National Institutes of Health

AUTOIMMUNE DISEASES COORDINATING COMMITTEE

Autoimmune Diseases Research Plan

U.S DEPARTMENT OF HEALTH
AND HUMAN SERVICES

AUTOIMMUNE DISEASES COORDINATING COMMITTEE

Autoimmune Diseases Research Plan

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Foreword

Autoimmune diseases result from a dysfunction of the immune system in which the body attacks its own organs, tissues, and cells. Physicians and scientists have identified more than 80 clinically distinct autoimmune diseases. Several are well known, including rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and systemic lupus erythematosus; others are less familiar, including autoimmune hepatitis, Sjögren's syndrome, autoimmune ear disease, and pemphigus. Collectively, these diseases afflict millions of Americans, an estimated 5 to 8 percent of the population – 14 to 22 million persons. The social and financial burdens imposed by these chronic, debilitating diseases include poor quality of life, high health care costs, and substantial loss of productivity.

The past two decades of research on the immune system have yielded a wealth of new information and extraordinary growth in conceptual understanding. As a result, opportunities now exist to identify genetic, environmental, and infectious causes of certain autoimmune diseases and to develop novel approaches for treatment and prevention. To achieve these goals, the National Institutes of Health (NIH) places a high priority on cross-disciplinary research and the participation of other government agencies and private organizations in these efforts. To facilitate collaboration among the NIH Institutes, other Federal agencies, and private organizations with an interest in autoimmune diseases, the NIH established the Autoimmune Diseases Coordinating Committee in 1998, under the direction of the National Institute of Allergy and Infectious Diseases. Since its inception, the Committee has analyzed a wide range of ongoing and planned research programs and developed crosscutting initiatives to address key aspects of autoimmunity. In developing this plan for autoimmune diseases research, the Committee analyzed the existing NIH research programs and sought the expertise of non-Federal scientists. An independent Expert Panel reviewed, contributed to, and endorsed the Plan in January of 2002.

The Research Plan highlights many unprecedented opportunities to increase our understanding of autoimmune diseases at the population, individual, and molecular levels, with a conceptual focus on the underlying mechanisms shared among many autoimmune diseases. This strategy should ultimately allow the translation of new knowledge into more effective treatments and prevention strategies.

Elias Zerhouni, M.D.
Director
National Institutes of Health

Executive Summary

Background

Over two decades of investment in intensive and productive research has yielded extraordinary opportunities to enhance our knowledge of the underlying causes of autoimmune diseases, develop more effective therapies, and design strategies to prevent the onset of these chronic and debilitating disorders. This strategic plan, as called for in the Children's Health Act of 2000 (P.L. 106-310) - Title XIX - NIH Initiative on Autoimmune Diseases, provides a comprehensive and long-term research agenda designed to capitalize on these opportunities and to build the infrastructure, human and research resources, and public-private partnerships critical to ensuring continued progress. This Research Plan highlights new programs and research areas in which future progress will benefit all autoimmune diseases.

The Nature and Impact of Autoimmune Diseases

Autoimmune diseases are chronic disabling disorders in which underlying defects in the immune response lead the body to attack its own organs and tissues. More than 80 autoimmune diseases have been identified. The most common of these diseases include systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes, autoimmune thyroid diseases (Graves' disease and Hashimoto's thyroiditis), myasthenia gravis, scleroderma, and rheumatoid arthritis. However, the immune response toward self can affect any organ or organ system, resulting in a wide variety of autoimmune diseases. Collectively, autoimmune diseases are thought to affect approximately 14–22 million people in the United States and represent a significant physical, emotional, social, and fiscal burden to the country's health care system. For example, annual medical costs for treating type 1 diabetes are estimated to range between $4.6 and $9.2 billion; for multiple sclerosis, annual costs have been estimated at $2.5 billion. For reasons that are not clear, the prevalence of autoimmune diseases appears to be rising

Most autoimmune diseases disproportionately affect women, and autoimmune diseases are among the 10 leading causes of death for women in every age group up to 64 years of age. All ages are affected, with onset from childhood to late adulthood. Persons of all racial, ethnic, and socioeconomic groups are affected, although the impact of racial background varies among autoimmune diseases. The burden imposed by these diseases includes a high cost to society in terms of lost productivity, chronic affliction, decreased quality of life, co-morbid mental illnesses, particularly depression and anxiety, and disruption of social and family structures due to the tendency to afflict women of childbearing age.

Federal Planning for Autoimmune Diseases Research

The NIH Autoimmune Diseases Coordinating Committee (ADCC) provides a forum for

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coordinating research efforts in the field of autoimmunity and autoimmune diseases and brings together the various stakeholders interested in autoimmune disease research, including the National Institutes of Health, the U.S. Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the Department of Veterans Affairs (VA), and private organizations. The research programs supported by these groups comprise a broad range of basic, preclinical, and clinical endeavors addressing many different diseases and aspects of autoimmunity.

The breadth of participation in the Autoimmune Diseases Coordinating Committee brings enormous strength to the task. The NIH is the Federal focal point for medical research in the United States and is uniquely positioned to coordinate research at all levels, from basic discovery research, to translational research, to clinical trials. NIH scientists work closely with scientists from other Federal agencies and from the academic community. Private organizations, which support research in autoimmunity and autoimmune diseases, represent the interests of patients and play a unique role in the research enterprise. These organizations support biomedical research and training programs independent of, and in collaboration with, the NIH, and provide valuable programs in education and information dissemination. They link patients and their families to research activities by helping to identify, recruit, and retain volunteers for clinical research and by providing information about developing therapies. Finally, these organizations are the public face of those directly affected by autoimmune diseases.

Key Implementation Principles

In developing this strategic plan, the Autoimmune Diseases Coordinating Committee and an Expert Panel, composed of independent academic and clinical scientists and laypersons, identified high priority areas for research and key principles essential for the effective implementation of the plan:

A focused program aimed at reversing the medical burden and impact of autoimmune diseases will require support for scientific activities, infrastructure, and technologies. Although certain needs are common to all autoimmune diseases, the impact on research progress varies by disease. The Autoimmune Diseases Coordinating Committee sought to identify opportunities that would be most likely to expedite discovery and clinical applications. Such a focus recognizes that advances in one autoimmune disease may facilitate progress in other diseases.

A coordinated structure will most efficiently manage the necessary resources. The recommendations in this Research Plan require a coordinated approach to establishing priorities and managing research funding and infrastructure. Such an approach will minimize duplicative activities, take advantage of economies of scale, and rapidly disseminate new scientific findings. This approach will enable more effective and efficient management of research endeavors that encompass multiple disciplines and span the missions of multiple government agencies and private organizations. The Autoimmune Diseases Coordinating Committee

should continue as the primary forum for coordination of Federal activities in autoimmune diseases research among NIH Institutes, Centers, and Offices, the CDC, the FDA, and other Federal agencies. The ADCC anticipates that member organizations will carefully evaluate and consider the recommendations in this Research Plan in their individual research priority-setting processes. Regularly scheduled ADCC meetings will focus on the sharing of information at early stages in the development of research solicitations in order to facilitate collaborations among ADCC member organizations on specific components of this Research Plan. Future reporting activities of the ADCC will also link ongoing and new research activities to components of this strategic research plan, providing benchmarks and metrics for collaborative activities. The ADCC would continue to function as an important locus for coordination of new activities.

Multidisciplinary approaches and both national and international partnerships of Federal, industry, and private entities will be important. Approaches that span a range of medical specialties and a variety of scientific disciplines will be essential. These efforts will require unprecedented cooperation and collaboration between scientists, clinicians, patients, and research sponsors. The NIH and its partners must develop innovative strategies to broaden participation and capitalize on the significant contributions that will be made by international collaborators and industry. Many of the new technical approaches, in addition to preclinical leads for new therapeutics, are being developed or tested in nonacademic settings. Thus,

partnerships with industry will be advantageous to ensure rapid progress.

Private organizations have a unique and important role in facilitating the research enterprise, and their continued participation should be encouraged. Private organizations disseminate medical and scientific information about autoimmune diseases and current research and are usually the first points of contact for patients after a diagnosis of an autoimmune disease. Such organizations promote the development of a cohesive community of affected individuals and their families; help to recruit and retain subjects for clinical research; and provide valuable information and perspectives to their members, the public at-large, research sponsors, and Congress. They also support biomedical research and training programs independent of, and in collaboration with, the NIH and other Department of Health and Human Services agencies.

Elements of the Strategic Plan

The Autoimmune Diseases Coordinating Committee highlighted the need for research in several thematic areas, focusing on those opportunities likely to have the greatest impact on accelerating discovery and clinical advances needed to prevent or cure autoimmune diseases. This process led to the identification of six high priority areas: Biomarker Development, Bioinformatics and New Technologies, Clinical Studies/Infrastructure, Etiology, Epidemiology, and Education.

Biomarker Development

An overarching need in autoimmune disease research is the development and validation of surrogate markers of the disease process. Biomarkers are laboratory markers that correlate with clinical status and facilitate clinical studies and patient management. Biomarkers can include specific genes and genetic polymorphisms, clinical laboratory tests, clinical signs, or immunologic assays. Biomarkers of disease onset, activity, or response to therapy would 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; 3) shorter and smaller clinical trials; and 4) more informative monitoring of agents for efficacy resulting in discontinuation of ineffective therapies.

Biomarkers of disease risk in unaffected individuals would allow clinical trials of preventive approaches. This has been done effectively in type 1 diabetes prevention studies. For example, the recognition that relatives of diabetics who also carry certain human leucocyte antigen (HLA) genes and autoantibodies are at high risk for disease development has allowed prevention trials to proceed in this population.

The development of biomarkers draws from 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. This developmental process requires a multidisciplinary and creative approach and the validation of candidate biomarkers requires rigorous clinical evaluation.

➡ Recommendation: Develop, test, and validate candidate biomarkers identified in epidemiologic, immunologic, and genetic studies and clinical trials.

Bioinformatics and New Technologies

A variety of new technologies should be applied to research on autoimmune diseases. Disease processes can now be characterized at a molecular level through the use of microarray technologies to study the expression of genes in tissue samples, proteomics to characterize the status of gene products in tissues, and novel labeling and high through-put technologies. Optimal utilization of the resulting data in the context of clinical outcomes, clinical laboratory assays, and population screening will require advanced computational capacities for data management and analysis.

These relational 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 the promise of significant advances in diagnosis, treatment, and prevention.

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 to progress in understanding the genetics of autoimmune diseases. Similarly, the existence of well-characterized individuals and families in clinical databases and registries housing serum and tissue samples, in addition to genetic and epidemiologic data, will greatly accelerate the application of these new technologies to the development of biomarkers.

➡ Recommendation: Develop and apply new technologies to explore pathogenesis and aid in clinical management of autoimmune diseases. Develop novel databases and computational capacity to analyze data from multiple sources, including clinical, genetic, epidemiologic, and immunologic studies.

Clinical Studies/Infrastructure

The overlapping nature of many autoimmune diseases allows advances in one disease to accelerate progress in others. However, despite similarities in underlying mechanisms, each disease has unique components. Impediments to the rapid and efficient conduct of clinical trials include the lack of: 1) standardized classification, diagnostic, and response criteria; and 2) national networks of physicians committed to collaborative clinical trials in autoimmune diseases.

For many diseases, the available therapies have not been rigorously tested to guide clinical care and management. In addition, although new agents have been approved for certain autoimmune diseases, testing of these agents in other diseases has lagged, resulting in potentially dangerous off-label use.

Professional organizations, including the American College of Rheumatology (ACR), have developed and validated disease classification criteria, e.g., ACR criteria for diagnosis of lupus, and disease response criteria, such as the ACR 20 and ACR 70 for rheumatoid arthritis. However, such classification and response criteria do not exist for most autoimmune diseases. The NIH and its partners have developed clinical infrastructures that could be utilized to expand such efforts. Examples include the Immune Tolerance Network, the Autoimmunity Centers of Excellence, Type 1 Diabetes TrialNet, Planning Grants of Clinical Trials in Rheumatic and Skin Diseases, and the Consortium for Autoimmune Disease Stem Cell Trials.

The infrastructure for the conduct of clinical trials provides a resource for advancing progress in the overlapping high priority areas of Biomarker Development, Bioinformatics and New Technology, Epidemiology, Etiology, and Education, including disease classification criteria, disease response criteria, and the availability of clinical data and biologic samples.

➡ Recommendation: Continue and expand support for existing and new networks to conduct clinical trials and associated mechanistic studies in a broad range of autoimmune diseases.

Epidemiology

Data on the incidence, prevalence, and health care costs of autoimmune diseases are generally not available. Much of the existing data is outdated or derived from flawed case definitions and small

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samples. More recent studies suggest that the collective impact of autoimmune diseases is greater than previously thought. Well-designed, multidisciplinary, longitudinal studies are needed to identify the relationships between autoimmune diseases and environmental and infectious agents and to determine their incidence and prevalence. 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 diseases within a single individual emphasize the need for coordinated, comprehensive, and integrated studies.

➡ Recommendation: Establish well-organized, multidisciplinary consortia to design and conduct integrated population-based epidemiology studies of autoimmune diseases with collection of data and subject samples in repositories. Provide investigator access to costly and sophisticated research tools that will speed the acquisition of data, but may not be widely available.

Etiology

Autoimmune diseases develop in genetically susceptible individuals and can be triggered by environmental exposures including exposure to infectious agents. Understanding the interactions of genetic and environmental factors that are necessary for disease development offers the promise of preventing or treating autoimmune diseases in novel ways.

Multiple genes contribute to disease susceptibility and overlapping genetic regions contribute to the development of several different autoimmune diseases. One family of immune response genes, the Major Histocompatibility Complex (MHC) genes, contributes to susceptibility in multiple autoimmune diseases. Other genes have been associated with particular autoimmune diseases, including the NOD2 gene in Crohn's disease and the insulin gene in type 1 diabetes.

Important steps in more fully characterizing the genes involved in autoimmune diseases include completion of the first draft of the human genome and the establishment of consortia to collect data from individuals and families with autoimmune diseases; e.g., the Multiple Autoimmune Diseases Genetics Consortium, the Type 1 Diabetes Genetics Consortium, and the North American Rheumatoid Arthritis Consortium. International consortia, with inclusion of larger numbers of subjects, will also be important. Cooperation and coordination among the consortia will be necessary to rapidly elucidate the genes involved.

To link exposure to infectious agents to the development of autoimmune diseases will require sensitive assays and careful population studies. The unique properties of the infectious agents, timing of infection, and host response are likely to be important parameters. Large, coordinated, multidisciplinary epidemiologic and surveillance studies will facilitate collection of this information.

Recent advances in the understanding of the immunologic processes leading to autoimmunity are paving the way for discovery of novel immunomodulatory treatments. The advent of anti-tumor necrosis factor therapies in rheumatoid arthritis, Crohn's disease, and ulcerative colitis is one

example that highlights the value of novel biologic therapies for autoimmune diseases. Further understanding of the immunopathogenesis of these diseases will allow development of more selective and effective therapies with lesser toxicities.

➡ Recommendation: Continue support of basic research on the etiology of autoimmune diseases, including identification of genes, infectious agents and other environmental factors, and the immune response to self with an emphasis on the interactions of these factors and translation of findings to clinical applications.

Education

Unfortunately, many affected individuals and health care providers are unaware of the relationships among autoimmune diseases. Many prominent persons in the political arena and the media and entertainment industries who are affected by these diseases have spoken openly of the need for increased information and research. For the most part, however, these individuals have emphasized one particular autoimmune disease, not the large family of disorders that have autoimmunity in common.

In addition to providing support services to patients and their families, private organizations distribute information about ongoing research efforts, including clinical trials. 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 and their families and for health care providers.

➡ Recommendation: In collaboration with voluntary health organizations, wage a high profile, vigorous and sustained public awareness campaign to provide up-to-date information about the nature of autoimmune diseases and the promise that coordinated and collaborative research holds for finding new treatments and prevention strategies. In collaboration with private and professional organizations, develop and disseminate professional education programs to increase professional awareness of autoimmune diseases.

