Network to Test Glucose Sensors in Children with Type 1 Diabetes Mellitus – a collaborative research consortium that will use new, continuous glucose monitoring devices to evaluate glycemic control, and the incidence, magnitude, and duration of hypoglycemia in children with type 1 diabetes.

Skin Diseases Research Core Centers – provides the resources to enable a number of established, currently funded investigators – many of whom are often from different disciplines – to adopt a multidisciplinary approach to common research problems in skin diseases.

Multidisciplinary Clinical Research Centers (MCRC) for Arthritis and Musculoskeletal and Skin Diseases – encourages prevention studies and research to assess and improve outcomes for patients with arthritis and other rheumatic diseases; musculoskeletal and orthopedic disorders, bone and muscle diseases; and skin diseases.

Rare Diseases Clinical Research Network – facilitates clinical research in rare diseases through support for (1) collaborative research, longitudinal studies, Phase I and II clinical trials and other clinical studies, and pilot and demonstration projects; (2) clinical investigator training in rare diseases research; and (3) distributed clinical data management incorporating novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms.

NIH Tetramer Facility – provides custom synthesis and distribution of soluble major histocompatibility complex (MHC)-peptide tetramer reagents that can be used to detect antigen-specific T cells.

Development of Immune Monitoring Reagents and MHC Typing Technologies for Non-human Primates – supports projects to develop, produce, and distribute new or improved nonhuman primate (NHP) immune monitoring and immune modulating reagents that are needed to (1) evaluate NHP immune responses in vaccine and adjuvant development for infectious diseases, transplantation research, and autoimmune and infectious disease models, and (2) develop novel immune-based therapeutics, vaccines, and adjuvants.

Islet Cell Resource Centers – promote the isolation, purification, and characterization of human pancreatic islet cells for transplantation into diabetic patients.

Type 1 Diabetes Mouse Animal Models – provides investigators with access to two animal repositories that maintain and distribute 52 mouse strains important to research on the pathogenesis of type 1 diabetes. The repository plans to maintain as many as 150 mouse strains.

NIH Clinical Trial Planning Grant Program – supports the development of Phase III clinical trials, including establishing the research team, developing data management and research oversight tools, defining recruitment strategies, and finalizing the protocol and other essential elements of the study, including an operations/procedures manual.

National Electronic Clinical Trials and Research (NECTAR) – a national network of new and existing clinical research sites, programs, and systems that aims to synergistically link clinical research networks in order to expand their utility, maximize connectivity among these sites, and provide scientists with unprecedented analytic capacity. NECTAR is a component of the NIH Roadmap thematic area, *Re-engineering the Clinical Research Enterprise.*

Chronic Graft-Versus-Host-Disease (GVHD) Consensus Criteria in Clinical Trials – supports NIH intramural, NIH extramural, and non-NIH scientists in developing consensus criteria for chronic GVHD in clinical trials.

International Histocompatibility Working Group (IHWG) – a multidisciplinary network of more than 200 laboratories in over 70 countries that is working to catalog the human leukocyte antigen (HLA) gene complex, and characterize the relationship between certain HLA genes and immune-mediated diseases, including autoimmunity and transplant-related diseases. (Note: also under Etiology of Autoimmune Diseases, page 103).

Clinical Trials

Immune Tolerance Network – a consortium of more than 80 investigators in the United States, Canada, Western Europe, and Australia dedicated to the clinical evaluation of promising tolerance induction therapies in kidney, liver and islet transplantation for type 1 diabetes; and medical treatments for all autoimmune disorders, and asthma and allergic diseases.

Autoimmunity Centers of Excellence – supports centers that bring together multiple clinical subspecialists and basic scientists to facilitate autoimmunity research collaboration.

Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) – a clinical trial testing the effects of statins – drugs used to lower low-density lipoprotein levels – against fat buildup in the blood vessels of children with lupus.

CombiRX trial – a randomized, controlled Phase III trial comparing the efficacy of combining glatiramer actetate and interferon-beta in treating relapsing forms of multiple sclerosis.

Diabetes TrialNet Consortium – provides infrastructure and support for clinical trials aimed at preserving insulin-producing cells in individuals at risk for type 1 diabetes and in those with new-onset type 1 diabetes. Multiple trials will be conducted simultaneously under its structure.

