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WHITE HOUSE STAFFING MEMORANDUM

DATE: 9/10/93 ACTION/CONCURRENCE/COMMENT DUE BY: _____

SUBJECT: FOURTH BIENNIAL REPORT OF THE DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH FOR THE PRESIDENT'S CONSIDERATION

	ACTION	FYI		ACTION	FYI
VICE PRESIDENT	<input type="checkbox"/>	<input type="checkbox"/>	PASTER	<input type="checkbox"/>	<input type="checkbox"/>
McLARTY	<input type="checkbox"/>	<input type="checkbox"/>	RASCO	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
NEEL	<input type="checkbox"/>	<input type="checkbox"/>	RUBIN	<input type="checkbox"/>	<input type="checkbox"/>
PANETTA	<input type="checkbox"/>	<input type="checkbox"/>	SEGAL	<input type="checkbox"/>	<input type="checkbox"/>
BAGGETT	<input type="checkbox"/>	<input type="checkbox"/>	SEIDMAN	<input type="checkbox"/>	<input type="checkbox"/>
EMANUEL	<input type="checkbox"/>	<input type="checkbox"/>	STEPHANOPOULOS	<input type="checkbox"/>	<input type="checkbox"/>
GEARAN	<input type="checkbox"/>	<input type="checkbox"/>	TYSON	<input type="checkbox"/>	<input type="checkbox"/>
GERGEN	<input type="checkbox"/>	<input type="checkbox"/>	VARNEY	<input type="checkbox"/>	<input type="checkbox"/>
GIBBONS	<input type="checkbox"/>	<input type="checkbox"/>	WATKINS	<input type="checkbox"/>	<input type="checkbox"/>
HALE	<input type="checkbox"/>	<input type="checkbox"/>	WILLIAMS	<input type="checkbox"/>	<input type="checkbox"/>
HERMAN	<input type="checkbox"/>	<input type="checkbox"/>	CLERK	<input type="checkbox"/>	<input checked="" type="checkbox"/>
LAKE	<input type="checkbox"/>	<input type="checkbox"/>	<u>Magazine</u>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
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NUSSBAUM	<input type="checkbox"/>	<input type="checkbox"/>	_____	<input type="checkbox"/>	<input type="checkbox"/>

REMARKS:

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JOHN D. PODESTA
Assistant to the President
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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

SEP 3 1993

The President
The White House
Washington, D.C. 20500

Dear Mr. President:

Enclosed for your consideration is the fourth Biennial Report of the Director of the National Institutes of Health (NIH). This report was prepared in accordance with the requirements of Sections 403, 406(g), and 407 of the Public Health Service Act as amended through June 30, 1992, which requires the NIH Director to submit a biennial report to the President and to the Congress. This two-volume report covers the period from the beginning of Fiscal Year 1991 through the end of Fiscal Year 1992.

The first volume contains NIH reports on (1) major research advances and opportunities in biomedical research; (2) research in disease prevention; (3) health-related behavioral research; (4) women's health research; (5) minority health research; (6) trans-NIH nutrition research; (7) NIH-wide science policy issues; (8) managing the costs of biomedical research; (9) activities to improve grant and contract accountability and peer review; (10) economic aspects of biomedical research; and (11) a compilation of biennial reports prepared by each of the research Institutes, Centers, and Divisions (ICDs). The second volume of the report contains the reports of the individual ICD advisory councils.

As required by the Act, the views expressed in the documents contained in the second volume are solely those of the members of the advisory councils and do not necessarily reflect the positions of the NIH, the Department, or the Administration.

Sincerely,

A handwritten signature in dark ink, appearing to read "Donna E. Shalala", is written over the typed name.

Donna E. Shalala

Enclosure

Biennial Report of the Director,
National Institutes of Health

Reports of the NIH Advisory
Councils and Boards

Volume II
1991–1992

U.S. Department of Health and Human Services
Public Health Service—National Institutes of Health

Background

This Biennial Report of the Director, National Institutes of Health (NIH), is the fourth report dealing with the Nation's biomedical research effort as submitted by the Secretary of the Department of Health and Human Services to the President and the Congress of the United States, pursuant to Section 403 of the Public Health Service Act as amended through June 30, 1992. The date for submission of the report is December 31, 1992. This report covers the period of fiscal years 1991 and 1992. The report was prepared at an estimated cost of \$80,000, which was shared by all NIH research institutes, centers, and divisions (ICDs), as well as the NIH Director's Office.

The report is organized around twelve major topics:

- Advances and opportunities in biomedical research
- NIH research in disease prevention
- Health-related behavioral research
- Women's health research
- Minority health research
- Trans-NIH nutrition research
- NIH-wide science policy issues
- Managing the costs of biomedical research
- Activities to improve grant and contract accountability and peer review
- Economic aspects of biomedical research
- Biennial reports of the Directors of each of the NIH institutes, centers, and divisions
- Biennial reports of the individual ICD national advisory councils and boards

The report is presented in two volumes. Volume I presents NIH policy issues and scientific reports; Volume II contains the biennial reports of the individual ICD national advisory councils and boards.

The views and opinions expressed on the following pages are solely those of the authors and do not necessarily constitute an endorsement, real or implied, by the U.S. Department of Health and Human Services.

Biennial Report of the Director,
National Institutes of Health

Reports of the NIH Advisory
Councils and Boards

Volume II
1991–1992

U.S. Department of Health and Human Services
Public Health Service—National Institutes of Health

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NATIONAL ADVISORY COUNCIL ON AGING

INTRODUCTION

The National Institute on Aging (NIA) was established in 1974 by the Research on Aging Act. The broad goals of the NIA programs are to understand aging processes in health and disease; to identify the many factors that influence aging; to develop methods for maintaining and improving health and productivity; and to enhance the quality of life in the later years. It is also expected that this new knowledge will assist in development of public health and social policies.

The rapid growth in NIA programs reflects the importance of its multiple missions and acknowledges the impact of the aging population on our society. Critical to this growth has been the recognition by Congress of the important health and social needs of older persons. In particular, with strong congressional support, research on Alzheimer's disease was designated as one of the Institute's highest priorities in 1979, and major research efforts are directed at developing methods for diagnosing, preventing, and treating the disease and uncovering its causes. Additional initiatives focus on the burden of caring for Alzheimer's disease patients, both in the home and in special care units in institutional settings.

The purpose of this Fourth Biennial Report to the Congress is to recommend areas for further development in order to meet the needs of the aging population and to recognize the accomplishments of the Institute and its programs.

THE NATIONAL ADVISORY COUNCIL ON AGING

The members of the National Advisory Council on Aging (NACA) are appointed by the Secretary of Health and Human Services. They are selected from the lay public, scientific, and education communities as individuals who are informed about the needs of older Americans. The NACA is the NIA's principal advisory body. It provides the second line of review for research, training, and career development applications; assesses research priorities; provides concept clearance for new research initiatives; recommends research directions and future research opportunities; represents the NIA on the Advisory Committee to the Director, NIH; and evaluates the progress of NIA intramural and extramural research programs.

RECOMMENDATIONS

The major advances that have occurred in aging research are remarkable when viewed in the context of the NIA's brief history and the rapidity with which its goals have been defined and implemented. However, this research is increasingly complex and requires state-of-the-art equipment, modern facilities, and an enhanced pool of senior and junior scientists with interests in aging research who can make major scientific advances in the field. The sophistication and diversity of NIA intramural and extramural research programs will require increases in funding consistent with the importance of the Institute's mission in order to meet the needs of our older population. Research in all areas is required now to prepare for their future needs. The following specific recommendations are developed from these needs.

1. Congress should establish a minimum appropriation of one billion dollars for the National Institute on Aging before the year 2000. It is imperative that the annual appropriation be sufficient to support growth in NIA research, education, training, and information dissemination programs and to take advantage of scientific opportunities that will lead to reduction of health care costs. It is essential that the budget permit full funding of awarded grants and provide sufficient staff to manage NIA programs in an effective manner.

2. Funding for research training of professional personnel engaged in disciplines related to aging should be expanded. The future of the field depends on increasing the number of well-educated and well-trained individuals who can continue to make scientific progress and implement the programs that result from these advances. As noted in earlier reports, there is an acute need for educators, health care providers, and scientists in the diverse disciplines that encompass aging research. The limited training budget allocated to the NIA has resulted in a reduction in the number of trainees rather than the increase planned. Moreover, it has precluded much-needed increases in trainee stipends. In addition, special consideration and additional funding should be given to attract individuals from underrepresented groups including minorities, women, and the disabled at all academic levels in aging-related research fields.

3. Support for research instrumentation and infrastructure should be expanded. In part this could be accomplished by restoration of the Biomedical Research and Support (BRS) and shared instrumentation grant programs. State-of-the-art facilities and equipment optimize scientific productivity, promote competitiveness of U.S. institutions, and help to maintain our Nation's preeminent position in science. Because recipient institutions often share in the acquisition and maintenance costs, such support is cost-effective. This program maximizes the use of facilities by many investigators and avoids duplication.

4. Funds are required to expand NIA efforts to establish and maintain centralized resources for aging research. These resources should include archives for social, behavioral, biological, and health data, as well as repositories for cells, tissues, and animals. Since considerable lead time is required to meet future needs, an investment in these resources is needed now. Centralized, standardized data and materials can hasten the progress of research by facilitating comparisons among research groups, allowing increased sharing of costly resources, and preventing duplication of effort.

5. Cooperative programs should be enhanced and expanded among the NIA and other agencies. The NACA commends NIA's leadership for identifying areas of mutual interest within the NIH and with other agencies. This approach is cost-effective, merges the interests of various groups, prevents duplication of research efforts and funding, and enhances collaborative interactions. Such programs optimize the applicability of diverse research findings to aging and, conversely, directly contribute to the missions of other research organizations.

6. The NIA appropriation should provide sufficient flexibility to take advantage of emerging scientific opportunities and changing public health needs related to aging. Research progress in many areas of geriatrics and gerontology is sufficiently rapid to

justify substantial rebudgeting of funds among NIA programs from one year to the next and occasionally within a single fiscal year.

RATIONALE

Our Nation's senior citizens form the most rapidly increasing segment of our society. Based on U.S. Census Bureau projections, the number of persons over 65 years of age will double from the present level and exceed 66 million by the year 2030. We must be prepared to help them maintain independent functioning, to meet their health care needs, and to provide the full range of social services they will require. These projected demands will have a major economic impact. The National Institute on Aging, through its mandated research programs, can provide the knowledge bases to address these projected needs. The funding requested will identify ways to prevent or ameliorate age-associated diseases. This funding will also promote the means by which our older population can maintain good health, functional independence, productivity, and effective interactions with their physical and social environment throughout their extended lifespan. Thus, this reservoir of vibrant, talented, and capable individuals will continue to make meaningful contributions to our society.

Research that can address the special needs of older persons has been outlined in a recent Institute of Medicine Report, "Extending Life, Enhancing Life." With considerable foresight, the National Institute on Aging also identified similar areas for research emphasis. Within its intramural and extramural programs, the NIA sponsors research that will (1) define the basic mechanisms underlying the biological, psychological, and social processes of aging; (2) determine the relationship between aging and the increased incidence of specific age-related diseases; (3) identify ways to enhance the ability of older persons to interact effectively with their environment by maintaining or improving their physical, sensory, cognitive, and social capabilities; (4) develop interventions for age-related diseases; (5) provide demographic data essential for resource allocation and economic planning; (6) implement a program of international activities in aging research; and (7) support programs of information dissemination and education both to health care professionals and to the general public.

Alzheimer's disease is an area of special emphasis. It has been estimated that 4 million Americans are affected by Alzheimer's disease at a cost to the Nation of approximately \$90 billion, in addition to the incalculable costs of human suffering. In no other disease are all the problems attendant with aging so clustered and brought into focus. The diminished physical and cognitive functions of those afflicted and the burdens of care for their families are well documented. Further, our health care delivery and support systems are presently inadequate to meet the physical, social, and environmental needs of Alzheimer's disease patients and their families. The NIA is dedicated to seeking the solutions for the diseases and disabilities of the aged through its unique blend of basic biomedical research with fundamental studies in the clinical, behavioral, epidemiologic, and social sciences, as well as research on the use of health services. Recent congressional increases in funding for the NIA have recognized the needs of our older citizens and facilitated the development of these important programs.

The Council continues to recognize that our rural and minority elderly have special needs. While the NIA has appropriately developed research programs that begin to address

the problems of these individuals, it is limited in the resources that can meet the needs. These initiatives require special congressional consideration.

The Council also emphasizes the urgent need for increased funding for NIA education and training programs. In the next decade there will be a growing demand for highly skilled researchers and professional and paraprofessional personnel in all fields of aging research. This need includes research scientists in the biological, psychological, social, and medical disciplines, health care and social services researchers and providers, as well as multidisciplinary personnel who can deal with the medical, psychological, and social needs of our aged. The key to NIA's continued success in aging research and the rapidity of translation of research findings to use depends upon this cadre of well-educated and well-trained scientists and service providers. The recommended funding should be targeted to the following areas.

Increases in both predoctoral and postdoctoral training programs and positions are required. Predoctoral programs should include traditional discipline-oriented as well as individual fellowships, both of which use established investigators as mentors. New initiatives for M.D./Ph.D. degree candidates that will fund both dissertation research and medical school are also required. The number of NIA full-time training positions has increased steadily over the past decade from 167 in FY 1980 to 426 in FY 1990. However, limited funding levels caused this number to decrease to 418 in FY 1991. Additional funding is required to stem this alarming downward trend.

The above needs are especially acute as regards underrepresented groups including women, minorities, and the disabled in the field of aging research. Initiatives that provide research grant supplements to established investigators for support of minority faculty and predoctoral and postdoctoral trainees should continue, although the present number of qualified individuals is small. Other approaches to "prime the pipeline" would be to support training programs in institutions with large enrollments of individuals from groups underrepresented as research scientists.

Sustained research progress and optimal environments in which to train our future scientists are crucially dependent upon maintenance of our research infrastructure. In recent years, because of competing priorities, the NIH has been forced to decrease its support for research resources and facilities. Because infrastructure costs are shared between the recipient institutions and government, these programs are extremely cost-effective. The presence of shared instrumentation and facilities promotes interdisciplinary research and training initiatives and minimizes costly duplication. The Council also emphasizes the importance of providing centralized resources that are unique for research in the field of aging. These resources (see Recommendations) are difficult for any single institution to acquire or maintain, and require significant time for their development. With considerable foresight, the NIA has established and maintains colonies of aging and calorically restricted animals that it provides to investigators around the Nation, and supports large data repositories of behavioral and social research on aging that are critical for further advances in understanding aging processes, as well as for demographic and economic projections. These two initiatives have demonstrated the effectiveness of such resources. Others that can be developed have been recommended above.

Equally important in enhancing research productivity is additional support for research programs that fulfill the goals and interests of more than one agency or organization. The NIA has been a leader in promoting cooperative studies and research programs with other NIH institutes. Some have had profound impact in defining ways in which interventions can improve health and functioning at an older age. One example is the Systolic Hypertension in the Elderly Program. In this clinical trial, a phenomenon that was thought to be an age-related pathologic entity, i.e., the rise in systolic blood pressure occurring in Western societies with increasing age, responds to pharmacologic treatment typically costing less than 25 cents per day. This treatment could result in 24,000 fewer strokes and 50,000 fewer cardiovascular events, including myocardial infarction, at a potential cost saving of \$200 million per year. The health benefits and cost savings that accrue from this type of study clearly justify others of a similar nature.

CONCLUSION

The accomplishments of NIA's intramural and extramural programs are impressive. The NIA-sponsored programs in the biomedical, behavioral, and social sciences have greatly expanded our understanding of normal and pathologic aging processes. Clinical research has already identified specific interventions that promise to alleviate suffering of older Americans and reduce the cost to society for their care. While such clinical breakthroughs are dramatic, it must be realized that they can only derive from a strong foundation of basic research. It is critical that NIA continue its strong support of investigator-initiated, basic research in the biological, psychological, and social sciences. This requires that NIA be given the flexibility to direct funds to scientifically outstanding projects across the diverse disciplines involved in meeting the NIA mandate. This flexibility will ensure a strong scientific base to support important future research applications. The next decade of the twentieth century provides an unprecedented opportunity to harness advances in basic molecular and cellular biology, neurosciences, geriatric medicine, and social and behavioral sciences to serve older Americans.

NATIONAL ADVISORY COUNCIL ON AGING

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NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

HOPE THROUGH NIAID RESEARCH

Infectious and immunologic diseases cause profound human suffering and place an enormous economic burden on both patients and the health care system. The combined effects of infectious diseases and malnutrition remain the most common cause of death for children worldwide, and disorders of the immune system are reported to affect more than 1 in every 10 Americans. Recent advances in biomedical research have led to the development of sophisticated technologies, such as gene therapy, that offer hope for treating a wide range of these devastating illnesses. Perfecting these technologies and ensuring their availability to affected individuals, however, will be expensive and could increase the portion of the gross national product dedicated to health care—a percentage that already is the highest in the world. Some of the most promising approaches to alleviating suffering from these illnesses are derived from research aimed at preventing disease and halting the progression of disease to disability or death. This strategy also is the most cost-effective use of resources.

Through its investigations of infectious and immunologic diseases ranging from allergies to AIDS, the National Institute of Allergy and Infectious Diseases (NIAID) has a unique opportunity to alleviate suffering and death caused by some of our Nation's most prevalent and most costly health problems. NIAID's foundation of basic research on microbes that infect people and on the immune system that protects us against these invaders underlies all of the Institute's prevention efforts. For example, NIAID's research in basic bacteriology and virology has enabled the Institute to make major contributions to the development of vaccines—one of the safest and most cost-effective measures for preventing infectious diseases. Vaccines have dramatically decreased or eradicated some infectious diseases, such as smallpox and poliomyelitis, that previously caused epidemics affecting millions of people. Yet only a fraction of the full potential of vaccines and other preventive measures has been realized. Investment in the development of new and improved vaccines alone has the potential to save hundreds of millions of dollars in direct and indirect health care costs by protecting vulnerable populations from diseases such as influenza, measles, and rotavirus.

As the Nation continues its ongoing battle to combat new pathogens such as human immunodeficiency virus (HIV) and reemerging diseases such as tuberculosis (TB) and measles, the need to commit resources for developing prevention and control measures to address these conditions becomes increasingly important. With its highly productive portfolio of basic, clinical, and applied research on infectious and immunologic diseases, NIAID offers the potential for dramatic reductions in human suffering and health care costs for a relatively modest investment.

ACTIVITIES OF THE NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

The National Advisory Allergy and Infectious Diseases Council (NAAIDC) plays a crucial role in advising the Institute on future directions for scientific research and policy emphasis. Working in partnership with NIAID and its leadership, NAAIDC has addressed several issues

presented by the Director of the Institute. For example, Council discussion following a presentation by the Director on issues concerning the funding of research grants led to the creation of the Council Working Group on Grant Issues. Working group members met with NIAID staff to consider the appropriate balance between awards made to new investigators and those made to established investigators. The group also examined the suggestion that NIAID develop a "triggering" mechanism to prompt automatically Council consideration of pending awards to individual researchers who already receive a specified level of funding from the Institute. The working group decided that the current ratio of 20 percent new investigators to 80 percent established investigators was appropriate and that the NIAID policy of funding 40 percent of First Independent Research Support and Transition (FIRST) Awards should be continued. After reviewing all awards made to individuals receiving NIAID funds of \$1 million or more annually, the working group decided that the Institute did not need to establish a triggering mechanism because essentially only two types of individuals received this level of support: those who were engaged in clinical studies of AIDS therapies, and those who had NIAID grants usually totaling less than \$300,000 but who also were credited with the entire amount of a Research Program Project award from another Institute.

In discussions following budget reports by the Director, NAAIDC expressed concern that providing resources for the repair of deteriorating infrastructures within the National Institutes of Health (NIH) and extramural research facilities could divert funds from awards supporting the research itself. The Council recognized that maintaining, improving, and expanding NIH and extramural facilities, while necessary, is very costly. The Council noted recent data on indirect costs indicating that facilities reimbursement is the fastest growing component of indirect costs in the extramural community. However, the Council viewed the trend of financing these expenditures at the expense of research as alarming and ultimately counterproductive. Consequently, NAAIDC recommended that the Federal Government find innovative ways of financing improvements to NIH and extramural facilities without jeopardizing the ultimate purpose of these infrastructures—namely, the support of biomedical research.

NAAIDC also provided advice regarding the need to maximize limited resources by supporting an appropriate balance of targeted and investigator-initiated research. The Council acknowledged the vital contribution of undifferentiated basic research in helping to identify specific research questions that need to be addressed in a particular field. For example, the expanding base of knowledge on HIV infection and vaccine development has revealed several important research questions that must be answered before scientists can create an effective AIDS vaccine. However, the Council expressed concern that efforts to find the answers to these questions should not be left solely to the initiative of investigators. It noted that the emergence of urgent research issues emphasizes the need to stimulate work in high-priority areas such as the control of drug-resistant cases of TB. Therefore, the Council encouraged NIAID to use Requests for Applications (RFAs) and other funding mechanisms to solicit more targeted research in areas needing immediate attention.

NAAIDC performs the important function of providing the first extramural review of NIAID concepts for the development of RFAs and Requests for Proposals (RFPs). In addition to making recommendations on whether to pursue particular concepts, the Council also offers suggestions at a broader policy level. For example, during a discussion concerning the plan for recompetition of the AIDS Clinical Trials Group, the Council suggested

strengthening linkages between adult and pediatric units and fostering the enrollment of underrepresented populations. A presentation by the Sexually Transmitted Diseases Branch led to the Council's recommendation that NIAID collaborate with other Institutes when conducting behavioral research.

NAAIDC also used concept review sessions to voice support for several ongoing programs. For example, a discussion of the Accelerated Development of Vaccines Program prompted NAAIDC to commend the potential of Cooperative Research and Development Agreements and to support the use of this mechanism for facilitating collaborative support of projects at all levels of research.

NIAID PROGRESS TOWARD ACHIEVING ITS OBJECTIVES

The Council is pleased to describe NIAID's progress toward its goal of preventing and treating a broad spectrum of infectious diseases as well as disorders of the immune system. Under the incisive direction of the NIAID Director, Institute-supported scientists are working to understand the causes of these conditions and to develop protective measures such as vaccines. Until prevention is possible, research efforts will include investigations aimed at improving diagnosis and treatment, thereby reducing the effect of these diseases on the Nation's health. During the past decade, NIAID's foundation in basic research has facilitated the Institute's response to newly emerging health problems such as AIDS and Lyme disease. It also has allowed NIAID to develop new approaches to preventing, diagnosing, and treating sexually transmitted diseases (STDs), TB, and other reemerging illnesses that are posing renewed threats to U.S. populations.

In addition to conducting and supporting longstanding scientific research programs in these areas, NIAID emphasizes studies on transplantation immunology, gene therapy, and other areas that are likely to have a profound effect on public health. Recognizing its global responsibility in the efforts to prevent disease, the Institute supports several collaborative international research projects. NIAID also focuses on efforts to address diseases that disproportionately affect minority groups and women and to enlist representatives of these groups to participate in clinical and epidemiologic studies. In addition, the Institute continues to place a high priority on training programs that seek to develop investigators qualified to conduct research in key scientific areas. The accomplishments described below are just a few examples of the results of NIAID's commitment to excellence in biomedical research and highlight the Institute's potential to make vital contributions to protecting our Nation's health.

Vaccine Development. In the ongoing battle to provide protection against infectious diseases, NIAID supports a broad spectrum of research aimed at developing new and improved vaccines. The Institute's basic research on the pathogenesis of infectious diseases is identifying new targets for immunologic attack and devising novel approaches to vaccines using innovative tools of biotechnology. NIAID is drawing on this knowledge and technology to provide scientific and programmatic direction for the Children's Vaccine Initiative, an international effort to ultimately develop a single oral vaccine that will provide lifelong immunity to the major infectious diseases of childhood. NIAID-supported scientists achieved a recent breakthrough in protecting children from disease by developing a new technology for producing vaccines that immunize infants against *Haemophilus influenzae*

type B (Hib), the leading cause of bacterial meningitis in young children. Additional NIAID research focuses on developing an improved vaccine for pertussis (whooping cough), a highly contagious childhood disease.

The dramatic increase in the incidence of STDs during the latter half of this century has increased the urgency for creating vaccines that will facilitate their control. NIAID-supported research in this area includes a phase II clinical trial to test the first genetically engineered vaccine for genital herpes.

The Institute also conducts and supports the clinical testing of several other new or improved vaccines, including those designed to provide immunization against malaria and hepatitis A.

HIV Infection and AIDS. Perhaps no prospective vaccine is more eagerly awaited than one to protect against HIV infection and AIDS. Because no cure for AIDS exists to date, the development of a safe and effective vaccine is an international health priority. NIAID supports collaborative groups that seek to conceptualize and develop candidate AIDS vaccines and to identify vaccine adjuvants. NIAID-supported scientists are investigating approximately 30 candidate vaccines, 6 of which are being evaluated for safety and efficacy in humans at five AIDS Vaccine Evaluation Units located throughout the United States. Recent research advances have increased optimism that the creation of an AIDS vaccine is feasible.

Until an AIDS vaccine is developed, research efforts also must focus on finding ways to treat HIV infection and its devastating progression to AIDS. NIAID supports treatment research through the AIDS Clinical Trials Group (ACTG), a network of 59 AIDS Clinical Trials Units (ACTUs) that evaluate promising therapies for AIDS and its associated opportunistic infections. Recent ACTG clinical studies have made significant contributions to the development of effective treatment for AIDS, HIV infection, and related opportunistic infections. The decision by the Food and Drug Administration (FDA) to approve the use of lower doses of azidothymidine (AZT) to treat AIDS and the early stages of HIV infection were based on two landmark ACTG studies. ACTG data also contributed to the recent FDA approval of dideoxyinosine, an antiretroviral drug licensed for treating HIV infection; foscarnet for treating retinitis caused by cytomegalovirus infection; and fluconazole, a less toxic drug for maintenance therapy to prevent recurrences of cryptococcal meningitis.

NIAID has broadened the base of its clinical investigations with a growing number of protocols conducted by the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) and the establishment of the Division of AIDS Treatment Research Initiative (DATRI). The CPCRA network of 17 community-based treatment programs enlists the participation of community health care providers and their patients in studies aimed at developing effective therapies and improving the quality of health care for HIV-infected individuals. CPCRA also provides a mechanism for addressing the needs of populations previously underrepresented in clinical studies. DATRI is a new clinical network designed to facilitate the rapid investigation of critical questions concerning AIDS therapeutic agents or innovative treatment approaches and of potentially effective treatments that may fall outside the immediate priorities of ACTG and CPCRA. The program will conduct phase I and phase

II clinical trials at sites throughout the United States, and treatments that show potential will go on to further testing in later-stage trials.

Sexually Transmitted Diseases. STDs are a critical global health priority because of their interrelationship with AIDS and the potentially devastating effect of their complications on women and infants. In addition to vaccine development efforts, NIAID supports an extensive portfolio of research on these diseases. For example, the Institute recently funded five STD Cooperative Research Centers (STDCRCs) to conduct research on the prevention and control of STDs. Each center addresses research questions on three or more STDs, using a multidisciplinary approach that combines basic science, clinical, and epidemiologic research as well as behavioral intervention strategies.