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Introduction

The Nature and Magnitude of Autoimmune Diseases

Autoimmune diseases represent a heterogeneous family of chronic, disabling diseases with different natural histories and a wide spectrum of clinical symptoms. More than 80 individual autoimmune diseases have been identified, including: type 1 diabetes; systemic lupus erythematosus; multiple sclerosis; rheumatoid arthritis; inflammatory bowel diseases, including both Crohn's disease and ulcerative colitis; hemolytic anemia; Graves' disease; scleroderma; and Sjögren's syndrome. These disorders share underlying defects in the immune response leading the body to attack its own organs and tissues. Immune-mediated injuries localized to a single organ or tissue, such as the pancreas in type 1 diabetes and the central nervous system in multiple sclerosis, characterize organ-specific autoimmune diseases. In contrast, non-organ-specific diseases, such as systemic lupus erythematosus, are characterized by immune reactions against many different organs and tissues resulting in widespread injury. Most of these diseases disproportionately affect women; however, persons of all racial, ethnic, and socioeconomic groups are affected. Certain diseases, including systemic lupus erythematosus and scleroderma, are more common in African Americans, whereas others, such as type 1 diabetes and multiple sclerosis, are more common in Caucasians. All ages are affected, with onset from childhood to late adulthood.

While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 5 to 8 percent of the United States population – 14 to 22 million persons. To provide a context to evaluate the impact of autoimmune diseases, cancer affected approximately 9 million people in the United States in 1997 (Surveillance, Epidemiology, and End Results [SEER] Registries, National Cancer Institute) and heart disease affected approximately 22 million people in the United States in 1996 (National Center for Health Statistics, Vital and Health Statistics, Series 10, No. 200, 1998).

Because of their chronicity, measured in decades, and their debilitating complications, autoimmune diseases exact high medical and socioeconomic costs. In addition, since autoimmune diseases affect women in their most productive years, their impact on families and society can be substantial. Although comprehensive national data on the incidence, prevalence, and medical and economic impact of autoimmune diseases do not exist in the aggregate, or for the majority of individual autoimmune diseases, the statistics that are available make clear that the impact of these diseases is significant. Some of the available data for specific diseases are highlighted below:

Rheumatoid Arthritis

- 2.1 million cases in the United States, including 30,000 to 50,000 children; afflicts twice as many women as men (Arthritis Rheum 41:778, 1998).

- 80 percent of cases have limitations in function (J Rheumatol 16:427, 1989; Primer on Rheumatic Diseases; 10th Edition, Arthritis Foundation, 1997).

- 211,000 hospitalizations per year (National Hospital Discharge Survey 1997, Vital and Health Statistics, Series 13, No. 145).

- Mortality is twice as high as expected in the general population and is associated with clinical severity (Arthritis Rheum 37: 481, 1994).

Type 1 Diabetes

- 300,000 to 500,000 cases in the United States – 123,000 patients are younger than 20 years of age (Diabetes in America, 2nd Edition, NIH, NIDDK, NIH Publication: 95-1468, p. 1, 1995).

- 30,000 new cases per year (Diabetes in America, 2nd Edition, NIH, NIDDK, NIH Publication: 95-1468, p. 1, 1995).

- Total estimated annual costs between $4.6 and $9.2 billion (Diabetes in America, 2nd Edition, 1995; National Diabetes Fact Sheet from the CDC, 1998).

Multiple Sclerosis

- 250,000 to 350,000 cases in the United States (Ann Neurol 31:333, 1992).

- 92,000 hospitalizations per year (National Hospital Discharge Survey, Vital and Health Statistics, 1997).

- $2.5 billion in estimated annual medical costs (Report of the NINDS Task Force, 1994).

Systemic Lupus Erythematosus

- Approximately 240,000 cases in the United States (Arthritis Rheum 41: 778, 1998).

- Disproportionately affects women and minorities (Arthritis Rheum 41:778, 1998).

- 102,000 hospitalizations per year (National Hospital Discharge Survey, 1997; Vital and Health Statistics, Series 13, No. 145).

Inflammatory Bowel Diseases

- Over 800,000 cases in the United States (Gut 28:402 1987; Gut 29:49 1988).

- More than two-thirds of cases due to ulcerative colitis and approximately one-third due to Crohn's disease (Gut 28:402, 1987; Gut 29:49, 1988).

- 32,000 hospitalizations for ulcerative colitis and 46,000 hospitalizations for Crohn's disease (National Hospital Discharge Survey 1997, Vital and Health Statistics, Series 13, No. 145).

Psoriasis

- Affects 2–4 percent of the population (Christophers, E. Clin Exp Dermatol 26: 314-320, 2001).

- Annual health care costs estimated at $2 billion (Fleischer AB, et al. Dermatol Clin 18:xv-xxi, 2000).

Themes in Autoimmune Disease Research

This Research Plan is divided into several thematic areas: Epidemiology and Burden of Disease; Etiology of Diseases; Diagnosis, Treatment, and Prevention; and Training, Education, and Information Dissemination. Additional overarching themes that appear throughout the plan and influence progress in each of the above areas include: identification of biomarkers of disease, stage of disease, and

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response to therapy; application of new technologies; and integration of bioinformatics and advanced computational tools.

The Importance of Research Coordination

Recognizing that autoimmune diseases span the interests of many public and private organizations, in FY 1998, Congress called for increased exchange of information and greater coordination of research activities across agencies of the Department of Health and Human Services. To help achieve these goals, National Institutes of Health established the Autoimmune Diseases Coordinating Committee under the direction of the National Institute of Allergy and Infectious Diseases (NIAID). The Committee includes: representatives of NIH Institutes, Offices, and Centers that support research on autoimmune diseases, the U.S. Food and Drug Administration, the Department of Veterans Affairs, the Centers for Disease Control and Prevention, and private organizations that sponsor research in this area (see Appendix A for a complete listing). The Autoimmune Diseases Coordinating Committee has assumed multiple and increasingly important functions, including: 1) information sharing; 2) development of research plans and more than a dozen specific research initiatives in response to Congressional interest in, and incremental funding for, targeted research on autoimmune diseases; and 3) preparation of reports.

The October 2000 Report of the NIH Autoimmune Diseases Coordinating Committee summarized major NIH-sponsored research programs by scientific categories, provided comprehensive data on the FY 1999 NIH investment by individual Institutes and Centers, and within each of 10 scientific categories identified promising research opportunities and highlighted the extensive collaboration of many Institutes and Centers in the development and oversight of research programs.

The Children's Health Act of 2000 (P.L. 106-310) – Title XIX - NIH Initiative on Autoimmune Diseases (see Appendix B for the full text) requires the expansion, intensification, and coordination of Federal activities related to autoimmune diseases. The Act calls for the Autoimmune Diseases Coordinating Committee 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. The Act mandates that elements of the strategic research plan should:

- Provide for a broad range of research and education activities relating to biomedical, psychosocial, and rehabilitative issues and describe the disproportionate impact of such diseases on women.
- Identify priorities within the programs and activities of the NIH regarding autoimmune diseases.

■ Provide for: 1) research to determine the reasons underlying the incidence and prevalence of autoimmune diseases; 2) basic research concerning the etiology and causes of autoimmune diseases; 3) epidemiologic studies to address the frequency and natural history of autoimmune diseases, including differences between the sexes and among racial and ethnic groups; 4) development of improved screening techniques; 5) clinical research for developing and evaluating new treatments; and 6) information and education programs for health care professionals and the public.

The Current NIH Investment in Autoimmune Diseases Research

NIH expenditures for autoimmunity and autoimmune diseases research totaled $435.3 million in FY 2000. Table 1 lists FY 2000 NIH expenditures by Institute and Center, along with expenditures of the Centers for Disease Control and Prevention and the Department of Veterans Affairs (VA), the two other Federal agencies with significant investments in autoimmune diseases research. Figure 1 displays FY 2000 NIH funding by scientific categories, and Figure 2 displays FY 2000 funding by disease or organ system involvement. Major private funding organizations supported an additional $157 million of research in FY 2000, through partnerships with NIH or independently. The President's FY 2003 Budget Request provides $608.6 million for research on autoimmune diseases.

Table 1. Total FY 2000 NIH, CDC, VA Expenditures for Autoimmune Diseases Research See Appendix C for list of acronyms.		
NIH		
	NIAID	$97,591,175
	NIAMS	$93,320,741
	NIDDK*	$84,799,557
	NEI	$47,744,035
	NINDS	$41,612,418
	NHLBI	$22,985,395
	NCRR	$13,847,313
	NCI	$6,397,619
	NIMH	$6,217,859
	NIDCR	$5,399,985
	NICHD	$5,290,852
	NIEHS	$3,621,000
	NINR	$2,803,241
	NIDCD	$2,014,276
	NIA	$853,874
	ORWH	$440,000
	NCCAM	$377,688
NIH	**Subtotal**	**$435,317,028**
VA		$6,514,167
CDC		$10,039,711
Grand Total		$451,870,906

*NIDDK figures do not include special type 1 diabetes appropriation of $27 million.

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Figure 1. NIH FY 2000 Autoimmune Disease Funds
By Scientific Category Code

Animal Models
3.0%
$12.9

Nursing, Behavioral,
Health Services
1.7%
$7.6

Resources
1.1%
$4.8

Not Coded
0.9%
$4.0

Therapy
16.4%
$71.3

Prevention
2.0%
$8.6

Target Organ–
Nonimmune
9.6%
$42.0

Epidemiology/Risk
Factors
4.4%
$19.0

Infectious
Environmental
Etiology
5.9%
$25.8

Genetics
9.5%
$41.3

Pathogenesis/Immune
Dysfunction
45.5%
$197.9
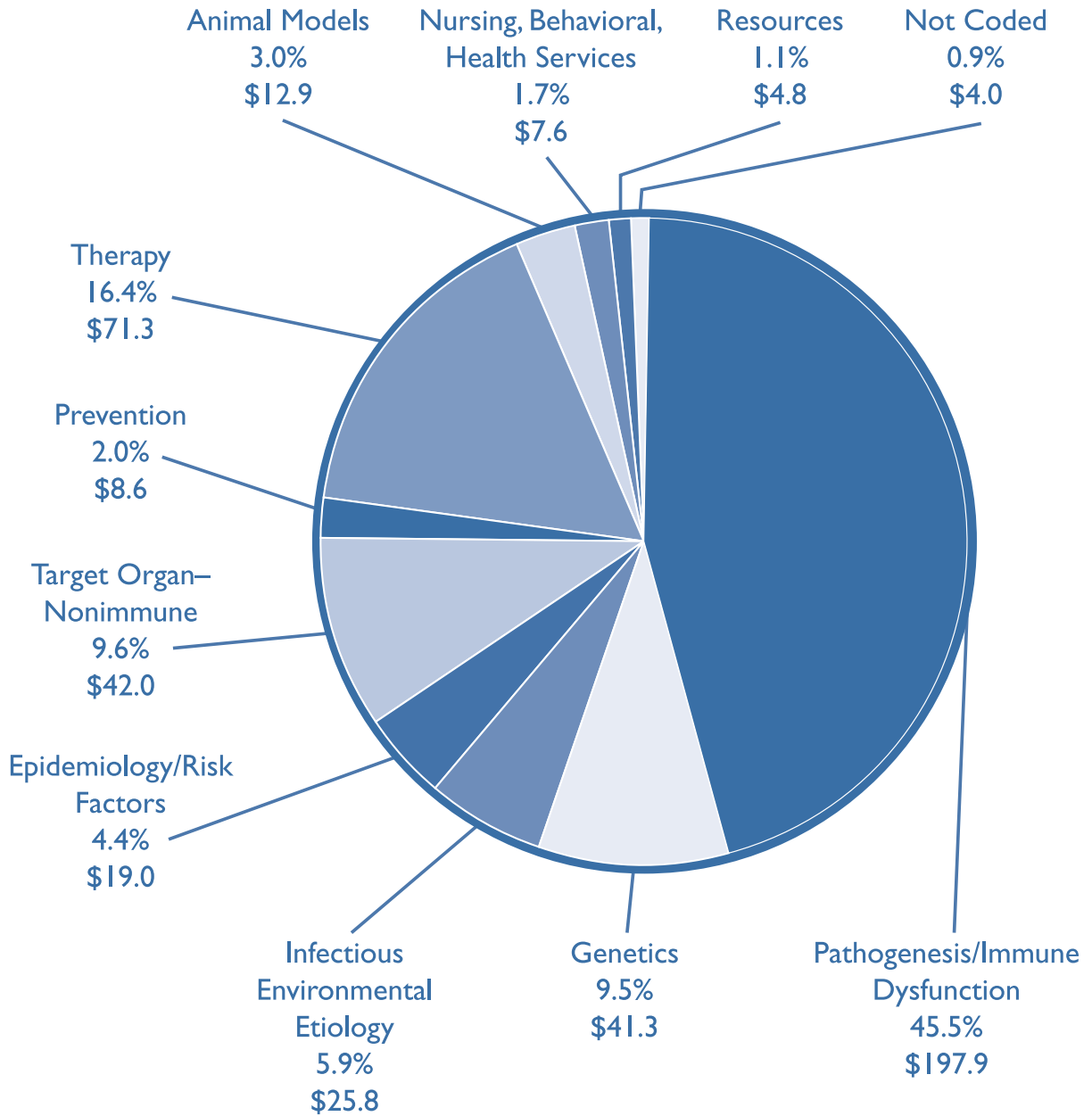
Total NIH FY 2000 Investment = $458.3M
(Dollars in Millions)

Figure 2. NIH FY 2000 Autoimmune Disease Funds
Research by Disease or Organ Involvement
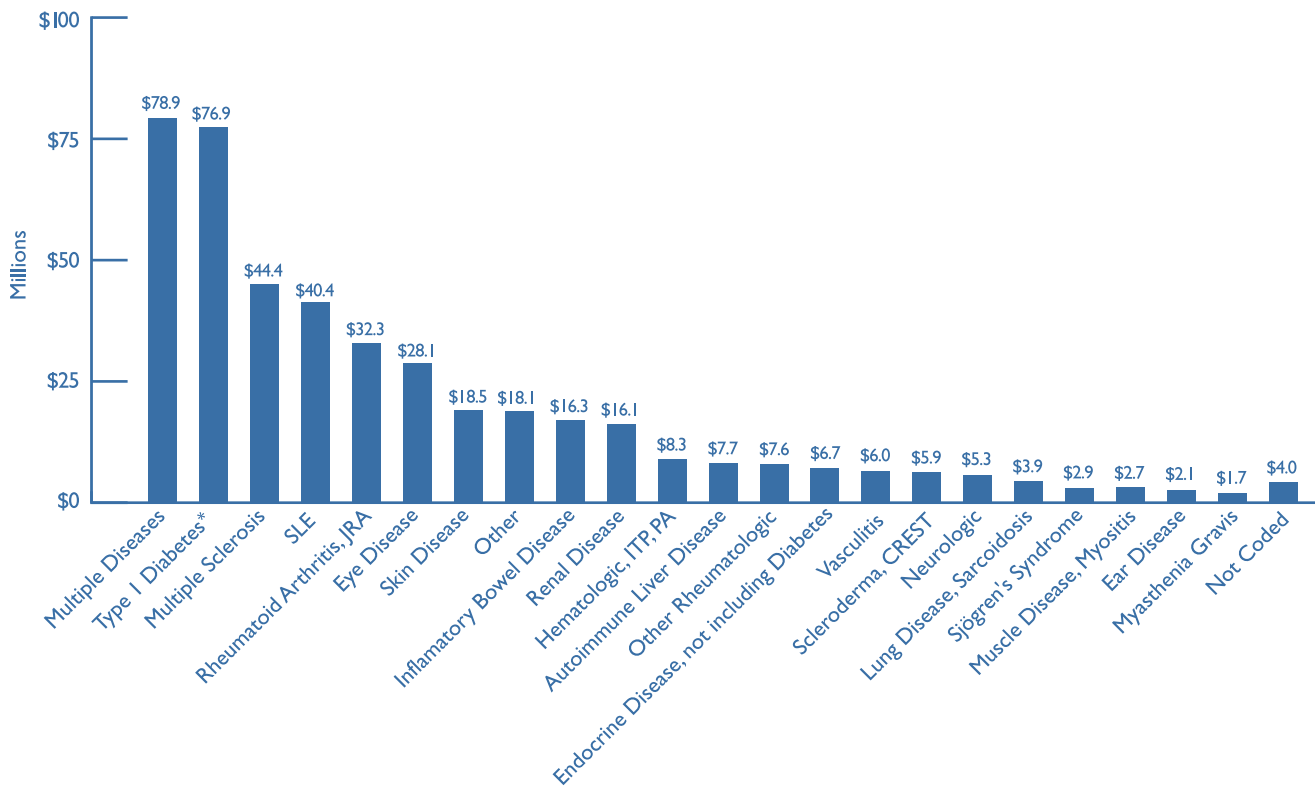
*Figures do not include special type 1 diabetes appropriation of $27 million.