Trial to Reduce the Incidence of Type 1 Diabetes Mellitus in the Genetically At-Risk (TRIGR) – a multisite, randomized, controlled clinical trial designed to determine if the onset of type 1 diabetes can be delayed or prevented by weaning genetically-susceptible infants to a hydrosylate of cow milk protein, instead of to a standard cow's milk-based infant formula (control group).

Stem Cell Transplantation for Autoimmune Disease Treatment Consortium – supports clinical trials designed to study the safety and efficacy of high-dose immunosuppressive or immunoablative therapy followed by autologous stem cell transplantation as a treatment for severe progressive autoimmune disease. In particular, these studies focus on severe systemic sclerosis (SSc), refractory systemic lupus erythematosus, and multiple sclerosis.

Innovative Therapies for Rheumatic and Skin Diseases – supports evaluations of innovative therapies for rheumatic and skin diseases, including Wegener's granulomatosis, rheumatoid arthritis, scleroderma, lupus, ankylosing spondylitis, and inflammatory, autoimmune, and genetic skin diseases.

Clinical Trials and Clinical Markers in Immunologic Diseases – focuses on orphan clinical trials of immunomodulatory treatments for immune-mediated diseases, including autoimmune disorders, and the development of biologic markers to measure disease activity, risk, and therapeutic effect.

Cyclophosphamide in Scleroderma Pulmonary Disease – supports an investigator-initiated five-year, 13-center, parallel-group, double-blinded, randomized, Phase III clinical trial of cyclophosphamide for the treatment of pulmonary fibrosis associated with systemic sclerosis.

Evaluation and Treatment of Salivary Gland Dysfunction – supports studies in patients with complaints of dry mouth or Sjögren's syndrome.

Natural History of Salivary Gland Dysfunction and Sjögren's Syndrome – focuses on patients with complaints of dry mouth or Sjögren's syndrome.

Complementary and Alternative Medicine studies – supports selected studies of clinical and basic science approaches using complementary and alternative medicine in multiple sclerosis, rheumatoid arthritis, fibromyalgia, and diabetic neuropathy. Some of these studies are randomized, controlled clinical trials of complementary and alternative medicine products, providing the scientific rigor that has previously been lacking in most studies of these therapies.

IV. Training, Education, and Information Dissemination

(The following includes selected listings of the many training and educational activities sponsored each year by NIH Institutes and Centers.)

Mentored Research Scientist Development Awards – provides researchers with an additional period of sponsored research experience as a way to gain expertise in a research area new to the applicant or in an area that would demonstrably enhance the applicant's scientific career. These awards are generally reserved for individuals interested in switching to a new research field, for individuals who have interrupted their career because of illness or pressing family care responsibilities, or for faculty at minority institutions who wish to enhance their capacity for independent research.

Independent Research Scientist Development Award – provides support for recently independent scientists with outstanding potential to become future leaders in biomedical, behavioral, or clinical sciences.

Mentored Clinical Scientist Development Award – provides support for clinicians who need an intensive period of mentored research experience.

Midcareer Investigator Award in Patient-Oriented Research – supports protected time for clinicians to enable them to conduct patient-oriented research and to act as mentors for beginning clinical investigators.

Mentored Patient-Oriented Research Career Development Awards – supports investigators focused on patient-oriented research. The initiative offers a non-renewable three- to five-year period of supervised study and research for clinically-trained professionals who may focus on mechanisms of disease, therapeutic interventions, new technology development, or clinical trials.

Small Grant Program for New Investigators – facilitates the entry of promising new investigators into research on arthritis and musculoskeletal and skin diseases and injuries. Both programs prepare investigators to compete successfully for independent research support.

Training and Career Development in Biopsychosocial Rheumatic, Musculoskeletal, and Skin Diseases Research – focuses on attracting promising behavioral researchers to the study of these disease areas, and encouraging biomedical researchers to adopt a biopsychosocial approach to research, with the ultimate goal of enhancing the quality of interdisciplinary research in these diseases.

Multidisciplinary Biobehavioral Rheumatic Diseases – fosters interdisciplinary communication and collaboration among behavioral scientists, physicians, and basic scientists with shared or overlapping interests in or expertise in rheumatic diseases. The goals of the workshops include promoting new collaborations, attracting investigators new to rheumatic disease research, and defining scientific needs and opportunities.