Tuberculosis. After decades of steady decline, the incidence of TB has begun to rise in the United States, especially among the underprivileged and minority populations. The increase in active disease among patients with AIDS and the emergence of drug-resistant cases of TB have raised additional concerns and prompted NIAID to place renewed emphasis on research aimed at diagnosing, preventing, and treating this illness. NIAID supports a full range of basic, clinical, and applied research projects on TB, including efforts to develop new and improved vaccines and diagnostic tests as well as more effective and less toxic anti-TB drugs. Clinical trials conducted through CPCRA are evaluating the safety and efficacy of drugs to prevent active TB in patients infected with HIV and *Mycobacterium tuberculosis*. In addition, the Institute cosponsored a workshop titled Future Directions in Tuberculosis Research, which brought together more than 80 scientists and other experts to develop goals for future research. In February 1992, NIAID also convened a meeting of outside experts to develop a scientific agenda for addressing the problem of TB.

Asthma. Effective prevention and control of noninfectious diseases continues to be a goal of NIAID's basic and clinical research efforts. For example, the Institute supports a number of studies on asthma, which affects an estimated 9 to 12 million Americans. Since the late 1970s, rates for hospitalization and death due to asthma have risen steadily in the United States, particularly among minority children and the economically disadvantaged in urban areas. NIAID is attempting to reverse this trend by supporting extensive research on the disease. The Institute has initiated the multicenter National Inner-City Asthma Study to identify factors that contribute to the increased incidence and severity of asthma among black and Hispanic children living in the inner city. NIAID recently funded eight centers in cities throughout the country to participate in the study.

Transplantation Immunology. An estimated 170,000 Americans currently have total and irreversible kidney failure or end-stage renal disease (ESRD) and must receive hemodialysis or kidney transplantation to remain alive. However, immunologic rejection of transplanted organs remains an obstacle to broader utilization of kidney transplantation. To help solve this problem and to improve the prognosis for patients with ESRD, NIAID supports studies to improve tissue typing and to develop ways of preventing graft rejection by fostering transplantation tolerance. The Institute recently launched the first NIH cooperative clinical trial in kidney transplantation, a multicenter prospective study designed to translate some of the most recent developments of basic research into new immunosuppressive modalities to prevent kidney graft rejection.

Gene Therapy. Another innovative area of research that may have a profound effect on public health is the use of gene therapy to treat inherited disorders. Recent advances in the molecular biology of immunodeficiencies have allowed NIAID researchers to develop methodologies for correcting certain inborn errors of immunity. For example, NIAID intramural scientists recently cloned the fourth and last gene that can cause chronic granulomatous disease (CGD), a rare childhood illness characterized by recurrent severe infections that often lead to death at an early age. The cloning of this gene provides researchers with the material needed to develop a genetically engineered therapy or cure for CGD. The resulting approach eventually may have broader applications for the treatment of other inherited immunodeficiencies. Basic research on CGD also has enabled NIAID intramural investigators to identify a successful chemotherapy for the disease.

Women and Minorities. Women and minority populations suffer disproportionately from certain infectious and immunologically mediated diseases and their sequelae. Consequently, NIAID has emphasized research on these diseases as well as efforts to encourage the participation of these groups in relevant clinical and epidemiologic studies. The Institute is responding to the growing number of minorities and women infected with HIV by investigating broader issues associated with the disease in these populations and by encouraging the representation of these groups in clinical trials. NIAID also has initiated three epidemiological investigations to study HIV in infected women, most of whom are members of minority groups. In addition, the Institute organized the first National Conference on Women and HIV to develop recommendations for future research. NIAID-supported research on STDs focuses on conditions such as pelvic inflammatory disease, human papillomavirus infection, and genital herpes, which have a disproportionately severe impact on women and minority populations. The Institute also supports research on the immune dysfunctions associated with systemic lupus erythematosus and other autoimmune diseases that disproportionately affect women and certain minority groups.

RECOMMENDATIONS FOR FUTURE PROGRAMS AND POLICY

The Council welcomes the opportunity to communicate concerns and recommendations that have arisen during the past 2 years of its activities. In its advisory role on policy development and program implementation, NAAIDC has considered several critical issues affecting the future direction of NIAID. The following discussion summarizes the Council's concerns and recommended approaches for addressing these issues.

Congressional Earmarking of Funds. NAAIDC views with concern the increasing tendency of Congress to include requirements for the support of specific research initiatives in its appropriations to NIAID. The Council appreciates the responsiveness of Congress to emerging public health issues. However, the Council believes that congressional earmarks should be supported by the scientific knowledge base as well as by funds to finance these new research priorities. The Council notes that NIAID recently has had to absorb a growing number of unanticipated charges to its budget for congressionally mandated research initiatives. Consequently, the Institute has found it increasingly difficult to address congressional priorities while sustaining its commitment to investigator-initiated research and critical research programs in vaccine and drug development, which contribute significantly to the basis for many advances in biomedical science and public health. The Council urges Congress to ensure the betterment of biomedical research by earmarking new

initiatives only when dictated by science and only when accompanied by additional funds to conduct the specified activities.

Staff Recruitment and Retention. NAAIDC also is concerned about Federal budget restrictions and policies that have had an adverse effect on NIAID's ability to recruit and retain qualified scientific and administrative staff. The Council recognizes the important contribution of NIAID staff in overseeing the Institute's extramural program and the outstanding accomplishments of the Institute's intramural scientists. NIAID's commitment to excellence in research has enabled the Institute to attract highly qualified investigators and administrators. However, NIAID's ability to recruit and retain the best staff has been hampered by limitations imposed on budget categories that include salaries. These restrictions force the Institute either to decrease the size of its staff or to decrease the salaries paid to staff members. NAAIDC believes that either alternative adversely affects NIAID's ability to fulfill its mission in biomedical research. Therefore, the Council discourages Congress and the Administration from imposing budget limitations that create barriers to the recruitment and retention of staff. The Council encourages the Administration to use the new Federal Employees Pay Comparability Act as the cornerstone of additional efforts to provide competitive salaries for Federal workers. The Council also recommends that Federal personnel structures, performance systems, and administrative requirements be simplified to provide more inducements for staff recruitment and retention.

Financial Management and Cost Containment. NAAIDC recognizes the importance of strict financial management and cost-containment strategies in an era of limited research dollars, escalating biomedical research costs, and Federal deficit reduction efforts. However, the Council is concerned with certain congressional approaches to achieving these goals. For example, the practice of specifically targeting the number of grants that must be funded each year without providing appropriations for these awards has forced NIAID and other NIH Institutes to make programmatic reductions in the grants they support. In addition, the congressional focus on research project grants tends to deemphasize other important funding mechanisms. For example, NIAID uses contracts to support some of its most outstanding research on vaccine and drug development. NAAIDC supports the approach taken by NIH in its financial management plan, which seeks to ensure an appropriate balance among all the various mechanisms of research support.

The Council also is concerned that congressional limits on the rate of funding increases for ongoing grants have been lower than the recognized inflation rates as indicated by the Biomedical Research and Development Price Index. These limitations are particularly detrimental to NIAID, which supports many important but expensive clinical and epidemiologic studies. Congress must recognize that unless it provides adequate resources to finance the full cost of scientific investigations, it faces a gradual but inevitable decline in the productivity of federally funded research.

Biomedical Research and Health Care. NAAIDC acknowledges that although the actual delivery of health care per se is not part of the NIH mandate, efforts to increase the application of NIH research are within the agency's purview. The Council also recognizes that growing constraints on domestic spending have prompted a corresponding increase in demands that biomedical research yield practical results, particularly in improved health care. NAAIDC is pleased to note that NIAID has sought the Council's advice regarding the

appropriate balance between support for basic research and for research leading to improvements in health care. The Council recommends that NIAID remain steadfast in its commitment to basic undifferentiated research, which provides the foundation for all improvements in public health. NAAIDC also urges the Institute to continue exploring its role in improving health care by conducting an ongoing dialogue with Congress, scientists, industry, constituency groups, and all relevant Federal agencies. The Council believes that NIAID's commitment to both aspects of biomedical research is needed to ensure that our Nation's people receive full and timely benefits from the Institute's advances in preventing, diagnosing, and treating disease.

MAXIMIZING RESEARCH RESOURCES THROUGH NIAID PREVENTION RESEARCH

The development of methods for preventing disease remains one of the most promising approaches to solving public health problems and improving the health status of U.S. populations. Vaccines and other prevention intervention strategies have led to dramatic declines in the incidence of diseases that once afflicted millions of American children and adults. Prevention measures also help relieve the economic burden to society and patients of using increasingly sophisticated and expensive technology for diagnosing and treating disease.

In addition to reducing morbidity and mortality associated with infectious diseases, dramatic reductions in illness and associated health care costs can be expected from the development of new and improved vaccines to prevent diseases such as STDs, rotavirus infection, and influenza.

With its long and fruitful history of basic research in immunology and microbiology, NIAID is uniquely positioned to maximize the return on dollars invested in biomedical research by increasing scientific knowledge about costly diseases and by accelerating the development of prevention and treatment methodologies for these illnesses. Increased support for these efforts offers one of the best hopes for realizing public expectations regarding the ability of biomedical research to alleviate and prevent suffering and death from human disease.

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

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NATIONAL ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES ADVISORY COUNCIL

INTRODUCTION

The Advisory Council of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is pleased to provide this report of its activities for fiscal years (FYs) 1991 and 1992. These have been remarkably productive years for NIAMS in terms of scientific advances, the development of its intramural program, and increased funding of its activities. Under the dynamic and forceful leadership of its Director and advisory bodies, our relatively young Institute has reached a critical phase in its history. While considerable progress has been made, much work remains to be done. We are pleased to outline this progress to the Congress of the United States on selected accomplishments of NIAMS and to provide recommendations for future activities.

NIAMS is responsible for research related to diseases and disorders of the joints, soft tissues, bones, muscles, and skin which, throughout life, affect virtually everyone and jeopardize the health and well-being of American people, including large segments of the female and black populations. The majority of these diseases inflict long-term pain and suffering, and severely limit an individual's ability to work. The suffering and disability they cause cost the taxpayers billions of dollars annually. Because the diseases and disorders addressed by NIAMS-funded scientists affect the fundamental structures necessary to human form and motion—the skeleton, skin, muscles, and joints—this research is fundamental to the health, happiness, and economic productivity of every working American.

In addition, these diseases increasingly affect the elderly. At least 24 million women in this country suffer from osteoporosis, a disorder that leads to deterioration of bone, with an estimated annual cost of \$10 billion. Back pain affects 80 percent of Americans at some time in their lives and is the most important cause of disability in otherwise healthy young people. More than 37 million Americans—1 in 7—are afflicted with one of the over 100 forms of arthritis or rheumatic diseases. As many as 60 million Americans, fully one-quarter of our population, suffer from one or more skin diseases, including a host of rare, disfiguring, and potentially fatal disorders. Furthermore, diseases affecting the skin are the leading cause of time lost from work because of occupational illness.

SUMMARY VIEW OF THE COUNCIL

The Council is deeply concerned about the future of biomedical research in the fields of arthritis, musculoskeletal, and skin diseases. Extraordinary opportunities abound for the development of new insights, as well as for identifying novel forms of therapy. Unfortunately, while we are on the threshold of momentous discovery, the support needed to achieve these triumphs is withering away. The scientific community, while deeply grateful to the Congress and the American people for their history of generous support for biomedical research, is, nonetheless, dismayed by the apparent unwillingness to follow through with the resources needed to accomplish these vitally important goals.

Biomedical research and biotechnology could well provide a major stimulus for resurging American leadership in world economic development while simultaneously affording the means for improving the health and quality of life of our people.

The Council believes that our scientific infrastructure in terms of people, facilities, and equipment is quietly lapsing into mediocrity and, without major new investment, our competitive position in this vitally important area will continue to slip.

OVERALL RECOMMENDATIONS

- NIAMS should make certain that its goals and direction are consistent with those of the *National Institutes of Health Draft Strategic Plan* that is currently being developed.
- NIAMS should strengthen its support of research, addressing diseases of the joints, muscles, bones, and skin of women consistent with the Women's Health Initiative.
- NIAMS should make every effort to communicate the scope and the success of its research agenda to the American people.
- NIAMS should do its utmost to attract and retain young scientists into its research programs. Particular attention must be paid to minorities and women in this regard.
- NIAMS should expand its support of research in rehabilitation of patients suffering from chronic diseases of the joints, muscles, bones, and skin.
- NIAMS should assure that strong innovative research is supported in the areas of epidemiology and prevention of disease.
- NIAMS should substantially increase its support of clinical trials and clinical investigators.

COMMENTS, CONCERNS, AND SPECIFIC RECOMMENDATIONS

Recommendation. In our judgment, levels of support for NIAMS programs should be increased over the FY 1992 levels by \$103.1 million in FY 1993 and an additional \$26.9 in FY 1994. The Council remains deeply concerned about the inadequate level of overall funding for the scientific programs of NIAMS. This situation persists despite the strong recommendations of previous Councils and in spite of the extraordinary advances achieved by those scientists who were fortunate enough to receive support from NIAMS. Furthermore, the congressional mandate for a fiscal management plan at NIH has imposed a financial straitjacket at the Institute by mandating fixed formulas for incremental funding of new, as well as competing and noncompeting renewal, applications. This results in an insidious undermining of the scientific review process and forces talented scientists with superb research programs to make arbitrary decisions about deleting promising areas of research. Greater flexibility in funding decisions is required.

The Council is particularly concerned by the arbitrary and capricious administrative actions necessitated to meet the mandated total number of grants to be funded from a restricted appropriation that is not adequate to support the recommended budgets required for the approved scientific projects.

Recent fiscal constraints have hampered the growth and development of current and future advances in arthritis, musculoskeletal, and skin diseases. In FY 1991, NIAMS received only 2.6 percent of NIH dollars for funding its extramural program.

NIAMS Recommended Budgets, FY 1993 and FY 1994

Dollars in Millions

	1992 Appropriations	1993 Recommendation	1994 Recommendation
Research project grants	138.2	198.8	213.6
Research centers	23.0	36.4	39.0
Other research	6.7	13.1	13.7
Research training	6.9	10.4	10.3
Research and development contracts	4.0	10.9	14.9
Intramural research programs	15.8	23.9	27.5
Research management and support	<u>9.4</u>	<u>13.7</u>	<u>14.9</u>
Total	203.9	307.0	333.9

Recommendation. Funding should be provided for research project grants sufficient to support 50 percent of approved new and competing applications (at recommended budget levels) and to fund all noncompeting applications at their recommended levels. Moreover, funding of meritorious "First Independent Research Support and Transition" (FIRST) awards should be ensured by increased funding of the NIAMS extramural research program at the levels recommended. Substantial cuts in requested funding levels are extraordinarily destructive to the national research effort. The perception of funding instability becomes a powerful deterrent to talented young investigators considering a career in biomedical research. This, in turn, diminishes the caliber of the next generation of scientific talent that is so vital to the future health of the American people.

The Council strongly believes that investigator-originated (RO1) research project grants are the Institute's bedrock and must remain its highest priority in its overall extramural program. The FY 1992 NIAMS budget levels are anticipated to permit funding of only 24.8 percent of approved research project applications. This is a deplorable state of affairs and virtually assures that the rate of future progress will be painfully slow and that the attractiveness of research careers for younger scientists will continue to decline.

Recommendation. One of the major deficiencies in the NIAMS research agenda has been the failure to support clinical trials, which play a vital role in our ability to transfer expeditiously developing scientific knowledge into effective new treatments and cures for diseases affecting the joints, muscles, bones, and skin. In addition, clinical trials are essential to develop and maintain this Nation's leadership in biotechnology. It is a source of great concern to the Council that so many of the clinical trials needed to verify the safety and efficacy of drugs and devices have been ceded to industry. We believe that NIAMS should be a leader in developing strong and mutually beneficial relationships with emerging biotechnology companies and the pharmaceutical industry.

NIAMS has developed a carefully considered agenda for clinical trials. Among those that are urgently needed include defining the safety and efficacy of bisphosphonates in the treatment of osteoporosis; identifying the long-term effects of exercise and diet on peak bone mass; assessing combination therapies for the prevention of osteoporosis during the immediate postmenopausal period; treating the late stages of Lyme disease; treating erythema migrans; early and aggressive combination therapies for rheumatoid arthritis; determining the safety and efficacy of cyclosporine for systemic sclerosis (scleroderma) and psoriasis; using retinoids in the treatment of psoriatic arthritis; efficacy of 13-cis retinoic acid and other retinoid derivatives in the treatment of keratinizing disorders; and safety and efficacy of bromhexine in the treatment of Sicca Syndrome associated with Sjögren's Syndrome.

Epidemiological studies are crucial to gauge the prevalence of diseases and health-related disabilities and disorders, and funding must be made available to support such studies.

Recommendation. Research excellence in the intramural program is essential to the success of NIAMS and should complement the excellence of its extramural program. The intramural program of NIAMS must be strengthened. The Council recommends funding at a level of \$23.8 million for FY 1993. Many of our Nation's current scientific leaders have had research training at NIH. The Council is pleased with the recent establishment of the skin research and structural biology intramural programs and urges the establishment of an orthopedic program.

Recommendation. The NIAMS Center's budget should be increased by \$13.4 million to permit the establishment of eight additional Centers. All Centers supported by NIAMS should be funded at recommended levels.

Recommendation. The Research Career Development Program should be expanded to permit funding of 29 additional positions in FY 1993. This would require an additional \$2.5 million and would provide support for approximately 50 percent of approved applications for clinical investigator awards, individual physician-scientist awards, and research career development awards. Funding for research training should be increased to permit support of 296 trainees, which will require an additional \$3.5 million.

The Council endorses the concept of a series of graduated awards to provide appropriate levels of support for talented young investigators to realize their full potential. The complexity of contemporary research requires sustained periods (4 to 5 years) of

training in rigorous environments where trainees are permitted maximum protected time to pursue their scientific development. Furthermore, efforts should be made to identify novel approaches to enhance the appeal of careers in biomedical science for young physicians. For example, the development of some type of financial incentives that would permit payback or forgiveness of educational loans could be helpful in this regard.

Finally, there should be a well-defined plan for the recruitment of women and minorities into biomedical research careers in arthritis, musculoskeletal, and skin diseases. This may include the development of training programs specifically geared toward supporting those groups and support for programs at the high school level.

FISCAL YEAR 1994 RECOMMENDED BUDGET

The budget for NIAMS presented in the table represents the Council's view of an adequate level of support for the Institute in 1994. It is further recommended that subsequent fiscal year budgets be increased by a minimum of 10 percent per year to maintain these levels of support.

RESEARCH ADVANCES AND OPPORTUNITIES

NIAMS supports an extraordinarily broad range of scientific investigation in the fields of arthritis, musculoskeletal, and skin diseases. The following section contains a few selected highlights of the Institute's richly varied research agenda.

Rheumatic Diseases

- *Animal model for arthritis discovered.* Genetically engineered (transgenic) rats have been created in which the B27 gene was introduced and these animals have been shown to develop a type of inflammatory joint disease that is strikingly similar to B27 associated arthritis that occurs in humans.
- *Genetic defect discovered for collagen failure in osteoarthritis.* A single base mutation has been identified in the gene that codes for Type II procollagen. This results in structural weakness that is associated with premature collagen failure and the development of osteoarthritis.
- *Molecular basis for antigen recognition by the immune system.* Genetic abnormalities and certain environmental triggers such as sunlight may facilitate the development of these autoantibodies directed against an individual's own body structures. Future studies could lead to the development of novel therapies to combat this process.
- *Systemic lupus erythematosus in various racial and ethnic groups.* Epidemiologic data indicate that systemic lupus erythematosus is three times more common in black women than white women in the United States. A major challenge is to discover the factors (genetic or socioeconomic) that are responsible for these differences.

- *Lyme arthritis is due to chronic persistence of the causative spirochete in tissues.* This disease provides an excellent model of the mechanisms whereby microorganisms can cause human arthritis.

Bone Diseases and Bone Biology

The relationship between bone generation and bone degradation activity and the influences of a wide variety of cytokines, mediators, and other molecular signals on bone mineralization are actively being investigated.

The use of stem cells, various growth factors, osteoconductive and osteoinductive substances, and biodegradable materials, is receiving intense study for use as bone activation and repair, bone graft, and ligamentous replacement.

- *Estrogen action on bone.* Estrogen deficiency after menopause is the major cause of postmenopausal bone loss; this loss can be prevented by exogenous estrogen replacement. Clinical trials are needed to define the safety and effectiveness of estrogen replacement in postmenopausal women and to define the optimal dose and best method of administration to achieve the effect.

Muscle Biology

Inherited conditions, such as Duchenne Muscular Dystrophy and myotonic dystrophy, are crippling and cause enormous pain and suffering. Other conditions, such as periodic paralysis and malignant hyperthermia, may have severe consequences. Acquired myopathies and injuries can initiate degeneration that severely limits motion and activity.

- Giant proteins related to myofilament assembly, including titin, dystrophin, and nebulin, have been identified. Abnormalities in these proteins have been linked to certain forms of muscular dystrophy.
- These advances indicate that understanding is at hand regarding the impairment and destruction of skeletal muscle function by certain genetic diseases.

Musculoskeletal Diseases

Great advances have been made in the area of joint replacement, and defining the interaction between foreign materials and host tissues. As a result, advances in design features of implants and their effects on the surrounding bone in terms of bone remodeling are being accomplished.

- Impairments of the spine are the leading chronic causes of limitation of activity among persons 17-45 years of age. Studies are needed to define the multiple causes of low back pain to include degeneration versus aging of the disc; development of mathematical and animal models; quantification of the types and functions of biological components of spinal connective tissue; evaluation of the distribution and function of nociceptors in the spine; and identification of risk factors.

Skin Diseases

- *Epidermolysis bullosa.* Remarkable advances in understanding the structure, function, and composition of the basement membrane zone and the abnormalities that underlie the three basic types of epidermolysis bullosa demonstrate the successful outcome of promoting targeted areas of research through dedicated funding and program emphasis.
- *Molecular genetic basis of psoriasis.* Recent evidence suggests that altered expression of histocompatibility antigens, such as HLA13 and 17, may occur in affected individuals.
- *Gene therapy for epidermolysis bullosa.* Missing or defective Type VII collagen is a component of dystrophic epidermolysis bullosa. By transfecting genes that code for the missing or defective element with keratinocytes obtained from the affected individual, it may be possible to achieve substantial improvement of this disease and avoid the problem of tissue rejection.
- *Photoaging and cancer of the skin.* Studies are needed to define the mechanism responsible for ultraviolet-induced aging and strategies to reverse these effects, and to prevent or reverse the development of cutaneous cancer.
- *Molecular basis of blistering diseases.* Several diseases that predominantly affect the skin of the elderly result in blister formation as a consequence of autoantibodies directed against structural components of the patient's own skin. The molecules against which these antibodies are directed have been identified in several of these diseases.

*NATIONAL ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
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NATIONAL CANCER ADVISORY BOARD

INTRODUCTION

By law, the National Cancer Advisory Board (NCAB) includes 18 members appointed by the President (12 leading representatives of the health and scientific disciplines and 6 from the general public) and officials of 12 other Federal agencies with cancer-related responsibilities as ex officio members. The Board conducts the final review of all National Cancer Institute (NCI) grant applications and advises the Secretary of the Department of Health and Human Services and the Director of NCI on the National Cancer Program. NCAB promotes scientific excellence and advises NCI on resource allocation and a broad range of policy and program issues. This report highlights selected program initiatives, research advances, and key Board activities and concerns during 1991-1992.

PROGRAM INITIATIVES AND POLICY ISSUES

Cancer Centers. The Cancer Centers Program is a cornerstone of the National Cancer Program and a key resource for transferring discoveries in basic research to human applications for prevention, diagnosis, and treatment. The Board notes the successful implementation of the new criteria for cancer center comprehensive designation and the increased emphasis on community service and outreach. Regional breast cancer education summits were sponsored at eight NCI-designated comprehensive cancer centers in 1992. Through cancer education grants, comprehensive cancer centers promote the transfer of state-of-the-art technology in cancer treatment, diagnosis, and prevention in their geographic regions. Cancer centers are expected to play a major role in a new initiative that will support multidisciplinary approaches to research on breast, lung, and prostate cancers. Specialized Programs of Research Excellence (SPOREs) for each of these cancers will foster basic/clinical research collaborations, develop research resources, provide career development opportunities, and encourage inter-institutional research. The Board has encouraged the establishment of new cancer centers in underserved areas. Twelve planning grants were awarded in 1992 to assist institutions, especially in States without a cancer center, to be able to compete successfully for cancer center core grants.

Education and Training. The Board is concerned that in recent years NCI's training budget has remained essentially flat, as investment in training is necessary to ensure a strong cadre of clinical and basic investigators. Recognizing that science education and training occur at many levels, NCI has developed a range of training opportunities for high school and undergraduate students as well as graduate students, postdoctoral, and new investigators. Enthusiasm has been especially high for NCI's Science Enrichment Program, a 5-week summer education experience to encourage underrepresented minority and underserved youth to pursue careers in scientific research. Beginning in FY 1992, regional programs are being supported to build on the success of the 2-year national program.

Particular efforts are directed at training a cadre of investigators for clinical and for cancer prevention and control research. A new cancer prevention and control education program trains clinical oncologists in the use of public health approaches and behavioral techniques for interventions in cancer prevention, detection, and diagnosis. It is also designed to orient health professionals toward careers in prevention and control research by

providing them with basic knowledge in cancer biology, prevention, and control, and the skills to execute intervention trials. Preventive Oncology Academic Awards support career development in cancer prevention for Ph.D., M.D., or equivalent professionals who are not yet fully independent investigators. The Clinical Oncology Research Career Development Program funds grants to prepare physicians for research careers.

Increasing Access to Cancer Treatment Information. Sharing the most up-to-date cancer treatment information with health professionals, cancer patients, and their families in the United States and other nations continues to be a high priority. NCI actively promotes its computerized data bases, Physician Data Query (PDQ) and CANCERLIT, which are available online through the National Library of Medicine and commercial vendors, and on CD-ROM discs that can be read with local equipment, avoiding telecommunications charges. CancerFax is a relatively new NCI service that provides cancer treatment information from PDQ using telefacsimile technology.

Improving the Health of Minorities in the United States. Cancer incidence and mortality rates for Black Americans are higher than for white Americans, for some sites markedly so. For selected malignancies, rates are disproportionately high among Hispanic Americans, Native Americans, Alaska Natives, and Native Hawaiians. Research indicates that at least some of these disparities are related to poverty rather than race or ethnicity. Limited access to health care, often a function of poverty, also contributes to higher cancer rates. NCI and NCAB are firmly committed to finding ways to address the special problems of cancer and poverty, while recognizing that a number of factors are beyond the NCI mission. The NCAB has encouraged initiatives to increase recruitment of minorities and the underserved to clinical trials, develop methods to overcome barriers to cancer screening and treatment, and provide information on health promotion to hard-to-reach populations. The National Black Leadership Initiative on Cancer, first proposed by Secretary Sullivan during his NCAB tenure, involves local community leaders in promoting cancer prevention, screening, and state-of-the-art care, and serves as a model for a new National Hispanic Initiative and Appalachia Initiative.

The Minority-based Community Clinical Oncology Program (MBCCOP) was created to give minority populations greater access to cancer treatment and control clinical trials. Twelve MBCCOPs are currently funded, each with greater than 50 percent of new cancer patients from minority groups. NCI also supports research to identify and remedy key factors that contribute to avoidable mortality from specific cancers, especially breast and cervical cancers, in Black Americans and Native Americans. NCI has developed and distributes numerous educational materials and health messages targeted to Hispanics and Black Americans.

Culturally sensitive researchers and clinicians can address the problems contributing to disproportionate cancer rates among minority and medically underserved groups. Cancer Control Research Networks have been established for Black Americans, Hispanic Americans, Native Americans, Alaska Natives, and Native Hawaiians to foster cohesive groups of researchers with experience in, and sensitivity to, the cancer control needs of these populations. Special grant supplements support the inclusion of minority investigators at all levels of their education and training on NCI-funded research grants. The new Minority

School Faculty Development Award will help minority institutions strengthen their training in cancer-related disciplines.