NIH Funding Mechanisms

NIH-supported extramural research includes grants and contracts awarded to medical schools, academic institutions, and other research organizations throughout the United States. Most NIH-funded research is through investigator-initiated, or unsolicited, grants that have been judged to be of extremely high scientific merit and technical feasibility by the NIH two-tiered review system. This peer review system includes initial review groups of scientific experts, as well as National Advisory Councils of each Institute and Center.

The NIH investment in highly productive investigator-initiated research projects over the past two decades has substantially increased our understanding of the underlying immune mechanisms involved in autoimmune diseases and has yielded increased knowledge that can now be applied to improvements in the diagnosis, treatment, and prevention of these serious and chronic disorders. Continued and expanded efforts to support unsolicited research in basic immunology, genetics, and the etiology and pathogenesis of autoimmune diseases will be important to facilitate new insights into the causes and factors associated with these disorders. Capitalizing on promising opportunities to improve the outcomes of patients with autoimmune diseases will require more targeted research programs, carried out under specific solicited research initiatives with dedicated funding. Such initiatives are already underway in multiple areas,

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including: animal model studies to assess the safety and efficacy of promising new therapeutic approaches; the establishment of multi-institutional clinical research programs to evaluate these promising therapies in humans; the development of biomarkers of disease stage, activity, and therapeutic effects; and the use of new and emerging technologies for identifying high-risk populations, as well as patient screening, diagnosis, and management. These solicited research programs are also vital to ensure collaboration among basic scientists, clinical investigators, and individuals from a host of other technological disciplines ranging from bioinformatics to the development of new imaging approaches.

Development and Organization of the Research Plan

The Autoimmune Diseases Coordinating Committee met early in 2001 to establish a process for developing the strategic research plan. The committee convened four working groups (see Appendix A), each responsible for one of the major themes of the plan: Epidemiology and Burden of Disease; Etiology; Diagnosis, Treatment and Prevention; and Training, Education, and Information Dissemination. Over 60 individuals

representing NIH Institutes and Centers, other Federal agencies, the academic research community, and private organizations participated in the working groups. Each working group met on multiple occasions. In January 2002, an advisory panel of non-Federal experts reviewed and contributed to the final report.

Following this introduction are chapters devoted to each of the four thematic areas noted above. Each chapter provides background information intended for an educated lay audience, a summary of existing or planned NIH programs relevant to that thematic area, and priority areas that constitute the recommendations of the Research Plan. The final section discusses implementation of the Plan and the need for centralized management of resources in order to optimize coordination, and it provides a roadmap for collaborations on specific programs and initiatives among NIH institutes, other Federal agencies, and private foundations.

The remaining sections of this report include Appendix A: Acknowledgments; Appendix B: Title XIX of the Children's Health Act of 2000; Appendix C: Acronyms; and Appendix D: Glossary of Scientific and Medical Terms.

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The Burden of Autoimmune Diseases

Introduction

Burden of disease is a general concept encompassing multiple ways in which a disease adversely affects individuals who are ill, their families, work and school life, and the public. Accurate assessments of disease burden require information on the number of affected individuals, duration and severity of disease, and disease outcomes. Such assessments fall within the scope of epidemiology, which uses quantitative methods to characterize the distribution of diseases within a population including information on incidence, prevalence, morbidity, and mortality. These types of rates help to identify and contrast variation in the occurrence and burden of disease within and between populations. Within a population, rates vary over time and by age, sex, race, ethnicity, socioeconomic status, occupation, and geographic location. Variations in rates among groups provide initial insights into conditions that alter disease occurrence and persistence.

Incidence, Prevalence, Morbidity, and Mortality of Autoimmune Diseases

Incidence represents how quickly new cases occur relative to population size and the passage of time. Incidence is calculated as the ratio of the number of new cases of a disease occurring within a population during a given time to the total number of people in the population. For example, there are an estimated 30,000 new cases of type 1 diabetes

in the United States annually, translating to an incidence rate of 10 new cases per year per 100,000 population.

Very limited data exist to estimate the incidence of autoimmune diseases on a national scale. While many published studies estimate incidence of individual autoimmune diseases, most of these estimates are derived from relatively small or geographically limited populations. For example, studies conducted in Olmstead County, Minnesota, an area served by the Mayo Clinic and affiliated providers, yield estimates of the incidence of multiple sclerosis, systemic lupus erythematosus, autoimmune thyroid diseases, and rheumatic fever. However, it is not possible to generalize from these data to the diverse population of the United States.

In a detailed review of the published literature, Jacobsen et al. (Clin Immunol Immunopathol 84: 223-243, 1997) identified 140 studies, published between 1965 and 1995, which include incidence estimates for one or more autoimmune diseases. These studies, conducted in a variety of locations throughout the United States, represent only 24 of the more than 80 known autoimmune diseases. Using data from these reports, Jacobsen et al. estimated that the total number of incident cases of these 24 autoimmune diseases in 1996 would be 237,200 new cases – approximately 172,700 in women and 64,500 in men. These figures translate to an 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. The autoimmune diseases with the highest incidence identified in reviewed studies were rheumatoid arthritis, autoimmune thyroid disease, and uveitis. However, it is likely that these statistics substantially underestimate the incidence of all autoimmune diseases on a national scale. Furthermore, several relatively common autoimmune diseases were not included in this analysis, e.g., psoriasis, ulcerative colitis, and Crohn's disease.

There are other important limitations to currently available data on incidence, including the following:

- Many of the studies on which incidence estimates are based were conducted 20 or more years ago.

- The majority of studies focus on relatively small populations residing in geographically localized areas.

- For most autoimmune diseases, scant information is available pertaining to non-Caucasians.

- Diagnostic criteria used to identify and confirm cases varied among different studies of the same autoimmune disease.

- For many autoimmune diseases, such as Sjögren's syndrome and vitiligo, incidence estimates are lacking altogether; for other diseases, such as myasthenia gravis and Addison's disease, all of the published incidence studies were conducted outside of the United States.

Prevalence is the ratio of all existing cases of a disease within a population at a specified time to the total number of persons in the population. Prevalence provides a measure of the frequency of

disease within a population. A prevalent case is a previously diagnosed case with persistent, unresolved disease attributes, i.e., an individual whose disease is ongoing or in remission, but has not been cured. For example, the prevalence for type 1 diabetes in 1990 was estimated at 1.2 per 1,000 population. Despite its frequent designation as a "rate," prevalence does not describe how quickly new cases of disease are occurring.

Prevalence is a function of both the incidence and duration of disease. In turn, duration is affected by the availability and effectiveness of curative treatments and by survival times of afflicted individuals. For most autoimmune diseases, cure is unusual, and survival is generally measured in years or decades. Hence, the chronicity of autoimmune disease leads to a high prevalence despite a relatively low annual incidence.

Household surveys are commonly used as a method to estimate prevalence. Such surveys involve contacting a random sample within a population and determining for all persons in the sample whether they have a specified disease. Provided the survey population is reasonably

Data on autoimmune diseases are extremely limited and based on small sample sizes and decades-old studies. The current paucity of data most likely results in significant underreporting in estimates of the overall incidence and prevalence of autoimmune disease.

representative, standard statistical methods can then be applied to extrapolate from the survey population to what is likely to hold true for the general population. This approach has been used to estimate prevalence for individual autoimmune diseases including scleroderma and lupus. The National Health Interview Survey involves contacting approximately 40,000 households each year and inquiring about acute and chronic health conditions experienced by household members. However, even a sample of this size is not large enough to accurately measure the prevalence of the less common autoimmune diseases. Most prevalence surveys are also limited by their reliance on self-reporting of disease status rather than a physician-confirmed diagnosis. Self-reporting of autoimmune diseases can result in misclassification and underreporting.

The existing data do not allow for reliable estimates of the prevalence of autoimmune diseases on a national scale. Based on over 130 published studies, Jacobsen et al. (Clin Immunol Immunopathol 84:223-243, 1997) 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 these studies. Prevalences for women and men were 5.0 percent and 1.4 percent, respectively. Despite data limitations, conservative estimates of the prevalence of all autoimmune diseases are in the range of 5 to 8 percent of the United States population – or 14 to over 22 million people.

Morbidity refers to the state of being diseased and the severity and impact of disease. Like prevalence,

measures of morbidity represent the burden that a disease places on a population. In contrast to prevalence, morbidity estimates use more complex approaches that are potentially more informative than a simple count of cases. Commonly used morbidity measures include number of hospitalization days due to a specific disease, number of days lost from work or school, number of physician visits associated with the disease, and days of restricted activity. These measures quantify the impact of a disease and often assess the nonmonetary costs associated with specific disorders.

There are significant limitations to the use of existing databases for estimating morbidity related to autoimmune disease. The National Hospital Discharge Survey provides data on primary and secondary diagnoses and reasons for hospitalization; however, these data are not linked in a manner that allows disease-specific estimates of individual

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> *There are no published studies of morbidity measures for autoimmune diseases in the aggregate, and the available data pertaining to most individual diseases are scant.*

morbidity or correlations between diseases. In addition, few studies have been conducted that examine the accuracy of hospital discharge data pertaining to autoimmune diseases, leaving unknown the true utility of these databases as indexes of morbidity. Furthermore, trends in data on hospitalizations and duration of hospital stays are

potentially misleading because hospitalizations for treatment of autoimmune diseases have decreased significantly as health care services have shifted considerably to outpatient settings. Sampling methods used in outpatient settings, such as those employed by the National Ambulatory Medical Care Survey, are insufficient to capture data on most autoimmune diseases.

Mortality measures deaths caused by a specific disease, deaths resulting from treatment for a specific disease, or deaths in which a specific disease is a contributing factor, but not the primary cause. Mortality is the number of deaths due to a disease during a specific time divided by the number of persons in that population at the beginning of the time period. Hence, mortality is a rate in the sense that it represents how quickly deaths occur relative to population size and the passage of time. It can be interpreted as reflecting the risk of death from a particular cause faced by persons within the population being studied.

As with hospital discharge data, few studies have assessed the accuracy of death certificate data with respect to autoimmune disease.

Only one research study has estimated total mortality from autoimmune disease in the United States. Using the same 24 diseases considered by Jacobson et al., Walsh and Rau (Am J Public Health 90:1463-1466, 2000) identified deaths in women in the United States during 1995, finding that 11,687

deaths from autoimmune disease occurred in that year. Autoimmune diseases were among the 10 leading causes of death for women in every age group up to 64 years of age. This study used data from the National Center for Health Statistics, a component of the CDC, which annually collects data from all death certificates filed in the United States. Only a very small number of studies have used this database to examine individual autoimmune diseases.

Mortality statistics generally reflect the combined effects of factors that: 1) cause the disease of interest; 2) influence the natural history of that disease; 3) influence the existence of effective treatments, access to health care, and adherence to treatment regimens; and 4) affect physician reporting on cause of death. In interpreting and contrasting rates of mortality, it is difficult to know which of these factors accounts for variability from one population to another. Furthermore, many research studies have documented serious problems with the accuracy and completeness of death certificates. This is particularly problematic for disorders that contribute to mortality as comorbid conditions, but are identified infrequently

Very limited data are currently available on racial or ethnic differences in the incidence and prevalence of autoimmune disease. Active surveillance and registry systems are needed to provide this fundamental information about disease patterns and risks.

as the immediate cause of death. As with hospital discharge data, few studies have assessed the accuracy of death certificate data with respect to autoimmune disease.

The Disparate Impact of Autoimmune Diseases: Effects of Age, Sex, Race, and Ethnicity

The majority of autoimmune diseases disproportionately affect women. In some diseases (e.g., thyroiditis, scleroderma, lupus, and Sjögren's syndrome), the disparity is substantial, with females representing 85 percent or more of patients. In other diseases, the difference is smaller; females represent 55 to 70 percent of patients with multiple sclerosis, myasthenia gravis, and inflammatory bowel diseases. The reasons for these gender-based variations are not known.

> **In some autoimmune diseases, women represent 85% or more of those affected.**

Some reports suggest differences in the rates of autoimmune disease among various racial groups, but the impact of racial background varies among individual autoimmune diseases. In the United States, African Americans are at higher risk than are Caucasians for systemic lupus erythematosus and scleroderma, but at lower risk for type 1 diabetes and multiple sclerosis. High rates of certain autoimmune diseases have been reported in certain

Native American groups; e.g., scleroderma in the Choctaw Tribe in Oklahoma and rheumatoid arthritis in Pima Indians. Asian Americans living in Hawaii have one of the lowest rates of some autoimmune diseases (multiple sclerosis and type 1 diabetes). Few data exist on disease rates in Hispanic populations in the United States, with the exception of type 1 diabetes, which appears less frequently in certain Hispanic populations (Diabetologia 28: 734-8, 1985) and more frequently in others (PR Health Sci J 20: 123-30 and 161-4, 2001).

Studies on race and autoimmune disease have focused primarily on genetic differences that may contribute to variations in disease risk, including genes affecting immune response and metabolism. Environmental factors that may be related to both race and risk of autoimmune disease include exposure to infectious agents, nutrition, individual and social stress (such as poverty and racism), and occupational and residential exposures related to residence in areas contaminated by industrial waste.

Disease Registries

Population-based disease registries for autoimmune diseases have the potential for advancing knowledge of epidemiology and etiology, as well as facilitating clinical research of new therapeutic and preventive strategies.

Descriptive Epidemiology. Registries can be important for facilitating research on the descriptive epidemiology of autoimmune disease, particularly when knowledge about sociodemographic and geographic aspects of disease occurrence is lacking. For example, registries established in the 1980's for

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diagnosed cases of type 1 diabetes documented clinical impressions that: the peak age of diagnosis is around the time of puberty; the peak time of diagnosis is during the winter months; rates in males and females are similar; most patients do not have a family history of type 1 diabetes; prevalence varies markedly internationally with the highest rates in Scandinavian countries and lowest rates in Asian populations; and incidence is increasing in some countries, but not in others. However, type 1 diabetes is an exception in terms of the quality and breadth of existing registry-based data. Similar approaches would be valuable for estimating incidence and trends for other autoimmune diseases.

Clinical Research. Many patients with autoimmune disease are seen at tertiary care referral centers where the focus is often on patients with severe clinical manifestations that are not representative of the natural history or typical spectrum of the disease. Therefore, population- or community-based registries generally provide a more representative group for clinical research studies.

Etiologic Research. The natural history of autoimmune disease is likely to involve a long asymptomatic period before clinical diagnosis. Population-based registries, with appropriate consideration of consent and confidentiality issues, can provide access to recently diagnosed patients and can contribute to understanding the risk factors for individual autoimmune diseases, identifying high-risk groups, and adopting appropriate prevention strategies.

Issues in the Design and Implementation of Disease Registries. The success of registries can be attributed, in part, to factors associated with the diseases themselves, public health importance of the disease, and the availability of standardized and validated diagnostic tools. One of the most successful examples is the Surveillance, Epidemiology, and End Results Registries, an extensive system of regional registries supported by the National Cancer Institute. For each region, newly diagnosed cases of cancer and information on patient survival over time are reported to the regional registry. SEER data have been used to estimate the incidence and mortality for various types of cancer, as well as changes over time and geographic and demographic variation in these rates. However, unlike autoimmune disease, registration of cancer cases is based on a solid foundation of relatively definitive radiologic and histopathologic studies with direct communication between pathology laboratories and regional registries. For autoimmune diseases, there is no single clinical or laboratory event equivalent to histopathologic identification of malignancy.

Other successful surveillance programs are currently in place for tracking reportable infectious diseases. State health departments, following guidelines issued by the Centers for Disease Control and Prevention, maintain lists of notifiable diseases. When a disease is so designated, physicians and clinical laboratories are required by law to report new cases to a local or State health official. The value of this approach is in detecting outbreaks and in identifying and tracking contacts. A similar rationale, based on the

Personal Profile

Liane Mark

Miss Waikiki 2001—Miss Downtown Honolulu 2002
First Runner Up Miss Hawaii 2001

The beautiful jazz vocalist, Miss Mark, was chosen Miss Downtown Honolulu 2002 and also named as one of Hawaii's three outstanding young persons of 2001. A cum laude graduate of Yale University with a B.A. in theater studies and psychology, she plans to earn a master of fine arts in acting and a master's degree and a doctorate in psychology. Liane was diagnosed with multiple sclerosis (MS) in February 2001.

After winning the Miss Waikiki Pageant in January 2001, she complained to her dad that her feet, accustomed to flip-flop slippers, had been terribly abused by the towering 4^1/$_2$-inch heels she wore for the pageant. Her feet felt numb and tingly. At first she thought it was nothing more than feet rebelling against torturous footwear, but the annoying sensation didn't go away and over the course of a month, it spread up her legs and torso and then to her hands. When she finally went to see a doctor, she was immediately referred to a neurologist, who hospitalized her for 5 days of testing.