Federal Working Group on Lupus (FWGL) – exchanges information and coordinates Federal efforts in lupus research and education. The working group is comprised of representatives from all relevant DHHS agencies and other Federal departments with an interest in lupus. The second meeting of the FWGL was held in the summer of 2004.

Biomarkers in Multiple Sclerosis – a meeting convened in April 2004 that discussed and evaluated current knowledge and the usefulness of biomarkers for diagnosing multiple sclerosis, monitoring specific disease processes, assessing therapies, and predicting disease course.

Genetics and Multiple Sclerosis: Future Prospects – an international workshop that explored the genetic underpinnings of multiple sclerosis, which to date have eluded definitive identification. The goal of the workshop was to create a collaborative multiple sclerosis genetics network that shares strategies, reagents, methods, data, and samples to accelerate the discovery of multiple sclerosis susceptibility genes.

Tenth International Conference, Myasthenia Gravis and Related Disorders: Biochemical Basis for Diseases of the Neuromuscular Junction – a cosponsored conference that explored autoimmunity issues in neuromuscular diseases, including myasthenia gravis, stiff person syndrome, and myositis.

Digestive Diseases Interagency Coordinating Committee (DDICC) – a group of Federal scientists who work to promote cooperation and collaboration among NIH Institutes and Centers and other Federal agencies that support research to combat digestive diseases. At the "Review of the Current State of Research on Inflammatory Bowel Disease" meeting, the DDICC reviewed current research activities and recommended new research directions and priorities.

Glutamic Acid Decarboxylase (GAD) Autoimmunity in Batten Disease – a workshop that facilitated the exchange and integration of ideas, new information, and technologies among experts in Batten disease, a rare and little understood hereditary nervous system disorder leading to neurologic impairment.

Multidisciplinary Biobehavioral Rheumatic Diseases – a workshop conducted to bring together behavioral scientists, physicians, and basic scientists with the aim of exploring current understandings and exchanging information on the etiology, course, and outcomes of rheumatic diseases.

Celiac Disease Consensus Conference – convened in June 2004 to assess current scientific knowledge on celiac disease and provide recommendations for its appropriate diagnosis and management.

Increasing Opportunities in Biobehavioral Research – a two-day working group meeting of behavioral, biological, and immunological science experts who examined current knowledge and provided recommendations to further advance biobehavioral research.

Promoting Research on Focal Cognitive Deficits in Non-Dementing Disorders – a meeting focused on reviewing current knowledge on these deficits in non-dementing central nervous system disorders and their effects on quality of life, health behaviors/decision-making, and health outcomes, identifying research gaps in this area, defining research challenges and emerging research methods, and identifying research opportunities in populations with these conditions. Multiple sclerosis is an example of the types of disorders discussed that would benefit from more research.

Appendix C
Autoimmune Diseases Coordinating Committee Roster

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Appendix D
Children's Health Act of 2000

Title XIX—NIH Initiative on Autoimmune Diseases

SEC. 1901. AUTOIMMUNE DISEASES; INITIATIVE THROUGH DIRECTOR OF NATIONAL INSTITUTES OF HEALTH.

Part B of Title IV of the Public Health Service Act (42 U.S.C. 284 et seq.), as amended by section 1001 of this Act, is amended by adding at the end the following:

SEC. 409E. AUTOIMMUNE DISEASES.

(a) EXPANSION, INTENSIFICATION, AND COORDINATION OF ACTIVITIES-

(1) IN GENERAL – The Director of NIH shall expand, intensify, and coordinate research and other activities of the National Institutes of Health with respect to autoimmune diseases.

(2) ALLOCATIONS BY DIRECTOR OF NIH – With respect to amounts appropriated to carry out this section for a fiscal year, the Director of NIH shall allocate the amounts among the national research institutes that are carrying out paragraph (1).

(3) DEFINITION – The term 'autoimmune disease' includes, for purposes of this section such diseases or disorders with evidence of autoimmune pathogenesis as the Secretary determines to be appropriate.

(b) COORDINATING COMMITTEE-

(1) IN GENERAL – The Secretary shall ensure that the Autoimmune Diseases Coordinating Committee (referred to in this section as the 'Coordinating Committee') coordinates activities across the National Institutes and with other Federal health programs and activities relating to such diseases.