Women's Health Issues. NCI is committed to a comprehensive approach to women's health that includes basic research, clinical trials, education and information dissemination, and the cancer centers. NCAB is dedicated to ensuring that vigorous research efforts address cancers unique to women or of special concern for women, and that women are adequately included in NCI-supported clinical research. In 1991 the Board created a new Subcommittee on Women's Health and Cancer, which may advise on all aspects of these issues.

The NCAB strongly supports two major initiatives to promote breast cancer screening around the Nation. In 1991, NCI and the Susan G. Komen Foundation sponsored a Women's Leadership Summit on "Women in the Workplace: The Challenge of Breast Cancer" to motivate and aid the business and labor communities to sponsor early detection and treatment programs for breast cancer. A series of regional summits were funded at NCI-designated cancer centers in 1992. With NCI collaboration, the National Basketball Association (NBA) players' wives will promote breast cancer screening in NBA cities through personal appearances before community groups and on television. The NCI Office of Cancer Communications has created superb culturally sensitive materials to promote breast and cervical cancer screening to various populations of women.

Tamoxifen is a hormonal therapy that can prevent recurrent breast cancer and the development of a second primary breast tumor when used as adjuvant therapy following surgical removal of a primary breast cancer. A clinical trial was activated in FY 1992 to assess the ability of tamoxifen to prevent breast cancer in 16,000 women at high risk for this malignancy. It is estimated that tamoxifen could reduce the incidence of primary breast cancer in postmenopausal women by 30 to 50 percent. Its effects on lipid metabolism and bone mineral density will also be explored in the study.

In December 1990, NCAB reviewed a proposal for a large-scale trial of the ability of a low-fat diet to prevent breast and other cancers and cardiovascular disease in women. The Board was concerned about the general applicability of the dietary intervention and advised that NCI first support studies of interventions targeted to minority and low-income women. This research has been initiated. Study findings and participants will be incorporated in the Women's Health Initiative, a trans-NIH study of strategies to prevent cancer, heart disease, and osteoporosis, leading causes of death and disability in women.

Cancer and Aging. Persons aged 65 and over comprise 12 percent of the population but account for 58 percent of all new cancer cases and two-thirds of all cancer deaths. For several malignancies, persons aged 65 and over are more likely to have advanced disease upon initial diagnosis. This suggests that targeted health promotion and early detection efforts could benefit this age group. Given the impact of cancer on older Americans and the fact that the over 65 population is growing rapidly, NCAB has encouraged increased research in areas such as early detection, diagnosis, and treatment of cancer for this age group. In 1991 a new NCAB Subcommittee on Aging and Cancer was empaneled to advise on research initiatives. The Board encourages continued collaboration with the National Institute on Aging, not only to address cancer in older individuals, but also to gain insights into the cancer process through knowledge of the basic biology of aging.

Encouraging Clinical Research. An increase in investigator-initiated clinical research is essential to hasten the translation of basic science advances to clinical application. The Board has encouraged NCI's efforts to stimulate high-quality, innovative clinical research proposals and to ensure their appropriate review. A program announcement was issued in 1991 seeking applications in all modalities of clinical therapeutic research, and NCI has sponsored education sessions at professional meetings on preparing competitive grant applications. The Board notes the positive response of the NIH Division of Research Grants to the need to ensure that the initial review group to which such applications are assigned includes the expertise needed to evaluate applications covering the full spectrum of clinical investigations.

Reimbursement for the Clinical Care Costs of Research. Board members stress the need for continued negotiation with insurers on the issue of reimbursement for clinical care for patients receiving investigational therapy in cancer clinical trials. Financial support for the clinical care costs of research is critical to being able to develop new and improved cancer therapy. The Board is encouraged by the Blue Cross/Blue Shield agreement to provide payment for four NCI-funded intergroup clinical trials of autologous bone marrow transplantation (ABMT) for women with metastatic or high-risk breast cancer. It is in the best interest of patients and payers to obtain a rapid answer regarding the effectiveness of this approach to "rescuing" the patient from potential lengthy bone marrow suppression that results from high doses of chemotherapy.

Budget/Funding Policies. The Board has been concerned about budget trends for NCI over the last 10 years. In 1980 constant dollars the entire NCI budget declined 6.2 percent from 1980 to 1991, while that for NIH as a whole rose 26.5 percent. Although the NCI budget for research project grants rose 29 percent and intramural research was up 21 percent in 1980 constant dollars during this period, it declined significantly for other mechanisms. The cancer centers budget fell 14.4 percent, and funding for clinical cooperative groups and prevention and control dropped 33 percent below the 1980 base. NCAB members note with appreciation the action of Congress in providing a 16 percent increase for FY 1992 over FY 1991. This increase, the largest in any single year since 1976, will enable the Institute to pursue the many important research opportunities using all the valuable components of the National Cancer Program.

Members have several concerns regarding the NIH Financial Management Plan developed during 1990 and 1991. The Board recognizes the existence of a multitude of exciting scientific opportunities and qualified researchers at a time of national budget constraint. Given this reality, flexibility in the use of funding mechanisms is highly desirable. The practice of specifying the number of research project grants that must be funded in a fiscal year limits NCI's ability to use the most suitable grant mechanisms, and its impact on program project grants is of special concern. Program project grants support three or more collaborative projects, often involving basic and clinical components. Despite the multiple subprojects, the mechanism counts as a single grant, creating a disincentive to use this more expensive, but productive, mechanism when trying to meet a grant target number. The Board requests that NCI be given sufficient flexibility in target numbers of competing awards to permit funding those meritorious program project grants that, in the Institute's judgment, promote the lab/clinic interface in cancer research.

ADVANCES IN RESEARCH AND TREATMENT

The Board is excited by the many recent advances in basic and clinical research. Following are highlights from research updates heard and discussed by the Board during 1991-1992.

Chemoprevention. The aim of chemoprevention research is the identification of specific chemical substances, many of them dietary micronutrients, that demonstrate anticancer activity in humans. Recent chemoprevention research has shown that vitamin A-related compounds, including retinoids and carotenoids, can prevent oral cancers and new malignancies in patients with previous head and neck cancers. Retinoids have been tested as possible chemopreventive agents for epithelial carcinogenesis, and preclinical and early clinical data have shown they can reverse precancerous oral cavity and lung lesions. As many as 10 percent of long-term survivors of non-small-cell lung cancer (NSCLC) may develop second primary lung tumors. A new study will test the ability of 13-cis retinoic acid to prevent second primary tumors in patients whose NSCLC has been completely resected.

Taxol. The development of taxol as an anticancer drug is of continuing interest to the Board. This compound, found in the bark of the Pacific yew tree, has been identified as the most active new agent for refractory ovarian and breast cancer. NCI has taken multiple actions to ensure an adequate current supply, to develop future supplies that do not require destroying trees growing in the forest, to define further the role of taxol in treating breast and ovarian cancer while exploring activity against other tumors, to learn more about its unique biological effects on the process of cell division, and to discover related chemical compounds with similar biologic effects. The Board strongly endorses this multifaceted initiative that includes collaborations with industry, the Departments of Interior and Agriculture, and the academic community.

Multidrug Resistance (MDR). Multidrug resistance refers to the ability of cancer cells to protect themselves from anticancer agents through the increased activity of a membrane protein that pumps the drugs out of cells before they can be damaged. The MDR gene has been identified, and researchers are working on ways to block its effects. A transgenic mouse system in which bone marrow expresses the human MDR gene has been developed. These animals are resistant to chemotherapy and can be used to evaluate pharmacologic agents, immunotoxins, and liposome-encapsulated anticancer drugs designed to circumvent this kind of multidrug resistance.

The use of multidrug resistance to benefit cancer patients is also being studied. Transplanting drug-resistant transgenic marrow confers drug resistance in animals, suggesting that introducing the MDR gene into human bone marrow cells could protect them from drug-induced cytotoxicity during chemotherapy. This would overcome a major chemotherapy-related toxicity and allow more dose-intensive treatment.

Gene Therapy. The Board has followed the evolution and clinical implementation of gene transfer studies to determine if genetically altered cells can be introduced in cancer patients to produce therapeutic results. The goal of these studies has been to develop a method for transfecting cells with genes that express immunomodulatory cytokines, which, in turn, mediate the immune-based rejection of human cancers. In the initial clinical experiments, immune cells (lymphocytes) capable of reacting against the patient's tumor are identified and

isolated, their number and antitumor activity are increased, and they are then returned to the patient in an attempt to produce greater antitumor effects. These tumor-infiltrating lymphocytes (TILs) have been isolated from a tumor, and upon reinjection into the patient, home to tumor deposits and increase in number at those sites. In the next generation of studies, begun in October 1991, patients are receiving transfusions of TILs into which the human gene for tumor necrosis factor (TNF) has been inserted. TNF has substantial antitumor effects in mouse models, but its use in humans has been limited by its toxic side effects. To enable the use of larger doses in humans, TILs are genetically modified to produce large amounts of TNF and deliver it to the tumor site.

The Board notes a growing interest in gene therapy in the research community and encourages NCI to support this field. NCAB notes that this exciting endeavor is built on many years of basic research on the cancer process and laboratory research on viruses and cancer, biological response modifiers, and recombinant DNA technology and other areas of biological engineering. Cancer patients will continue to benefit from advances in these areas.

Tumor Suppressor Genes. These genes retard the development of cancer; their deletion or mutation is related to the development of malignancy. The most common cancer-related genetic change known at the molecular level is mutation in the p53 tumor suppressor gene, which is implicated in lung, breast, colon, liver, and many other cancers. The p53 mutational spectrum appears to differ among various cancers, and analysis of these mutations is providing clues to tumor etiology and to the function of specific regions of p53. Recent research has linked exposure to aflatoxin B, a carcinogenic mold product, to a specific alteration of the p53 gene. This observation provides the first strong evidence for a molecular mechanism for chemical carcinogenesis. A germ line p53 mutation has been found to be the genetic defect underlying the Li-Fraumeni syndrome, a familial cancer syndrome (including breast, soft tissue, brain, bone, and adrenocortical cancers and leukemia). This finding may help elucidate the genetic basis of cancer predisposition. Researchers are also studying the frequency of p53 mutations in the general population and their potential for cancer screening.

OTHER NOTABLE EVENTS

NCAB sponsored an anniversary symposium in November 1991 to observe the twentieth anniversary of the National Cancer Act, a time to reflect on research achievements that have expanded our understanding of the cancer process, improved detection, diagnosis, and treatment for many patients, and given us important clues for prevention. At the same time, much work remains to alleviate the burden from the group of diseases labeled cancer. This is a time for renewed dedication, but also for optimism.

Dr. Paul Calabresi was appointed Chairman of the NCAB in 1991, succeeding Dr. David Korn. Dr. Harold Freeman was appointed Chairman of the President's Cancer Panel in 1991 after the death of Dr. Armand Hammer. Dr. Hammer's enthusiasm and dedication to the National Cancer Program will be remembered. Also in 1991, Dr. Bernadine Healy was confirmed as Director of the National Institutes of Health. Board members salute her appointment and will work with her to promote excellence in biomedical research and its application to improving human health, as described in the *National Institutes of Health Draft Strategic Plan*.

NATIONAL CANCER ADVISORY BOARD

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NATIONAL ADVISORY CHILD HEALTH AND HUMAN DEVELOPMENT COUNCIL

INTRODUCTION

The National Advisory Child Health and Human Development Council (NICHD) again welcomes the opportunity to report to the Congress on the outstanding accomplishments and promise of research supported by this Institute. A superficial glance at a few disease statistics, particularly those concerning women and infants, suggests that the health of America's children—and thus the Nation's future—is in grave jeopardy:

Infant Mortality and Morbidity. In the United States, nearly 10 infants of every 1,000 die within the first year of life.

Genetic Disease. Reliable estimates indicate that genetic diseases strike 37 to 53 individuals out of every 1,000.

HIV Infections, AIDS, and Mortality in Women and Children. An estimated 1,500 to 2,000 HIV-infected children were born in 1989 as the result of maternal transmission of AIDS. If current trends continue, HIV/AIDS will soon be one of the five leading causes of death in children 1 to 4 years of age.

Disability. About 2.5 million children and 43 million adults suffer some form of physical disability.

Childhood Trauma and Injury. Injury and trauma are the leading cause of death and disability in American children and young adults, accounting for about half of all deaths in those under 15 years of age—and 80 percent of all deaths in the 15- to 24-year age group.

Infertility. Conservative estimates indicate that about 15 percent of all couples attempting pregnancy have difficulty conceiving and are defined as infertile. Female reproductive disorders associated with infertility include endometriosis (five to 15 percent of reproductive-age women), ovulation failure, and uterine fibroids (20 percent of reproductive-age women).

Unintended Pregnancy. More than half of all pregnancies in the United States are unintended, about 40 percent of them due to contraceptive failure.

These data depict only some of the problems that plague Americans along the continuum of human development. Although these health problems do not represent an exhaustive accounting of the needs served by NICHD, they do provide a context for appreciating the Institute's ongoing achievements—and the challenges that comprise its agenda for the immediate and long-term future.

In reviewing this report of the National Advisory Child Health and Human Development Council, it is important to remember that the morbidity and mortality statistics cited throughout this document provide only a glimpse of the impact of disease and disability on the lives of Americans. Health problems take a disproportionate toll on the millions

whose adverse socioeconomic circumstances are further marred by inadequate health care. Effective solutions will thus require advances not only in scientific and clinical investigation but also in social research and initiatives to ensure that the needs of the medically underserved are successfully addressed and met.

Biomedical progress is yielding improvements in the outlook for individuals struck by certain life-threatening conditions such as high-risk newborns and the victims of accidents and trauma. Although clinical research advances are saving their lives, many of these individuals must then contend with a lifetime of disabling problems. They thereby join a growing subset of the population whose health care needs can be met only through a more concerted, national effort in rehabilitation research and treatment. These needs were recognized in 1991 with the establishment of the National Center for Medical Rehabilitation Research (NCMRR) within NICHD.

PRIORITIES AND CHALLENGES FOR THE FUTURE

NICHD's programmatic priorities and challenges for the immediate and long-term future are best appreciated within the context of four interrelated domains: (1) maternal and child health research; (2) behavioral research; (3) population research; and (4) rehabilitation research.

Maternal and Child Health. The social and economic barriers to adequate access and utilization of health care services are alarmingly evident in this country's exceedingly high rate of infant mortality and morbidity. Low birth weight and prematurity, the two principal causes of infant mortality within the first year of life, are associated with these barriers in many parts of the population. Among the National Institutes of Health, the NICHD has primary responsibility for basic and clinical research concerning maternal and child health. These investigations have had substantial and positive impact on pregnancy outcome and support the conviction that every expectant mother should have ready access to perinatal health care services and that every child should have access to health care for at least one year after birth.

Research priorities for the Institute include the following clinical problems: high-risk pregnancy, fetal abnormalities, pre-term labor and birth, and abnormal adaptations of the newborn. These research activities draw on the collaborative expertise and knowledge of a broad base of scientific disciplines including molecular and cellular biology, obstetrics, neonatology, and the social and behavioral sciences.

Behavioral Research. Little is known about the subsequent, long-term effects of nutritional deficiencies, a poor nurturing environment, and exposure to drugs and other toxins during infancy and early childhood. There is reliable evidence that these hazards are associated with learning disabilities, mild mental retardation, and behavioral problems that usually are not detected until ages 8 to 10. Further analysis and evaluation are needed to provide a rational basis for intervention and clinical strategies.

In 1988, more than 10.5 million children under the age of 6, including 6.6 million under the age of 3, had mothers in the work force; another 18 million children between the ages of 6 and 13 had working mothers. According to reliable projections, the number of

working mothers with infants and young children will continue to rise in the course of this decade, and daycare will become an even more prominent setting for early childhood development. NICHD initiatives to study and assess the effects and quality of daycare need to be sustained and expanded. Focused on the medical, demographic, and psychological dimensions of daycare, these initiatives include a 10-site investigation, "The NICHD Study of Early Child Care." This study is assessing the development of children in varying child care arrangements, from exclusive parental care to extensive reliance on daycare during the first three years of life; the aim is to determine the health, social, emotional, linguistic, and cognitive outcomes associated with these different child care settings.

Population Research. Under the rubric of population research, NICHD has defined three priority research areas:

Fertility Regulation: Our current contraceptive methods and our understanding of the behavioral aspects of contraceptive use are inadequate. Improvement can come only from intensive population, laboratory, and clinical studies. Basic and clinical research should be directed at the development and evaluation of

- New and safer contraceptives, including oral contraceptives and new barrier devices for both men and women;
- Antifertility drugs for men;
- Immunocontraceptive vaccines;
- RU 486 and other antiprogestin drugs as contraceptives;
- Improved, reversible, and nonsurgical techniques for sterilization in men and women;
- Development of a contraceptive that is acceptable to adolescents.

Fertility and Infertility: Several key biologic and sociologic factors are now thought to underlie the widespread incidence of infertility in the United States. Sexually transmitted diseases, which can result in lasting injury to reproductive organs, and environmental toxins, which can adversely affect impregnation, may be examples of these factors. The current trend toward delayed childbearing appears to be closely related to increases in the actual number of infertile women. Population research in this area should include large-scale studies to define more precisely the causes of infertility and their relative incidence. Epidemiological studies to define normal fecundity and the relationship of natural fertility to age should also be conducted. Intensive laboratory research is needed to determine the basic pathophysiology of both male and female infertility.

Additional research into the technology, biology, and effectiveness of medically assisted conception is needed. A large number of couples could benefit from in vitro fertilization (IVF), but the success rate for this procedure has remained virtually unchanged in the past five years.

Reproductive Health: Endometriosis, uterine fibroids, and chronic pelvic pain in women, and impotence and varicocele in men are the major reproductive disorders that adversely affect not only fertility but the general health of men and women in this country. Comprehensive investigations at the basic and clinical levels are needed to

- Define the natural course of endometriosis and its causal nexus with infertility; determine the etiology of this condition, particularly the role of immunologic factors;
- Better define the etiology and hormonal regulation of uterine fibroids and develop enhanced methods for their surgical and nonsurgical management;
- Define the etiology and pathophysiology of chronic pelvic pain and develop and evaluate methods for its more effective management;
- Develop noninvasive diagnostic strategies for symptomatic, atypical, and subclinical forms of pelvic inflammatory disease (PID); develop new modalities to treat PID and reduce the incidence and severity of its sequelae.

Rehabilitation Research. The prefatory data on disability provide only a glimpse of the prevalence, various dimensions, and consequences of this problem. Twenty-two million Americans are hearing-impaired; 2 million of these are deaf. Such developmental disabilities as cerebral palsy and mental retardation affect 9.2 million. Partial or complete paralysis disables 1.2 million Americans. The Federal Government spends approximately \$40 billion annually to assist people with disabilities with medical and income support. The economic cost of disability is estimated at 6.5 percent of the gross national product.

By promoting medical rehabilitation research training in the United States, the NCMRR aims to fill a major void in our Nation's human resources for addressing the complex problems of disability in both the scientific and clinical domains. Courses on disability and rehabilitation are absent from most medical school curricula; the delivery of essential health care services to the disabled is limited by personnel shortages including shortages of physicians in the specialty of physical medicine. Basic and clinical rehabilitation research, a vital component of the foundation for new strategies to solve the problems of disability at the individual and social levels, suffers a dearth of investigators and infrastructural supports. Thus, NCMRR's priorities emphasize research training, including

- Increasing the number of new and established investigators entering the field, the diversity of research specialties, and the participation of groups now underrepresented;
- Creating research incentives and enhancing the priority of rehabilitation research;
- Increasing opportunities for single-investigator and collaborative, interdisciplinary studies of rehabilitation problems and related issues.

Medical rehabilitation research has traditionally focused on the causes of disability. Although this focus is vital, additional research is also needed to understand and alleviate the

functional consequences of the many disabling impairments for which current treatment is inadequate. These include neurophysiological dysfunction, musculoskeletal disorders, cancer rehabilitation, and geriatrics. Moreover, NCMRR is also committed to research involving the developmental aspects of disability, including long-term studies to illuminate the changing nature of disability over the lifespan and basic and clinical investigations to determine the role of maternal environmental factors in the pathogenesis of birth defects.

CONCLUSION

In light of the enormous health problems that face America's children, the Advisory Council is proud of the accomplishments of the NICHD and the research efforts it has planned for the future to attack aggressively the roots of these problems. The Advisory Council, however, wishes to underscore the vital importance of four key aspects of the Institute's programs for basic and clinical research.

The first is funding for the intramural and extramural programs of the Institute. The benefits of research for mothers, infants and children, and persons with disabilities have been clearly established, but adequate resources for developing new knowledge are still needed. Indeed, the gap between the promise of research and the resources required to attain that promise has created an atmosphere of crisis including loss of motivation and frustration in the American biomedical research community. Among the precipitants to this crisis is the congressional mandate that NIH fund 6,000 new grants annually. An adverse consequence of this arbitrarily fixed target is this: although only one-fourth of the research initiatives deemed meritorious by peer review panels eventually receive financial support, this funding is often inadequate. Thus, it is in the best interests of the Nation to seek and implement more flexible funding guidelines for use by NICHD and other NIH Institutes.

The Advisory Council also urges continued increases in Federal appropriations for biomedical research. In an era marred by unrestrained inflation in the cost of health care, the economic rationale for investing in biomedical research is unassailable. A sterling example is NICHD-sponsored research that developed screening for neonatal hypothyroidism. Nearly 900 newborns can be saved every year from a lifetime of arrested physical and mental development through screening for this condition. The total cost of the applied research and clinical trials required to develop this screening program was \$1.2 million; the annual savings in health care costs are estimated at \$206 million. Another example is the NICHD-sponsored Pittsburgh Tonsillectomy and Adenoidectomy Study, which demonstrated that these common procedures are *not* indicated in the great majority of cases; according to conservative estimates, this study accounted for 50 percent of the reduction in these procedures between 1981 and 1987.

The second key aspect of research that the Advisory Council wishes to underscore and safeguard is the importance of animal experimentation. Animal research has played—and will continue to play—an essential role in the progress of biomedical science and health care. It is simply naive to argue that tissue culture or computer modeling alone can provide an adequate substitute for investigating the causes and mechanisms of disease. Although such research must proceed within guidelines that prevent abuse and misuse, the essential role of animals in basic and clinical research must be recognized and preserved.

Third, the Advisory Council wishes to emphasize the importance of both fetal tissue research and fetal research. Ongoing controversies now cloud the immense potential of scientific activities in these two areas. Fetal tissue research holds enormous promise for our understanding of the cellular and molecular biology of health and disease, as well as for effective therapies for disorders of the brain and other organ systems. Fetal research has a demonstrated promise for the medical and surgical treatment of disorders in utero—and thus for improving the opportunities for health at one of the most critical junctures in human development. Research in these areas must be conducted in the context of ethically sound guidelines that serve to protect the needs and interests of parents, the unborn, and society at large. Guidelines for such research should be the focus of dialogue and discussion within and beyond the Federal sphere.

Finally, the Advisory Council must again state its opposition to the recently experienced limitations placed on funding surveys of sexual behavior and studies involving human in vitro fertilization. The limitations on the surveys prevent our full understanding of behaviors underlying contraceptive practices and the behaviors associated with the transmission of HIV and other sexually transmitted diseases. Without such an understanding of sexual behaviors, we are hindered in our ability to provide effective and acceptable contraception, to prevent risky behaviors, and to promote safe ones. Without research involving in vitro fertilization, we are limiting our ability to redress infertility through a promising new technology. Placing such limitations on research proposals, which, like these, have passed through a rigorous scientific peer review process and have been approved, compromises the integrity of the scientific peer review process and undermines both the work of investigators and the ability to make progress against major public health problems.

Rational approaches to all of these key aspects of research are vital to the health and well-being of children yet to be born, who will be cured or helped tomorrow by what NICHD does today.

NATIONAL ADVISORY CHILD HEALTH AND HUMAN DEVELOPMENT COUNCIL

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NATIONAL DEAFNESS AND OTHER COMMUNICATION DISORDERS ADVISORY COUNCIL

INTRODUCTION

The National Deafness and Other Communication Disorders Advisory Council is pleased to report on its activities for fiscal years 1991-1992 and to present to the Congress of the United States its views and recommendations relative to the areas of responsibility of the National Institute on Deafness and Other Communication Disorders (NIDCD). The areas of responsibility for NIDCD are research and research training on the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. The NIDCD also supports efforts to create devices that substitute for lost and impaired sensory and communications functions and conducts and supports research and research training that is related to disease prevention and health promotion. NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders and is committed to understanding how certain diseases may affect women, men, and members of minority populations differently. The majority of the Institute's support goes to a program of research grants, individual and institutional research training awards, center grants, and contracts to public and private research institutions and organizations. In accordance with the legislation that established NIDCD in October 1988, the NIDCD National Information Clearinghouse was established to collect and disseminate information to health professionals, patients, industry, and the public on research findings related to deafness and other communication disorders. Following the mandate of the legislation, National Multipurpose Research and Training Centers have been established.

Council Responsibilities. A responsibility of the Council is the review of applications for grants, contracts, and cooperative agreements. After preliminary review by scientific study sections, the Council assesses the relevance of the application to program priorities and considers the recommended funding of these grants. The Council also has an important responsibility to review the Institute's Implementation Plans. Being cognizant of the fiscal constraints imposed upon all government programs, as well as the high quality of research of the applicants, the NIDCD Advisory Council has made every effort to ensure that the NIDCD funds the best science as a means of accomplishing its mission.

The primary concern of the Council is the current inability to fund all excellent research. The Council expressed concern 2 years ago (*Third Biennial Report for Fiscal Years 1989-1990*) that the funding would only permit support of one in three applications that were recommended for support. The Council continues to be concerned because that ratio has worsened. It is a growing concern as the Council recognizes the increasing instability of scientific activity in this field and the missed opportunities to fund excellent science that would expand knowledge about the devastating diseases and disorders of hearing, balance, smell, taste, voice, speech, and language that directly impair the economic well-being and the quality of life for some 44 million Americans.

The National Strategic Research Plan. The NIDCD has developed The National Strategic Research Plan and instituted a mechanism to assure its regular updating. The National Strategic Research Plan is a volume that was created by more than 100 scientists and clinicians, that is driven by the scientific community, and that identifies needed research in

the areas of human communication. The work of updating is done by representative scientific panels. These expert panels update two of the six research areas in the NSRP each year so that no part of the plan will be more than 3 years without revision. This National Strategic Research Plan provides the scientific base for establishing the priorities for development and growth of the NIDCD.

RECOMMENDATIONS FOR FUTURE PROGRAM AND POLICY DIRECTION

The Council recognizes the special programmatic accomplishments of this new Institute: the NIDCD is supporting five National Multipurpose Research and Training Centers; the NIDCD has increased Minority Supplement Training; and the Institute has established the National Institute on Deafness and Other Communication Disorders Information Clearinghouse as a national resource.

The NIDCD Council makes several recommendations for future program and policy direction. The NIDCD Advisory Council recommends that

- The NIDCD place emphasis on funding research in all seven of the areas of human communication within the NIDCD's mission as provided for by the National Strategic Research Plan;
- Investigations in molecular medicine include programs related to hereditary hearing impairment and the molecular genetics of specific language impairment and dyslexia;
- Vaccine development, especially related to a vaccine for otitis media, be intensified; and that
- The structural biology of the Organ of Corti (hearing organ in the inner ear) will yield important information that will be extremely helpful not only in understanding the process of hearing but in investigating the best assistive devices to use based on the hearing loss of an individual. Investigation in biotechnology includes relating changes of genetic information to specific proteins in the auditory system.
- The Council recommends that diseases that affect the health of women, men, and members of minority populations differentially need to continue to be studied.