A wise tea drinker once observed that people are like tea bags—you have to put them in hot water before you know how strong they are. At first, Liane was too numb and scared to even cry, and then she was too determined to find out everything about the disease and its treatment to remain so. A call the next day to the National MS Society, and to some friends, soon produced stacks of information at her bedside. The information encouraged her to take immediate action and begin therapy with the medication beta-interferon 1a, one of at least three treatments approved by the FDA that can now affect underlying disease process and help control MS and its progress.

Though Liane's symptoms so far have been mild, despite the fact that her MRIs showed extensive lesions on both sides of her brain and a big lesion that goes up and down her spine, she has been lucky enough to be able to maintain a full schedule of activities, including preparations for the 2002 Miss Hawaii Pageant. She hasn't had to, and certainly doesn't intend to, give up her dreams!

Because of her experiences, she has made it her mission to promote early diagnosis and treatment of MS. Liane is confident that there will be a cure for multiple sclerosis in the not-too-distant future.

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importance of protecting public health, could not be invoked for noncommunicable disorders such as autoimmune disease.

Ideally, registries should support comprehensive, multidisciplinary approaches to analyze relationships among autoimmune diseases and their association with malignancies and immune deficiency syndromes.

Current Research Investment

The CDC, NIH, and private foundations currently support a range of autoimmune disease research related to the epidemiology and burden of disease. Many of the currently funded registries are not population based and have been designed to address particular research questions. Examples of currently-funded research include:

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 southeast United States are recruiting African Americans to join the registry.

DAISY (Diabetes Autoimmunity Study in the Young) is a longitudinal study of two cohorts: 1) healthy siblings and offspring of persons with type 1 diabetes, and 2) healthy newborns with type 1 diabetes-associated MHC genes who lack a family history of diabetes. The study is collecting and analyzing data on infections, vaccination, diet, MHC genes, and autoantibodies to beta cell antigens in these cohorts.

The Research Registry for Neonatal Lupus provides material for basic research on the causes of this disease. It is hoped that the registry will facilitate improved methods of diagnosis, as well as prevention and treatment. The registry tracks important data such as recurrence rates in subsequent pregnancies and facilitates family counseling.

The 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.

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 concerned with diagnosis and treatment. 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.

The National Epidermolysis Bullosa Registry focuses on the underlying causes, improving methods of diagnosis, and developing effective methods of treatment and prevention. Over 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.

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The New Onset Juvenile Dermatomyositis Registry collects, characterizes, and makes available to the research community cases of new onset juvenile dermatomyositis and investigates geographic and seasonal clustering of new cases.

The 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.

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 (SLE). SLE is an autoimmune disease that adversely affects women, especially African American women. Reasons for the African American excess risk are not known. The National Institute of Environmental Sciences and the National Center on Minority Health and Health

Disparities have joined together to support this examination of hormonal, occupational, and environmental risk factors in a previously understudied population. These efforts may help illuminate etiological 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 disease risk will also be assessed.

SEARCH is developing a uniform, population-based approach to ascertainment of type 1, type 2, and other forms of diabetes in a population of approximately 5 million children. SEARCH centers are expected to have access to about 7,000 prevalent cases and 800 incident cases of diabetes per year over a 5-year period. The majority of cases are expected to be type 1 diabetes. SEARCH is led by the Centers for Disease Control and Prevention and co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases.

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Components of the Plan

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 nongenetic 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.

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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.**

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The Etiology of Autoimmune Diseases

Introduction

Knowledge of the causes and origins (etiology) underlying autoimmune diseases allows for the design of prevention strategies and the development of targeted treatment approaches that have the potential for increased efficacy and minimal toxicity. Many observations support a role for genetics, infectious and non-infectious environmental factors, hormones, and the immune response in the pathogenesis of these diseases. Ultimately, understanding the pathogenesis of one disease may provide insights into the mechanisms operating in others.

Immune Dysfunction

The principal role of the immune system is to defend against infection, a function that depends on the ability to destroy pathogens and toxins while, at the same time, not attack the body's own tissues. Understanding the natural processes by which the body prevents the immune system from attacking itself is enabling investigational studies of new approaches to treat and prevent autoimmune disease.

The safeguards that the immune system naturally possesses to protect from harming self are collectively termed "immune tolerance." Central tolerance is the process by which potentially autoreactive immune system cells are eliminated before they mature into active cells and enter the circulation. Central tolerance of immature B and T cells (two types of lymphocytes) occurs in the primary lymphoid organs (bone marrow and thymus) during the process of maturation. This process is "leaky," and T and B cells capable of reacting against self-tissues are found in the blood of every individual. Peripheral tolerance is the process by which these cells are controlled so as not to damage tissues; peripheral tolerance constitutes the major mechanisms to control autoreactive cells.

Three distinct processes are used to control these dangerous cells in the periphery: 1) elimination, 2) inactivation, and 3) regulation of such cells. Activation of self-reactive immune cells requires several steps. If cells are stimulated without other important survival or activation signals, they die or may survive in an unresponsive state, called anergy. Synthetic blockers of the molecular pathways needed for complete T and B cell activation are currently being tested. Each of these agents blocks a particular part of the costimulatory pathway preventing activation of T cells. These agents have been used successfully for treatment and prevention in animal models of autoimmune diseases and are now in clinical trials in humans. The third mechanism of peripheral tolerance is through regulatory T cells that block the activation of autoreactive cells in their vicinity. Current thinking holds that regulatory cells may be defective in autoimmune diseases, a topic only now beginning to

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be studied in the clinic. Many studies have defined a role for regulatory cells in the control of self-reactive T cells in animal models of type 1 diabetes, multiple sclerosis, and Crohn's disease. Recent data suggest that other regulatory immune cells may control autoimmune disease by preventing the migration of pathogenic T cells into target organs. Additional regulatory cell populations can release substances called cytokines that counteract tissue-destructive inflammation induced by self-reactive cells. Researchers are only beginning to grasp the complexity of regulatory cell control of autoimmune responses. By understanding how to induce regulatory responses, it may be possible to prevent autoimmune diseases as well as treat them.

Autoreactive B lymphocytes can produce antibodies against self-tissues, called autoantibodies. Antibodies normally help the body eliminate foreign invaders such as bacteria. However, when antibodies are directed against the body's own tissues, they can initiate inflammatory processes that lead to destruction of tissues and organ failure. These autoantibodies are the major mechanism by which some autoimmune diseases, including myasthenia gravis and systemic lupus erythematosus, cause dysfunction. Autoantibodies may be present but are less important in other diseases where the damage is caused by T lymphocytes, such as type 1 diabetes and multiple sclerosis. Measurement of autoantibodies is frequently used in the diagnosis of disease, and certain therapeutic approaches target the elimination of disease causing autoantibodies.

The immune system produces a number of soluble mediators, called cytokines or chemokines. These mediators, when present in the tissues, through interaction with their receptors present on other immune cells or other types of cells and tissues, influence the type of immune response that develops. Information about the identity and role of these mediators and their receptors continues to grow. Treatment with a number of recombinant mediators or agents that block their actions are entering treatment and prevention trials and biologics that block the activity of one such mediator (tumor necrosis factor-α TNF-α) are licensed for rheumatoid arthritis and Crohn's disease. Other inflammatory mediators, including prostaglandins, complement proteins, and acute phase response molecules, are also capable of activating or amplifying an autoreactive immune response. Agents that modulate these mediators are also being developed for use in autoimmune diseases.

The mucosal barriers of the respiratory, gastrointestinal, and genitourinary tracts and the specialized immune cells found in these tissues represent the first sites of contact with pathogens, bacterial commensals, and benign foreign materials, including food and sperm. Understanding the normal mechanisms leading to immunity and tolerance to these materials may lead to new approaches to induce tolerance to self. In animal models, presentation of self-proteins, or peptides, by the oral/mucosal route can induce oral tolerance and prevent autoimmune diseases. Several human clinical trials are ongoing, including a large multicenter trial of oral insulin to prevent or delay the onset of type 1 diabetes.

Genetics

Evidence for the importance of genes in the etiology of autoimmune diseases has been provided by studies showing that 1) identical twins are more likely to suffer from the same autoimmune disease than fraternal twins; 2) relatives of patients with autoimmune diseases are at higher risk for development of the same or another autoimmune disease; and 3) certain races or ethnic groups are disproportionately affected by particular autoimmune diseases. In both human and animal models, studies suggest that multiple genes are involved in conferring either susceptibility to, or protection from, autoimmune disease and that specific autoimmune diseases may share a set of susceptibility genes. In contrast to an inherited disease such as cystic fibrosis that results from a disease-causing mutation in a single gene, the inherited genes involved in autoimmune diseases do not individually lead to disease but in combination determine susceptibility to one or another autoimmune disease.

> *Specific autoimmune diseases may share a set of susceptibility genes.*

Particular genes within the major histocompatibility complex, a family of genes that regulate immune responses, are associated with susceptibility to type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus. Other genes that play a role in immune function are under active investigation for association with autoimmune diseases, including those for cytokines, cytokine receptors, and other regulators of the immune response.

Multiple studies have identified the general location of several regions on different chromosomes that are associated with autoimmune disease susceptibility, but have not identified the specific gene(s) or gene families within these regions. Recently developed tools will greatly facilitate studies to narrow these regions and determine their importance. The mouse and human genomic maps will greatly aid in finding specific genes in these susceptibility regions.

Studies of the genes involved in animal models of autoimmune disease are as important as studies of humans. Selective breeding, which isolates particular regions that are associated with autoimmune disease susceptibility, and genetic engineering can be performed only in animals. Once disease susceptibility genes are identified in animals, related genes can be examined in humans for their role in autoimmune diseases. This parallel path is likely to allow researchers to more quickly identify genes and families of genes involved in autoimmune diseases. The interaction of genes is more easily studied in animals and may offer insights valuable in understanding genetic interactions in humans.

The identification of a gene involved in Crohn's disease illustrates how genetic research builds upon advances in related fields. Susceptibility to this disease was linked first to chromosome 16 and then to a specific locus on this chromosome, designated as IBD1. Recently, two groups using

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Personal Profile

ARE ALL MY FAMILY'S DISEASES CONNECTED?

Kathy Morland Hammitt

When my sister was diagnosed as having Meniere's, an autoimmune disease that affects the middle ear and causes vertigo, my family and I were amazed to learn how little was known about the disorder and how few treatments were available. Then a diagnosis of lupus followed that of Meniere's. We learned more. Could they be connected?

At the time, some doctors thought they could; others did not. I myself had suffered from swollen parotid glands (known as the "mump" glands) for years and was often the brunt of jokes in the newsroom where I worked because I particularly swelled up around cigarette smoke. I went from doctor to doctor, but no one could explain the reason.

When my daughter was born, I developed a low-grade fever that wouldn't go away, joint and muscle pain, and an incredible fatigue that I could only describe as the bone-tired feeling one has when one's pregnant. I thought, "Having fatigue confined to the months of pregnancy is hard enough, but who wants to feel that way for a lifetime?" When my daughter was 18 months old, I was finally diagnosed with Sjögren's syndrome. I was also suspected of having non-Hodgkins lymphoma, which occurs with greater frequency in autoimmune diseases and in particular Sjögren's syndrome, and we continue to watch for its possible development. Because I was positive for autoantibodies that can cause fetal heartblock, my husband and I lived in as much fear for the welfare of our second child as joy. It would be years before I developed the devastating dryness that is considered the hallmark symptom of the disease. Over the years, I developed many autoimmune symptoms and disorders, some of which can be considered separate disorders and occur on their own but can also occur as a part of Sjögren's. I have Raynaud's, antiphospholipid antibody syndrome, vaculitis, purpura, and debilitating neuropathies.

Then my sister developed autoimmune thyroid while another developed autoimmune symptoms that have yet to be definitely diagnosed. Was my family really struck unfairly out of the blue? Can one person really have all these multiple disorders? As research has progressed, we've learned about the tremendous overlap and genetic propensity of autoimmune disorders and symptoms. I've also learned that I am not alone: I have autoimmune disease, and the name mine has been given is Sjögren's syndrome. Relatives from earlier generations might or might not have suffered from autoimmune disease. Could the great aunt who was always referred to as a hypochondriac have had autoimmune disease? Possibly. Our diagnostic tools and knowledge have improved tremendously. Drugs that specifically target Sjögren's syndrome are coming on to the market for the first time as we cross into a new century. For the first time, I have hope for my sisters, myself, and most of all, for my children.

different methods identified a specific susceptibility gene, NOD2, in this region. NOD2 is also associated with lupus, psoriasis, and type 1 diabetes, providing further evidence that individual genes may predispose to different autoimmune diseases.

Environmental Factors

The concordance of autoimmune disease in identical twins is frequently less than 50 percent and is often in the 25 to 40 percent range. This observation supports the idea that the etiology of autoimmune disease involves both genetic and environmental factors. Various exogenous environmental factors, including infectious agents and chemical toxins, have been associated with the development of several autoimmune diseases.

Infectious Agents

Infectious agents are suspected triggers or modulators of autoimmune diseases. The classic example is streptococcal infection leading to development of an autoimmune cardiomyopathy. In addition, chronic reactive arthritis (Reiter's syndrome) follows a variety of infections that

Table 2. Selected Infectious Etiologies of Autoimmune Diseases

Autoimmune Disease	Proven or Postulated Infectious Etiology
Reactive arthritis (also called Reiter's syndrome)	*Chlamydia trachomatis, Salmonella, Shigella, Yersinia, Campylobacter jejuni*
Ankylosing spondylitis	*Klebsiella*, other bacteria
Crohn's disease	*Mycobacterium avim, paratuberculosis sbsp*, enteric bacteria, *Yersinia, Listeria*, other microbes
Diabetes mellitus, type 1	*Coxsackie virus, Rubella virus*, other enteroviruses, other viruses
Lyme arthritis	*Borrelia burgdorferi*
Guillain-Barré Syndrome	*Campylobacter jejuni*
Multiple sclerosis	*Human herpes virus 6* [HHV-6], *Chlamydia pneumoniae, Epstein-Barr virus*, other viruses and bacteria
Wegener's granulomatosis	*Staphylococcus aureus*
Cardiomyopathy	*Coxsackie B virus*, other enteroviruses, other microbes
Uveitis or retinitis	*B. burgdorferi, Toxoplasma gondii*
Vasculitis (e.g., polyarteritis nodosa, small vessel vasculitis, cryoglobulinemia)	*Hepatitis B virus, Hepatitis C virus*, other viruses

include sexually transmitted *Chlamydia trachomatis* as well as gastrointestinal *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter.* The frequency of reactive arthritis following either symptomatic or asymptomatic infection has not been established across geographic regions and racial/ethnic groups in the United States population. A pilot, prospective, population-based study sponsored by the CDC of incident and persistent reactive arthritis following documented enteric infections is underway at two state FoodNet sites. Guillain-Barré syndrome, an acute autoimmune demyelinating polyneuropathy, has been associated with viral or *Campylobacter jejuni* infections. Other examples include the epidemiologic association between type 1 diabetes mellitus and various infectious agents, including rubella and Coxsackie viruses. The increased incidence of the disease in the winter and spring supports an association with common respiratory infections. Table 2 provides a partial list of proven or postulated infectious causes of some autoimmune diseases.

The mechanism by which infectious agents may trigger or modulate the autoimmune process is not clear. Molecular mimicry, in which the immune cells that develop in response to pathogen infection cross react with normal self-tissues leading to autoimmunity, has been shown only in an animal model of autoimmune keratitis. Another mechanism has been proposed, in which the immune response to a pathogen leads to the production of mediators that then damage normal tissues. Further, it is not clear that an infectious organism must be continuously present to induce autoimmunity; in some settings it appears more

likely that an organism may induce autoreactive responses that then become self-sustaining. A role for superantigens, antigens found on bacteria or viruses that can activate a large number of T cells nonspecifically, also has been suggested. New technologies that allow detection of pathogens at low levels are being developed, as are techniques that may allow for the detection of past infection. Application of these technologies to the study of autoimmune diseases may lead to new prevention or treatment approaches.

The age at which the infection occurs may also influence the development of autoimmune disease. Some hypotheses suggest that infection at a later age (in later childhood or after childhood) predisposes the individual to abnormal immune consequences of infection, whereas other hypotheses focus on infection in the prenatal or neonatal stages as the critical event or time period. Others suggest that an initially normal immune system attacks self-tissues only after repeated infections or in the presence of persistent infection.