(2) COMPOSITION – The Coordinating Committee shall be composed of the directors or their designees of each of the national research institutes involved in research with respect to autoimmune diseases and representatives of all other Federal departments and agencies whose programs involve health functions or responsibilities relevant to such diseases, including the Centers for Disease Control and Prevention and the Food and Drug Administration.

(3) CHAIR-

(A) IN GENERAL – With respect to autoimmune diseases, the Chair of the Committee shall serve as the principal advisor to the Secretary, the Assistant Secretary for Health, and the Director of NIH, and shall provide advice to the Director of the Centers for Disease Control and Prevention, the Commissioner of Food and Drugs, and other relevant agencies.

(B) DIRECTOR OF NIH – The Chair of the Committee shall be directly responsible to the Director of NIH.

(c) PLAN FOR NIH ACTIVITIES-

(1) IN GENERAL – Not later than 1 year after the date of the enactment of this section, the Coordinating Committee shall develop a plan for conducting and supporting research and education on autoimmune diseases through the national research institutes and shall periodically review and revise the plan. The plan shall—

A) provide for a broad range of research and education activities relating to biomedical, psychosocial, and rehabilitative issues, including studies of the disproportionate impact of such diseases on women;

(B) identify priorities among the programs and activities of the National Institutes of Health regarding such diseases; and

(C) reflect input from a broad range of scientists, patients, and advocacy groups.

(2) CERTAIN ELEMENTS OF PLAN – The plan under paragraph (1) shall, with respect to autoimmune diseases, provide for the following as appropriate:

(A) Research to determine the reasons underlying the incidence and prevalence of the diseases.

(B) Basic research concerning the etiology and causes of the diseases.

(C) Epidemiological studies to address the frequency and natural history of the diseases, including any differences among the sexes and among racial and ethnic groups.

(D) The development of improved screening techniques.

(E) Clinical research for the development and evaluation of new treatments, including new biological agents.

(F) Information and education programs for health care professionals and the public.

(3) IMPLEMENTATION OF PLAN – The Director of NIH shall ensure that programs and activities of the National Institutes of Health regarding autoimmune diseases are implemented in accordance with the plan under paragraph (1).

(d) REPORTS TO CONGRESS – The Coordinating Committee under subsection (b)(1) shall biennially submit to the Committee on Commerce of the House of Representatives, and the Committee on Health, Education, Labor and Pensions of the Senate, a report that describes the research, education, and other activities on autoimmune diseases being conducted or supported through the national research institutes, and that in addition includes the following:

(1) The plan under subsection (c)(1) (or revisions to the plan, as the case may be).

(2) Provisions specifying the amounts expended by the National Institutes of Health with respect to each of the autoimmune diseases included in the plan.

(3) Provisions identifying particular projects or types of projects that should in the future be considered by the national research institutes or other entities in the field of research on autoimmune diseases.

(e) AUTHORIZATION OF APPROPRIATIONS – For the purpose of carrying out this section, there are authorized to be appropriated such sums as may be necessary for each of the fiscal years 2001 through 2005. The authorization of appropriations established in the preceding sentence is in addition to any other authorization of appropriations that is available for conducting or supporting through the National Institutes of Health research and other activities with respect to autoimmune diseases.

Appendix E
Acronyms

ABCoN	Autoimmune Biomarkers Collaborative Network
ADCC	Autoimmune Diseases Coordinating Committee
APS	Antiphospholipid syndrome
CDC	Centers for Disease Control and Prevention
CLEAR	Consortium for the Longitudinal Evaluations of African Americans with Early Rheumatoid Arthritis
CREST	CREST syndrome (an acronym for the cardinal clinical features of the syndrome: **c**alcinosis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia.
DAISY	Diabetes Autoimmunity Study in the Young
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FY	Fiscal year
HHS	Department of Health and Human Services
HLA	Human leukocyte antigen
HRSA	Health Resources and Services Administration
IHWG	International Histocompatibility Working Group
ICRs	Islet Cell Resources
ITP	Idiopathic Thrombocytopenic Purpura
JRA	Juvenile rheumatoid arthritis
MADGC	Multiple Autoimmune Diseases Genetics Consortium
MHC	Major Histocompatibility Complex
MS	Multiple sclerosis
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NCMHD	National Center on Minority Health and Health Disparities
NCRR	National Center for Research Resources
NEI	National Eye Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAID	National Institute of Allergy and Infectious Diseases

NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other 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
NIGMS	National Institute of General Medical 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
NLM	National Library of Medicine
NMA	National Medical Association
NMSS	National Multiple Sclerosis Society
ORD	Office of Rare Diseases
ORWH	Office of Research on Women's Health
PA	Pernicious anemia
SLE	Systemic lupus erythematosus
SCCOR	Specialized Centers of Clinically Oriented Research
SCOR	Specialized Centers of Research
VA	Department of Veterans Affairs

Appendix F
Glossary of Scientific and Medical Terms

Addison's disease: a disorder due to autoimmune-induced destruction of the adrenal cortex that results in deficiency of aldosterone and cortisol; it is fatal in the absence of replacement therapy.

Adjuvant: A component of vaccines used to increase the potency of an antigen in inducing an immune response.

Allele: Any of two or more alternative forms of a gene that occupy a specific site on a chromosome.

Antibody: A molecule (also called an immunoglobulin) produced by B cells in response to an antigen. The binding of antibody to antigen leads to the antigen's destruction.

Antigen: A substance or molecule that is recognized by the immune system. The molecule can be from a foreign material such as a bacterium or virus, or the molecule can be from one's own body and called a self-antigen.

Apoptosis: Programmed cell death – a normal process by which aged or unwanted cells are eliminated.

Autoantibodies: Antibodies that are made against the body's own organs and tissues rather than foreign parts of bacteria or viruses.

Autoimmune disease: Condition in which the immune system mistakenly attacks the body's own organs and tissues.

Autologous: Related to self; the components of the same individual organism.

Central tolerance: Process by which potentially autoreactive immune system cells are eliminated before they can mature and be released to circulate in the body.

Chemokine: A cytokine with chemotactic activity (see cytokine, see chemotaxis).

Chemotaxis: The movement of a cell (usually a leukocyte) or an organism in response to a chemical signal.

Clone: The progeny of a single cell such as a B cell or T cell.

Cohort: In epidemiology, a group of individuals who share a common characteristic. In cohort studies, subjects are followed over time in order to study information about the incidence of a disease and the relative risk of incurring the disease (the ratio of disease incidence in subjects exposed to certain predictors, risk factors, against those not exposed).

Co-stimulatory: A signal required for complete activation of lymphocytes, required to generate many immune responses.

Crohn's disease: An autoimmune inflammatory bowel disease.

Cytokines: Chemical substances released by several types of cells in the body that have varied effects on many cells of the body. For example, some cytokines can cause growth and activation of the immune system cells.

Determinant: The component of an antigenic molecule that is responsible for a specific interaction with antibody or T cells.

Dimorphic: Existing in two different forms.

Enteroviruses: A family of viruses that can infect the respiratory and intestinal tracts.

Epidemiology: The science concerned with the study of the factors determining and influencing the frequency and distribution of diseases and their causes in a defined human population for the purpose of establishing programs to prevent and control their development and spread.

Epitope: Same as Determinant.

Genome: Complete genetic complement of an organism.

Genotype: The genetically inherited characteristics of an individual.

Glomerulonephritis: Nephritis accompanied by inflammation of the capillary loops in the glomeruli of the kidney.

Guillain–Barré syndrome: An acute autoimmune demyelinating polyneuropathy.

Haplotype: A group of linked genes contributed by either parent.

Hashimoto's thyroiditis: A progressive autoimmune disease of the thyroid gland, with lymphocytic infiltration of the gland and circulating anti-thyroid antibodies. Patients may develop hypothyroidism.

HLA: Human leukocyte antigen, the major histocompatibility complex (MHC) in humans (see MHC).

Homeostasis: The tendency of the body to maintain a stable internal environment.

Homologue/homolog: Corresponding in structure, position or origin.

Immune tolerance: The safeguards that the immune system naturally possesses to protect from harming self.

Incident case: A new case of a disease; that is, someone who has just become symptomatic or who has just been diagnosed.

Inflammation: A localized protective response induced by injury or infection, classically associated with pain, heat, redness, and swelling.

Leukocyte: A white blood cell.

Lipopolysaccharide: A component of bacterial cell wall, comprising lipid and carbohydrate portions.