COUNCIL ACTIVITIES, FY 1991-1992

- Reviewed grant applications, including special attention to those from foreign institutions and to applications with potential problems involving the use of human and/or animal subjects or biohazards.
- Research subcommittee recommended (1) a yearly cap of \$1 million in direct costs for National Multipurpose Research Training Centers; (2) support of separate paylines for regular research projects and centers; and (3) a \$750,000 cap on program project and center grants to contain costs.

- Suggested future efforts to (1) examine and recommend mechanisms for promoting research in NIDCD program areas; (2) discuss specific research areas or questions raised by outside agencies and Congress; and (3) retain and improve the integrity of the Institute's programs by monitoring the distribution of support across the different scientific areas and mechanisms.
- Reviewed the Implementation Plan, as amended, for fiscal year 1993.
- Developed, through the National Advisory Council's Training Subcommittee, a report that recommended several activities to ensure a steady supply of investigators in the field of NIDCD research, including (1) compiling information on the success and effectiveness of previous and current mechanisms of training support; (2) encouraging vestibular researchers to train at facilities outside their institutions as a means of extending the use of the existing limited and uniquely equipped facilities as national resources for vestibular research; and (3) developing ways to contain tuition payments in order to increase the number of predoctoral students.
- Approved a recommendation to publicize the availability of the Senior Fellowship (F33). These fellowships are excellent opportunities for seasoned investigators who need to learn new techniques. This is a training opportunity for established investigators to change the area of his or her scientific focus.
- Recommended a total of five investigators for the NIDCD Claude Pepper Awards.
- Approved the recommendation that the project period for active RTC grants be extended from three to five years and that the Council would receive a periodic progress report on these grants. This action was recommended in order to provide stability for the research programs of the Centers during their initial award period, allow recruitment of high-level trainees, and ensure sufficient experience in continuing education and public information dissemination for adequate evaluation of their effectiveness.

Training and Career Development. The National Advisory Council Training Subcommittee developed a report that made several recommendations that the Council

(1) Gather information on the efficacy of training mechanisms that have been used in the past by (a) contacting current grant holders to determine which mechanisms were used to support their training, and (b) utilizing information from broader surveys of scientists from other sources in the fields covered by NIDCD;

(2) Promote multisite training for vestibular investigators to (a) attract additional scientists to vestibular research and (b) allow vestibular scientists to utilize the limited number of unique specially equipped facilities for their training and research;

(3) Promote the use of already available mechanisms (the Senior Fellowship, F33) and explore the development of new mechanisms not constrained by the limitations of current mechanisms to retrain seasoned investigators who need to learn new techniques;

(4) Explore possible mechanisms to expose students to research in the fields of human communication at much earlier stages of their education, including special training for high school teachers and development of possible training units for use in elementary or high school classrooms;

(5) Increase the number of predoctoral trainees by implementing, in cooperation with all the ICDs at NIH, a common cost containment plan to support tuition costs.

After monitoring the training and career development activities of the Institute and the efforts of the NIDCD to implement the NIH goals for minority representation and to achieve the recommendations of a special panel of advisors that had been convened in July 1989, the primary concern of the subcommittee was maintaining and enhancing the supply of highly qualified investigators for the future. The training of a sufficient number of predoctoral students in the communication sciences to provide highly qualified candidates for NIDCD postdoctoral training programs becomes the current goal.

There has been increased activity in these recommended areas, including

- Major institutions of higher education have augmented or designed new predoctoral training programs to meet this national need as outlined in the National Strategic Research Plan. In FY 1990, more predoctoral training positions were awarded for the support of candidates in speech, language, hearing, basic neurosciences, and medical genetics in the area of communication disorders than in the 5 previous years. Information provided to the scientific community regarding the availability of such support is starting to achieve the desired results. The major problem with this predoctoral initiative is the high cost of tuition. Many institutions that have the best record of educating high-quality students geared to biomedical research tend to be the very institutions that charge the highest tuition rates.
- NIDCD is cooperating with all the ICDs at NIH to maintain a common cost containment plan to support tuition costs. The results of this aggressive plan to increase well-trained doctoral students are not expected to be evaluated until FY 1996.
- The use of the short-term (3-month) training experience for medical students, minorities, and communicatively-impaired individuals is increasing at a rate much greater than expected when it was initiated in FY 1990. Of particular significance is the program to assign deaf students to the laboratories of basic scientists studying hearing, smell, and taste. Last year, five deaf students from Gallaudet University interviewed for four positions, and this year 27 deaf students interviewed for seven positions, and one student extended her stay to a full year of academic and laboratory and research training. This year, two persons who stutter will receive similar training in laboratories of basic speech scientists. It is intended that these programs will serve as models and be extended to a number of universities throughout the country and in government and industrial laboratories.

- The involvement of minority students in both short-term and predoctoral training has been increased with last year's award of the National Multipurpose Research and Training Centers. The recruitment of African-American, Native American, and Hispanic students has received special emphasis by these multidisciplinary centers. Since an informal evaluation of the contribution of minority investigators to NIDCD-supported research showed approximately six percent participation, the National Advisory Council recommends the early recruitment and training of these potential researchers if the Institute expects to achieve a reasonable commitment to minority researchers in the communication sciences.
- The career development program of NIDCD, which provides salary support to allow new investigators to be released from their clinical or academic responsibilities to pursue research, is showing two clear trends: Investigators pursuing clinical research, such as physicians and speech-language pathologists, are increasing while investigators pursuing the basic sciences related to hearing (balance, smell, taste, voice, speech, and language) are decreasing in the career development program. These trends are being experienced by all of the other ICDs and may reflect the 1988 requirement that the career development candidate must obtain other funds to support the actual laboratory work, i.e., equipment costs, supplies, travel, and other related research costs. Given the current tight funding situation, it is an unusual candidate who is capable of preparing a successful research grant before he/she has had adequate time to build a laboratory and accomplish meritorious research. No answer to this dilemma is offered in this report, but the National Advisory Council will continue to report new trends and attempt to determine a solution to the problem.

The NIDCD Advisory Council adopted specific recommendations to publicize the availability of the Senior Fellowship (F33) to support retraining of experienced investigators and recommendations to publicize the opportunities for multisite training and research in the vestibular area.

PROGRESS IN ACHIEVING INSTITUTE OBJECTIVES

Molecular Medicine. The NIDCD has made recent progress on two syndromic forms of hereditary deafness, Usher syndrome and Waardenburg syndrome, and an NIDCD grantee has recently announced the discovery on the long arm of chromosome 5 of the gene for a late-onset hereditary form of deafness found in a family in Costa Rica.

NIDCD-supported scientists are making progress on understanding the regeneration of sensory cells, unlocking the way to accelerate their repair and return to normal function. The NIDCD is focused upon the study of auditory and balance-related hair cells and the study of the olfactory neuroepithelium.

NIDCD investigators, in collaboration with a group of scientists from the Karolinska Institute and the University of Umea in Sweden, will soon embark on a major international research project to find the gene for dyslexia. Utilizing techniques of molecular biology and molecular genetics, NIDCD investigators will analyze DNA from blood samples received from Sweden to determine linkage.

Neuroscience and Behavior. A recent study, supported by NIDCD and the National Institute of Child Health and Human Development (NICHD), has shown that a mother's consumption of even small amounts of alcohol shortly before nursing changes the odor and, thus, the flavor of breast milk, causing the feeding infant to consume less. This research refutes popular folklore suggesting that drinking alcohol before nursing benefits the infant's feeding. While these beliefs have encouraged nursing mothers to drink alcohol as an aid to lactation, this new study provides the first scientific evidence that shows infants actually drink less breast milk when alcohol is present. In another study by the same investigator, garlic enhanced nursing behavior. These studies demonstrate the important practical applications of human chemosensory research.

A current longitudinal study is following a large number of preschool-aged children who stutter to determine factors that can be used for early identification of stuttering. This study will differentiate subtypes of stutterers and identify children at risk for severe stuttering who are, therefore, in need of intensive early intervention.

Prevention, Health Education, and Control. Preliminary results of an NIDCD-supported study of severely and profoundly deaf adults who first learned American Sign Language (ASL), either during or after childhood, indicate that there is a critical period that applies to the learning of sign languages, as well as to spoken languages. Researchers have also discovered that the age boundaries on language acquisition are much greater for first, or native, language learning compared to secondary language learning. These findings underscore the importance of language intervention very early in life for any child who is at risk for delayed language acquisition.

Health of Women, Minorities, and Underserved Populations. NIDCD intramural scientists have demonstrated that botulinum toxin injections are effective in restoring the voice in the treatment of spasmodic dysphonia, diseases that affect women disproportionately more than men.

Vaccine Development. *Haemophilus influenzae* is one of the three most common pathogens in the development of otitis media. Medical treatment of otitis media has been largely limited to antibiotics or surgical procedures. An NIDCD-supported project is the development of vaccines to provide immunity against the most common pathogens responsible for acute otitis media. These vaccines would provide early immunogenicity so that infants could be protected against otitis media and its associated hearing impairment during the period critical for speech and language development. Two promising antigens are being evaluated for potential vaccines. Otitis media is one of the major causes of hearing loss among minorities.

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NATIONAL ADVISORY DENTAL RESEARCH COUNCIL

INTRODUCTION: THE BROADENED SCOPE

The work of the National Institute of Dental Research (NIDR) touches the health of everyone in the United States and, through growing collaborations, touches the lives of individuals worldwide. In the early years, research efforts were oriented toward dental caries and periodontal diseases, the costly, painful, and prevalent conditions that were responsible for the widespread toothlessness of past generations. Dental research soon revealed the nature of these diseases and, importantly, what could be done to prevent them. These findings led to the widespread use of fluorides, a better-informed public, improved oral hygiene, and major dietary changes. As a result, we are seeing remarkable changes in the pattern of oral diseases—dramatic declines in caries in children and younger adults; milder and less extensive forms of periodontal disease in adults. These changes in turn are having a significant impact on the practice of dentistry, moving the profession further along the road to prevention, away from costly and extensive restorations and extractions. Although economists estimate that the application of research advances by dental practitioners accounts for over \$39 billion in savings in the Nation's oral health care bill from 1979 to 1989, it should be noted that the Nation's annual dental bill was estimated to be \$35 billion in 1991 and that caries and periodontal diseases remain the major culprits.

The Nation's oral health problems are not over. Everyone remains at risk for oral diseases and disorders. Everyone is in need of regular oral health care. The mouth is the major entryway into the body, an environment that must be kept healthy to protect the oral tissues and, beyond that, the body itself. This is accomplished by defense mechanisms that counter potentially harmful invaders and maintain the proper balance.

For millions of Americans, however, this balance is not maintained. We know that 20 percent of the Nation's schoolchildren experience the bulk of the tooth decay that remains in young people. Blacks and Hispanics are in worse oral health than whites. We also know that our oldest citizens experience the worst oral health of any age group, with all that that means in pain, suffering, and loss in the quality of life. Since low-income groups cannot afford conventional dental care, it is incumbent upon oral health researchers to develop more cost-effective methods of prevention and treatment of oral health problems.

Thus, NIDR must continue to work to reduce the impact of caries and periodontal diseases, exploring the opportunities for prevention and treatment that have opened up as a result of adopting the techniques of genetics and molecular biology. The emphasis is on groups and on individuals at high risk for oral health problems, whether because of age, lack of education, and access, or because of systemic diseases or handicapping conditions.

Important among these diseases are oral cancers, one of the more lethal forms of cancer, responsible for 10,000 deaths annually; diabetes; genetic disorders such as the ectodermal dysplasias, in which teeth are missing or malformed; autoimmune disorders such as Sjögren's syndrome, in which the salivary and tear glands are progressively destroyed; chronic orofacial pain; and AIDS, where oral signs and symptoms are often the earliest signs of HIV infection and of progression of disease.

These expanded horizons for oral health research emphasize the intimate connection between the mouth and the rest of the body in normal development, maturity, and aging, as well as the importance of oral and systemic interactions in the course of disease and disease treatments. This perspective has been detailed in the Institute's long-range research plan for the nineties, *Broadening the Scope*, published in 1990. The plan identifies 19 areas of science of primary importance to the Institute, where investigators are ready, willing, and able to pursue new leads and approaches that can pay off in improvements of the oral and general health of all Americans.

RESEARCH PROGRESS AND BRIDGES TO THE FUTURE

Making Bone to Order. Recently, NIDR staff scientists and collaborators combined natural and synthetic materials to generate new bone tissue—essentially “making bone to order.” Working with rats, the investigators took muscle tissue flaps containing stem cells (capable of conversion into a variety of cell types) and combined them with bone precursor materials and osteogenin, a bone growth factor discovered at NIDR. These ingredients were placed in silicone molds and implanted in the rats in such a way that arteries and veins from the implanted muscle could be reconnected to the animal's blood supply. Ten days later the contents of the molds were analyzed. Those containing the experimental ingredients had formed a spongy bone mass that completely filled the shape of the mold. The implications of this research are that patients in need of bone replacements may be able to convert their own muscle tissue to bone, obviating the need for bone grafts or foreign tissue.

Vaccine Research. The availability of biotechnology techniques to generate highly purified molecules has revived interest in developing vaccines for a number of diseases. Recognizing the potential of such methods for oral health, NIDR recently convened a major international workshop on Genetically Engineered Vaccines: Prospects for Oral Disease Prevention. Participants agreed that there is sufficient expertise and progress in the field to warrant an expanded research effort to develop genetically engineered vaccines for dental caries, periodontal diseases, herpes and papillomavirus infections, and other oral diseases. Such vaccines are particularly needed for populations at high risk, including rural and low-income groups that have limited access to regular oral health care.

Technology Assessment of Dental Restorative Materials. In August 1991, NIDR cosponsored with the Office of Medical Applications of Research, NIH, a major technology assessment conference on the Effects and Side Effects of Dental Restorative Materials. This conference employed an expert panel to assess the state of the science in relation to the risks and benefits of dental amalgam and other materials currently used in dental restorations. These assessments were based on papers presented by leading investigators along with a set of specific questions to be addressed. The panel concluded that there was no evidence to warrant the removal of dental amalgam as a health hazard, but that more research is needed, not only on amalgam but also on the newer biomaterials used in dentistry. A major recommendation was to accelerate the search for alternative biomaterials and new restorative procedures. Indeed, although the United States is the world leader in oral health research, it is lagging behind other countries in the development and testing of new dental biomaterials. A strengthened government-academia-industry cooperation will help bring U.S. leadership to this field.

“Window of Infectivity.” NIDR-supported researchers can now point to a specific time period, between 19 months and 33 months of age, when infants are most likely to become infected with the principal decay-causing bacteria, *Streptococcus mutans*. These bacteria are not normally present in the mouths of babies but are commonly transmitted from mother to infant in the course of contacts in which saliva is exchanged. This predisposition to infection by the mother is also related to the fact that characteristics of the mother's immune system are passed on to the infant. Thus the bacteria able to resist the child's immunological defenses and colonize the oral tissues are more likely to resemble those found in the mother. An oral vaccine administered at this critical time period could provide a potent means of protection. Alternatively, investigators have shown that treatment of the mother with an antimicrobial mouth rinse such as chlorhexidine can also prevent the spread of infection.

An Expanded Focus in Epidemiology. NIDR has long recognized the importance of public health needs as a driving force for basic and clinical research. To better define those needs, the Institute is giving new impetus to its Epidemiology and Oral Disease Prevention Program. Recently reorganized, the program is emphasizing “molecular epidemiology”—a program to develop and test biologic and environmental markers of oral disease or of the risk for disease through the sampling of easily obtained oral tissues (e.g., saliva) obtained in epidemiologic studies. The Epidemiology Program also plays a key role in the NIDR Research and Action Program to Improve the Oral Health of Older Americans and Other Adults at High Risk, and maintains an active outreach effort for health promotion and disease prevention.

STRATEGIES AND NEEDS

The world leadership of the United States in oral health can and should be used to strengthen the overall position of the U.S. with global partners. Industrialized and developing nations share our concern for oral disease and general health and are eager to benefit from emerging technologies and treatments made possible through NIDR-supported projects. NIDR leadership is already generating leveraged international financial and scientific support directed toward oral health problems that can best be studied through international collaboration. Examples include studies of oral cancers, research to determine optimal levels of fluoride for the human organism, studies of craniofacial anomalies, and research to develop alternative biomaterials to replace amalgam. NIDR is also cooperating with the World Health Organization in epidemiological and surveillance studies on the oral manifestations of AIDS. Recognition of the NIDR as the world leader in oral health research will give U.S. private-sector organizations a distinct advantage in the commercialization of biotechnology.

Accomplishment of this goal requires the development of strategies that can maintain the leadership of U.S. oral health research. With the full support of its Council, NIDR proposes to address the full range of diseases that affect the oral tissues and to capitalize on the relatively easy access of the orofacial tissues to promote the development of useful models of systemic diseases and disorders.

The Council believes that the way to carry out this expanded agenda is to increase our ability to support basic research and to invest in the development of human resources in science and technology. The former should be through the optimal use of current

mechanisms of support and through expanded collaborations with the private sector and with other countries. The latter requires approaches aimed at stimulating the training of promising talent, particularly among minority and historically underrepresented populations. NIDR has already recognized this imperative, and a subcommittee of this Council has been actively studying the issues of minority health and minority representation in the professional force.

The national investment in biomedical research is largely associated with the NIH system, which provides for a unique and productive partnership between the Federal Government and extramural participants. With congressional support, this has led to the development of a highly productive national research system. The Council believes that such support should be expanded to maintain the partnership and the country's leading role in biomedical science. Accordingly, the Council makes the following recommendations:

1. Adequate growth and stability of funding should be maintained for all mechanisms in the Extramural Program.
2. A stable level of support should be provided for the intramural research program of NIDR and of NIH overall.
3. A balanced portfolio of support mechanisms to extramural partners should be maintained, including research project grants, research centers, research training awards, small grants, career development awards, and research and development contracts. Within this context, the Council recommends that funding for small grants be expanded in order to provide funding for innovative and "high-risk" research, as well as to support the research of new investigators, especially among women and minorities. The Council also recommends further enhancement of the centers program to reach the total of 30 projected in the 1985 report to Congress concerning the Institute's use of centers and other large grant programs. Note that this total does not include the projected regional centers for research on minority health. (See Recommendation 7.)
4. Adequate support should be provided through the contract mechanism to conduct clinical trials to promote the transfer of advances from the laboratory to dental practice and health care.
5. Adequate support should be provided for new initiatives aimed at individuals at high risk, including older Americans, minorities, and special care populations. This should include epidemiological and intervention studies.
6. The Council recommends that initiatives common to both the NIDR long-range research plan and the *National Institutes of Health Draft Strategic Plan* be supported to the extent possible.
7. The Council recommends that the new initiative of Regional Research Centers for Minority Oral Health be supported aggressively and fully.

8. The Council enthusiastically endorses initiatives aimed at increasing the career development and research training opportunities for women, minorities, and historically underrepresented populations.

9. The Council recommends investment in upgrading research facilities both inside and outside NIH and continued support for instrumentation/equipment awards to extramural laboratories.

10. The Council endorses the NIDR's long-range research plan for the nineties, *Broadening the Scope*, as the primary vehicle to guide Institute planning for the decade.

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NATIONAL DIABETES AND DIGESTIVE AND KIDNEY DISEASES ADVISORY COUNCIL

INTRODUCTION

The National Diabetes and Digestive and Kidney Diseases Advisory Council is pleased to report to the Congress of the United States on its activities during fiscal years 1991 and 1992 and to comment on the state of biomedical science in its areas of responsibility. A roster of the Council is attached to this report.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports both clinical and basic research on an extensive range of diseases that have major impacts on the health of the American people.

Basic research, the preface to advances in clinical medicine, is yielding an unprecedented mosaic of discoveries about vital biologic processes. The Council applauds and supports the Institute's commitment to basic research as a cornerstone for curing and treating human disease. Many of the recent developments in structural biology and molecular medicine, areas strongly represented in the Institute's portfolio of extramural support, highlight the dependence of clinical advances on basic research.

The NIDDK leads the Federal research effort to conduct and support research on the causes, diagnosis, treatment, and prevention of diabetes mellitus and its complications. Diabetes is the sixth leading cause of death by disease in the United States, affecting about 13 to 14 million Americans and costing the country between \$20 and \$40 billion annually. Similarly, the Institute supports research on a large variety of endocrine diseases including disorders of the thyroid and parathyroid glands, the pituitary gland, and the adrenal glands. The NIDDK also is the lead agency in the support of research on cystic fibrosis, the most common lethal inherited disease in Caucasians, and supports research on a wide variety of less common but devastating metabolic diseases as well.

The digestive diseases for which the Institute bears research responsibility exact an enormous toll in terms of disability, suffering, and economic costs. They include gastric and duodenal ulcers, ulcerative colitis and ileitis, and pancreatitis. These disorders cause over 200,000 absences from work each day at a total cost to the Nation of over \$50 billion annually. Nutrition and obesity are the foci of large NIDDK research support efforts and are areas of investigation that are critical to understanding, treating, and preventing many human diseases.

Kidney and urinary diseases and disorders are among the most critical and costly public health problems in the country, affecting more than 13 million Americans and accounting for over 80,000 deaths each year. Treatment accounted for an estimated \$50 billion in direct health care costs in 1992, and more than 200,000 individuals in the United States suffered from end-stage renal disease. Benign prostatic hyperplasia and urinary incontinence alone cost Americans over \$12 billion. Polycystic kidney disease, interstitial cystitis, benign prostatic hyperplasia, and conditions attending end-stage renal disease and kidney transplantation are special areas of research interest for the NIDDK. The Institute also supports research on a broad range of basic and clinical topics in hematology including those

related to anemias caused by nutritional, genetic, and other factors (such as sickle cell disease and thalassemia); disorders of blood cell production; and immune diseases involving the blood.

SUMMARY OF RECOMMENDATIONS

1. The Council enthusiastically endorses the strategic planning process initiated by the NIH, and urges that it continue as a close collaboration between the NIH and the scientific and lay health communities.
2. As the Council has emphasized in previous reports, the NIH and the NIDDK must address the problems of ensuring the continuing supply of well-trained scientists; ensuring the continuing use of animals, where required, in research; and reversing the deterioration of the Nation's biomedical research infrastructure.
3. Investigator-initiated research must be preserved within the context of cost management. First priority must always be the support of the best research to improve the Nation's health.

DISCUSSION AND RECOMMENDATIONS REGARDING NIDDK PROGRAMS

The Council is grateful to the Congress for its continued support of the NIDDK even in the difficult recessionary environment of the past 2 years. During that period, the Institute has continued to lead the scientific community to solve the problems of many chronic diseases and thereby improve the health of the American people. Unfortunately, the gap between the demand imposed by compelling scientific opportunities and the resources available to fund research has widened. When these opportunities are missed or incompletely exploited, there are direct and observable negative effects on the Institute's quest to improve the health status of the American people.

Within the NIDDK's extramural support program, three specific categories of support have been of great concern to the Council over the past decade. The following sections represent our status report on each area.

Research Project Grants. In its previous reports, the Council expressed alarm that the gap between the funds recommended for any given research project grant and those actually awarded appeared to be steadily widening, and we emphasized the damaging effect that this practice can have on laboratories if continued year after year. Unfortunately, instead of improving, this situation has deteriorated at an accelerating rate. The following table shows the trends over the last several years:

Fiscal Year	1986	1987	1988	1989	1990	1991	1992
Total grants	2049	2069	2083	2073	2027	2036	2141
Competing grants	637	686	579	504	420	518	638
Percentile payline	33	35	31	24	17	23	27
Award rate	35%	40%	34%	29%	22%	27%	29%
Cuts from recommendations	-11%	-7%	-10%	-11%	-12%	-17%	-22%

The good news is that the total number of regular research grants supported by NIDDK has risen from a low of 2027 in FY 1990 to a high of 2141 in FY 1992, and the number of competing awards has gone from 420 to 638 in the same period. The bad news is that in FY 1991, the average award was only 83 percent of that recommended by the peer review system and in FY 1992 the figure declined even further to 78 percent.

While a number of factors contribute to the inability of the NIDDK to fully fund grants at recommended levels, the Council believes that the most important single factor has been the implementation of the NIH-wide "Plan for Managing the Costs of Biomedical Research," which includes coupling the size of the average research project grant award to the Biomedical Research and Development Price Index rather than allowing it to be determined by the needs of the scientific community as expressed in applications judged highly meritorious by the peer review system. This move has eroded the influence of science and the peer review system as the primary determinant of the support to be awarded to each project and has meant that the majority of awards are made at levels patently insufficient to support the work proposed and recommended by this Council. Also, it has placed enormous pressure on the NIDDK to give preference to small projects instead of large ones, regardless of the relative scientific and health potential of each. Eventually, this strategy will almost certainly lead to an underrepresentation in the Institute's portfolio of such crucial types of research as clinical and epidemiological studies.

While the Council applauds the Congress' and NIH's efforts to better manage the public's biomedical research dollar, we believe that patterns of research funding must be determined primarily by the merit and potential health significance of the proposed work and not by adherence to a fiscal policy insensitive to these factors. We recommend that the NIH reconsider its approach to cost management and reformulate it in closer consultation with the scientific community. This Council would be pleased to play a role in that effort.

Research Centers. Previous reports of this Council have pointed out the important roles that research centers play in the NIDDK's extramural support programs but have indicated that their funding has averaged 25 percent below Council-recommended levels (e.g., in FY 1990). The Council is pleased to report that in FY 1992, the picture has improved somewhat with centers being funded at an average of 16 percent below peer-recommended levels. It should be noted that this improvement has been due chiefly to the adoption of a policy that limits the amount of funds that a center application can request. While the goal of full funding for centers is still far from a reality, the Council approves of the progress made

toward that end and reiterates its recommendation that centers be funded at recommended levels.

Training and Career Development. In the last decade, funding for training and career development has fallen from approximately 9.7 percent of the Institute's budget to 7.4 percent. Meanwhile, the sophistication and complexity of biomedical science continue to increase at a rapid pace, placing demands for ever longer and more arduous training on young people entering research.

Overall, little or no progress has been made toward the training and career development goals set by the Council in its previous reports, i.e., funding for 250 individuals in the career programs and 1,000 positions in the National Research Service Award (NRSA) programs. (In FY 1992, the Institute supported 178 career development awards and 834 full-time equivalent NRSA positions.) The Council firmly believes that larger numbers of positions must be supported in both the training and career programs in order to ensure the appropriate number and quality of researchers in the future; thus, the Council reiterates its recommendations for supporting 250 and 1,000 positions in NIDDK career development and training programs, respectively.

ADDITIONAL PUBLICATIONS

For several areas of the Institute's responsibility, additional discussions of scientific advances and opportunities, as well as program needs and plans, may be found in the following publications:

- The National Diabetes Advisory Board 1991 Annual Report (NIH Publication No. 91-1587, March 1991).
- The National Digestive Diseases Advisory Board 1991 Annual Report (NIH Publication No. 91-2482, March 1991).
- The National Kidney and Urologic Diseases Advisory Board 1991 Annual Report (NIH Publication No. 91-3004, March 1991).

SUMMARY OF COUNCIL ACTIVITIES

The functions and responsibilities of the Council are primarily to assist the Director, NIDDK, in overseeing the activities of the Institute and to provide advice and counsel with regard to the Institute's budget and scientific goals and programs.