Genetic factors also contribute to susceptibility to autoimmune disease following infection as only a small number of persons who are infected with various viruses or other microbes develop autoimmune disease. Gene-environment interactions may be the key to proposed associations between type 1 diabetes and *Coxsackie virus*/enteroviruses or to the notion that infectious agent(s) may be causally related to the development of multiple sclerosis, rheumatoid arthritis, and numerous other autoimmune diseases.

Chemicals and Toxins

Relatively few studies have been conducted on the relationship between occupational exposure to chemicals and toxins and development of autoimmune disease. Most likely, this reflects the tendency of autoimmune diseases to disproportionately affect women, and occupational exposure assessment techniques are not as well developed for women as for men.

> **Increased coordination and communication between experimental researchers and epidemiologic researchers is critical for timely advancement.**

Exposure to mercury has been shown to cause autoimmune disease in both humans and animals. Few epidemiologic studies have been conducted of occupational exposures to other metals in relation to specific autoimmune diseases. Epidemiologic studies suggest a possible link between solvents and a variety of autoimmune diseases, but such an association remains speculative. Increased communication and coordination between the disciplines of epidemiology and immunology are needed to fully explore these associations.

The experimental and epidemiologic literature relating to crystalline silica (quartz) exposure and autoimmune disease is quite extensive. Silica has a strong adjuvant effect on immune responses, resulting in increased proinflammatory cytokine

production and immune cell activation. Studies of highly exposed individuals (such as miners, granite workers, and silicosis patients) have shown strong associations (a relative risk of 3.0 and higher, with some studies reporting more than a tenfold increased risk) with rheumatoid arthritis, scleroderma, lupus, and glomerulonephritis. Improved exposure assessment techniques, designed specifically to assess low to moderate exposures (particularly in women), are needed.

Lifestyle Factors

Lifestyle factors contribute to the development or progression of autoimmune disease. For example, nutritional factors that affect immune function and the interaction 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 have delayed onset of symptoms or prolonged survival with antioxidant supplementation or with reduction in total fat and caloric intake and manipulation of the fatty acid content (for example, omega-3 fatty acids) of the diet. The potential role of diet in the development and treatment of 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 systemic lupus erythematosus. 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 diseases and why different effects are seen across the spectrum of diseases.

Sex Differences

Differences in the immune response of men and women may be related to sex hormones, such as androgens and estrogens. However, the effects of these hormones on specific immune responses are less clear. Estrogens can stimulate B cell growth and antibody and cytokine production and, therefore, may be important stimulators of B cell immunity and may play a role in increased susceptibility to autoimmune disease. Understanding the role of estrogens and other hormones in autoimmune disease is particularly important in light of the increasing number of people exposed through medical interventions or unintentionally to a wide range of synthetic chemicals that have estrogenic or anti-estrogenic activity. These include hormone supplementation, pesticides, insecticides, fungicides, and foods and herbal products.

> **Basic research on the role of hormones in modulating the immune system is needed.**

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 through interactions with specific cell-surface hormone receptors. Alternatively, they may mediate their effects through modulation of the hypothalamic-pituitary-adrenal/gonadal axes. It will be important to explore these factors in more detail and to determine whether additional sex-based differences in neuroendocrine function contribute to autoimmune disease.

Many autoimmune diseases occur most often before puberty or after menopause, suggesting that changes in hormone levels may be an overly simplistic explanation for the sex differences in the incidence of these diseases. In some autoimmune diseases affecting children (such as type 1 diabetes), the sex ratio is fairly even; however, females predominate in other juvenile autoimmune diseases. Additional explanations for female predominance in autoimmune disease should be explored and should address the variation in age- and sex-specific patterns in the incidence of specific autoimmune diseases.

Microchimerism is defined as the presence in an individual of a population of cells derived from another human being. Cells pass from mother to fetus and vice versa during pregnancy. After pregnancy, some of these cells may remain – some maternal cells remain in the child and some fetal cells remain in the mother. Several researchers reported the presence of fetal progenitor cells in women with scleroderma and advanced the notion that the persistence of microchimerism allows the

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development of autoimmune disease. However, it is still not known whether fetal cells have a causal role in the etiology of autoimmune disease.

Scientific Accomplishments

- Recognition that regulatory T cells modulate the immune response to self-antigens.

- Identification of the importance of the innate immune system in immune response to self.

- Identification of overlapping genetic susceptibility regions in multiple autoimmune diseases.

- Increased understanding of the interaction of the T and B cells in tolerance to self.

- Recognition that non-protein antigens may be involved in autoimmunity.

Current Research Investment

The NIH supports a large number of investigator-initiated research grants studying basic mechanisms of autoimmunity and various autoimmune diseases, including studies of the genetics, immune mechanisms, and role of environmental agents. Studies of human and animal models are supported. Several recent initiatives and ongoing programs are cited below.

Sex-Based Differences in the Immune Response. This initiative focuses on the identification, characterization, and definition of differences in the immune response between males and females, supporting multidisciplinary research of sex-based differences that may be important in autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and scleroderma. The National Institute of Allergy and Infectious Diseases, National Institute of Neurological Disorders and Stroke, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Office of Research on Women's Health, NIH, and the National Multiple Sclerosis Society cosponsor this program.

Environment/Infection/Gene Interactions in Autoimmune Disease. This initiative supports innovative basic or population-based research to determine the role of environmental and infectious agents in the initiation and/or exacerbation of autoimmune diseases, including the role of exposure in development of disease and the interaction of genetic, hormonal, and environmental factors. The National Institute of Environmental Health Sciences, National Institute of Allergy and Infectious Diseases, National Institute of Child Health and Human Development, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Office of Research on Women's Health, National Institute of Child Health and Human Development, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, National Eye Institute, National Heart, Lung, and Blood Institute, and National Institute of Mental Health cosponsor this program.

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Target Organ Damage in Autoimmune Diseases. This initiative supports research on the genetic basis and molecular pathways of target organ damage in rheumatic and autoimmune diseases. The National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Allergy and Infectious Diseases, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, National Institute on Deafness and Other Communication Disorders, National Eye Institute, National Heart, Lung, and Blood Institute, National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, and Office of Research on Women's Health, NIH cosponsor this program.

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Multiple Autoimmune Diseases Genetics Consortium (MADGC). This consortium of investigators is collecting over 100 families that include at least two members with at least two different autoimmune diseases. This resource of clinical data and repository of immortalized cells and serum samples is available to investigators to identify and characterize those genes that predispose to autoimmunity and autoimmune diseases.

The International Histocompatibility Working Group (IHWG). The IHWG supports development, standardization, and distribution of highly sensitive reagents for tissue typing, worldwide. These efforts enhance identification of healthy individuals at risk for development of certain autoimmune disorders.

The North American Rheumatoid Arthritis Consortium is a national repository dedicated to the collection and characterization of sibling pairs with rheumatoid arthritis. The goals of the registry are to collect at least 1,000 families in which two or more siblings are afflicted with rheumatoid arthritis and to search for genes that predispose to rheumatoid arthritis with the ultimate goal of understanding the cause of this disease, leading to better diagnosis and treatments.

The Research Registry for Juvenile Rheumatoid Arthritis supports the collection of data on multicase families with affected sibling pairs and the development of a related genomics program to identify all of the susceptibility genes.

The Lupus Registry and Repository supports a core facility dedicated to the collection and characterization of multiplex lupus pedigrees. Clinical information, genotypes at over 300 loci, and family relationship structure are available from 102 pedigrees containing 592 family members. An additional 25 pedigrees are made available each succeeding year. Limited amounts of DNA, plasma, and serum are also available from these pedigrees.

Autoimmunity Centers of Excellence. This cooperative program includes four research centers to support 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 subspecialists (e.g., neurologists, gastroenterologists, and rheumatologists), as well as basic scientists, to increase collaboration in autoimmunity research. This group is currently

conducting clinical trials of immune modulating therapies in systemic lupus erythematosus and multiple sclerosis, with trials in type 1 diabetes planned. The National Institute of Allergy and Infectious Diseases and multiple NIH Institutes and Offices support this program.

Innovative Research on Human Mucosal Immunity. The Crohn's and Colitis Foundation of America joined the National Institute of Allergy and Infectious Diseases and the National Institute of Dental and Craniofacial Research in sponsoring this FY 2000 research initiative to promote innovative investigations of the human mucosal immune system and its role in the pathogenesis of autoimmune diseases, including inflammatory bowel disease.

Type 1 Diabetes Mouse Animal Models are being made available to investigators through two repositories. The NIDDK has established a repository at the Jackson Laboratories to maintain and distribute at least 150 mouse strains important to research on the pathogenesis of type 1 diabetes. The NIAID with the Welcome Trust and Merck Foundation are transferring all the Wicker/Todd

congenic NOD mouse strains to Taconic where they will be available to investigators. Many of these mice have proven to be useful in study of several autoimmune diseases in addition to type 1 diabetes.

Innovative Partnerships in Type 1 Diabetes Research. This initiative to support collaborations between investigators who focus their research efforts on type 1 diabetes or its complications and researchers from other research areas with expertise relevant to type 1 diabetes research was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, the National Eye Institute, the National Institute of Nursing Research, and the National Heart, Lung, and Blood Institute. The purpose of this RFA was to attract new research talent to type 1 diabetes research, strengthen the ongoing efforts of type 1 diabetes researchers by providing access to specialized expertise or technologies relevant to their research, and facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes.

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Components of the Plan

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 leucocyte 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

Introduction

Autoimmune diseases are a heterogeneous group of chronic disorders with different natural histories and a wide range of clinical symptoms. Individuals with the same autoimmune disease exhibit distinct clinical phenotypes and variability in the course of their disease. Despite these differences, many autoimmune diseases appear to share underlying immunologic mechanisms and the potential to respond to treatment with the same, or related, therapeutic agents. Important advances of the past decade include the development of more selective and less toxic immunosuppressive and immunomodulatory agents and the identification of promising approaches for the induction of immune tolerance. Improved knowledge of the etiology and natural history of autoimmune disorders and the clinical staging of patients will be important in evaluating new immune-based therapies in clinical trials and in bringing safe and efficacious treatments into the clinic. The recommendations in this area provide many opportunities but will require a new infrastructure to accelerate clinical application of new findings.

Natural History and Progression of Autoimmune Diseases

The natural history of disease refers to the course of disease over time, unaffected by treatment. In autoimmune diseases, biologic onset precedes the development of clinical symptoms, often by months

> **In autoimmune diseases, biologic onset precedes the development of clinical symptoms, often by months or years.**

or years. The point at which a person is considered "diseased" is somewhat arbitrary and depends on the sensitivity and specificity of diagnostic tools. Furthermore, many autoimmune diseases follow a course of alternating exacerbations and remissions, but with progressive deterioration even under treatment. For example, approximately 85 percent of patients with multiple sclerosis begin with a relapsing and remitting pattern of disease that may be ameliorated by a number of recently licensed agents. Relapses are characterized by acute attacks of neurologic symptoms, such as blurring of vision, numbness or tingling of body parts, or loss of coordination. Relapses may be followed by periods of stability and finally by partial or complete recovery. This relapsing-remitting pattern repeats at varying intervals, compounding the difficulties in diagnosis and clinical staging.

Multiple or progressive organ system involvement can complicate the pattern of alternating exacerbation and remission. For example, in systemic lupus erythematosus, the joints, skin, kidneys, and central nervous system may be affected together or individually. Rheumatoid arthritis involves primarily the joints, characteristically beginning in the small joints of the hands and feet

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and progressing to the larger joints later in the course of disease. Some patients have brief periods of acute arthritis followed by low-grade activity, whereas others have sustained progression of active disease. Remission rates for rheumatoid arthritis are 5 to 7 percent, with a median remission duration of ~10 months. Alternating periods of remission and exacerbation, characteristic of many autoimmune diseases, have implications beyond those related to the physical condition of the patient. Psychological health, ability to work, and eligibility for public and private disability programs can also be affected by these patterns.

Lack of standardized disease definitions and accurate diagnostic tools are major impediments in natural history studies. For example, reviews of the natural history of rheumatoid arthritis showed significant discrepancies between population-based studies and rheumatology clinic-based studies. Population-based studies, in which less stringent disease criteria are used, suggest little evidence for persistent disease after 5 years in 75 percent of patients. A far worse prognosis is seen in clinic-based studies where after 10 years of followup, most patients present a picture of marked disease progression.

At present, the factors that can affect the course of autoimmune disease are not fully understood. In diseases with periods of remission and exacerbation, relatively little is known about specific environmental triggers involved in the transition between states. Older age of onset appears to be associated with slower progression of type 1 diabetes and with a more favorable prognosis in rheumatoid arthritis. In addition, sex is not only a

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> *Increased knowledge of the natural history of autoimmune disease will allow for earlier and more accurate recognition, diagnosis, and staging of patients, leading ultimately to more effective treatments and improved outcomes.*

susceptibility factor for many autoimmune diseases but may also affect disease course. For example, although women are more likely than men to suffer from autoimmune disease, recent analyses suggest that men with multiple sclerosis experience increased acceleration of disease and increased mortality compared with women. Evidence from a variety of studies implicates a role for sex hormones in modulating the course and severity of certain autoimmune diseases. For example, clinical remissions often occur during pregnancy in multiple sclerosis and rheumatoid arthritis, whereas disease activity is increased postpartum. In contrast, pregnancy may either precipitate or ameliorate symptoms in patients with lupus.

Increased knowledge of the natural history of autoimmune diseases will allow for earlier and more accurate recognition, diagnosis, and staging of patients, leading ultimately to more effective treatments and improved outcomes. For example, in relatives of patients with type 1 diabetes, a combination of genetic markers, antibody assays, and metabolic testing can identify individuals at high risk for development of disease and can be used to assign probabilities that an individual will develop

clinical disease within a period of 1 to 5 years. However, type 1 diabetes is an exception in terms of the availability of validated tools for preclinical identification and staging. In contrast, detection and characterization of patients in the preclinical period remains a serious limitation in the management of patients with most other autoimmune diseases.

Diagnosis of Autoimmune Diseases

Diagnosis of most autoimmune diseases is complicated by the absence of signs and symptoms specific for a given autoimmune disease and the lack of validated and standardized diagnostic criteria and biomarkers of early disease. For example, patients with lupus may present with arthralgias, fatigue, rash, psychiatric syndromes, or renal failure, while patients with multiple sclerosis may present with symptoms shared by a variety of infectious diseases, trauma, or malignancy. Patients frequently present with only a subset of the clinical signs that may be associated with a particular disease. Many of these patients will progress over time to manifest additional signs and symptoms leading to a definitive diagnosis, while others will not. Definitive diagnosis of autoimmune diseases can be a lengthy process that requires repeated evaluation and monitoring over time.

> *Definitive diagnosis of autoimmune diseases can be a lengthy process that requires repeated evaluation and monitoring over time.*

Professional societies have developed classification criteria for several autoimmune diseases. Although these classification criteria have generally been developed for use in clinical trials, they have also proved useful as guidelines for practicing physicians. For example, the American College of Rheumatology has developed classification criteria for rheumatoid arthritis, lupus, and several other rheumatologic diseases. These criteria are developed through an established procedure involving the publication of draft criteria representing the consensus of a group of medical experts and a validation process in which physicians throughout the country classify clinical cases using these criteria. Criteria for the diagnosis of multiple sclerosis have been developed through consensus among experts in the field and have recently been revised by consensus of an international panel. For the first time, magnetic resonance imaging is included among the tools that can supplement clinical examination and history in establishing a diagnosis of multiple sclerosis. Unfortunately, consensus diagnostic criteria are not available for most autoimmune diseases, despite their clear value not only for diagnosis but also for clinical trial design.

Definitive diagnostic markers do not exist for most autoimmune diseases. Even where laboratory markers are available, such as the presence of antinuclear antibodies or elevation of the erythrocyte sedimentation rate (a marker of ongoing inflammation), their specificity, sensitivity, and correlation with specific diseases are limited. In addition, many different methods may be used by clinical and research laboratories to measure the same disease markers. The autoantibodies

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Personal Profile

Could I Lead the Life I Envisioned?

Kim Vaughn
Mrs. Georgia America

The happiest and most memorable day of my life was not the day I was crowned Mrs. Georgia America, but the day my first child was born. Little did I know that within a few months of becoming a new mother, I would begin experiencing the symptoms of an autoimmune disease. I thought being a new mom meant feeling extremely tired, weak and aching, but as my son grew, I began to feel even worse. My vision was blurred, my hands and feet were numb, and swallowing became increasingly difficult. What was happening to me? Could I continue caring for my young son? Lead the life I had envisioned? Have more children? Continue my career as a professional model?