Lupus: Specifically, systemic lupus erythematosus – a chronic, relapsing, inflammatory, and often febrile multisystemic autoimmune disorder. It can affect the joints, skin, kidneys, lungs, heart, or brain. A less serious form of lupus is discoid or cutaneous lupus, which mainly affects the skin.

Lymphocytes: Small white blood cells that are critical components of the immune system. There are several types of lymphocytes: B cells are primarily involved in the production of antibodies; T cells attack infected cells or release chemicals that activate and direct the movements of other cells to help fight infection or attack foreign matter.

Macrophage: A differentiated mononuclear cell found in tissues; macrophages ingest microbes and are potent antigen presenting cells.

Major Histocompatibility Complex (MHC) molecules: Molecules that are found on cell surfaces and display antigen; the antigen-MHC molecules may then interact with a T cell receptor. (see also HLA)

Microchimerism: The presence in an individual of a population of cells derived from another human being.

Monoclonal antibody: A population of antibodies derived from a single B cell clone.

Multiple sclerosis: A disease in which there is demyelination of the white matter of the central nervous system, typically causing severe weakness, fatigue, uncoordination, burning or prickling sensations, speech disturbances, and visual complaints.

Myasthenia gravis: A disorder of neuromuscular function due to the presence of antibodies to acetylcholine receptors.

Myositis: Inflammation of muscle.

Natural history of disease: The course of disease over time, unaffected by treatment.

Pathogenesis: The processes involved in the development of a disease.

Pemphigus: A disease of the skin resulting in large blisters.

Peptide: A small molecule comprising a number of amino acids; the constituent part of a protein.

Peptidoglycan: A molecule comprising a peptide and carbohydrate portion.

Peripheral tolerance: The process by which potentially autoreactive cells are controlled after they reach the bloodstream.

Phenotype: The characteristics of an individual (or group) that can be seen and that result from the interaction of its genetic constitution and environmental factors.

Polymorphism: The presence of multiple alleles at a specific locus of a chromosome.

Proteomics: State-of-the-art methods that combine genomics, molecular biology, and protein chemistry.

Reactive arthritis: See Reiter's syndrome.

Receptor: A structure on the surface of a cell with the capability of combining specifically with a structurally matched cognate molecule. Depending on the specific receptor, the latter may be a drug, a cytokine, or an antigen.

Reiter's syndrome: Reactive arthritis, that is, arthritis that is manifested after an infection, such as urethritis caused by *Chlamydia trachomatis* or enteritis caused by Campylobacter, Salmonella, Shigella, or Yersinia. Associated features may include inflammatory eye lesions, oral ulcers, and skin lesions.

Rheumatoid arthritis: A chronic systemic disease primarily of the joints, marked by inflammatory changes in the synovial membranes and articular structures.

Scleroderma: Chronic hardening, thickening, and tightening of the skin, occurring in a localized or local form and as a systemic disease. Systemic scleroderma also attacks the body's organs, including the blood vessels, heart, lungs, and kidneys.

Sjögren's syndrome: An autoimmune disease targeting moisture-producing glands and causing dryness in the mouth and eyes. Other parts of the body – the stomach, pancreas, intestines, and ovaries – can be affected as well.

Stroma: A supporting tissue element or structure.

Stromal cells: A network of cells providing the structure of a tissue or organ.

Synovial: Pertaining to joints or the fluid within joints.

T cell: A type of lymphocyte. T cells have T cell receptors and, sometimes, costimulatory molecules on their surfaces. Different types of T cells help to orchestrate the immune response and can issue orders for other cells to make cytokines and chemokines.

Telerogenic: Generated from a distance.

Teratogenic: Producing a teratoma, a tumor made up of a number of different types of tissues.

Transgenic: The experimental insertion of a segment of DNA from one genome onto the DNA of a different genome. This technique is used to make genetically modified mice.

Tumor necrosis factor alpha (TNF-α): A cytokine produced by macrophages and T cells having multiple functions in regulating the immune response (see cytokine).

Type 1 diabetes: A condition in which the pancreas makes little or no insulin because the beta cells have been destroyed by an autoimmune reaction. Because the body is unable to use glucose for energy, insulin must be replaced through injection or by another mechanism.

Uveitis: The inflammation of part or all of the uvea, the middle (vascular) section of the eye.

Vitiligo: A usually progressive, chronic pigmentary anomaly of the skin manifested by depigmented white patches that may be surrounded by a hyperpigmented border.

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