Review of Grant Applications. Primary among the Council's roles is its statutory responsibility to provide the second level of peer review for applications for assistance. During FY 1991 and 1992 the Council reviewed a total of 5,756 applications. On 64 of these applications, the Council's recommendations differed from those of the Initial Review Groups.

Program Planning and Oversight. The principal focus of the Council's scientific planning and oversight function involves the development and review of the Institute's annual plan.

This plan identifies the current states of knowledge, the science bases and opportunities, and the needs perceived by the Council and the scientific community in the various areas within the mission of the Institute. While the Council believes that the general direction of biomedical research is best determined by investigator-initiated projects and not by centralized administrative decisionmaking, it recognizes the occasional need to create special opportunities for investigators to capitalize on new scientific advances and situations. Staff and Council members identify the recent major research advances in each field that might indicate the emergence of new needs and opportunities for program initiatives. Also identified are critical areas not well represented in the NIH's portfolio of funded projects. These perceived needs and opportunities, along with ideas for possible program initiatives, are discussed in detail during the May Council meeting and form a basis for Institute staff actions in the subsequent fiscal year.

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DIABETES RESEARCH AND TRAINING CENTERS PROGRAM

INTRODUCTION

As a result of recommendations by the National Commission on Diabetes, the first Diabetes Research and Training Centers (DRTC) grants were awarded in September 1977 in conformity with authorizing legislation (Public Law 93-354). At present, there are six DRTCs that are located at Albert Einstein Medical College (Bronx), University of Chicago (Chicago), University of Indiana School of Medicine (Indianapolis), University of Michigan Medical School (Ann Arbor), Vanderbilt University (Nashville), and Washington University (St. Louis).

DRTCs are evaluated continually through several varied but complementary processes. These include NIH peer review, program review by the National Diabetes Advisory Board (NDAB), staff review of progress reports and staff visits to centers, special evaluation projects by Institute staff, scientific merit review associated with presentations at annual meetings and publication of research results in scientific journals, and in-house evaluations by the centers themselves.

CENTER FEATURES

The basic requirement for establishment of a DRTC is excellence in biomedical research as evidenced by a substantial base of high quality, NIH-funded research projects. The resources furnished by center funding allow for enhancement of collaborative and multidisciplinary endeavors, which span the spectrum of basic and clinical research to the transfer of new knowledge through training of primary care health professionals. In view of these basic DRTC characteristics, this report will focus on new research and training-based efforts by the centers, as well as on center evaluation.

A major advantage of DRTC funding to the recipient diabetes centers is the establishment of shared resources (cores) for use by the investigators of the center. In addition, funds are provided for a limited number of modest research projects, pilot and feasibility research studies, and other activities to enhance the centers' research and training programs. The cores provide services to funded investigators whose area of research or training interest is diabetes or related areas of the biomedical sciences. These combined resources allow for greater efficiency, better quality control, cost saving through bulk purchase, and fostering collaboration and multidisciplinary efforts. Funds for pilot and feasibility studies of modest amount and limited duration are provided following peer review to young investigators who do not yet have their own individual support. Also, pilot and feasibility funding is provided to established investigators either from other fields who have become interested in diabetes research or established diabetes researchers with innovative ideas for new research directions. In addition, a small amount of funding is allowed for enhancement of the multidisciplinary environment through seminars and conferences and through the exchange of information with consultants and lecturers from outside the center institution. The DRTCs have provided accordingly for the consolidation of common interests and activities of basic and clinical scientists, practicing physicians, nurses, nutritionists, and other health care professionals in the diabetes area.

NIH PEER REVIEW

During fiscal years 1990-91, one DRTC was awarded funds following successful competition. A detailed application was submitted in FY 1989 that summarized the progress made during the previous project period. The application was then reviewed by a special initial review group of 15 expert consultants who conducted a 2-day project site visit at the center to evaluate each component of the application in detail. A written summary of the findings and recommendations from the site visit team was then provided to the National Diabetes and Digestive and Kidney Diseases Advisory Council for final review and approval. Only a center that is recommended for support with the very highest enthusiasm receives funding. This peer review process ensures that each center submitting an application is subjected to a rigorous and objective external evaluation of scientific and technical merit at least once every 5 years. During FY 1991 two RFAs were published in the NIH Guide to Grants and Contracts that announced competition for three DRTCs (DK-91-11) and five DRTCs (DK-91-12). Awards are expected to be made in FY 1992.

SPECIAL EVALUATIONS UNDERTAKEN IN FY 1990-91

The DRTCs submit annual special reports in response to a series of specific questions. These relate to research highlights, use and changes in biomedical cores, status of the Pilot and Feasibility Program, and highlights and accomplishments in training and education. The responses are carefully evaluated by staff, and selected information is used in the preparation of this report.

CENTER ACTIVITIES

There are basically two main thrusts for the DRTCs: (1) biomedical research and (2) training and/or education of health care professionals involved in treatment and management of people with diabetes.

Advances in Biomedical Research. Major advances in biomedical research have been supported during 1990 and 1991 by the DRTCs. A few representative descriptions of these advances will be presented.

The Washington University DRTC has operated a Human Pancreatic Islet Isolation Core for 3-1/2 years. This laboratory processes fresh human pancreata to isolate viable, highly purified human pancreatic islets for distribution to diabetes researchers within Washington University as well as select investigators in other centers. It is the only laboratory in the world that offers this type of service to the research community at large.

The development of automated techniques for the mass isolation of human islets has allowed studies in purified human islets previously cultured and tested for viability *in vitro* and then transplanted into diabetic patients with established kidney transplants. During the last year one transplant recipient, previously shown to be incapable of producing d-peptide, was able to maintain normal hemoglobin A_{1c} concentrations and remain insulin independent for 11 months. These results extend a previous report from the Washington University Center demonstrating clearly that human islet allografts can function effectively for prolonged periods in immune-suppressed patients.

Studies supported by the University of Chicago and University of Michigan DRTCs identified the gene responsible for diabetes susceptibility in a large family from Michigan with a form of non-insulin-dependent diabetes mellitus (NIDDM) termed maturity-onset diabetes of the young. The diabetes-susceptibility gene identified on chromosome 20 is likely to be only one of several. The identification of other diabetes-susceptibility genes using similar genetic strategies will result in NIDDM being defined as a series of different diseases, all of which are characterized by impaired uptake and utilization of glucose. Knowing the cause of NIDDM in an affected individual, it will then be possible to devise new and specific therapeutic modalities for treating the many different forms of this disorder.

Advances in Training and/or Education. Advances in the transfer of new knowledge through training has occurred at each of the DRTCs. Two examples will be presented here.

The University of Chicago DRTC has developed a program centered on self-management for children with insulin-dependent diabetes mellitus (IDDM) and their parents. The focus is on enabling children to take more responsibility for the daily management of their diabetes. Parents are taught to foster and support their children's self-management practices. Children with IDDM and their parents must make major adjustments in their lifestyles to reduce the threat of future life-endangering and disabling complications. It is generally accepted that children should assume as much responsibility for the self-management of their diabetes as possible. The management of IDDM in children requires extensive education for both the children and their parents, which this program attempts to develop most effectively.

At the Vanderbilt DRTC, a main focus of the training component has been to improve diabetes patient care through improving the patient education process. Activities relating to this goal include development and validation of methodologies to assess educational methods and outcomes, development of innovative instructional strategies and materials, and development of training programs to improve the teaching skills of health professionals. Toward this end, a training program, "Effective Patient Teaching," has been developed for all health professionals. Research and observation led to generating a list of 19 specific teaching skills felt to be required of health professionals in general and specifically those devoted to diabetes care. The program is 4-1/2 days in length and evaluation of the program is ongoing. About one-half of the program is devoted to didactic presentations of the important teaching skills. In the remaining half of the program, participants practice teaching skills in small group sessions. All practice teaching sessions are videotaped for later review. Each participant also receives a 75-page notebook for subsequent use.

COLLABORATIONS

The DRTCs have established collaborations within their own group and with Federal and private agencies and organizations with missions relating to education and training in diabetes. Active collaborations currently exist with Federal agencies (e.g., Centers for Disease Control and Indian Health Service), professional and voluntary health organizations (e.g., American Diabetes Association, Juvenile Diabetes Foundation, American Association of Diabetes Educators), State and city health departments, local colleges, local hospitals, other voluntary organizations, and community health centers.

SUMMARY

This report briefly addresses the extent to which the DRTC's have fulfilled the original goals set for them by the National Commission on Diabetes. New developments since the last report are described and indicate the great potential for DRTC's in stimulating progress in research and education related to diabetes. The Department of Health and Human Services finds that the Diabetes Research and Training Centers are continuing to progress toward their objectives and views them as a national resource for achievement in research and education related to diabetes.

DIGESTIVE DISEASES AND NUTRITION CENTERS PROGRAM

INTRODUCTION

The Division of Digestive Diseases and Nutrition (DDDN) Centers Program was initiated in 1979 with the award of five Clinical Nutrition Research Units (CNRUs) and expanded in 1984 with the award of six new Digestive Diseases (DD) core center grants. The centers program has evolved over the past decade, expanding to a total of 18 centers: 5 CNRUs, 1 obesity center, and 12 DD centers. The 18 centers are located in 16 different universities in 12 different cities. The 12 DD centers include the Gastrointestinal Hormone Research Core Center of University of Michigan (Ann Arbor, MI); the Hepatobiliary Center at University of Colorado Health Sciences Center (Denver, CO); the Harvard Digestive Diseases Center at Harvard Medical School (Boston, MA); the Liver Research Center at Albert Einstein College of Medicine (Bronx, NY); the Center for Gastroenterology Research on Absorptive and Secretory Processes at Tufts University (Boston, MA); the Center for the Study of Inflammatory Bowel Disease at Massachusetts General Hospital (Boston, MA); the Center for Ulcer Research and Education (CURE) at UCLA (Los Angeles, CA); the Yale Liver Research Center at Yale University (New Haven, CT); the Digestive Diseases Center at Stanford University (Palo Alto, CA); the Center for Liver Research at the University of California (San Francisco, CA); the Center for Study of Cell and Molecular Biology of the Gastrointestinal Tract at the University of Chicago (Chicago, IL); and the Center for Study of Intestinal and Bowel Disorders at the University of North Carolina (Chapel Hill, NC). The five CNRUs include centers at the University of Washington (Seattle, WA), the Oregon Health Sciences Center (Portland, OR), the University of Chicago (Chicago, IL), the University of California at Davis (Davis, CA), and Vanderbilt University (Nashville, TN). The Obesity Center is located at St. Luke's-Roosevelt Hospital in association with Rockefeller and Columbia Universities (New York, NY).

The DD, CNRU, and Obesity Center grants are 5-year awards that become available as existing grants compete for renewal. The competition is open through published requests for applications. The centers program provides support for research centers at institutions where there is an existing base of excellent biomedical research and where it can be demonstrated that the use of shared resources will lead to (1) cooperative and collaborative research efforts, (2) enhanced efficiency and low-cost routine services, (3) new cooperative and collaborative efforts among investigators, (4) routine availability of services and resources hitherto unavailable to investigators, and (5) expanding the capabilities and potential for research accomplishments greater than that possible through individual projects.

DIGESTIVE DISEASES CORE CENTERS

Biomedical Research Component. The biomedical research component at the DD centers focuses on research areas such as liver disease; abnormal liver metabolism; problems related to liver transplantation; cholesterol gallstone disease; peptic ulcer disease; Crohn's disease and inflammatory bowel disease; normal and abnormal gastrointestinal motility; infectious diarrheal diseases; and absorption, secretion, and regulatory processes in the gastrointestinal tract. Research at all centers is directed toward enhancing the

understanding and knowledge of digestive diseases leading to improvement in the care of patients with these conditions.

Biomedical Core Facilities. The biomedical research core at DD centers provides center investigators with shared resources to conduct biomedical research in an efficient and cost-effective manner. Among the benefits from these shared resources are a greater potential for collaboration, availability of expert consultation and use of state-of-the-art facilities, lower cost for services rendered, and the means to pursue limited pilot and feasibility research.

Core facilities at DD centers have included conventional transmission, freeze-fracture electron microscopy, immunocytochemistry, autoradiography, cell culture, molecular biology, peptide synthesis, protein purification, radioimmunoassay, and laboratory animal facilities.

Pilot and Feasibility Studies. The core center grant mechanism provides for support of a limited number of innovative pilot and feasibility research projects that relate to the center's overall research focus. As the name suggests, these projects are supported to test new hypotheses, provide opportunities for new collaborations, and explore new methods or procedures as they apply to research problems in digestive diseases. These studies, when fruitful, lead to research and grant applications for fuller exploitation of the initial concept.

Advances in Research at Digestive Diseases Centers. The directors of the 12 DD centers meet yearly to discuss administration and research issues. The research advances presented are numerous and demonstrate how the center core grant can augment the effectiveness of biomedical research in the institution. The center grant is particularly effective in drawing new investigators into a field and allowing established investigators to pursue innovative lines of investigation. Some examples from advances made in the last year will show these features.

At the University of California, Los Angeles, Dr. John Walsh (principal investigator) and his colleagues have studied peptic ulcer, a common disease that has multiple causes and contributing factors. Among these factors are heredity, gastric acid secretion, brain influences on the stomach, gastric infection with a bacterium known as *Helicobacter pylori*, ingestion of nonsteroidal antisecretory drugs, and smoking. Center researchers have made substantial contributions to understanding the importance and mechanisms responsible for each of these factors in the causation of ulcers. Among the most exciting new developments are new insights regarding *H. pylori* as an infectious cause of ulcers, the ways in which anti-arthritis drugs damage the stomach, the pathways by which stressful stimuli are transmitted from the brain to the stomach, and the effects of smoking on blood circulation to the lining of the stomach.

At the University of North Carolina, Dr. Robert Sandler (acting director of the center) and his coworkers have found that the peptidoglycan polysaccharide polymers of bacterial cell walls cause inflammation in the mucosa of the intestine and scarring of the bile ducts, changes that are typical of ulcerative colitis and sclerosing cholangitis. These inflammatory changes could be blocked by treating the bacterial cell wall polymers with an enzyme. This work, which was supported by the center core grant, promises to shed light on the cause of inflammatory bowel disease, one of the most important gastrointestinal diseases.

CLINICAL NUTRITION RESEARCH UNITS

Advances in the knowledge of human biochemistry and physiology have placed clinical nutrition on a sound, scientific base. Many nutritional deficiency states, consequences of inborn errors of metabolism, and diet-related diseases are now understood and may be treatable or preventable. However, there remain many unanswered questions on the relationship of diet to health and disease, chronic diseases, and aging.

Advances in research to help answer questions about nutrition and disease are derived from many disciplines such as biochemistry, molecular biology, genetics, and physiology and from medical specialties such as internal medicine, pediatrics, and surgery. Nutrition science is interdisciplinary and complex and is dependent upon the close interaction among research investigators, health service providers, and educators. As a means of encouraging a multidisciplinary approach to clinical nutrition research, DDDN is part of an NIH-wide program of CNRU support. Specific objectives of the CNRU are (1) to create or strengthen foci in a biomedical research institution for multidisciplinary research in clinical nutrition to develop new knowledge on specific nutrients in health and on the prevention and treatment of disease; (2) to strengthen training environments to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition; and (3) to enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutritional information for the public.

The essential components of a CNRU are (1) research with human subjects and populations; (2) laboratory investigations; (3) research training; (4) shared facilities and research services; (5) education programs for medical students, house staff, practicing physicians, and allied health personnel; (6) research components of nutritional support services; and (7) public information activities.

CNRU Research Core Facilities. Core facilities of CNRUs are developed to support research in the broad areas of fundamental and clinical nutrition. Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged to increase knowledge concerning function and requirement of nutrients, relationship of diet (and nutrients) to health and disease, and prevention and treatment of diseases as an outgrowth of nutrition research.

Fundamental research supported by NIDDK generally has been nutrient centered rather than focused on a particular disease, organ, or life cycle. In contrast, clinical investigation usually concerns problems interrelating nutritional status with the biochemical and physiological function of a cell population, organs, or the whole individual.

Advances in Research at CNRUs. The CNRU provides a powerful means of augmenting research in nutrition, particularly as nutrition research tends to be spread among many medical disciplines. Thus, nutrition expertise and research may be carried out in departments of biochemistry, physiology, psychology and psychiatry, gastroenterology, cardiology (lipids/atherosclerosis), oncology, pediatrics and geriatrics. The CNRU provides a home and focus for these diverse groups to collaborate and stimulate innovative approaches to dealing with nutritional issues. Some examples of recent advances that were presented at the yearly meeting of CNRU directors are given here.

At Vanderbilt University, Dr. Faye Ghishan has recently shown that there is a phosphate transporter in the small intestine and this transporter may be deficient in the severe crippling inherited disease known as vitamin D-resistant rickets. Using the molecular biology core at the Vanderbilt CNRU, this investigator is attempting to isolate, characterize, and clone the gene of the phosphate transporter; this would aid greatly in diagnosis, understanding, and treatment of this disease.

At the University of Washington, Dr. Robert Knopp is carrying out a large study on diet and atherosclerosis, looking at the effect of different levels of fat content in the diet (18-30% of calories) on cholesterol concentrations including high-density lipoprotein and low-density lipoprotein cholesterol. The CNRU grant allows for the comprehensive dietary assessment of patients needed to verify whether changes in fat intake occur in different groups of patients. The center also provides for the accurate estimations of serum lipids and lipoproteins. These studies will help to show what level of decrease in fat content in the diet is important in lowering cholesterol and the risk of heart attack and stroke.

OBESITY RESEARCH CENTER

Advances in obesity research are derived from, and thus are dependent on, many disciplines such as biochemistry, molecular biology, genetics, and physiology and on medical specialties such as internal medicine, pediatrics, and surgery. Obesity research is interdisciplinary and is dependent on the close interaction among researchers, health services providers, and educators to achieve stated goals.

There is growing public desire for more information on the development, treatment, and prevention of obesity. NIDDK has performed and supported research relating to obesity and continues to have a major commitment to developing new nutritional information and imparting this information to physicians, other health professionals, and the public.

The objectives of an Obesity Research Center include (1) to create or strengthen a focus in biomedical research institutions for multidisciplinary research in obesity to develop new knowledge about the development, treatment, and prevention of obesity and related eating disorders throughout the human life cycle; and (2) to strengthen training environments to improve the education of medical students, house staff, practicing physicians, and allied health personnel in obesity and related eating disorders.

DDDN supports one Obesity Center, which is located at the St. Luke's-Roosevelt Institute for the Health Sciences. This center is evaluated each year as a part of the DDDN Centers Program. This center has played a key role in progress being made in the understanding of obesity and its treatment. One of the major areas of research in the St. Luke's-Roosevelt Obesity Center has been on developing the best technology for measuring body composition in obese persons. Body weight does not accurately reflect obesity because increases in muscle, water, or bone can change weight as much as increases in body fat. The Obesity Center investigators are evaluating the full spectrum of techniques of measuring body fat, body composition, and energy expenditure including underwater weighing, bioelectric impedance, stable isotopes, dual photon absorptometry, and neutron activation in lean and obese patients of various races and ages with and without dietary and exercise modifications. These studies are beginning to show what determines a propensity to obesity.

Thus, these investigators have recently shown, using the obesity center facilities, that the resting metabolic rate decreases when obese persons lose weight, but this decrease is not due to a defect in energy regulation in obese persons but rather is due to loss of lean body mass (which determines resting metabolic rate) in addition to fat when weight is lost.

ASSESSMENT AND EVALUATION

In 1984, the National Digestive Diseases Advisory Board (NDDAB) held a workshop to explore possible mechanisms for evaluating and monitoring the DDDN Centers Program. NDDAB suggested criteria and mechanisms for monitoring programmatic activity and suggested methods of obtaining evaluation information, including the adoption of a standardized reporting method.

In February 1988, the DD, CNRU, and Obesity Center directors met with DDDN and senior NIDDK staff to consider the development of guidelines for the centers and related issues. NIDDK has completed the preparation of formal administrative guidelines for centers as a product of this meeting. The utilization of these guidelines has facilitated uniform reporting of progress and accomplishments from the centers.

SUMMARY

The DDDN Centers Program provides the assessment mechanisms and reporting procedures that, in concert with the NIDDK peer review process, have supported a highly effective community of research centers of excellence. The role of DDDN centers is to improve the understanding of the causes of digestive diseases and nutritional metabolism in health and disease states. This understanding will lead to improved methods for early detection, diagnosis, and treatment of digestive diseases and nutritional disorders with consequent improved patient care and lower health care costs. The Department of Health and Human Services finds that the DDDN Centers Program continues to progress toward its objectives and views it as a national resource for achievement in its special research and training areas.

KIDNEY AND UROLOGIC DISEASES RESEARCH CENTERS PROGRAM

INTRODUCTION

The Kidney and Urologic Diseases Research Centers (KURC) Program was initiated in September 1987, when six centers were established. These centers were established to conduct biomedical research into the cause of kidney and urologic diseases in order to improve early detection of these diseases, to improve their treatments, and to find the means of prevention and possible cure. The location, title, and the director for each center is listed in Table 1.

CENTERS DESCRIPTION

Brigham and Women's Hospital Kidney and Urology Research Center is a comprehensive, multi-institutional, interdisciplinary center where research efforts are devoted to studies of diabetes mellitus and the kidney and nephrotoxicity/toxic cell injury. Four other institutions, operating under a consortium arrangement with Brigham and Women's Hospital, also participate: Beth Israel Hospital, Massachusetts General Hospital, Joslin Diabetes Center, and Tufts New England Medical Center. Dr. Barry M. Brenner at Harvard University is the director of this center.

The Research Center at the University of New York at Syracuse focuses its research efforts on defining the pathogenetic mechanisms of vesical, ureteral, and renal dysfunctions in obstructive uropathy through biochemical, morphologic, and functional studies. Research activities are conducted in collaboration with: SUNY at Syracuse, University of Michigan at Ann Arbor, and University of Pennsylvania at Philadelphia. Dr. Ahmad Elbadawi, at SUNY, serves as center director.

TABLE 1

Location	Research	Center Director
Harvard University	Diabetes, Hypertension	Dr. Barry M. Brenner
Northwestern University	Prostate Gland	Dr. John T. Grayhack
University of Michigan	Acute Renal Failure	Dr. Roger Wiggins
State University of New York at Syracuse	Urinary Obstruction	Dr. Ahmad Elbadawi
Vanderbilt University	Biology of Progressive Nephron Destruction	Dr. H. R. Jacobson
University of Alabama	Hypertension and Renal Disease	Dr. D. G. Warnock

The Northwestern University Kidney and Urology Research Center concentrates its research efforts on the study of cellular and chemical aspects of prostate growth. The basic thrust of this center is to elucidate the mechanisms responsible for benign prostatic hyperplasia. Dr. John T. Grayhack serves as center director.

The Vanderbilt University Kidney and Urology Center's main objective is to study the cellular basis of renal immune injury to define the basic putative mechanisms resulting in progressive glomerulosclerosis. Dr. Harry R. Jacobson serves as center director.

The University of Alabama Kidney and Urology Research Center conducts basic and clinical research studies on the mechanisms and consequences of renal dysfunction associated with or stemming from renal hypertension. Dr. David G. Warnock serves as center director.

The University of Michigan at Ann Arbor Kidney and Urology Research Center's goal is to bring together senior scientists working primarily outside the renal area to interact with individuals with a nephrology background and to focus such integrated expertise on the sequence of events leading from initial immune- or non-immune-mediated glomerular injury to sclerosis of the glomerulus. Dr. Roger Wiggins serves as center director.

SUMMARY

Public Law 99-158, the Health Research Extension Act of 1985, gave NIDDK the authority to provide for the development and substantial expansion of centers for research in kidney and urologic diseases. NIDDK, through its Division of Kidney, Urologic, and Hematologic Diseases, opened a national competition to establish a limited number of KURCs to investigate the epidemiology, causes, prevention, and treatment of kidney and urinary tract disorders. Six centers that demonstrated significant potential for successful research were established in September 1987 and are actively pursuing studies toward achievement of the goal of preventing, reducing, or eliminating the major causes of specific kidney and urologic diseases. The Department of Health and Human Services finds that the KURC program continues to progress toward its objectives and views it as a national resource for achievement in its special research area.

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

INTRODUCTION

People are exposed to environmental agents throughout their lives, from the moment they are conceived until they die. The ability of these agents to interact with genetic and cellular material translates into a tremendous spectrum of potential environmentally caused diseases and dysfunctions. Included in this list would be cancer, birth defects, reproductive disorders, neurological diseases, and respiratory problems. The extremely broad scope of environmental health sciences dictates that, given limited resources, careful choices must be made to ensure that emphasis is placed on research areas that are important public health problems and hold the most promise for resolution. It is the National Advisory Environmental Health Sciences Council's responsibility to oversee the efforts of the National Institute of Environmental Health Sciences (NIEHS) in dealing with its ambitiously large mandate and to guarantee that the focus of these efforts is appropriate given the resources and the current state of environmental health knowledge.

In 1991-1992, the Council convened its fourth task force to evaluate the current state of environmental health sciences and to recommend new areas of research. Task Force IV had the following goals: (1) to assess future research needs in environmental health, with particular reference to those problems warranting special attention within the coming decade; (2) to identify areas of scientific challenge and promise, with particular reference to emerging concepts and methods applicable to environmental health problems; and (3) to recommend the training activities needed to assure adequate numbers of qualified scientists in the disciplines critical to solution of the environmental health problems of the coming decade, with particular attention to needs and opportunities for women and minority students. Recommendations made by Task Force IV are summarized below; a complete copy of the report can be obtained from the Office of Communications, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

GENERIC ISSUES

Task Force IV identified three general directions that environmental health efforts needed to follow. They were the need to define environmental components of human disease, to improve the current data base used in environmental risk assessment, and to develop the ability to predict individual risk, thus maximizing the utility of intervention and prevention schemes.

Shift to Disease-Oriented Research. Currently the NIEHS is focused on looking at the potential adverse effects of a particular chemical or physical agent. Task Force IV recommended that research efforts shift to focus on studying the environmental components of specific disease states. Specific research questions to be addressed include

- what etiologic roles do the environment and specific environmental agents have in the major classes of human diseases other than cancer?

- do appropriate disease registries exist, or can they be created, so that investigations into the environmental origins of the major classes of human diseases can be carried out?
- can the exposure status of both diseased and healthy populations be established to the extent needed for studies of exposure-disease response?

Improve the Size and Quality of the Data Base on the Health Effects of Environmental Agents. The two principal sources of toxicology data on environmental chemicals are epidemiological studies and animal bioassays. While efforts to understand underlying mechanisms of toxicity are of fundamental importance, collecting reliable data on the toxic effects of a wide variety of environmental agents remains an objective of utmost importance to the advancement of our understanding of the impact of the environment on human health. It is essential that substantial research be devoted to improving the validity and utility of both epidemiological studies and animal bioassays.

Improve Methods to Define Individual Risks. Currently risk assessment involves extrapolating our knowledge of environmental health effects in laboratory animals or in the general population to the probability of these effects developing in a subset of the population. There is a real need to refine risk assessment procedures so that we can define risks for an **individual**, as well as groups or populations. Critical to this endeavor are the development and validation of biomarkers of environmental exposures and effects, development of assays that can determine who is more susceptible to environmental effects, and use of risk assessment methodologies that are more mechanistically based. Armed with these improved techniques, improved intervention strategies can be developed that address the needs and exposures of each individual.

ENVIRONMENTAL VECTORS

Important routes of environmental exposures are too numerous to list in a meaningful way in this document. However, four vectors of environmental exposure merit mention because they hold significant promise for improving the public health and should receive increased research emphasis. These vectors are air pollution, soils and dusts, diet, and physical energy.