I began in earnest to try to figure out what was wrong with me. During the long year and a half it took me to receive the correct diagnosis, I was stuck, spinal tapped, x-rayed, and probed and had electric currents run through my body. Meanwhile, my younger sister began experiencing symptoms similar to mine.

Finally, we discovered the diagnosis: Sjögren's syndrome, a common but unfamiliar autoimmune disorder. Those of us with Sjögren's are all different, with different stories, symptoms, abilities, and disabilities. That's one of the reasons this disease is so tough to diagnose. Some of us are very sick, while others, like myself, manage better to struggle with day-to-day symptoms.

Fortunately for me, medical research had shown that an anti-malarial drug called plaquenil helped those with other autoimmune diseases. I tried it; it helped; and I continue to take it. Now there are two new drugs on the market for the dry mouth caused by Sjögren's syndrome and several in the final stages of development that might help my dry eyes. Others tell me the new Cox-2 inhibitors are helping them, and they don't have to rely as heavily on corticosteroids such as prednisone. I have to take prednisone occasionally—but very reluctantly—because it can have devastating side effects for so many of us.

The more we learn about autoimmune disease and Sjögren's syndrome, the more many of us will be able to live productive and happy lives. Since our first son was born, we have had a second wonderful and healthy child. My health has remained relatively stable, and I live with the promise I hope all of us with autoimmune disease will have – that some day, we will have even better medications, greater knowledge, and, best of all, a cure.

measured in type 1 diabetes are an exception, with several international workshops having established standards for the performance of these markers.

The absence of definitive markers of early disease affects patients and their families in medical, personal, and socioeconomic terms. Delays in diagnosis also lead to underestimates of incidence and prevalence and of costs to society. The resulting delays in treatment may increase morbidity and heath care costs. Self-esteem, family acceptance, employment, disability support, and involvement in society may be adversely affected with delays in definitive diagnosis.

> *The absence of definitive markers of early disease affects patients and their families in medical, personal, and socioeconomic terms.*

Treatment of Autoimmune Diseases

Therapeutic approaches to autoimmune disease can be broadly divided into three general areas: 1) therapies to improve signs and symptoms, 2) therapies to modify the natural course of disease, and 3) therapies directed at complications resulting from organ damage brought about by the disease. In many instances, agents are anticipated to have activities that will span these broad categories. For example, in type 1 diabetes, a number of agents are currently being evaluated for the prevention of

disease in at-risk individuals. Similar or closely related agents are being evaluated for the preservation of beta cell mass and function in individuals with new-onset disease. If effective, these agents can be expected to both improve the signs and symptoms of diabetes and alter the course of disease.

> *The range of potential therapeutic approaches available to treat autoimmune disease is expected to expand rapidly during the next decade as a consequence of progress in genetic and immunologic research conducted in the public and private sectors.*

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The range of potential therapeutic approaches available to treat autoimmune disease is expected to expand rapidly during the next decade as a consequence of progress in genetic and immunologic research conducted in the public and private sectors. These therapies are likely to include drugs, biologic agents, gene-based delivery systems, immunomodulation, cell-based treatments, and tissue and organ engineering procedures, as well as therapies based on complementary and alternative medicine. For example, new approaches to isolate, purify, and transplant human islet cells, coupled with less toxic post-transplant immunosuppressive regimens, show promise for treating patients with brittle diabetes. Another promising strategy involves reconstitution of the immune system by stem cell transplantation. Antigen-specific and other

approaches are being tested in a number of other autoimmune diseases including multiple sclerosis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and psoriatic arthritis. Many of these approaches have been successful in rodent or larger animal models of autoimmune disease or in pilot clinical studies. However, to date, the achievements in larger clinical trials have been modest. Individualized therapy, based on genetic markers of prognosis, drug responsiveness, and drug toxicity, is another highly promising area of research in autoimmunity.

Success in developing new therapies will rely increasingly on an in-depth understanding of the etiology and pathogenesis of individual autoimmune diseases. Moreover, the ability to conduct well-designed clinical trials to assess the efficacy of such therapies will require the identification of clinically relevant endpoints and the development of sensitive and specific measurement tools that accurately reflect the course and stage of disease. As a consequence, therapeutics can be regarded as a final common pathway that is heavily dependent on support and progress in virtually all aspects of basic and clinical research related to autoimmunity.

A major factor for further advancement of therapeutic research is development of biomarkers to determine the stage, activity, and progression of disease and to assess response to therapy. Biomarkers would enable clinicians to target particular therapies to those patients most likely to respond and would inform researchers and clinicians about the relationships between certain

therapies and outcomes. Identification of biomarkers specific for certain autoimmune disorders will also permit earlier identification of individuals with disease, thereby allowing earlier intervention. Improved, validated outcome measures and surrogate markers will also improve the effectiveness of clinical research, allowing for shorter studies, smaller research cohorts, and better focused trials.

> **For most autoimmune diseases, multicenter studies are necessary to enroll sufficient numbers of subjects in a timely manner.**

Various classification criteria have proven useful in categorizing and enrolling subjects in clinical trials. While reliance on such criteria can simplify clinical trial design and analysis of data, the resulting study populations may not reflect the true heterogeneity of the disease as seen by practicing physicians. Hence, this practice may severely limit the application of new discoveries.

Patients with autoimmune diseases frequently have an impaired quality of life due to loss of function of organs targeted by the disease. For example, patients with rheumatoid arthritis lose joint mobility due to progressive destruction of joints, and patients with multiple sclerosis lose the ability to walk or control bowel and bladder function due to

Personal Profile

An Unwanted Family Tradition

Abby Bernstein

I was diagnosed in 1994 with autoimmune hepatitis, a chronic inflammatory disease where the immune system attacks the liver. It was several years from the onset of my symptoms until my diagnosis was finally made.

My first symptoms occurred in 1988 when I was traveling and became ill with what appeared to be flu-like symptoms. An initial blood test showed extremely elevated liver enzymes. After several weeks of diagnostic tests looking for illnesses such as mononucleosis and Epstein-Barr, they discovered that I was having an allergic reaction to the drug Minocin. I had been taking Minocin for several years for cystic acne. Once the drug was eliminated from my system, I began to recover quickly. However, I still never felt "quite right" and several years later while taking the drug Prilosac, I once again experienced elevated liver enzymes. This time, however, I did not recover when I stopped taking the drug. My liver enzymes continued to rise, and I eventually experienced swelling and a loss of circulation in my hands and feet.

After seeing four different doctors, I was finally diagnosed with autoimmune hepatitis. A liver biopsy confirmed that diagnosis. For about 4 years, I worked with my doctors to employ a variety of treatments from Prednisone to acupuncture to keep my disease under control. Unfortunately, 3 years ago I was diagnosed with another autoimmune disease—rheumatoid arthritis. I suffer from pain and swelling in virtually every joint in my body. This autoimmune disease has been particularly challenging because my autoimmune hepatitis limits the drugs I can take. Last August I started taking the drug Enbrel, and so far both my liver and joints seem to be doing well.

But my story of autoimmune disease is not the only one for our family. My mother, who passed away 7 years ago of cancer, had rheumatoid arthritis and lupus. My father has rheumatoid arthritis, and my 10-year-old niece was diagnosed 2 years ago with autoimmune hepatitis. She was diagnosed quickly because her doctors asked for a family profile and immediately recognized the prevalence of autoimmune disease in our family. When I was first diagnosed with autoimmune hepatitis, I struggled to obtain information on my disease. Most of the books I found stated that my life expectancy was about 10 years. In my quest for more information on my disease, I became active with the American Autoimmune and Related Diseases Association. Currently I work as a member of their advocacy committee to bring needed awareness about these diseases to Congress and to lobby for increased funding for autoimmune diseases. I am hopeful that treatments for these diseases will improve. My heart aches for my 10-year-old niece who has had to take large amounts of Prednisone to help keep her body from destroying her liver. Hopefully, if not in my lifetime, we will see a cure in hers.

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destruction of the myelin sheath on nerves. The development of new strategies to reverse loss of function is needed.

Prevention of Autoimmune Diseases

One of the overriding principles and greatest challenges in all areas of biomedical research and public health is the prevention of disease prior to onset. Primary prevention generally yields the greatest public benefit at the lowest health care costs. Among the major achievements of modern medicine is the marked reduction or eradication of infectious diseases, such as smallpox, polio, viral hepatitis, and respiratory and enteric infections, either through prevention of exposure with improved sanitation and living conditions or through immunization programs.

Primary prevention requires the identification of individuals at risk; the development of new knowledge about underlying mechanisms of disease; and the design of safe, efficacious, and cost-effective interventions. A striking example is prevention of rheumatic fever, once a leading cause of death and serious disability in the United States, through prompt recognition and treatment of streptococcal infections. However, with other autoimmune disorders, only limited progress has been achieved in the identification of at-risk individuals and the prevention of disease. Effective strategies for prevention will require identification of environmental triggers and development of markers that accurately identify individuals at high risk before the onset of clinical disease.

Type 1 diabetes is the only autoimmune disease in which a cohort of individuals can be identified who are at significantly increased risk for development of the disease within the next 5 years, thus allowing testing of agents for prevention of disease. A European study, the ENDIT trial, includes more than 500 at-risk relatives of diabetics and is testing whether nicotinamide will prevent the development of disease. A large NIH-supported multicenter trial is currently testing whether the administration of oral insulin to at-risk relatives will delay or prevent development of type 1 diabetes. Based on promising studies in animal models of type 1 diabetes, additional NIH-sponsored trials to prevent

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Scientific Accomplishments

- FDA approval of first biologic agents for treatment of autoimmune diseases; e.g., etanercept for rheumatoid arthritis and infliximab for Crohn's disease.

- Development and adoption of clinical response criteria for an autoimmune disease: ACR 20, 50, and 70 for rheumatoid arthritis.

- Identification of criteria that define individuals who are at risk for development of an autoimmune disease; e.g., type 1 diabetes.

- Successful completion of the first definitive prevention trial in at-risk individuals for type 1 diabetes clearly demonstrated that subcutaneous insulin does not prevent onset of disease.

- Successful transplantation of human islets with insulin independence in patients with type 1 diabetes.

type 1 diabetes are currently in the planning phases using a variety of immunologic approaches. Reliable predictors of risk for disease are needed before prevention studies can proceed in other autoimmune diseases.

Current Research Investment

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

Diabetes Prevention Trial – Type 1. Under the sponsorship of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the National Center for Research Resources, the Juvenile Diabetes Research Foundation International, and the American Diabetes Association, this national multi-site cooperative clinical trial is evaluating the use of oral insulin for prevention of type 1 diabetes in intermediate-risk relatives of patients

with type 1 diabetes. The network of investigators recently reported that parenteral insulin does not prevent or delay the onset of type 1 diabetes in relatives at high risk.

Diabetes TrialNet. This large consortium of basic and clinical investigators is expanding on the major advances of the Diabetes Prevention Trial – Type 1. In collaboration with the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the Juvenile Diabetes Research Foundation, and the American Diabetes Association, the National Institute of Diabetes and Digestive and Kidney Diseases established Diabetes TrialNet. This national network has capabilities for spanning recruitment and detailed clinical evaluation of new onset diabetics and at-risk individuals and conduct of multi-site trials of promising immune-based therapies.

Immune Tolerance Network. In collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International, the National Institute of Allergy and Infectious Diseases established a consortium of more than 40 institutions in the United States, Canada, Western Europe, and Australia dedicated to the clinical evaluation of promising tolerance induction therapies in four areas: kidney transplantation, islet transplantation for type 1 diabetes, autoimmune disorders, and asthma and allergic diseases (http://www.immunetolerance.org). The network is also developing assays and biomarkers to measure the induction, maintenance, and loss of immune

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tolerance in humans and is studying underlying mechanisms as an integral part of all clinical trials. Trials are open or in development for multiple sclerosis, type 1 diabetes, and psoriatic arthritis.

Autoimmunity Centers of Excellence. This cooperative program includes four research centers to support 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 subspecialists (e.g., neurologists, gastroenterologists, and rheumatologists), as well as basic scientists, to increase collaboration in autoimmunity research. This group is currently conducting clinical trials testing immune-modulating therapies in systemic lupus erythematosus and multiple sclerosis, with trials in type 1 diabetes planned. The National Institute of Allergy and Infectious Diseases and multiple NIH Institutes and Offices support this program.

Stem Cell Transplantation for Autoimmune Disease Treatment Consortium. Several studies of the safety of hematopoietic stem cell transplantation have been completed. However, case-controlled studies of efficacy have not yet been conducted. This consortium, sponsored by the National Institute of Allergy and Infectious Diseases, is supporting clinical trials of the safety and effectiveness of these treatment regimens for multiple sclerosis, scleroderma, and systemic lupus erythematosus. Basic research studies of immune reconstitution and its effect on disease activity will be an integral component of these trials.

Pilot Clinical Trials on Innovative Therapies for Rheumatic and Skin Diseases. Established in FY 1999, under the sponsorship of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, this program is evaluating innovative therapies for the treatment of rheumatic and skin diseases, including Wegener's granulomatosis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and ankylosing spondylitis.

Nonhuman Primate Immune Tolerance Cooperative Study Group. Through this cooperative research program, the National Institute of Allergy and Infectious Diseases and National Institute of Diabetes and Digestive and Kidney Diseases support studies to evaluate the safety and efficacy of promising tolerance induction treatment regimens in nonhuman primate models of kidney and islet transplantation. The knowledge gained from this research effort is proving critical to the translation of successful tolerance induction strategies from small animal models to applications in human clinical trials.

Human Pancreatic Islet Cell Resources (ICRs). The National Center for Research Resources supports Islet Cell Resources for the isolation, purification, and characterization of human pancreatic islets for transplantation into diabetic patients. These Centers are responsible for the procurement of whole human pancreata, isolation and quality control of islet cell preparations, and distribution of islets for approved research or clinical protocols. Each ICR will facilitate the translation of this promising technology into an effective

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treatment and will also assist in making it available to the large numbers of patients for whom insulin injections are inadequate to maintain a healthy life.

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

Bench to Bedside Research on Type 1 Diabetes and Its Complications. This initiative, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, the National Eye Institute, and the National Heart, Lung, and Blood Institute, will support partnerships between clinical and basic biomedical researchers to translate advances in our understanding of the molecular basis of type 1 diabetes and its complications into new therapies for the prevention, treatment, and cure of this disease.

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

Autoimmune Diseases Prevention Centers. In FY 2001, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Child Health and Human Development, the Juvenile Diabetes Research Foundation, and the NIH Office of Research on Women's Health funded four new Autoimmune Diseases Prevention Centers focused on prevention of autoimmune diseases. This multidisciplinary program supports an interactive and collaborative network of investigators to advance understanding of immune homeostasis in health and in autoimmune states and to develop interventions for the prevention of human autoimmune disease. The Centers will support preclinical research, pilot innovative projects, and clinical studies.

Autoimmune Biomarkers Collaborative Network. Funded in 2001 by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the goal of this project is to develop biomarkers for two major rheumatic diseases,

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rheumatoid arthritis and systemic lupus erythematosus, that can be used reliably in a clinical setting to define disease subsets or follow disease activity and progression. New tools may assist in the diagnosis of these diseases, may help physicians better guide and manage therapy, and could provide important predictive information regarding flares of disease and long-term outcome.

Clinical Trials and Clinical Markers in Immunologic Diseases. The National Institute of Allergy and Infectious Diseases sponsored this research initiative focused 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. Several contracts focused on development of biomarkers are currently supported.

Complementary and Alternative Medicine. Therapies based on complementary and alternative medicine are largely unproven for autoimmune disease, but selected studies are currently being supported by the NIH National Center for Complementary and Alternative Medicine. Investigators are evaluating clinical and basic science approaches using complementary and alternative medicine in multiple sclerosis, rheumatoid arthritis, fibromyalgia, and diabetic neuropathy. Some grants are supporting randomized, controlled clinical trials of complementary and alternative medicine products.

Beta Cell Imaging Initiative was launched by the National Institute of Diabetes and Digestive and Kidney Diseases to stimulate the development of techniques or reagents to image or otherwise noninvasively detect pancreatic islet beta cells *in vivo* to measure their mass, function or evidence of inflammation, or to monitor engraftment of transplanted isolated pancreatic islets. The ability to make these measurements would potentially be very useful in monitoring individuals at high risk for type 1 diabetes and assessing response to preventive therapy.

The Collaborative Islet Transplant Registry was established by the National Institute of Diabetes and Digestive and Kidney Diseases to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America.