Air Pollution. The health effects of air pollutants remain a significant public concern. More than half of the U.S. population lives in areas where National Ambient Air Quality Standards are exceeded. Changes in technology are anticipated to create new exposures of concern. It is vital to the public health that these exposures be anticipated and their health impact evaluated before large populations are exposed to them.

Soils and Dusts. Poor hazardous waste management, intensive agricultural activities, and extensive mining enterprises have all contributed to soil contamination by organic and inorganic chemicals. These contaminated soils and dusts are now identified as important media through which hazardous substances reach people. Children constitute the most vulnerable portion of the exposed population because they ingest greater quantities of soil and dust than do adults. Clearly, chemical exposures occurring from chemically

contaminated soils and dusts should receive study to the same extent that has occurred for air, water, and food.

Diet. To advance research in this area, closer cooperation is called for between scientists in the environmental health disciplines and those studying the effects of various nutritional and dietary alternatives. Such collaboration is needed to understand how dietary patterns influence the susceptibilities of various population groups to environmental agents, including individual constituents of the diet, and to determine the contributions of different dietary patterns to the impact of toxicants on the rates of the major human diseases. Of increasing importance is research into the health benefits and risks of natural, as well as artificial, nonnutritive constituents of foods, particularly those of plant origin, which display the same range of toxic properties as do synthetic substances.

Physical Energy. Physical energy to which we are all exposed includes ionizing radiation, UV light, microwaves, electric and magnetic fields, sound, light, lasers, and vibration. Most of these environmental agents are known to be capable of causing injury at some exposure levels. Major research questions center around the nature and mechanisms of their effects, the relevant exposure-risk relationships, the extent to which they pose risks to populations at ambient levels of exposure, and the degree to which they may modify susceptibility to the action of other noxious agents.

EMERGING CONCEPTS, METHODS, AND RESEARCH OPPORTUNITIES

Recent advances in techniques for studying molecular and structural biology, coupled with improved software capacity in computer sciences, hold great promise for refining environmental health studies and developing a more mechanistic understanding of the interactions between environmental agents and biological systems.

Molecular Genetics. The advent of polymerase chain reaction (PCR) techniques and transgenic animal models will enable scientists to better define the consequences of environmental exposures at the cellular and molecular level. Outgrowths of these research efforts would include improved biomarkers of environmental exposures and effects and development of genetically engineered microorganisms capable of destroying otherwise persistent, hazardous compounds.

Macromolecular Modeling. The recent explosion in computational capacity and sophistication provides tools to assist in the establishment of the molecular basis of toxicology. Also, it has become possible, through the new tools of structural and molecular biology, to identify the molecular basis of a toxic effect and to provide adequate amounts of the target macromolecule for three-dimensional characterization at the atomic level of resolution. This enhanced understanding should provide better metabolic approaches for detoxifying chemicals, as well as potential inhibitors of toxic effects.

Application of New Techniques in Probing Specific Diseases. A number of these new techniques can be targeted in studying the environmental etiology of specific diseases. The ability to analyze cell-cell interactions responsible for the acute and chronic pulmonary injury produced by environmental exposure to inhaled agents will benefit the study of pulmonary disease. Environmental components of neurological disorders will potentially be

defined through use of newly developed stable, differentiated neuronal cell cultures and the use of transgenic animals to study the role of particular genes encoding enzymes, receptors, or transcription factors implicated in the expression of neurotoxic damage. Environmental causes of immune disorders can be better defined by exploiting advances in monoclonal antibody technology, cell sorting, in vitro cell culture, and specific inbred mouse strains, which offer possibilities for studying specific lymphoid cells, receptors, and differentiation signals in developmental models and in selected xenobiotic-exposed populations. Environmental disturbance of the endocrine system could be better understood by encouraging the use of X-ray crystallography, multi-dimensional nuclear magnetic resonance, infrared spectroscopy, high-resolution microscopy, electron/tunneling microscopy, and molecular adsorption techniques to study the molecular mechanisms by which environmental agents act on this system.

All of the above work could potentially lead to development of biological indicators (biomarkers) of an individual's risk of developing a particular environmentally caused disease. Cancer researchers are already poised to capitalize on the use of biomarkers. Urinary markers of genotoxic exposures have been successfully used (e.g., nitrosoproline as an indicator of exposure to N-nitroso compounds), as have the detection of adducts of genotoxic agents with hemoglobin in occupationally exposed populations (e.g., 3-hydroxy-histidine and 3-hydroxyvaline as indicators of ethylene oxide exposure). Methods are available that can detect and characterize a variety of genetic alterations, ranging from base-substitution mutations to chromosomal rearrangements and deletions. These include mutation markers based on altered phenotype (e.g., hypoxanthine phosphoribosyl-transferase (HPRT) deficiency in peripheral leukocytes); altered gene product (e.g., mutant glycophorin in erythrocyte membranes); gene inactivation (loss of specific mRNA); or altered DNA sequences (restriction fragment length polymorphism (RFLPs) and translocations involving oncogene or regulatory sequences). These methodologies need to be developed and evaluated in epidemiological studies so that their potential as screening tools for intervention and prevention programs can be realized.

TRAINING AND EDUCATION

Training. The NIEHS is the Federal Government's principal supporter of training in the environmental health sciences. Identifying the disciplines for which advanced professional training is needed is challenging because environmental health science draws upon every branch of science, engineering, medicine, and public health. The task force identified several fields in which current professional training curricula either do not exist or are inadequate for addressing newly emerging environmental health science opportunities. These fields are environmental epidemiology, human exposure assessment, and clinical environmental medicine. The NIEHS should encourage new training programs to meet the future need for trained professionals in these fields.

There is also a need to recruit more nonphysician women and minorities into professional environmental health training programs. Such efforts would not only address the historic underrepresentation of these groups in the sciences, but would also serve to bring to the field a fresh perspective on environmental problems faced by these groups and on workable solutions to these problems. Among the strategies to consider would be

support of undergraduate students from predominantly minority colleges for participation as summer research trainees at NIEHS and at NIEHS-supported academic centers.

Public Education. NIEHS can and should do more to disseminate knowledge on the nature and extent of human disease resulting from, or exacerbated by, exposures to physical and chemical agents in the environment. In doing so, it should specifically target the health care community, the health education community, and the public at large. One way to reach these audiences would be to prepare and distribute summary versions of the proceedings of topical symposia that are currently distributed in specific volumes of *Environmental Health Perspectives* (EHP). A corollary effort would be to prepare one or more brief summary documents on the information presented in detail in EHP on a specific topic and target the presentation so that it is appropriate to particular groups, such as primary care physicians, health educators, high school science students, or the general public.

The NIEHS should also investigate how public education campaigns about environmental risks can lead to behavioral changes. Key questions to address are (1) what specific public agency actions and education programs are most effective, (2) how much time and effort does it take to convince significant numbers of people that their individual actions matter, and (3) what governmental actions are effective in getting people to recognize the benefit of behavioral change and act on that benefit?

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

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NATIONAL ADVISORY EYE COUNCIL

INTRODUCTION

The research activities of the National Eye Institute (NEI) continued in 1991-1992, as they have for 20 years, to be guided by a national strategic planning process that culminates in the publication of a long-range plan for vision research. These plans are prepared, updated, and revised in consultation with the vision research community. The latest in this series of vision research plans is currently in draft and will be published in 1992. The National Advisory Eye Council (NAEC), through its Vision Research Program Planning Subcommittee, oversees the development of these plans and uses them in making recommendations on funding priorities.

The current NEI draft plan has been particularly useful in developing vision research initiatives for the *National Institutes of Health Draft Strategic Plan*, carried out in 1991-1992. The following are examples of some of the research priorities from the NEI draft plan. These are categorized under two of the five broad trans-NIH objectives—critical science and technology and research capacity. At the time this biennial report was prepared, the term critical science and technology consisted of molecular medicine, structural biology, molecular immunology and vaccine development, and biotechnology. The term research capacity is used to encompass a wide array of “cross-cutting areas that are of particular importance to all of NIH.” These include such topics of particular importance to NEI as neuroscience and behavior, chronic and recurrent illness and rehabilitation, and aging.

RECOMMENDED NEI PROGRAM INITIATIVES

Objective 1—Critical Science and Technology

Repair of Damaged and Developmentally Deficient Visual System:

- identify gene loci that control repair and regeneration of the visual system;
- conduct research on the efficacy of transplanting retinal and other central nervous system tissues to damaged sites;
- identify factors that ensure integration of transplants into host tissues and identify factors that specify appropriate rewiring of damaged connections.

Aldose Reductase Inhibition and Somatic Gene Therapy for the Prevention of Diabetic Complications:

- develop techniques to inhibit aldose reductase (AR) activity at the protein or gene level;
- determine the structure of the AR protein and identify its active sites;
- investigate the structure of the AR gene and the details of its regulation in normal and diabetic tissue.

Regulation of Corneal Wound Healing:

- develop an understanding of the regulation of cellular interactions that lead to normal healing of the ocular surface;
- investigate biologically based strategies to enhance the permanent resurfacing of the wounded cornea.

Inherited Retinal Degenerations:

- identify the molecular defect(s) in various forms of inherited retinal degenerations, such as retinitis pigmentosa, gyrate atrophy, choroideremia, color blindness, and progressive rod/cone degeneration.

Molecular Basis of Signaling in Retinal Photoreceptor Cells:

- establish the complete molecular basis of visual signaling, signal termination, and adaptation in photoreceptor cells;
- define the structure and function of the molecular components of the biochemical pathways through which light is converted to electrical impulses sent to the brain.

Lens Crystallins:

- investigate the role of the interactions between the various crystallins of the lens.

Objective 2—Critical Health Needs

Age-Related Cataract:

- determine the causes and mechanisms of age-related cataract formation, and develop new preventive and therapeutic strategies;
- address the biochemical characterization of cataract formation and the identification of interventions that can prevent or delay cataract formation.

Environmental Risk Factors That Contribute to Cataract Development:

- identify and quantify environmental factors and associated molecular mechanisms that lead to increased risk for the development of age-related cataracts.

Neural Basis of Visual Perception:

- determine how the activity of individual neurons and groups of neurons relate to perception;
- examine how visual information is encoded by nerve cells and localized in centers of the brain.

Neural Modeling of the Visual System:

- encourage the development and use of computational models of the visual system, which provide information on how the visual system functions.

Assessing Treatments for Infant Vision Disorders:

- develop and apply techniques to measure the vision of infants and young children in order to study normal development, screen for and diagnose visual disorders, and monitor the effects of treatment;
- determine the most effective roles of pharmacological, optical, behavioral, and surgical approaches to the treatment of different forms of strabismus.

Educating the Public and Health Professionals About Rehabilitative Services and Devices for People with Low Vision:

- initiate public and professional information and education activities on the availability of low vision resources;
- encourage individuals who could benefit from low vision services and devices to take advantage of available resources.

Education of Hispanics and Native Americans About Diabetic Eye Diseases:

- initiate public and professional education activities for Hispanics and Native Americans with diabetes that convey the importance of early detection and timely treatment of diabetic eye disease in preventing blindness and will encourage comprehensive eye examinations through dilated pupils.

Molecular Mechanisms of Age-Related Macular Degeneration:

- determine the cause of the aging-related destruction of photoreceptor cells in the macula, the small specialized area of the central retina that is responsible for sharp, crisp vision.

Strategies for Rehabilitation in Visual Impairment:

- investigate the role vision plays in everyday tasks and develop standardized tests to provide a profile of residual visual capacities and their relationship to common clinical measures of vision;
- determine how the visual system adapts to progressive deterioration of important neural or optical components that result in visual impairment.

Glaucoma:

- ameliorate the impact glaucoma has on Black Americans in terms of disease risk and economic hardship;
- apply recent advances in the biology of ciliary body fluid production to find better ways to treat glaucoma;
- develop the use of noninvasive assessment of the optic nerve head as a diagnostic tool for early detection of glaucoma.

Dry Eye or Keratoconjunctivitis Sicca:

- investigate the causes of insufficient tear secretion by the lacrimal gland resulting in dry eye or keratoconjunctivitis sicca.

FUTURE FUNDING CONSIDERATIONS

The NAEC is very concerned that these research priorities, which represent important opportunities for progress in vision research, might be lost because the NEI lacks the funds necessary to support a larger portion of the excellent research grant applications it receives. This lack of adequate funding has resulted in several disturbing trends: some of the best young scientific talent is not entering our disciplines, superbly trained young scientists—especially clinician scientists—are leaving the community of vision researchers, and the quantity of funded research programs, as well as the quality, are being adversely affected by multiple years of budget reductions. The net effects are not in the best interest of the Nation.

Research advances have already resulted in cost savings of extraordinary dimensions in health care related to the eyes and visual system. For example, the Optic Neuritis Treatment Trial, the first randomized clinical trial to evaluate corticosteroid therapy for optic neuritis (a debilitating inflammation of the optic nerve), recently reported that oral prednisone alone was ineffective in treating optic neuritis and actually increased a person's risk for future attacks. If these results cause a change in current treatment practice in favor of not treating the optic neuritis, the potential annual savings in medical management costs would be approximately \$32.4 million. Ongoing and future studies of this type hold potential for even greater savings in cost as well as sight.

Research at all levels—fundamental, clinical, and epidemiological—may one day lead to a means to prevent cataract, which alone could reduce health care costs by hundreds of millions of dollars annually. Progress in developing effective treatments for other aging-related eye diseases also could have a significant impact in reducing future health care costs as the number of people over age 65 doubles within the next 40 years. Additional research support may help gain an understanding of the precise molecular basis of inherited blinding diseases, so that we can improve our ability to provide early and prenatal diagnosis and genetic counseling. In some of these diseases, gene therapy might even be possible, thereby avoiding blindness with its enormous personal and public costs.

Through these difficult fiscal times, the NAEC has witnessed the dedicated efforts of the NEI staff and Director. Their commitment to excellence has served the public and the research community extremely well. The members of the NAEC have worked closely with NEI staff in developing funding options and ensuring that the maximum amount of high-quality research is pursued, given the limited resources available. However, we feel that it is imperative that the NEI budget be more closely aligned with current research opportunities and those opportunities that could be exploited over the next 5 years (Table 1). The NAEC also believes these increased investments would be more than repaid through savings in health care costs. The Council's budget would eliminate the harmful effects on research quality and quantity caused by the current reductions in research grants, fund additional promising research, rekindle interests in vision research careers, and ensure training of future vision scientists. These steps are essential for future continued progress against the blinding and disabling eye and visual diseases that cause so much suffering and economic burden to our Nation.

TABLE 1
NATIONAL ADVISORY EYE COUNCIL
Planning Budget
(Dollars in Thousands)

	First Year		Second Year		Third Year		Fourth Year		Fifth Year	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
<i>Research Grants</i>										
Research Projects										
Noncompeting	778	\$149,361	902	\$182,014	1,028	\$217,772	1,157	\$257,492	1,254	\$293,082
Competing	<u>425</u>	<u>81,592</u>	<u>468</u>	<u>94,311</u>	<u>515</u>	<u>109,171</u>	<u>515</u>	<u>114,640</u>	<u>515</u>	<u>120,384</u>
Subtotal	1,203	230,953	1,370	276,325	1,543	326,943	1,672	372,132	1,769	413,466
Research Centers	36	12,597	36	13,237	36	13,909	36	14,606	36	15,338
Other Research	<u>300</u>	<u>44,212</u>	<u>325</u>	<u>51,831</u>	<u>350</u>	<u>59,915</u>	<u>376</u>	<u>68,462</u>	<u>403</u>	<u>77,550</u>
Total	1,539	287,762	1,731	341,393	1,929	400,767	2,084	455,200	2,208	506,354
<i>Training</i>										
Individual	94	2,586	94	2,820	103	3,260	114	3,765	125	4,349
Institutional	<u>195</u>	<u>5,868</u>	<u>195</u>	<u>6,435</u>	<u>215</u>	<u>7,438</u>	<u>236</u>	<u>8,592</u>	<u>260</u>	<u>9,924</u>
Total	289	8,454	289	9,255	318	10,698	350	12,357	385	14,273
<i>Res. & Dev. Contracts</i>		10,000		10,508		11,042		11,595		12,176
<i>Intramural Research</i>		30,705		33,776		37,153		40,868		44,955
<i>Res. Mgt. & Support</i>		12,632		13,643		14,734		15,913		17,186
<i>Ext. Construction</i>		10,000		10,508		11,042		11,595		12,176
TOTAL		<u>359,553</u>		<u>419,083</u>		<u>485,436</u>		<u>547,528</u>		<u>607,120</u>

NATIONAL ADVISORY EYE COUNCIL

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NATIONAL ADVISORY GENERAL MEDICAL SCIENCES COUNCIL

INTRODUCTION

In this, its fourth biennial report to Congress, the National Advisory General Medical Sciences Council (NAGMSC) wishes to highlight the research training grant programs of the National Institute of General Medical Sciences (NIGMS) and to express concern for what is seen as a developing crisis in these programs if present trends are not reversed. The NAGMSC believes that "benign neglect" in research training programs has potentially long-term serious consequences for the entire biomedical research enterprise.

RELATIONSHIP OF RESEARCH TRAINING NEEDS TO NIH STRATEGIC PLAN

The Council's concern is an affirmation of the *National Institutes of Health Draft Strategic Plan*, most particularly the plan objective entitled Intellectual Capital, which addresses, in part, "the renewal and growth of the intellectual capital base essential to the biomedical research enterprise." This objective proposes to examine issues that are critical to maintaining and enhancing the talent pool of science, including strengthening research training and career development and ensuring the recruitment and retention of underrepresented groups into science. Because these issues are central to the future of the biomedical research enterprise in the United States, the NAGMSC strongly endorses the continued attention to and support of research training and career development programs at all levels—undergraduate, predoctoral, and postdoctoral, and particularly with regard to talented members of minority populations.

BACKGROUND

National Institute of General Medical Sciences. The NIGMS supports research and research training in the sciences that form the foundation needed for advances in understanding disease. In this way, the Institute helps supply new knowledge, theories, and concepts for disease-targeted studies supported by other components of the NIH. As a vital part of its mission, the NIGMS funds over one-half of the predoctoral trainees and about one-third of all trainees who receive assistance from the NIH. In all of its programs, both research and research training, the NIGMS stresses the importance of laying the basic foundations for disease-oriented research as well as for further fundamental biomedical studies.

The NIGMS is also the focal point at NIH for activities designed to increase the number of minority biomedical scientists. In 1991, the NIGMS established the Minority Opportunities for Research (MORE) Programs Branch to serve as an administrative umbrella for the Institute's new and existing programs related to minorities in biomedical research. The branch is the focus of planning and coordination of the activities of the Minority Access to Research Careers (MARC) Program and the Minority Biomedical Research Support (MBRS) Program, as well as of special initiatives, including a new National Predoctoral Fellowship Program for Minority Students. The leadership and administrative oversight provided by this new branch promises to enhance the success of the current NIGMS programs and create new opportunities for expanding the participation of minorities and minority institutions in sponsored research.

National Advisory General Medical Sciences Council. The NAGMSC was authorized in 1962, concurrent with establishment of the NIGMS, and it was chartered in 1963. The Council provides for second-level review of grant applications assigned to NIGMS and recommends to the Secretary of the Department of Health and Human Services and to the Director, NIH, approval of those projects that merit funding. In addition, the Council advises on matters relating to the biomedical sciences, assesses the state of research in areas relevant to the NIGMS mission, and advises the Director, NIGMS, on the nature and future direction of the Institute's activities and priorities.

NIGMS ROLE IN RESEARCH TRAINING OF UNDERREPRESENTED GROUPS

Research training and career development are central to the mission of the NIGMS, which provides the largest share of NIH predoctoral research training and is the steward of the NIH programs designed to strengthen biomedical research expertise in underrepresented populations. The Institute has long led the NIH in support of programs designed to increase the number of minority biomedical scientists. The Council is pleased to report the success of the new NIGMS National Predoctoral Fellowship Program for Minority Students that was first announced in February 1991. Similar in concept to the Minority Access for Research Careers Predoctoral Fellowships (which, since its inception in 1981, has provided support for 171 fellowships), the National Predoctoral Fellowship Program expands eligibility for these graduate fellowships to minority graduates of any college or university. In its first year, the NIGMS made 65 awards under this program; another 36 were funded by the Office of Minority Programs, NIH, and several other NIH institutes and centers. Additional components of the NIH have joined with the NIGMS in reannouncement of the program for future awards in FY 1992.

Illustrative of the value of investment in such young people, the Council cites with pride the accomplishments of Dr. Charles Richard Neal. Dr. Neal participated in the NIGMS MARC and MBRS programs as an undergraduate. He spent 2 years at the University of New Mexico, then moved to the University of California, Santa Cruz. At Santa Cruz, he first received support from the MBRS program and later became a MARC honors undergraduate research trainee. Following his graduation with a B.A. in psychobiology, Dr. Neal received a MARC predoctoral fellowship and went to the University of Michigan where he began study in the NIGMS Medical Scientist Training Program (MSTP). Recognized as an accomplished teacher, Dr. Neal was a sought-after tutor and was noted for providing valuable assistance to students. He was cofounder of the Latin American/Native American Medical Association and was also an active member of the medical school admissions committee. In recognition of his many accomplishments, the school awarded him its 1991 Medical Scientist Training Program Award, which honors one graduating student who demonstrates outstanding achievements in research and who exhibits the personal and professional qualities desired in a physician.

RESEARCH TRAINING IN BASIC AND CLINICAL SCIENCES

It is widely recognized that rapid research progress has created opportunities in biomedical science that were inconceivable a decade ago. Today, largely as a result of support of basic science, cell biologists, pathologists, and clinical oncologists can capitalize on advances in the fields of genetics, molecular biology, and structural biology to answer questions about

normal and abnormal cellular function and growth. Advances in computer technology and optics also have enabled researchers to adapt existing biological tools, such as the light microscope, to examine dynamic processes in living cells. Advances in cell cycle research, including the construction of a cell-free system to help scientists purify the cyclin-kinase complex essential to cell division, has enabled biologists to work with geneticists in discovering the links between cell cycle machinery and tumor suppressor genes.

These opportunities and advances would not have been realized without the existence of a cadre of broadly trained personnel. And, as described above, many of the most important new and exciting discoveries in basic and clinical science would not be possible without collaboration among trained personnel in many different disciplines.

Modern biomedical research requires individuals who have been well trained, not in traditional, narrow disciplines (although rigorous mastery of specific areas is crucial), but in a manner that enables them to transcend disciplines and move capably from field to field as new scientific opportunities are presented. The Council believes that the NIGMS has made a significant contribution to the rapid developments in biomedical sciences of the last several decades through support of programs for research training of qualified and motivated biomedical scientists. As one stellar example, the Council acknowledges the work of Dr. Alfred Gilman of the Department of Pharmacology, University of Texas, Southwestern Medical Center, who received the 1989 Lasker Award for Basic Medical Research. Dr. Gilman discovered a family of proteins known as the G proteins. His remarkable work combines physiology, pharmacology, molecular biology, and chemistry. Dr. Gilman's broad background and training enabled him to move from discipline to discipline as scientific knowledge unfolded. Dr. Gilman exemplifies the value of NIGMS-supported research training. He holds a combined M.D.-Ph.D. degree from Case-Western Reserve Medical School in a program that was a predecessor to the highly successful Medical Scientist Training Program now funded by the Institute, and he is a graduate of the small, but outstanding, NIGMS intramural research training activity, the Pharmacology Research Associate Training Program. After Dr. Gilman was awarded the Lasker prize, Nobel Laureate Dr. Michael Brown said of Dr. Gilman's contributions to the understanding of the nature and function of G proteins, "What's so interesting about [Gilman's] work is that it turns out to be central to all areas of biology. Development, cancer, disorders of metabolism—everything seems to lead back to receptors and intracellular signaling. It's equal to the study of genetics in terms of its pervasiveness in biology." The universality of Dr. Gilman's contribution is a highlight that illuminates the value of cross- and multidisciplinary research training.

Over the last several decades, institutional research training grants provided by NIGMS changed the model of American biomedical education even before the boundaries between disciplines began to fade. Instead of the numerous narrow Ph.D. programs, students were exposed to a range of potentially interactive modern disciplines and technologies. With the explosion of biotechnology and other new fields at the interfaces of several older disciplines, there is an even greater demand for such scientists. An example of the Institute's recognition of these emerging needs is the recently announced initiative for predoctoral research training at the chemistry-biology interface. This new program will provide for predoctoral institutional training grants to increase the level of participation of chemists in predoctoral training commensurate with the level of support provided by NIGMS for chemistry research. There is a compelling argument in support of this new training

program—the diminishing pool of scientists trained in chemistry is considered a problem of considerable urgency by the pharmaceutical and biotechnology industries. Modern research in these industries is accomplished by interdisciplinary teams, and currently industry must provide for interfacial training. One of the goals of this new program is to create a “partnership” with industry in training critically needed scientific talent at the interface of chemistry and biology.

The NIGMS also developed and supports the congressionally mandated Biotechnology Research Training Program. Concerned with our ability as a Nation to meet the growing demand of the biotechnology industry for well-trained scientific personnel, the Congress directed the Institute to establish a research training program to remedy the critical shortages of experts in biochemical engineering, macromolecular structure, protein engineering, separation technologies, and other areas that coincide with the major biotechnology research needs. NIGMS support for new biotechnology programs is intended to help fill this need by providing research training that focuses on the applications of engineering, physics, chemistry, mathematics, and biology in those areas of biomedical research related to biotechnology.

Since its inception in FY 1989, however, the program’s growth has fallen short of annual goals—and in fact, support is woefully insufficient to meet the program’s 5-year plan target of 1,500 trainees by FY 1995.

Unless new programs like these just described can go forward and, indeed, unless the NIH and NIGMS have the opportunity to capitalize on emerging needs for scientifically trained personnel, the excellence of the pharmaceutical and biotechnology industries and of basic medical research in the United States will be jeopardized.

SUMMARY

The Council wishes to emphasize the need for scientists who can address the problems of tomorrow and who are offered sufficiently inviting and effective training situations that they become committed to this challenging endeavor. Twenty years ago, HIV infection and AIDS were unrecognized, and yet, because of NIH support of multidisciplinary research training, the manpower was available to initiate innovative and responsive research programs to ultimately address the AIDS crisis. We cannot know the specific problems that will arise in the coming century and beyond—nor can we predict what new technologies will fundamentally alter research opportunities. But, research training programs in which investigators at today’s cutting edge train young scientists in creative, broad-based, rigorous approaches to problems are an absolute requirement for the health of the Nation’s people.

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NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL

INTRODUCTION

The goals of the National Heart, Lung, and Blood Institute (NHLBI) are to prevent, diagnose, treat, and cure heart, blood vessel, lung, and blood diseases and to provide for an adequate and safe blood supply for the Nation. To achieve these goals, the Institute supports a comprehensive and balanced program that incorporates basic and clinical investigations, clinical trials, epidemiologic studies, and demonstration and education projects. These efforts have resulted in extraordinary progress in the quest to improve the public health and have led, in turn, to new and exciting avenues for research. This document, the 17th report of the National Heart, Lung, and Blood Advisory Council, focuses on new scientific opportunities, on issues related to research cost considerations, and on several specific mechanisms of research support.

SCIENTIFIC OPPORTUNITIES

This year, the NHLBI has been a major and enthusiastic participant in the development of the *National Institutes of Health Draft Strategic Plan*. This plan was conceived to identify areas of research that promise significant dividends for the Nation's future health, to nurture the intellectual base of biomedical research and the conditions that lead to breakthroughs on the cutting edge of science, and to provide approaches for addressing broad administrative and science policy issues that affect the ability of the NIH to carry out its mandate. The plan identifies promising areas of science to be pursued and details specific initiatives within each area. The NHLBI initiatives developed for this plan comprise the most auspicious opportunities for research on the heart, blood vessels, lungs, and blood—the collective forward thinking of the Institute and its scientific advisors. The maintenance of strong research training and career development programs that encourage young investigators to focus upon cardiovascular, lung, and blood diseases is essential to the plan's success.

In the area of biotechnology, for example, the ability to create new animal models of human diseases by disrupting the expression of endogenous genes or by introducing defective human genes into the animal offers a host of exciting possibilities for understanding basic pathogenetic mechanisms of many diseases. The *Draft Strategic Plan* includes an NHLBI initiative to develop and use the full range of transgenic animal approaches to understand normal and altered cardiovascular and pulmonary function at the molecular, biochemical, cellular, and physiological levels; to elucidate gene-environment interactions; and to develop and evaluate innovative therapies and diagnostic procedures.

The NHLBI leads the NIH effort in gene therapy and bone marrow transplantation research, a key feature of the *Draft Strategic Plan* panel report on molecular medicine. In that promising area, an initiative is proposed to expand research on identification of the genetic basis of human disease, on the use of animal models (particularly nonhuman primates) to develop gene therapy for human disease, on the use of hematopoietic bone marrow cells as a general target of therapeutic genes, and on the mechanisms of transferring genes into other specifically targeted tissues and cells.

Another promising area of science is structural biology, a discipline that has, over the past decade, evolved tools and techniques for understanding the highly organized interactions of molecules in the living cell. Of critical interest to the NHLBI is a new initiative to determine the structure of the active sites of growth factors, cytokines, and their cellular receptors to understand their role in cardiovascular, pulmonary, and blood diseases. This information will eventually enable the molecular design of growth factors useful in the prevention and treatment of cardiovascular and pulmonary diseases and in the treatment of blood cell production abnormalities, immunologic defects, and marrow suppression due to cancer chemotherapy.

The *Draft Strategic Plan* panel report for prevention, health education, and control includes a special emphasis on diet and fitness to promote good health, with particular reference to racial and cultural differences. Within this context, an NHLBI initiative will evaluate the effects of a wide range of dietary components and physical activity regimens on blood lipids and blood pressure, with an eye to developing a scientific basis for new recommendations to prevent cardiovascular diseases. This is an area of research that has enormous public health potential and will flower with enhanced scientific attention. A second prevention initiative focuses upon the role of exposure to oxidants in the development and clinical consequences of atherosclerosis. This research would include animal studies to assess oxidant and free-radical effects on the heart and the arteries and on longevity; small studies in humans of production of, protection from, and effects of oxidized low-density lipoprotein; and a full-scale clinical trial of antioxidant and antithrombotic therapy in the prevention of cardiovascular diseases. Other studies, such as identification of risk factors and optimal management strategies for asthma, are important aspects of prevention research.

The initiatives described above represent only a sampling of the many exciting and timely scientific opportunities that exist today. Building upon a solid foundation of basic and clinical research, the Institute has achieved a balanced and comprehensive program that continues to gather momentum as new ideas, discoveries, and disciplines come into play. Maintaining that momentum, within the fiscal and administrative constraints that currently prevail, is a major challenge to the Institute. During the past year, the NHLBI and its Advisory Council addressed a range of issues that relate to sustaining its continued vitality and growth. The remainder of this report will elaborate upon these topics.

COST CONSIDERATIONS

An issue of particular concern is the funding of new and competing renewal research project grants. Over the past several years, the NHLBI has wrestled with the increasingly difficult problem of selecting—from among numerous highly meritorious investigator-initiated grant applications—those that would allow the Institute to meet congressional mandates for numbers of competing awards, without going over budget. In the past, the strategy was to pay grants according to scientific merit (that is, in order of their percentiled priority scores) but to limit costs through downward negotiation of the actual amount awarded.

Recent events made it clear that other approaches were needed. Specifically, the Congress directed NIH to consider the total cost of research project grant applications and to avoid any downward negotiations in arriving at funding decisions. These additional

constraints stimulated exploration of a number of methods for introducing the concept of cost-effectiveness into the assessment of grant applications. Specifically, the NHLBI developed a "value function" model that can be used to rank grants according to a mathematical score that reflects both scientific merit and cost, with scientific merit receiving the lion's share of weight. Application of this function makes it possible to highlight a gray area of grants near the margin that merit closer examination in terms of cost-effectiveness. When faced with grants having similar percentile ranks but widely varying resource requirements, for example, the Institute may opt to fund a handful of modestly priced grants rather than a single costly grant. On the other hand, it may elect to support an expensive grant if it is in an area of high program priority.

This approach was discussed in detail at the September 1991 meeting of the Advisory Council. The Council expressed its support through passage of the following motions:

- That cost be made a factor in funding considerations; that is, adopt the concept of the value function model;
- That the scientific judgment of staff members be inserted into the funding decision, given their overview of all applicants, the variability of judgments between the study sections, and their knowledge of where the science is and, hence, the need for support. It is also recommended that the Director report on this issue to the Council as appropriate;
- That NIH, by all means possible and appropriate, educate the Congress, the Administration, the health professions, and the public as to the NIH's efforts to improve the management and the use of fiscal resources they are responsible for and that a special effort be made to present the achievements of the biomedical enterprise and its contribution to the economic well-being of the Nation.

The value function approach was subsequently used for the first time to assist NHLBI funding decisions following the October 1991 Council meeting. Had the Institute made awards according to straight percentile ordering, only 139 applications that had percentile scores of 18.9 or less could have been funded within the available dollars. Using the value function, the Institute was able to identify a number of grant applications for special programmatic and cost review. After much thought and discussion, the decision was made to skip over three relatively costly applications near the margin. As a result, a total of 161 applications could be funded, all of which had percentiles of 21.8 or less. Thus, the net impact of the value function analysis was an increase of 18 awards over what would have been funded had the NHLBI continued to rely solely upon percentiles.

PROGRAM PROJECTS

Certain funding mechanisms, by virtue of their inherent high cost, tend to be identified by the value function as possible candidates for special consideration. The program project grant, with an average yearly cost in excess of \$1.2 million, is such a mechanism and has, thus, been the focus of considerable discussion. Beginning with fiscal year 1992, the NHLBI instituted new procedures for handling program projects that fall within the gray area of the value function described above and would not be selected for funding. Such grants are

disaggregated into their component research subprojects, each of which has an individual percentiled priority score and a cost that includes a proportionate share of the program project's core costs. These research subprojects, now reborn as regular research grants (R01s), are then reintroduced into the value function model and considered for funding as any other grant. This strategy enables the Institute to preserve the most meritorious aspects of program projects with moderate priority scores, yet meet its goal of paying the congressionally specified number of research project grants within the available budget.

The Advisory Council strongly endorses continued support for this vital mechanism. The program project grant has proved to be a very important mechanism for accomplishing research that the NHLBI is mandated to support. These grants not only enable support of a large number of investigators from a diversity of disciplines but also facilitate maintenance of an appropriate balance between cardiovascular, pulmonary, and hematologic research.

RESEARCH CENTERS

The previous Advisory Council report highlighted research centers as a critical area of progress and opportunity, and the message bears reiteration. Overall, 70 to 80 percent of NHLBI-supported clinical research is conducted in its research centers; for a number of disease areas, centers are the exclusive source for NHLBI support of clinical research. Over the years, the research conducted by Institute-supported centers has contributed directly to improvements in the public health and reductions in health care costs by developing new approaches to diagnosis, treatment, and prevention.

Currently, the Institute supports 64 centers in 15 subject areas. Our last report urged development of centers in four new areas: vascular biology and medicine, sudden cardiac death, heart failure, and bone marrow transplantation. A fifth topic, pediatric cardiovascular disease, is an additional area of scientific opportunity that should be addressed by a new centers program. Pediatric cardiovascular diseases, including congenital heart disease, rheumatic heart disease, Kawasaki disease, and arrhythmias, are a significant source of morbidity and mortality in the United States. The advancing state of knowledge in many basic science areas—biochemistry, molecular biology, genetics, bioengineering—presents new opportunities for understanding normal and abnormal cardiac development. Establishment of multidisciplinary research centers in pediatric cardiovascular disease will facilitate the full and rapid expansion of these opportunities.

POPULATION-BASED STUDIES

The past year marked the successful conclusion of three major NHLBI clinical trials: the Systolic Hypertension in the Elderly Program (SHEP), the Studies of Left Ventricular Dysfunction (SOLVD), and the Cardiac Arrhythmia Suppression Trial (CAST). SHEP found that treatment of isolated systolic hypertension, a common condition in older persons, resulted in average 5-year reductions of 36 percent for stroke, 27 percent for coronary heart disease, and 32 percent for all cardiovascular events. SOLVD demonstrated that treating chronic congestive heart failure with an angiotensin-converting-enzyme inhibitor, enalapril, reduced overall deaths by 16 percent and deaths or hospitalization for heart failure by 26 percent. CAST was halted upon determination that use of the drug moricizine resulted in a significant number of excess deaths in heart attack survivors who had mild arrhythmias.

The results of these trials have enormous implications, not only for the survival and quality of health of patients with such conditions but also for the costs associated with their care.

Because many interventions—pharmacologic, surgical, or hygienic—are employed without an adequate scientific basis, an urgent need exists for clinical trials to evaluate experimental interventions. Given sufficient funds, the NHLBI has developed plans for trials in such diverse areas as evaluation of prevention and treatment strategies for peripheral arterial disease, comparison of various regimens of beta-2 agonist therapy for asthma, determination of the risks and benefits of T-cell depletion of bone marrow for allogeneic transplantation, and the use of hydroxyurea in sickle cell disease. The Advisory Council expresses its strong support for clinical trials and other population-based studies as research mechanisms of demonstrated utility that can rapidly bring new scientific knowledge into clinical practice.

CONCLUSION

Considerable progress has been made in the Institute's quest to reduce the toll of heart, blood vessel, lung, and blood diseases and to meet the Nation's need for blood resources. But so much more remains to be accomplished. In this age of great progress and promise for biomedical research, the Council supports the Institute in its efforts to capitalize fully upon the myriad scientific opportunities that unfold.

NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL

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NATIONAL ADVISORY NEUROLOGICAL DISORDERS AND STROKE COUNCIL

INTRODUCTION

Neurological disorders are some of the most dreaded, disabling, and highly prevalent health problems facing our Nation. For example, severe traumatic head injury is the leading cause of death and disability for people under age 45 and is a significant cause of physical, cognitive, and psychological disabilities. There are 5,000 new cases of epilepsy each year as a result of traumatic head injury. Between 1 in 10 to 1 in 20 children enter adult life with a handicap due to a brain disorder. Malignant brain tumors are almost uniformly fatal; they are more common in adults, but are the second most common cancer of children. Since these disorders most often strike persons at a young age, plans for lifelong objectives are altered, careers are ended, and exceptional stress is placed on families and personal relationships. Additionally, they represent immense national health care costs, as illustrated by the following examples:

Disorder Group	Est. Incidence/Prevalence	Annual Cost <i>in Billions</i>
• Head Injury	2 million+ new cases per year	\$25.0
• Spinal Cord Injury	10,000 per year/250,000 existing cases	2.0
• Epilepsy	2 million existing cases	4.0
• Stroke	350,000 per year/2 million existing	25.0
• Huntington's Disease and other Genetic Disorders	125,000 existing cases	Unknown
• Developmental Disorders	10 to 15 percent of children	20.0
• Brain Tumors	35,000 new cases per year	Unknown
• Dementias, including Alzheimer's Disease	5,000,000 existing cases	90.0
• Multiple Sclerosis	10,400 per year/300,000 existing	2.5
• Nerve & Muscle Disorders	400,000+ existing cases	Unknown
• Parkinson's Disease & Motor System Disorders	In excess of 1 million existing	6.0
• Chronic Pain	Over 10 million office calls annually	Unknown

There are many other equally devastating neurological disorders, including cerebral palsy, shingles, tremor, neuro-AIDS, and other infections of the brain. This year some 50 million Americans—1 out of 5—will be affected by one or more neurological disorders, costing this Nation more than \$150 billion annually. As alarming as these statistics are, they only hint at the disabling impact of these disorders on individuals, families, and our society.

Responding to the disastrous consequences of the neurological disorders on our Nation, and recognizing the great, realistic potential we now have to understand, treat, and prevent them, Congress and the President declared in law that the 1990s are designated the "Decade of the Brain." Enactment of the "Decade of the Brain" was a declaration of war on neurological disorders. Now it is time to enlist the full force of the Nation's resources on strategies to defeat these illnesses and to prevent their resulting disabilities.

OBJECTIVES AND RECOMMENDATIONS FOR FUTURE DIRECTIONS

Following the Presidential Proclamation, the National Advisory Neurological Disorders and Stroke (NANDS) Council immediately constructed a strategy for use by the National Institute on Neurological Disorders and Stroke (NINDS). The *Implementation Plan* for the "Decade of the Brain" that it produced provides the structure for the conduct of successful research. The Council identified the most compelling neurological disease areas and research issues for which the opportunity exists to make beneficial and extraordinary advances within the next few years; a plan of priorities based upon opportunity and need. The focus of the *Plan* is on the major disease categories for which the field of neurobiological research is poised for a breakthrough. To take advantage of newly developed opportunities, we must take further decisive action now. The following recommendations are the highest priority issues that, if adequately pursued, will have a profound effect—in our own time—on the drive against neurological disorders:

The Genetic Basis of Neurological Disorders. Many brain disorders are genetically influenced. Of all human genetic disorders, at least one-fourth primarily affect the brain and the nervous system; in many more the brain is damaged as a result of the genetic abnormality governing other organ systems. By understanding the genetic basis of the nervous system, we increase understanding of how it develops and works and how we can repair or treat neurogenetic defects. We can expect even today to be able to manipulate genes for therapeutic purposes as when the brain is injured by trauma or disease. The flourishing of molecular genetics has made possible the very exciting discovery of the genetic defect responsible for Duchenne's muscular dystrophy and may well lead to treatment—possibly a cure—for the thousands of children and adults with this and other neuromuscular diseases. The dramatic advances in genetic research have great implications not only for specific neurodegenerative diseases but also for exploring the genetic influences in diseases such as multiple sclerosis, the dementias, memory disorders, and stroke.

Understanding Brain Structure and Organization. Within the past decade, imaging of the anatomy and metabolism of the functioning human nervous system and its nerve cells has provided extraordinary information heretofore unthinkable. Brain imaging techniques such as Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), and ultrasonography are now indispensable tools for neuroscience research as well as clinical diagnosis. They are responsible for much of what is known about brain activity and

structure in diseases such as stroke, Parkinson's disease, Alzheimer's disease, brain tumors, and epilepsy. Increasingly, neurological scientists are expanding the scope of imaging techniques to study the higher cognitive functions of learning, thinking, and memory. New ultrarapid, high-resolution techniques must be developed in the next few years to enable the noninvasive study of the structure, metabolism, and blood flow of the normal and affected brain from intrauterine life and infancy throughout adulthood. As a tool of research and for better understanding of virtually every disease that affects the brain, imaging will play a vital role.

Mechanisms of Repair. How the brain and spinal cord achieve ultimate restoration after being damaged is still very poorly understood. Thus, additional studies of mechanisms of repair are essential. We also need to know more about the normal nervous system as it is organized during early development and as it evolves throughout life, so that we might consider how to reprogram it for repair.

Animal Models Leading to Clinical Studies. The brain and its disorders must be studied in the living animal in as humane and effective ways as possible. Computer simulations and tissue culture techniques are useful adjuncts that help the scientist frame the question; in vivo animal studies help answer the question. If we are to understand the fundamental effects of disease and test the safety and efficacy of medications and other therapeutic agents, the use of animal models is critical.

Basic Neurological Research. The history of advances in science indicates that fundamental research has often led to discoveries that have far-reaching implications for a variety of different diseases. The foundation of our present knowledge about disorders of the brain and nervous system is built upon basic neurological research. For example, the development of monoclonal antibodies has opened up whole new research approaches to both the normal and abnormal nervous system. Additional studies in neurochemistry, neurogenetics, neuropathology, and other fundamental neurosciences are needed to identify the yet undiscovered secrets of the brain and the nervous system that will lead the way to further clinical advances. We must maintain our focus on the basic research that leads to clinical applications, for it is only through a strong science base that we will realize the potential of the "Decade of the Brain."

Controlled clinical trials and clinical testing of therapeutic procedures are essential. The extraordinary results of NINDS-supported trials within the last two years illustrates their importance for disease and disability prevention and treatment. They require adequate funding, and costs should be widely shared. We recommend that the Congress promote interagency and private sector joint sponsorship of clinical trials. This can be done through the use of the "demonstration funds" already identified in Medicare, other health care funds, and through legislation encouraging joint efforts.

Replenishment of Scientists. As a requisite for success in reaching the goals of the *Implementation Plan* for the "Decade of the Brain," a commitment must be given to the replenishment of the scientists whose inventiveness fuels discovery. Fellowships, training grants, and career development awards prepare the next generation of physician-investigators and scientists. We must increase our commitment to training programs to provide basic and clinical researchers who can continue to explore the neurological sciences

and exploit the enormous potential for therapeutic intervention in neurological diseases and disorders.

The Equipment of Research. We must encourage the continuing development of the extraordinarily sophisticated equipment required for nervous system research. Research space and equipment of the Nation's most prestigious bioscience laboratories are becoming dilapidated and obsolete. The development of new tools for research is part of every initiative recommended in the *Plan*.

In shaping the *Implementation Plan* for the "Decade of the Brain," the opportunities for the NINDS have been stated with precision, viewed as being achievable, and presented with realistic budget requirements. Total cost estimates for this national initiative on neurological disorders were derived by identifying the level of research effort required to fully implement each of the recommendations. The Council recommends that to carry out these activities efficiently and economically would require a total budget increment of \$410 million above the current NINDS operating budget. This is a relatively small investment when compared to the more than \$100 billion these disorders cost our society annually. Because of the inherent interaction in neurological research, the more these activities can be pursued simultaneously, the greater the efficiency and the reward from our investment.

ACTIVITIES AND PROGRESS DURING FISCAL YEAR 1991-1992

As of this writing, less than two years after the beginning of the "Decade of the Brain" and the implementation of our strategic *Plan*, we can report that there have been many major, concrete victories in the battle against neurological disorders:

Stroke: Aspirin/Warfarin. The results of a study supported by NINDS revealed that therapy with aspirin or warfarin—an anticoagulant drug—is effective in reducing the risk of stroke in elderly patients with atrial fibrillation. Both drugs were so beneficial that the risk of stroke was decreased by 50 to 80 percent. The striking results obtained suggest that 20,000 to 30,000 strokes can be prevented each year with proper treatment. The resulting savings from health care costs and continued productivity will be in the millions of dollars.

Spinal Cord Injury. An NINDS-supported clinical trial demonstrated that methylprednisolone, given within 8 hours of a spinal cord injury, improves recovery of function. The study showed for the first time that effective treatment of acute spinal cord injury was possible. It also emphasized the vital importance of prompt treatment of spinal cord injured patients. Hospitals throughout the country have adopted the regimen of high-dose methylprednisolone as the treatment of choice for acute spinal cord injury, and treatment by emergency medical teams at the accident scene is becoming more common. Great opportunity exists to refine this and develop other treatments to limit secondary damage from head and spinal cord injury.

Type I Gaucher's Disease. Gaucher's disease, a little-known but devastating genetic disorder, afflicts approximately 20,000 persons in the U.S. NINDS scientists have demonstrated the ability to reverse the features of Type I Gaucher's disease by enzyme replacement, providing the patients with remarkable clinical benefit. Their anemia has been corrected, the size of the enlarged spleens and livers has decreased, and there is skeletal

improvement. In addition, many have been able to return to normal daily activities, and they all emphatically state that the quality of their lives is greatly improved. Studies are underway to establish minimal dosages necessary and to learn of efficacy in treatment of another form of the disease (Type III). Scientists also have now successfully used enzyme replacement therapy in the treatment of Fabry's disease.

Parkinson's Disease. An NINDS-supported clinical trial revealed that treatment with the drug deprenyl delays the progression of symptoms in patients with early Parkinson's disease and postpones the need for L-DOPA therapy. This is the first time that we have evidence of a drug that may slow the progression of a neurodegenerative disease. Deprenyl was also found to increase significantly the time patients remained gainfully employed, a benefit that will yield increased productivity and millions of dollars of annual savings in health care costs.

Stroke: Carotid Endarterectomy. Overwhelming evidence from an ongoing clinical trial shows that the surgical removal of fatty deposits from the carotid artery reduces the risk of stroke by two-thirds in patients with 70 percent to 99 percent obstruction. As part of a 5-year trial funded by the NINDS, investigators at 50 centers in the United States and Canada studied 595 patients. Those who received the operation had a 78 percent reduction in their risk of suffering a major or fatal stroke on the side of the operation. The findings are a major advance in our battle to treat and prevent stroke.

Genetic Basis of Nervous System Function. Recently, NINDS scientists have developed the technology that can isolate and sequence 10,000 to 12,000 human brain genes per year. A large cDNA library of human brain clones and sequences is being established. A computer is used to compare these sequences tags with known protein sequences and identify unknown gene products. Within a few years, current research efforts should result in the partial sequencing of most genes expressed in the human brain.

Neurofibromatoses. The neurofibromatoses (NF) are common, serious, neurogenetic disorders. Two forms of NF have been described. NF1 is the most common type and is caused by a genetic defect that has been isolated on chromosome 17; NF2 is caused by a gene defect on chromosome 22. Both cause tumors of the nervous system for which there currently exists no medical treatment. The location on chromosome 22 of the genetic defect underlying NF2 suggests that it involves a tumor suppressor gene like that in some forms of cancer. Studies to identify the responsible gene may yield important new information regarding the development of malignancy outside the nervous system. Additionally, the information gained concerning the basic defect in this disorder may lead to the development of therapies for both inherited and sporadic brain tumors.

ALS—Lou Gehrig's Disease. A gene responsible for familial amyotrophic lateral sclerosis, also called Lou Gehrig's disease, has been located on chromosome 21 by a team of investigators supported by NINDS. This is the first time that hard evidence has been discovered about the cause for the disorder, which afflicts approximately 20,000 people in the United States.

Epilepsy: Genetics. The genetic basis of epilepsy and seizures has been intensively studied. A large four-generation family with benign familial neonatal convulsions has been identified. Chromosome studies show that the gene is tightly linked to two DNA markers on

the long arm of chromosome 20. Other investigators have localized DNA markers for juvenile myoclonic epilepsy on the short arm of chromosome 6.

Epilepsy: Phenytoin. A clinical trial addressing the use of Phenytoin in preventing epilepsy following serious head injury showed that, although early seizures were prevented, the later development of epilepsy was not. This finding has implications for treatment after severe head injury or brain surgery.

Epilepsy: Phenobarbital. Findings from another NINDS study show that phenobarbital given for the prevention of seizures in young children with high fevers (febrile seizures) appeared to lower their scores on intelligence tests. This finding is markedly affecting the therapies used for febrile seizures.

Head Injury. A national network of comprehensive, multidisciplinary head injury research centers has been established across the country. These centers have already contributed significantly in assessing the effectiveness of treatment procedures being used by the Nation's trauma centers.

The measure of success for the Nation's commitment to neurological research can be seen concretely in the thousands of survivors of stroke, head injury, spinal cord injury, Gaucher's disease, and other disorders, and the millions of persons whose lives are less painful and disabled because of the new therapies that have been developed through NINDS-sponsored research. Their lives testify to personal courage and to the reality that knowledge gained from our investment in research can be translated into more effective treatments.

These early successes only increase our resolve to press on to locate and defeat the faulty genes, the viruses, the poisons, and the other organisms and mechanisms that cause neurological disorders. Much has been accomplished, but much remains to be done.

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BOARD OF REGENTS OF THE NATIONAL LIBRARY OF MEDICINE

INTRODUCTION

The National Library of Medicine (NLM) was created to "assist the advancement of medical and related sciences, and to aid the dissemination and exchange of scientific and other information important to the progress of medicine and to the public health." NLM's mission is fully supportive of the mission of the National Institutes of Health: "Science in pursuit of knowledge to extend healthy life and reduce the burdens of illness and disability." NLM is entrusted with the responsibility and the privilege of making this knowledge accessible to health professionals so that it may be used to alleviate suffering and improve the lives of all Americans.

Together with the Nation's medical libraries, the NLM has made great strides in improving the dissemination of biomedical information to health professionals, and has been at the forefront in the development of new information technology in the health sciences. The environment of the 1990s and beyond will demand more broadbased and timely communication modes that meet the needs of the multiplicity of audiences, such as research scientists, health practitioners, educators, students, and a wide variety of health professionals located in both the public and private sectors.

Through its Long-Range Plan, the NLM Board of Regents has directed the growth of the Library and its entry into emerging areas such as biotechnology information and high performance computing and networking applications. NLM's initiatives described in this report will contribute to the success of the development of the *National Institutes of Health Draft Strategic Plan* and focus particularly on trans-NIH objectives having to do with biotechnology; structural biology; impact of research on the Nation's economy; the health of women, minorities, and underserved populations; and communications and information flow.

SUMMARY AND RECOMMENDATIONS

The Board of Regents is well pleased with the achievements of the Library in meeting the goals of its own Long-Range Plan. Much progress has been made, and, with adequate resources, the provision of information services has a tremendous potential for improving health care and biomedical research. Specific recommendations of the Board follow.

The Board recommends strong support for basic library services as the necessary underpinning of all the Library's new initiatives in outreach, high performance computing and communications, biotechnology, and other areas. The Board also recommends that NLM continue its role as a national leader in library technology.

The Board recommends increased support for NLM's outreach programs as a way to improve the health and well-being of the American people through the expeditious communication of new knowledge.

The Board recommends increased support for NLM's High Performance Computing and Communications programs, and by extension the related programs of the NIH, to help

the biomedical community to translate its research and practice needs to benefit from the power and usefulness of new modes of communication.

The Board recommends increased support for biotechnology information data bases and tools on which the field of biotechnology is vitally dependent for its survival and growth.

The Board strongly supports the work of the NLM Planning Panel on Toxicology and Environmental Health and underscores the importance of expediting the panel's work with respect to defining the near- and long-term responsibilities of the Library.

BASIC LIBRARY SERVICES

Basic library services—such as collection building, maintenance, and preservation, indexing and cataloging, improvements to NLM's online services—are at the heart of NLM's congressional mandate “to assist the advancement of medical and related sciences, and to aid the dissemination and exchange of scientific and other information important to the progress of medicine and to the public health.” Success of the exciting new initiatives described in this report are dependent upon a strong underpinning of the library services that provide essential information products and services.

The NLM budget must ensure that NLM can maintain and preserve the quality of its collection, perform the indexing and cataloging essential to create current and accurate online data bases, and incorporate the results of the Unified Medical Language System (UMLS) project into basic operations. The success of NLM's Outreach initiative depends on the currency and quality of the NLM collection and its online data bases. If practitioners and researchers cannot find the most recent literature in NLM's data bases or obtain comprehensive backup document delivery service from the NLM collection, then the Library's outreach efforts will suffer. Other major initiatives—such as high performance computing and communications—also depend upon the existence of the core library services.

NLM has long been a pioneer in the field of library technology and automation. It has an important role to play in developing and disseminating library technologies, within the medical library community and to other libraries as well, in the United States and worldwide.

IMPROVING ACCESS TO BIOMEDICAL INFORMATION

The major “product” of the NIH is new knowledge about health and disease. As it discusses the impact of research on the Nation's economy, the *Draft Strategic Plan* is based on the notion that the full and appropriate application of NIH research results is critical to many groups: scientists engaged in biomedical and behavioral research; health care practitioners of all types, whose responsibility to their patients requires that information concerning biomedical and behavioral advances be applied appropriately and in a timely manner; and all members of the public, specifically those in high-risk groups facing health problems.