New Strategies for Treatment of Type 1 Diabetes, an RFA issued by the National Institute of Diabetes and Digestive and Kidney Diseases, supports regular and pilot projects of new approaches including immune modulation to arrest or reverse type 1 diabetes, gene transfer approaches to enhance islet transplantation or alter immunity, and new approaches to treat or prevent complications of diabetes.

Components of the Plan

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 *in 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;

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- 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

Introduction

To capitalize on advances in biomedical research, such advances must be translated into clinical practice. Successful translation requires training of current and future basic science and clinical researchers, continuing educational activities for health care providers, and effective communication and information dissemination to patients, their families, and the public. The multidisciplinary nature of autoimmune disease offers a significant, but exciting, challenge to achieving these goals.

Training

Training for health care providers about autoimmune diseases will require targeted approaches, since these diseases cross many health care disciplines, with varying degrees of patient care responsibilities and interactions. Primary care physicians must be able to recognize the often intermittent and nonspecific symptoms of autoimmune diseases. Other medical specialists treat individual autoimmune diseases within their areas of expertise. Dentists may be the first to recognize Sjögren's syndrome in patients with an increase in dental caries, often a presenting sign of this disease. Allied health professionals play an important role in helping patients deal with their diseases and the side effects of treatments. Nontraditional therapists, such as acupuncturists, may help alleviate some of the symptoms of these diseases. Thus, training

programs should involve all stakeholders, including patients and their families, health care providers, researchers, professional associations, and nonprofit health organizations that are advocates for and assist patients with autoimmune diseases.

The involvement of multiple specialists in treatment of individual patients can result in lack of coordination, discontinuity of care, increased health care costs, and increased drug toxicity. Challenges facing the clinician are compounded when a patient presents with multiple autoimmune diseases, a not-uncommon occurrence, since the presence of one specific autoimmune disease increases the risk of developing others. When this occurs, dealing with complications outside the clinician's area of training and specialization presents additional challenges. Crucial to delivery of quality medical care is a cadre of well-trained professionals who work together as a multidisciplinary team to translate discoveries into public benefit. The NIH supports a variety of individual and institutional training awards to meet the needs of new and established investigators.

Education

Continuing education of health care professionals and allied health care workers is essential. Public education and education of patients and their families are likewise critical components of the National Institutes of Health and Centers for Disease Control and Prevention missions. Highly successful venues for continuing medical

education include NIH-sponsored symposia, consensus development conferences, and NIH collaborations with professional societies and voluntary patient organizations.

Information Dissemination

An effective communication and information dissemination strategy requires an understanding of how people access and use information and the discrepancies between what is known and what is practiced. Health care for patients with autoimmune disease will be improved by effective translation of information about risk factors, signs and symptoms, diagnostic tools, prevention, and treatment to health care providers, patients and their families, and the public. A broad range of formats and technologies should be employed to maximize access to and use of information on all aspects of autoimmune disease. Health care providers and patients would benefit greatly from having the most accurate and current information about diagnosis and best practices for treatment and prevention.

Most consumers are unaware of available information and resources until confronted with an immediate and urgent need. At that stressful point, it is difficult for patients to adopt an organized approach for obtaining relevant information. Easy-to-understand guides to information, including Internet resources, can help patients through the challenges of diagnosis, early treatment, and life with a chronic disease.

In addition to the NIH Institutes' and Centers' Web pages, the National Library of Medicine provides two important information resources for patients and their families, health care providers, and the public: MEDLINEplus and ClinicalTrials.gov. MEDLINEplus is a Web-based system designed to assist consumers in locating authoritative health information. Its pages contain carefully selected links to Web resources with health information, as well as links to preformulated searches of MEDLINE. ClinicalTrials.gov is a Web-based system that provides the public with access to information about clinical trials and opportunities to participate in the evaluation of new treatments and includes both federally and privately funded clinical trials.

Recent Activities

The NIH Institutes and Centers sponsor a variety of scientific, educational, and informational activities, often in collaboration with private sector partners. Examples include the following:

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

Linking Environmental Agents and Autoimmune Diseases. This workshop defined state-of-the-art future research to understand the

mechanistic links between environmental agents and development or exacerbation of autoimmune disease. Sponsoring organizations included the National Institute of Environmental Health Sciences, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, Office of Research on Women's Health, NIH, Office of Rare Diseases, Environmental Protection Agency, American Autoimmune Related Diseases Association, and Juvenile Diabetes Research Foundation International.

New Immunotherapies for Autoimmune Diseases. A unique, dual-track symposium highlighting research advances and opportunities for a combined lay and scientific audience. Sponsors of this symposium included the National Institute of Allergy and Infectious Diseases, National Institute of Environmental Health Sciences, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, Office of Research on Women's Health, NIH, Office of Rare Diseases, American Autoimmune Related Disease Association, Juvenile Diabetes Research Foundation International, Arthritis Foundation, Crohn's and Colitis Foundation of America, Myositis Foundation, Sjögren's Syndrome Foundation, and the National Pemphigus Foundation.

Annual Arthritis Research Conference. This annual conference brings together NIH and privately supported trainees and their mentors to highlight ongoing research in rheumatologic

diseases, sponsored by the Arthritis Foundation, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Allergy and Infectious Diseases, and the American College of Rheumatology.

Information Resources.

- MEDLINEplus (http://www.nlm.nih.gov/medlineplus)
- ClinicalTrials.gov (http://clinicaltrials.gov)
- NIH Institutes and Centers Web pages
- NIH Institute Clearinghouses
- CDC Morbidity and Mortality Weekly Report (http://www.cdc.gov/mmwr/).

Development of Pediatric Endocrinologists is supported by a joint program of the National Institute of Diabetes and Digestive and Kidney Diseases, the Juvenile Diabetes Research Foundation, and the American Diabetes Association for research training and career development to prepare pediatric endocrinologists for careers in research in type 1 diabetes. This program fosters development of pediatric endocrinologists to assume leadership roles related to type 1 diabetes.

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Components of the Plan

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 mid-career 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.

Implementation

Recent accomplishments offer the promise of major advances in the diagnosis, treatment, and prevention of autoimmune diseases. However, gaps still exist in current knowledge, and new research programs and infrastructures will be needed to fully capitalize on the existing and future opportunities. In the judgment of the Autoimmune Diseases Coordinating Committee and non-Federal advisors to the ADCC, the nation is falling short of achieving its maximal potential in addressing the challenge of these diseases. This Autoimmune Diseases Research Plan highlights a conceptual and mechanism-based understanding of autoimmune diseases that emphasizes shared features and a multidisciplinary approach to translation of research advances into clinical applications.

Since its inception, the Autoimmune Diseases Coordinating Committee has been a forum for the coordination of research supported by multiple NIH Institutes, Centers and Offices, other Federal agencies, and a wide range of professional and private organizations. The present Autoimmune Diseases Research Plan builds extensively on existing programs, new research initiatives planned for implementation in FY 2002 and 2003, and the strategic plans of individual NIH Institutes and other Federal agencies. The table, located at the end of this chapter (Table 3), provides a "roadmap" of the activities recommended in this Research Plan and a matrix for collaborative activity among research sponsors. Efficient information exchange, formal short- and long-range collaborative planning, and

cosponsorship of activities will facilitate successful implementation of these recommendations. Greater coordination between NIH and other Federal agencies, in particular with the Centers for Disease Control and Prevention, Food and Drug Administration, Department of Veterans Affairs, Agency for Healthcare Research and Quality, and Health Resources and Services Administration, will significantly enhance the efficient use of resources. In addition, many public-private partnerships in support of autoimmune diseases research have been highly productive and should be expanded.

Implementing this research plan poses many challenges for the responsible stewardship of Federal research programs. Chief among these are the need to formalize collaborations and coordinate activities among potential partners. Logistical hurdles also exist, including the need to rapidly solicit, review, and award funds for meritorious research in a relatively short time. In the field of autoimmunity, several models already exist for effective management of new resources. In FY 1999, the Autoimmune Diseases Coordinating Committee played an instrumental role in identifying promising research opportunities and participated in the development of seven new trans-NIH initiatives and expansion of an additional nine planned programs. The Autoimmune Diseases Coordinating Committee continues to serve as a forum for sharing of information among organizations at early stages of program planning and development of research solicitations.

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Through the Balanced Budget Agreement of 1997, Congress provided an additional $30 million per year over 5 years to enhance Department of Health and Human Services activities leading to the prevention and cure of type 1 diabetes. The FY 2001 Consolidated Appropriations Act increased mandatory funding to the Secretary of Health and Human Services (HHS) under this program by $70 million per year in each of FY 2001 and 2002 and extended this support at a level of $100 million in FY 2003. The Consolidated Appropriations Act charged the Secretary, HHS, with development, implementation, and administrative oversight of a coordinated trans-NIH research plan for type 1 diabetes research. The Secretary delegated these responsibilites to the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, who used the Diabetes Mellitus Interagency Coordinating Committee to gather recommendations and suggestions for the research plan. The ability to centrally coordinate and manage project development and allocation of resources was critical to the successful implementation of an ambitious research plan spanning the missions of multiple NIH Institutes and other Federal agencies. Similarly, the Autoimmune Diseases Coordinating Committee believes strongly that centralized NIH coordination will be equally important for autoimmune diseases research.

In the event Congress appropriates additional funds to support research in autoimmunity, the ability of the Autoimmune Diseases Coordinating Committee to serve as a forum for prioritization and coordination of new programs through a centralized NIH mechanism will ensure successful and coordinated implementation of the components of this Research Plan.

TABLE 3. PROPOSED COLLABORATORS FOR IMPLEMENTING RESEARCH RECOMMENDATIONS

POTENTIAL PUBLIC AND PRIVATE COLLABORATORS
See Appendix C for the list of acronyms.

BURDEN OF AUTOIMMUNE DISEASE RESEARCH PLAN COMPONENTS	Federal Agencies																										Private Organizations
	NCCAM	NCMHD	NCRR	NEI	NHGRI	NHLBI	NIA	NIAID	NIAMS	NIBIB	NICHD	NIDDK	NIDCD	NIDCR	NIEHS	NIMH	NINDS	NINR	NLM	ORD	ORWH	AHRQ	CDC	FDA	HRSA	VA	
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.		●		●				●	●			●			●		●						●				AARDA
Design and conduct multidisciplinary, population-based, epidemiology and surveillance studies with sufficient racial, ethnic, socioeconomic, and geographic diversity to identify incidence, prevalence, morbidity, and mortality of autoimmune diseases in the United States.				●		●		●	●		●	●	●	●	●	●	●				●		●			●	ACR AF CCFA NMSS SSF, ADA ALR JDRF SLE
DISEASE REGISTRIES																											
Establish new and improve existing methods to identify and track patients with autoimmune diseases.						●		●	●			●					●						●				ACR AF CCFA NMSS SSF, ADA ALR JDRF SLE
Expand support for non-population-based autoimmune disease registries to enhance collection and analysis of data on causation, natural history, morbidity, and mortality of autoimmune diseases.				●		●		●	●		●	●	●	●	●	●	●				●		●			●	AARDA ACR AF CCFA NMSS SSF, ADA ALR JDRF SLE

TABLE 3. PROPOSED COLLABORATORS FOR IMPLEMENTING RESEARCH RECOMMENDATIONS

POTENTIAL PUBLIC AND PRIVATE COLLABORATORS
See Appendix C for the list of acronyms.

ETIOLOGY OF AUTOIMMUNE DISEASE RESEARCH PLAN COMPONENTS	NCCAM	NCMHD	NCRR	NEI	NHGRI	NHLBI	NIA	NIAID	NIAMS	NIBIB	NICHD	NIDDK	NIDCD	NIDCR	NIEHS	NIMH	NINDS	NINR	NLM	ORD	ORWH	AHRQ	CDC	FDA	HRSA	VA	Private Organizations
GENETIC FACTORS																											
Identify genetic factors that influence autoimmune diseases.				●	●	●		●	●		●	●	●	●	●	●	●				●		●			●	AARDA, ACR, ADA, AF, ALR, CCFA, JDRF, NMSS, SLE, SSF
Provide resources for production, storage, and distribution to the research community of materials and probes for genetic research.			●	●	●	●		●	●		●	●	●	●	●	●	●				●		●			●	AARDA, ACR, ADA, AF, ALR, CCFA, JDRF, NMSS, SLE, SSF
ENVIRONMENTAL FACTORS																											
Identify environmental factors.								●	●			●			●		●						●			●	AARDA, ACR, ADA, AF, ALR, CCFA, JDRF, NMSS, SLE, SSF
Establish mechanistic relationships between environmental factors and autoimmunity.								●	●			●			●						●		●				AARDA, ACR, ADA, AF, ALR, CCFA, JDRF, NMSS, SLE, SSF
IMMUNOLOGIC STUDIES																											
Identify and characterize immune mechanisms underlying autoimmune diseases.						●	●	●	●		●	●		●			●				●		●			●	AARDA, ACR, ADA, AF, ALR, CCFA, JDRF, NMSS, SLE, SSF
Promote development and appropriate use of animal models.			●	●	●	●		●	●		●	●					●										AARDA, ACR, ADA, AF, ALR, CCFA, JDRF, NMSS, SLE, SSF

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TABLE 3. PROPOSED COLLABORATORS FOR IMPLEMENTING RESEARCH RECOMMENDATIONS

POTENTIAL PUBLIC AND PRIVATE COLLABORATORS
See Appendix C for the list of acronyms.

DIAGNOSIS, TREATMENT, PREVENTION RESEARCH PLAN COMPONENTS	NCCAM	NCMHD	NCRR	NEI	NHGRI	NHLBI	NIA	NIAID	NIAMS	NIBIB	NICHD	NIDDK	NIDCD	NIDCR	NIEHS	NIMH	NINDS	NINR	NLM	ORD	ORWH	AHRQ	CDC	FDA	HRSA	VA	Private Organizations
CLINICAL RESEARCH INFRASTRUCTURE																											
Develop clinical research infrastructures with the capacity to conduct multi-institutional, multidisciplinary clinical studies.	•	•	•	•		•		•	•		•	•	•	•	•	•	•				•					•	AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF
Support research and shared facilities to accelerate screening for identification of individuals at risk for autoimmune diseases.			•	•		•		•	•		•	•	•	•	•	•	•				•					•	AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF
Expand support for bioengineering and bioimaging research and development, and procurement of large instruments and shared facilities.			•					•	•	•		•		•			•									•	AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF
Promote collaborations among engineers, chemists, physicists, and the immunology research community through workshops, symposia, and research solicitations.								•	•	•		•								•	•		•				AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF

TABLE 3. PROPOSED COLLABORATORS FOR IMPLEMENTING RESEARCH RECOMMENDATIONS

POTENTIAL PUBLIC AND PRIVATE COLLABORATORS
See Appendix C for the list of acronyms.

DIAGNOSIS, TREATMENT, PREVENTION RESEARCH PLAN COMPONENTS

CLINICAL TRIALS

Plan Component	NCCAM	NCMHD	NCRR	NEI	NHGRI	NHLBI	NIA	NIAID	NIAMS	NIBIB	NICHD	NIDDK	NIDCD	NIDCR	NIEHS	NIMH	NINDS	NINR	NLM	ORD	ORWH	AHRQ	CDC	FDA	HRSA	VA	Private Organizations
Develop new rehabilitative strategies to address loss of function.	●	●	●	●		●		●	●		●	●	●	●	●	●	●	●			●			●		●	AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF
Support carefully designed clinical trials of FDA-approved agents for nonapproved indications.	●	●	●	●		●		●	●		●	●	●	●	●	●	●	●			●		●	●		●	AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF
Define diagnostic and disease classification criteria for multiple autoimmune diseases and promote their use in research studies and in clinical practice.			●	●		●		●	●		●	●	●	●		●	●	●			●		●			●	AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF
Promote public-private partnerships for support of pivotal clinical trials.				●		●		●	●		●	●	●	●		●	●	●			●		●			●	AARDA ACR ADA AF ALR CCFA JDRF NMSS SLE SSF

TABLE 3. PROPOSED COLLABORATORS FOR IMPLEMENTING RESEARCH RECOMMENDATIONS

POTENTIAL PUBLIC AND PRIVATE COLLABORATORS
See Appendix C for the list of acronyms.

Private Organizations listed: AARDA, ACR, ADA, AF, AMA, ALR, CCFA, JDRF, NMA, NMSS, SLE, SSF

TRAINING, EDUCATION, INFORMATION DISSEMINATION RESEARCH PLAN COMPONENTS	NCCAM	NCMHD	NCRR	NEI	NHGRI	NHLBI	NIA	NIAID	NIAMS	NIBIB	NICHD	NIDDK	NIDCD	NIDCR	NIEHS	NIMH	NINDS	NINR	NLM	ORD	ORWH	AHRQ	CDC	FDA	HRSA	VA	Private Organizations
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.	●	●	●	●		●		●	●		●	●	●	●		●	●	●			●		●			●	●
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 diseases.	●	●	●	●		●		●	●		●	●	●	●		●	●	●			●		●			●	●
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.	●	●	●	●		●		●	●		●	●	●	●		●	●	●		●	●	●	●		●	●	●

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TABLE 3. PROPOSED COLLABORATORS FOR IMPLEMENTING RESEARCH RECOMMENDATIONS

POTENTIAL PUBLIC AND PRIVATE COLLABORATORS
See Appendix C for the list of acronyms.

TRAINING, EDUCATION, INFORMATION DISSEMINATION RESEARCH PLAN COMPONENTS	NCCAM	NCMHD	NCRR	NEI	NHGRI	NHLBI	NIA	NIAID	NIAMS	NIBIB	NICHD	NIDDK	NIDCD	NIDCR	NIEHS	NIMH	NINDS	NINR	NLM	ORD	ORWH	AHRQ	CDC	FDA	HRSA	VA	Private Organizations
INFORMATION DISSEMINATION																											
Develop communication and information dissemination strategy 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.	●	●	●	●		●		●	●		●	●	●	●		●	●	●	●	●	●	●	●		●	●	AARDA ACR ADA AF AMA ALR CCFA JDRF NMA NMSS SLE SSF
Provide information about clinical trials to evaluate prevention and treatment regimens that will enable patients and their physicians to make informed choices.	●	●	●	●		●		●	●		●	●	●	●		●	●	●	●		●		●			●	AARDA ACR ADA AF AMA ALR CCFA JDRF NMA NMSS SLE SSF
Develop culturally sensitive public awareness information materials aimed at patients, families, and health care providers of diverse races.	●	●		●		●		●	●		●	●	●	●		●	●	●			●	●	●		●	●	AARDA ACR ADA AF AMA ALR CCFA JDRF NMA NMSS SLE SSF
Establish a centralized, consolidated autoimmunity/autoimmune disease information center accessible to professionals and the public via the Internet.	●		●	●		●		●	●		●	●	●	●	●	●	●	●	●	●	●	●	●			●	AARDA ACR ADA AF AMA ALR CCFA JDRF NMA NMSS SLE SSF

Federal Agencies

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Appendix A: Acknowledgments

The Autoimmune Disease Research Plan is the culmination of efforts by numerous individuals and organizations. All members and representative members of the congressionally mandated Autoimmune Diseases Coordinating Committee and its working groups have made major contributions to the Research Plan. Their efforts, insights, contributions, and commitment have helped to ensure that this document represents a comprehensive strategic research plan for all NIH-funded autoimmune disease research, as directed by the Congress. This Research Plan is intended to help increase the effectiveness, comprehensiveness, and collaborative nature of autoimmune disease research. The Committee and working groups are composed of scientific experts in the field within and external to the government, as well as lay leaders in the autoimmune disease communities.

Autoimmune Diseases Coordinating Committee

Members

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

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

Elizabeth Gretz, Ph.D.
National Institute of Arthritis and
    Musculoskeletal and Skin Diseases

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

Stephen P. James, M.D.
National Institute of Diabetes and
    Digestive and Kidney Diseases

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

Rebecca A. Fuldner, Ph.D.
National Institute on Aging

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

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

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

Guo H. Zhang, Ph.D.
National Institute of Dental and
    Craniofacial Research

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

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

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

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

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

Paul Coulis, Ph.D.
National Institute of Drug Abuse

Kathleen Michels, Ph.D.
Fogarty International Center

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

Jerrold Heindel, Ph.D.
National Institute of Environmental
    Health Sciences

AI

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

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

Lisa Begg, Dr.P.H., R.N.
Office of Research on Women's Health

Henrietta D. Hyatt-Knorr, M.A.
Office of Rare Diseases
National Institutes of Health

Neal B. West, Ph.D.
National Center for Complementary and
    Alternative Medicine

Jeffrey N. Siegel, M.D.
Center for Biologics Evaluation and Research
Food and Drug Administration

Sahar M. Dawisha, M.D.
Center for Devices and Radiological Health
Food and Drug Administration

Kent Johnson, M.D.
Center for Drug Evaluation and Research
Food and Drug Administration

Barbara White, M.D.
VA Maryland Health Care System
Department of Veterans Affairs

Patricia W. Mueller, Ph.D.
National Diabetes Laboratory
National Center for Environmental Health
Centers for Disease Control and Prevention

Karen K. Steinberg, Ph.D.
National Center for Environmental Health
Centers for Disease Control and Prevention

Siobhán O'Connor, M.D., M.P.H.
National Center for Infectious Diseases
Centers for Disease Control and Prevention

Alicia Scott-Wright, M.D., M.P.H., M.T.M.&H.
Health Resources and Services Administration

Representative Members

Virginia Ladd
American Autoimmune Related Diseases
    Association

Stanley M. Finger, Ph.D.
National Coalition for Autoimmune Patient Groups
American Autoimmune Related Diseases
    Association

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

Patricia O'Looney, Ph.D.
National Multiple Sclerosis Society

Carolyn Doyle, Ph.D.
Arthritis Foundation

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

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

Margaret Dowd
The S.L.E. Foundation

Michael Holers, M.D.
American College of Rheumatology

Janice Wherry, M.D., Ph.D.
PhARMA
Schering-Plough Research Institute

Katherine Morland Hammitt, M.A.
Sjögren's Syndrome Foundation

Arthur Grayzel, M.D., MACR
Sjögren's Syndrome Foundation

Elaine Alexander, M.D., Ph.D.
Sjögren's Syndrome Foundation

Richard Kahn, Ph.D.
American Diabetes Association

A2

Autoimmune Diseases Coordinating Committee Working Groups

Epidemiology Working Group

Denise Wiesch, Ph.D., Chair
National Institute of Allergy and Infectious Diseases

Glinda Cooper, Ph.D.
National Institute of Environmental Health Sciences

Catherine Cowie, Ph.D.
National Institute of Diabetes and Digestive and
    Kidney Diseases

Margaret Dowd
The SLE Foundation

Maureen Harris, Ph.D.
National Institute of Diabetes and Digestive and
    Kidney Diseases

Jerrold Heindel, Ph.D
National Institute of Environmental Health Sciences

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

Siobhán O'Connor, M.D., M.P.H.
National Center for Infectious Diseases
Centers for Disease Control and Prevention

Christine Parks, Ph.D.
National Institute of Environmental Health Sciences

Stephen Walsh, Sc.D.
Sjögren's Syndrome Foundation

Etiopathogenesis Working Group

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

Elizabeth Gretz, Ph.D.
National Institute of Arthritis and Musculoskeletal
    and Skin Diseases

Beena Akolkar, Ph.D.
National Institute of Diabetes and Digestive
    and Kidney Diseases

Elaine Alexander, M.D., Ph.D.
Sjögren's Syndrome Foundation

Henry Chang, M.D.
National Heart, Lung, and Blood Institute

Geoffrey Cheung, Ph.D.
National Center for Research Resources

Carolyn Doyle, Ph.D.
Arthritis Foundation

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

Rebecca A. Fuldner, Ph.D.
National Institute on Aging

Arthur Grayzel, M.D.
Sjögren's Syndrome Foundation

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

Charles Hackett, Ph.D.
National Institute of Allergy and Infectious Diseases

Jerrold Heindel, Ph.D
National Institute of Environmental Health Sciences

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

Steve McDougal, M.D.
National Center for Infectious Diseases
Centers for Disease Control and Prevention

Patricia W. Mueller, Ph.D.
National Center for Environmental Health
Centers for Disease Control and Prevention

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

Siobhán O'Connor, M.D., M.P.H.
National Center for Infectious Diseases
Centers for Disease Control and Prevention

Ursula Utz, Ph.D.
National Institute of Neurological Disorders
    and Stroke

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

A3

Lois Winsky, Ph.D.
National Institute of Mental Health

Clinical Studies Working Group

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

Lisa Begg, Dr.P.H., R.N.
Office of Research on Women's Health
National Institutes of Health

Geoffrey Cheung, Ph.D.
National Center for Research Resources

Philip Fox, D.D.S.
Sjögren's Syndrome Foundation

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

Stephen P. James, M.D.
National Institute of Diabetes and Digestive
    and Kidney Diseases

John H. Klippel, M.D.
Arthritis Foundation

Curt Meinert, Ph.D.
Johns Hopkins University
American Autoimmune Related Diseases Association

Barbara Mittleman, M.D.
National Institute of Arthritis and Musculoskeletal
    and Skin Diseases

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

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

Susan Swedo, M.D.
National Institute of Mental Health

Fred Vivino, M.D.
Sjögren's Syndrome Foundation

Neal West, Ph.D.
National Center for Complementary and
    Alternative Medicine

Training, Education, and Information Dissemination Working Group

Stanley M. Finger, Ph.D., Chair
National Coalition of Autoimmune Patient Groups
American Autoimmune Related Diseases
    Association

Debbie Ader, Ph.D.
National Institute of Arthritis and Musculoskeletal
    and Skin Diseases

Belinda Ash-Shaheed, M.S.
National Institute of Allergy and Infectious Diseases

Janet Austin, Ph.D.
National Institute of Arthritis and Musculoskeletal
    and Skin Diseases

Stephanie Clipper
National Institute of Neurological Disorders and Stroke

Jane DeMouy, Ph.D.
National Institute of Diabetes and Digestive
    and Kidney Diseases

Marian Emr
National Institute of Neurological Disorders and Stroke

James Hadley
National Institute of Allergy and Infectious Diseases

Henrietta D. Hyatt-Knorr, M.A.
Office of Rare Diseases
National Institutes of Health

Natasha Leskovsek, R.N., J.D.
Heller, Ehrman
American Autoimmune Related Diseases Association

Katherine Morland Hammitt, M.A.
Sjögren's Syndrome Foundation

Ann Parke, M.D.
Sjögren's Syndrome Foundation

Sam Perdue
National Institute of Allergy and Infectious Diseases

Patricia Pletke, M.D.
University of Virginia
American Autoimmune Related Diseases Association

Constance Raab
National Institute of Arthritis and Musculoskeletal
    and Skin Diseases

Steering Committee

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

Elaine Alexander, M.D., Ph.D.
Sjögren's Syndrome Foundation

Lisa Begg, Dr. P.H., R.N.
Office of Research on Women's Health
National Institutes of Health

Glinda Cooper, Ph.D.
National Institute of Environmental Health Sciences

Elizabeth Gretz, Ph.D.
National Institute of Arthritis and Musculoskeletal
    and Skin Diseases

Charles Hackett, Ph.D.
National Institute of Allergy and Infectious Diseases

Natasha Leskovsek, J.D.
Heller, Ehrman
American Autoimmune Related Diseases Association

Stanley M. Finger, Ph.D.
National Coalition of Autoimmune Patient Groups
American Autoimmune Related Diseases Association

Barbara Mittleman, M.D.
National Institute of Arthritis and Musculoskeletal
    and Skin Diseases

Katherine Morland Hammitt, M.A.
Sjögren's Syndrome Foundation

Siobhán O'Connor, M.D., M.P.H.
National Center for Infectious Diseases
Centers for Disease Control and Prevention

Noel Rose, M.D.
Johns Hopkins University
American Autoimmune Related Diseases Association

Denise Wiesch, Ph.D.
National Institute of Allergy and Infectious Diseases

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Expert Panel Members

Gerald T. Nepom, M.D., Ph.D., Chair
Director
Virginia Mason Research Center
Seattle, WA

Mark A. Atkinson, Ph.D.
Professor
Department of Pathology
University of Florida
Gainesville, FL

Henry N. Claman, M.D.
Professor
University of Colorado
Denver, CO

Betty Diamond, M.D.
Professor
Albert Einstein College of Medicine
Bronx, NY

Peter K. Gregeren, M.D.
Professor and Center Director
North Shore Long Island Jewish Research Institute
Manhasset, NY

Michael Holers, M.D.
Professor
University of Colorado Health Sciences Center
Denver, CO

Stuart S. Kassan, M.D.
Clinical Professor of Medicine
University of Colorado Health Sciences Center
Denver, CO

Samia Khoury, M.D.
Professor of Neurology
Brigham and Women's Hospital
Boston, MA

Virginia Ladd
President
American Autoimmune Related Diseases Association
Eastpointe, MI

Edward K. Wakeland, Ph.D.
Professor and Director
University of Texas Southwestern Medical Center
Dallas, TX

Stephen S. Rich, Ph.D.
Professor and Vice Chair
Public Health Sciences
Wake Forest University School of Medicine
Winston Salem, NC

Caroline Whitacre, Ph.D.
Chair and Professor
Molecular Virology, Immunology and Medical Genetics
Ohio State University
Columbus, OH

National Institute of Allergy and Infectious Diseases Staff Support

Daniel Rotrosen, M.D.
Director
Division of Allergy, Immunology, and Transplantation

Elaine Collier, M.D.
Chief, Autoimmunity Section
Acting Chief, Clinical Immunology Branch

Nancy Blustein
Director
Office of Program Planning, Operations,
   and Scientific Information
DAIT

Jean McKay
Deputy Director
Office of Program Planning, Operations,
   and Scientific Information
DAIT

L. Jeanne Borger
Program Analyst
Office of Program Planning, Operations,
   and Scientific Information
DAIT

Contract Support

Health Research Sciences, Inc.
Rockville, Maryland

Gail Herzenberg, M.P.A.
Project Manager and Managing Editor

Donna R. Savage, M.Ed., ELS
Senior Editor

Naomi Levy
Senior Editor

Betty Bennett Gilmore
Editor and Administrative Manager

Keith Deverin
Data Specialist

IQ Solutions, Inc.
Rockville, Maryland

Hope Levy Kott
Project Manager

Tiffany Hayes
Meeting Planner

Appendix B: Congressional Language: Children's Health Act

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.

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(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 C: Acronyms

AARDA	American Autoimmune Related Diseases Association
ABCoN	Autoimmune Biomarkers Collaborative Network
ACR	American College of Rheumatology
ADA	American Diabetes Association
ADCC	Autoimmune Diseases Coordinating Committee
AF	Arthritis Foundation
AHRQ	Agency for Healthcare Research and Quality
ALR	Alliance for Lupus Research
AMA	American Medical Association
APS	Antiphospholipid syndrome
CCFA	Crohn's and Colitis Foundation of America
CDC	Centers for Disease Control and Prevention
CLEAR	Consortium for the Longitudinal Evaluations of African Americans with Early Rheumatoid Arthritis
CREST	CREST syndrome
DAISY	Diabetes Autoimmunity Study in the Young
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIC	John E. Fogarty International Center

HHS	Health and Human Services
HLA	Human leucocyte antigen
HRSA	Health Resources and Services Administration
IHWG	International Histocompatibility Working Group
ICRs	Islet Cell Resources
ITP	Idiopathic Thrombocytopenic Purpura
JDRF	Juvenile Diabetes Research Foundation International
JRA	Juvenile rheumatoid arthritis
MADGE	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

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NIAID	National Institute of Allergy and Infectious Diseases		NIH	National Institutes of Health
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases		NIMH	National Institute of Mental Health
NIBIB	National Institute of Biomedical Imaging and Bioengineering		NINDS	National Institute of Neurological Disorders and Stroke
NICHD	National Institute of Child Health and Human Development		NINR	National Institute of Nursing Research
NIDA	National Institute on Drug Abuse		NLM	National Library of Medicine
NIDCD	National Institute on Deafness and Other Communication Disorders		NMA	National Medical Association
NIDCR	National Institute of Dental and Craniofacial Research		NMSS	National Multiple Sclerosis Society
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases		ORD	Office of Rare Diseases
NIEHS	National Institute of Environmental Health Sciences		ORWH	Office of Research on Women's Health
NIGMS	National Institute of General Medical Sciences		PA	Pernicious anemia
			SEER	Surveillance, Epidemiology, and End Results
			SLE	Systemic lupus erythematosus
			SSF	Sjögren's Syndrome Foundation
			VA	Department of Veterans Affairs

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Appendix D: 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.

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

Antibodies: 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.

Antigens: 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.

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.

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

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).

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.

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.

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.

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.

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.

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

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are several types of lymphocytes: B cells are primarily involved in the production of antibodies; T cells release chemicals that activate and direct the movements of other cells to help fight infection or attack foreign matter.

Macrophage: any of the many forms of mononuclear phagocytes found in tissues.

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.

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

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 that occur in the development of a disease.

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.

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.

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.

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.

Type I 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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