Outreach to Health Professionals in Underserved Areas. Strategies to be employed by NLM involve promoting access to national information resources that contain the results of scientific research conducted at the NIH and in laboratories worldwide. A special focus of

these efforts is aimed at extending health-related knowledge, and the information technology that makes this transfer possible, to underserved persons who lack or have limited access to health care, a pressing need that is also underscored by the *Draft Strategic Plan* as it considers the health of women, minorities, and underserved populations. The Board of Regents continues to view outreach as a highest priority for NLM. NLM invests both its fiscal and intellectual resources not only in acquiring scientific information but in devising new and more efficient and effective methods for making it readily available to the health and scientific community. Large numbers of health professionals in our Nation do not have easy access to biomedical information—because of geographic isolation, nonaffiliation with a hospital or medical school library, or lack of information about available services. With the increased funding available for outreach, and with the guidance of the Board's own Outreach Planning Panel report, NLM has developed an active and successful outreach program.

Data Base Searching. The explosion of scientific knowledge in recent years has been accompanied by a revolution in information technology that has itself become an indispensable part of the research process at all stages. For example, data base searches are absolutely critical for molecular biology research, and as the data bases grow and become more comprehensive, their effectiveness in this process grows as well. As an example, using the information resources of NLM's National Center for Biotechnology Information, an international team of investigators recently identified the gene responsible for Kallmann syndrome, an important discovery that may ultimately result in the development of new drugs to promote accurate nerve regeneration in humans.

It is critically important not only to produce scientific information that will affect the work of researchers, but also to devise better methods for making the results available for use by health practitioners. It is the peer reviewed journal literature that constitutes the scholarly record and is the authoritative statement of what is known. The published journal literature continues to be the preferred means of disseminating new information from "bench to bedside." Studies have shown that access to the published literature and state-of-the-art knowledge, via online computer data base services such as MEDLINE and PDQ, has had beneficial—even life-saving and limb/organ-sparing—consequences for patients. Striking benefits deriving from the use of such services have also been demonstrated in terms of reduced costs of care, the quality of care given, the efficiency and safety of health care institutions, and the public's understanding of health care issues.

The widely available "Grateful Med" software for personal computers, NLM's easy-to-use microcomputer interface to the MEDLARS system, remarkably easy to use and extremely economical, is changing how health practitioners keep abreast of the literature. Since its introduction in 1986, nearly 40,000 copies have been distributed. The newest enhancement to Grateful Med now allows any health professional not only to search through millions of MEDLINE records, but actually to place an online order for a copy of the entire journal article to be mailed or faxed. This service, called "Loansome Doc," truly gives "fingertip control of the literature" to the health practitioner.

The successful Integrated Academic Information Management System (IAIMS) initiative, by bringing information from diverse sources to the bench and to the bedside, strengthens the research infrastructure and disseminates the most current clinical information to the point of care.

Clinical Alerts. At times, new research advances may be so extraordinary and have the immediate potential to literally save lives or avert crippling disability that clinicians should be alerted before their formal publication. Within recent months, a new product, "Clinical Alerts," has been released. This is a coordinated approach for expedited release of new research information when it is determined that any delay in its dissemination could adversely affect patient care. NLM and the NIH Office of Communications have charted a plan for cooperating with individual research institutes in issuing "Clinical Alerts." Seven such alerts have been made available over NLM's online network since January 1991.

HIGH PERFORMANCE COMPUTING AND COMMUNICATIONS

The *Draft Strategic Plan* acknowledges the critical role computers play in scientific research in many fields and recommends a strong NIH role in high performance computing. NLM's own planning process has reached similar conclusions; high performance computing and communications are essential for a number of key initiatives in the Board's Long-Range Plan, including molecular biology computing; creation, transmission, and storage of digital electronic images; the linking of academic health centers via computer networks; the creation of advanced methods to retrieve and store information from life sciences data bases; and training in biomedical computer sciences. The development of new and faster computers, advanced software, a national research and education computer network, and expanded training of scientists in the use of computer-based tools, are critical to many advances in science, such as the analysis of the human genome, prediction of protein structure and function from genetic code, and rational drug design.

The President's Office of Science and Technology Policy (OSTP), through the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET), has initiated a multiagency High Performance Computing and Communications Program (HPCC) to strengthen the Nation's research computing enterprise. As stated by D. Allan Bromley, Director of the Office of Science and Technology Policy, in the preface to *Grand Challenges: High Performance Computing and Communications*,¹ "The goal of the Federal High Performance Computing and Communications (HPCC) Program is to accelerate significantly the commercial availability and utilization of the next generation of high performance computers and networks. Recent advances offer the potential for a thousand-fold improvement in useful computing capability and a hundred-fold improvement in available computer communications capability by 1996. These advances will come through improvements in hardware and software. This increased capability will greatly expand the availability of these resources for research and education."

The HPCC initiative and investment by large telecommunications corporations in digital data services will stimulate dramatic change in the national infrastructure for communications for research and education through the decade of the 1990s. These new information resources will facilitate access to and delivery of health sciences information via

¹Office of Science and Technology Policy, *Grand Challenges: High Performance Computing and Communications, The FY 1992 U.S. Research and Development Program*. A report by the Committee on Physical, Mathematical, and Engineering Sciences, Federal Coordinating Council for Science, Engineering, and Technology.

electronic pathways employing the most up-to-date and effective computer and telecommunications technology available. There needs to be a catalytic effort by NIH to help the biomedical community to translate its research and practice needs to benefit from the power and usefulness of these new modes of computing and communication. Moreover, there must be concerted efforts to ensure that every health professional, regardless of setting, has access to the new technology if the goal of promoting the full and appropriate application of NIH research will be realized.

BIOTECHNOLOGY INFORMATION AND COMPUTATIONAL TOOLS

The rapid pace of progress in biotechnology and molecular biology presents a challenge to computer and information science to collect, analyze, and make available an ever-increasing body of knowledge. Sequence and three-dimensional structural data are being generated at rates that are accelerated by technological advances and the directed support of the Human Genome Initiative. Not only the volume, but the complexities of the data as well, create new demands for innovative solutions to represent and retrieve the data. Access to these data has now become an essential component in planning, conducting, and evaluating laboratory work.

As is underscored in the *Draft Strategic Plan*, the field of biotechnology is vitally dependent on the flow of information for its survival and growth. Breakthrough discoveries on the molecular basis of cancer, heritable diseases, and the immune system would never have occurred without computer searches of data bases. Traversing the links among sequence, genetic and physical map, and bibliographic information will be essential for capitalizing on these discoveries. In practical terms, this means that members of the biotechnology community must be able to access and utilize the information derived from basic research, which in turn requires ready access to the data itself and to the tools needed to extract and analyze such data. With the increasing availability of high performance computing systems and high-speed networking through the High Performance Computing Initiative, powerful computing resources are no longer limited to computer centers but have entered the laboratory.

PLANNING PANEL ON TOXICOLOGY AND ENVIRONMENTAL HEALTH

In accordance with NLM's longstanding interest in improving access to biomedical information and learning more about its users and their information needs, the Library has launched a new Planning Panel on Toxicology and Environmental Health at the request of the Board of Regents, as part of its efforts to update and expand upon the NLM Long-Range Plan. Since its inception in 1967, the goals of NLM's Toxicology Information Program have been quite straightforward: to create and maintain automated data banks of information on toxicological subjects and to disseminate that information widely. In the intervening years, "toxicology" has developed meanings and societal importance far beyond those envisioned 24 years ago. In parallel, the demand for access to comprehensive, accurate information about the subject has expanded rapidly. There is growing awareness of the dangers associated with the release of hazardous chemicals into the environment. Dramatic disasters in locales such as Bhopal have alerted the world community to the acute toxicity of certain chemicals. More recent reports have highlighted the devastating effects of prolonged exposure of populations in Eastern Europe to industrial contaminants. Public scrutiny is

increasingly directed to more subtle hazards to populations exposed to low doses of marginally harmful agents over long periods of time.

The time is propitious for reevaluating the goals, objectives, and scope of the NLM's Toxicology Information Program. The Board expects to derive from this effort a plan of what can and should be done by the Library in this area within a 20-year timeframe. The Board notes the importance of expediting the panel's work vis-a-vis identifying the Library's responsibilities in this increasingly global confluence of toxicological and environmental health effects.

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NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH

INTRODUCTION

The National Center for Human Genome Research (NCHGR) was established on October 1, 1989, to manage the NIH component of the Human Genome Project, a worldwide effort with the ultimate goal of analyzing the structure of human DNA and identifying the genetic information residing in its sequence, including the localization of all human genes. In parallel with this effort, the DNA of a set of model organisms will be studied to provide the comparative information necessary for understanding the functioning of the human genome.

The Human Genome Project is a bold initiative with far-reaching implications for all of biomedical science. It will spawn new research tools—chromosome maps, DNA sequence information, laboratory technology, and computer data bases—that should form the foundation of 21st-century biomedical science. Knowledge gained from the genome project will facilitate research and lead to improved prevention, diagnosis, and treatment of many diseases. Since all cellular processes are ultimately governed by genes, understanding the structure and function of human genes will provide powerful new approaches to understanding human health and disease. Virtually every component of the NIH supports genetic research. The fruits of NCHGR-supported research are expected to facilitate and complement these efforts dramatically.

The NIH and the Department of Energy are the key agencies managing the Human Genome Project in the United States. In FY 1990, the NCHGR and the Department of Energy issued a joint research plan for the first 5 years of the Human Genome Project. Five-year goals have been identified for the following areas, which together encompass the Human Genome Project: mapping and sequencing the human genome; mapping and sequencing the genomes of model organisms; data collection and distribution; ethical, legal, and social considerations; research training; technology development; and technology transfer.

The National Advisory Council for Human Genome Research was established by the Secretary, Department of Health and Human Services, on May 8, 1990, and held its first meeting on January 22, 1991. The Council has been impressed at how rapidly and effectively the NCHGR has taken on the task of managing a unique, novel, and sometimes controversial program that has received a great deal of public attention. Much of the early opposition to the program has dissipated, in large part due to the high quality of the research supported by NCHGR, the evident usefulness of the results that are beginning to flow, and the caliber of the staff and their management of the Center's programs. The Council endorses the goals set forth in the 5-year plan and believes they have been effective in focusing the efforts of the scientific community as well as the management of the genome program on the essential immediate objectives.

NIH STRATEGIC PLAN

The Council notes with satisfaction that, during the development of the *National Institutes of Health Draft Strategic Plan*, the importance of genetic research was emphasized throughout most of the scientific panel reports and concurs with the high priority assigned to these approaches. The Human Genome Project will clearly be of immense value to all

these areas. In particular, the following panels' proposed initiatives will rely heavily on the efforts of the NCHGR: Molecular Medicine, Structural Biology, Biotechnology, Chronic and Recurrent Illnesses and Rehabilitation, Basic Biology and the Environment, Neuroscience and Behavior, Molecular Basis of Embryonic Development.

The Council is also pleased that the strategic planning exercise has identified considerable interest in the NIH intramural program for expanded activities in human genome research. This is highly commendable. Such activities would greatly strengthen the research programs on the NIH campus in manifold ways and complement existing strengths in structural biology and gene therapy. Considering the high priority accorded genome research in the extramural program and, indeed, throughout the world, it would be most appropriate to have in the NIH intramural laboratories a strong program in genomic research focused on the goals specified in the 5-year plan for the genome project and the applications of the fruits of this research to medical problems. While the applications research would span the programs of all Institutes, the Council concurs with the position of the NCHGR, that this Center would be the only appropriate unit at the NIH to manage a laboratory dedicated to the genetic and physical mapping activities that would provide the foundation for expanded genome research at NIH.

RECOMMENDATIONS

Although the Council is extremely pleased with the progress achieved by the NCHGR to date, there are concerns for the future that need to be addressed.

Budget. The Council is disappointed that the budget for the NCHGR has not achieved the levels specified in either the 5-year plan or the Budget Plan prepared for the House Appropriations Committee. The difference between the budget envisioned and the budget achieved is substantial enough that progress will be affected. In particular, the Council expects that the physical mapping of human chromosomes will be significantly slowed at the current level of funding. The Council believes that a critical mass of activity, as reflected in the 5-year Budget Plan, is needed to solve the technical problems that remain and move this research forward. Therefore the Council urges that future appropriations for the Center be at the levels recommended in the 5-year Budget Plan, which represents the recommendations of leading experts in genomics research.

Uniqueness of Genome Research. Genome research is of necessity different in some respects from most of the basic research supported by NIH. In order to achieve the very ambitious goals that attend this program, research needs to be carefully planned and monitored. Only in this way can we assure that research results will be compatible with each other and will be obtained in the most economical way. Coordination of research projects is essential, as is rapid dissemination of information and integration of results into consensus maps. Many projects demand interdisciplinary research teams of substantial size in order to make effective progress. The need for significant technology development in all aspects of genome research also calls for the funding of highly innovative work, sometimes in areas not traditionally favored by the NIH.

Certain funding mechanisms are better suited for this type of research than others. Thus, although the traditional NIH research project grant (R01) will continue to play a

significant role in the genome project for the foreseeable future; other mechanisms must necessarily play an increasing role. These include the research center grants as well as contracts—mechanisms that allow for coordinated large multidisciplinary projects and for more input into their research direction by staff. The use of Requests for Applications is also expected to increase. The Council thus strongly urges that the NCHGR be given every flexibility in allocating its budget among the mechanisms that will best serve the interests of the human genome program, rather than being held to distribution formulas that reflect the needs of NIH as a whole. Such formulas do not apply to the genome program and will be detrimental to accomplishing its goals.

In addition to flexibility in the use of mechanisms, the genome program requires adequate staffing and adequate resources for the staff to carry out their necessary functions. The Council and the Program Advisory Committee on the Human Genome provide active oversight of the project and need to be able to meet, create working groups, conduct site visits, and carry out other activities as needed. In this regard, restrictions on travel funds or personnel ceilings are counterproductive to the aims of the genome program. Only through careful management of the monies appropriated will this program succeed and provide the payoffs that we all look for. The expenses associated with program management and oversight are well worth the investment and indeed essential to the efficient conclusion of the project.

Peer Review. The special nature of genome research, with its emphasis on innovation, interdisciplinary research, and technology development, requires attention during peer review. In general, the Council notes that peer review of genome grants has improved since the program was started, but continues to be a challenge. Reviewers on the whole have a better understanding of the needs of genome research. However, there is still a reluctance to take chances with novel ideas and sometimes a lack of appreciation of the contribution a particular approach could make to achieving the goals of the program. When dealing with a goal-oriented area of science, such as the genome program represents, constant vigilance is required to assure that peer review supports the objectives of the program.

RESEARCH AND PROGRAM HIGHLIGHTS

Genetic Linkage Maps. The Council is pleased with the Center's initiative to develop a framework linkage map for each human chromosome, consisting of 300 evenly spaced index markers of very high quality. Progress on this initiative is excellent to date. These maps will provide a series of highly informative landmarks that can be used to rapidly localize each new marker to a particular interval on a chromosome.

Physical Maps. In recent years, physical maps have played a key role in the isolation of the genes involved in a number of important genetic diseases, including the genes for the Fragile X Syndrome, Familial Adenomatous Polyposis, Charcot-Marie-Tooth Syndrome, and Kallmann Syndrome. The Council notes that the search for each of these genes was greatly aided by the products of the Human Genome Project. However, in view of budget limitations, the Council notes that the 5-year goal for physical mapping may not be achieved for all chromosomes.

DNA Sequencing. At present, DNA sequencing is too expensive to consider sequencing large regions of human DNA. The Council affirms the Center's strategy of supporting pilot DNA sequencing projects with the goal of reducing the cost significantly by improving current technology and/or developing new approaches to DNA sequencing. The Council believes the 5-year goal for DNA sequencing is still realistic: to improve current methods and/or develop new methods for DNA sequencing that will allow large-scale sequencing of DNA at a cost of \$0.50 per base pair.

Informatics. The Human Genome Project will produce data bases as well as tools for analyzing data. The Council supports the NCHGR's sponsorship of the Genome Data Base at The Johns Hopkins University and encourages the Center to continue to pursue international funding and oversight of this vital resource in future years. The support of additional data bases focused on model organisms is also encouraged.

New Technology. The Council notes the need for new technology to speed up and simplify both chromosome mapping and DNA sequencing. In addition, the accuracy and reliability of the results must be improved. The Council supports the Center's emphasis on high-risk, high-payoff projects that may lead to order-of-magnitude improvements in the cost and rate of DNA sequencing or chromosome mapping.

Ethical, Legal, and Social Implications. The Council is very pleased with the speed with which the Ethical, Legal, and Social Implications (ELSI) program of the Center has been established and the significant impact it has already made. This program is the first at the NIH to address social implications of science in the context of a biomedical research program.

Realizing the benefits that will derive from research supported by the NCHGR will require professional and public deliberations over an important set of bioethical questions about the use of genetic information. The numerous issues that are emerging raise policy questions at multiple levels within society. The Council endorses the focus the ELSI program has placed on privacy of genetic information, safety and efficacy of new genetic testing options, and fairness in the use of genetic information. The Council also applauds the efforts of Center staff in launching the new program on cystic fibrosis testing. This program, in collaboration with the National Center for Nursing Research and the National Institute of Child Health and Human Development, is seeking to define the best methods for educating and counseling individuals who want to be tested for the gene that causes cystic fibrosis. Professional practices and public policies established with respect to cystic fibrosis testing will provide important precedents for the introduction of new genetic tests into medical practice.

INFORMING THE PUBLIC

Effective dissemination of accurate and useful information about the genome program to the public and to various professional groups is essential to the success of the program. In this regard the Council endorses the activities of the Center's Office of Communications in reaching out to various groups with a variety of informative materials. The recently released videotape and the pamphlet "New Tools for Tomorrow's Health Research" are particularly

effective vehicles for a wide-ranging audience, and the Center is encouraged to continue these efforts.

CONCLUSION

The Human Genome Project is one of the most important and far-reaching initiatives in biomedicine today. Genes play a role in many of today's most common diseases, including heart disease, hypertension, cancer, Alzheimer's disease, arthritis, diabetes, and birth defects, diseases that are believed to result from complex interactions between genes and environmental factors. The improved understanding of these diseases, resulting from genome research, will lead to novel preventive modalities and therapies, which in turn will result in marked decreases in illness and suffering for the American people. A coordinated and goal-oriented project such as the NCHGR has undertaken is the most effective, economical, and expeditious approach to achieving these results. The Council commends the NIH for its foresight in establishing a Human Genome Program and the NCHGR for the quality of the program that has been mounted.

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NATIONAL ADVISORY COUNCIL FOR NURSING RESEARCH

INTRODUCTION

The National Advisory Council for Nursing Research views the past 2 years as a time of dynamic growth for the National Center for Nursing Research (NCNR). Council members believe that the NCNR is fulfilling its commitment to improving the health of the American people and ameliorating the effects of illness, injury, and disability by achieving breadth and depth in the scientific base for nursing practice. The Council commends the NCNR for its leadership in developing and implementing strong programs in nursing research, research training, and dissemination of results for nurses and other health professionals in research and clinical practice.

RECOMMENDATIONS FOR FUTURE DIRECTIONS

In order to strengthen the leadership role played by the NCNR and enable it to meet the many health challenges ahead, the Advisory Council members make the following recommendations with respect to the structure of the NCNR, its research and research training programs, and its human and fiscal resources.

Structure of the NCNR

1. The Council strongly recommends that the National Center for Nursing Research be elevated to the status of an institute. The NCNR has already launched extramural and intramural research and research training programs equal in scope and depth to those of a full institute. The results of these programs are being translated into effective patient care by nurses, the largest discrete group of professional caregivers in the American health care system. Institute status for nursing research, with access to the full range of funding mechanisms and special congressional appropriations, would immeasurably help researchers and practitioners provide scientifically sound, economical health care for patients and their families.

Research and Research Training

2. The Advisory Council applauds the NCNR's outstanding efforts to recruit minorities in undergraduate, graduate, postgraduate, and faculty nursing research and research training programs. The Council encourages the NCNR to amplify its support for activities that increase the number of minority nurse investigators. This is not only a matter of equity; it is also a matter of bringing to nursing research the special knowledge, experience, and sensitivities of minority persons from various cultures. The cultural aspects of care are an important part of nursing research when the community and family are considered.
3. The Advisory Council believes that NCNR's establishment of specialized and exploratory centers at strategic locations around the Nation is an outstanding strategy for building depth in basic, clinical, and targeted research in priority health care problems. Through such centers, nursing research can make vital contributions to the health of women, minorities, infants and children, older persons and the frail elderly, and other vulnerable patient populations, their families, and their communities. The NCNR supports two specialized

centers, each at \$500,000 in total costs per year, and five exploratory centers, each at \$100,000 total costs per year. The Advisory Council recommends that funding for each specialized center be increased to \$750,000 in total costs per year and that the number be increased to 10 by 1996. Members also recommend that the funding for each exploratory center be increased to \$150,000 in total costs per year and that the number be increased to 15 by 1996.

4. The Advisory Council commends the NCNR for its accomplishments thus far in intramural research, with special praise for its clinical research program on the special needs of HIV-infected individuals and the Honolulu-based study of caregivers of patients with Alzheimer's disease. The NCNR must now be able to expand its intramural program substantially in order to address critical nursing research questions such as symptom management, compliance with therapeutic regimens, improved administration of treatments, facilitation of positive patient outcomes, and maximum quality of life.

5. The Advisory Council applauds the leadership taken by NIH in establishing a trans-NIH Women's Health Initiative. The Council further recognizes the notable contribution of the NCNR to this initiative; that is, research on normal growth and development in midlife women. The Council encourages the NCNR to continue its commitment in this regard, with special emphasis on the health care needs of minority women of all ages.

6. The Advisory Council encourages the NCNR to continue its efforts to include nursing-related elements in existing NIH multisite studies and to explore the development of other multisite studies (with common data bases) to address more effectively the health care issues that cut across diverse ethnic, racial, socioeconomic, and regional components of American society. Multisite studies not only reflect our Nation's heterogeneity but also yield important information on the effects of these diverse factors on human health.

7. The Advisory Council is deeply concerned about the inadequacy of funds for training and career development in nursing research. These funds are critical to the preparation of investigators who will form the foundation of improved nursing practice over the remainder of this decade and into the 21st century. The Advisory Council recommends a fivefold increase in the number of career development awards, from 12 in FY 1992 to 58 in FY 1996. Council members also advocate that predoctoral and postdoctoral training positions be raised from 245 in FY 1992 to 375 in FY 1996, with an appropriate stipend increase.

8. The Advisory Council applauds the NCNR's interest in facilitating networks with nurse researchers in other countries. Cooperative international research can accelerate the development of new knowledge in areas of global concern such as maternal and child health and the transmission of HIV infection.

9. The Advisory Council emphasizes the fact that the investment of taxpayer funds in nursing research is of little value to the ultimate beneficiaries—the American people—unless the results of that research are widely circulated to other scientists, practicing nurses, and others engaged in patient care. The Council, therefore, encourages the NCNR to continue to increase its efforts to disseminate research findings through demonstration projects and professional and public media.

Human and Fiscal Resources

10. The Advisory Council is concerned that the NCNR's rapid expansion of research and research training programs has placed extraordinary demands on the NCNR's outstanding staff of public servants. The Council strongly recommends, therefore, that steps be taken to ensure that staffing is commensurate with the growth of NCNR's programs and associated administrative responsibilities.

11. The Advisory Council has reserved its strongest language for this final but critically important recommendation: that the National Center for Nursing Research receive appreciably higher levels of appropriations over the next 5 years in order to bring its resources into balance with the health care needs of the American people and with the scientific needs of an increasingly sophisticated nursing profession. The Advisory Council is profoundly concerned that the NCNR is able to fund only a modest number of the excellent applications it receives. The NCNR's success rate for research project grants is far below the aggregate NIH success rate. The estimated success rate for NIH in FY 1993 is 26.4; NCNR's estimated success rate for the same year is 15.5, a full 10.9 points lower. The effect of this funding constraint is twofold: (1) worthy investigations are not carried out and their potential benefit is lost; and (2) investigators may become discouraged and look elsewhere for support or turn away from research altogether. Either result is extremely damaging to the growth of the nursing research domain; both results wreak havoc on any long-range plan for the nursing research and research training enterprise. The Advisory Council's recommended funding to sustain appropriate levels of nursing research through FY 1996 has been provided in Table 1.

ACTIVITIES OF THE ADVISORY COUNCIL

During 1991 and 1992, the Council met six times. Council members' principal tasks are to provide second-level review for grant applications and advice on policy development. During the period of this report, issues inherent in the second phase of the NCNR's long-range plan and the *National Institutes of Health Draft Strategic Plan* received critical attention.

The Council participated in planning for the NCNR's 1993 Conference on Research Priorities, which provides a forum for nurse scientists and scientists from related disciplines to evaluate and update the National Nursing Research Agenda.

By the end of 1992, reports were completed on five of the initial priority areas designated in the National Nursing Research Agenda: HIV Infection—Prevention and Care; Low Birth Weight—Mothers and Infants; Symptom Management; Long-Term Care for Older Adults; and Nursing Informatics—Enhancing Patient Care. A panel of experts was convened to review the state of the science in an additional priority area, "Health Promotion for Children and Adolescents."

The Advisory Council received and approved two special reports: (1) the report of the NCNR Biological Sciences Task Force, which provides a 10-year plan for linking nursing research and the biological sciences; and (2) the report of the Task Force on Patient

Outcome Measures, which suggests directions the NCNR might take to develop research initiatives on patient outcomes.

NCNR'S PROGRESS ACROSS THE RESEARCH SPECTRUM

The Council members are gratified with the NCNR's progress over the past 2 years in the following key research areas:

Low Birth Weight Infants and Their Mothers. NCNR research has focused on preventing low birth weight and improving methods of nursing care for these infants. This research is of major significance in view of the magnitude of the problem of low birth weight in the United States. Funded projects have examined different nursing approaches to the education and counseling of minority, low-income, and single pregnant women, who comprise the maternal population at highest risk. Other studies explore preventive, intensive, and other models of postpartum nursing support for low birth weight infants and their mothers.

HIV Infection. The Advisory Council strongly supports NCNR's identification of the prevention of HIV transmission and the care of HIV-infected individuals as priority research areas. Current HIV-related research (1) seeks culturally sensitive prevention strategies for high-risk minority populations, (2) searches for better caregiving practices for persons infected with HIV, and (3) studies the needs of AIDS patients and their families as they cope with the physiological and psychosocial problems that arise at every stage of the illness.

Women's Health. In addition to the focus on maternal health care, the NCNR is addressing other women's health issues. This research focuses on altered functions associated with the menstrual cycle and premenstrual syndrome. These studies will be expanded to include inadequately understood syndromes of midlife women that are characterized by musculoskeletal changes, fatigue, insomnia, gastrointestinal problems, and flushing. Because there is a lack of knowledge about these syndromes, women often receive inappropriate treatment. The Advisory Council endorses this line of research as one that will contribute significantly to the health and well-being of American women. This research is particularly important because it addresses the concerns of a population group that has previously been ignored.

Long-Term Care for Older Adults. The Advisory Council notes that nurses provide most of the professional care given to chronically ill older Americans, both at home and in institutions. Since nurses have the greatest potential to improve the delivery of quality, cost-effective, long-term nursing care for our society's rapidly growing population of older and "frail elderly" men and women, the Council strongly supports the NCNR's commitment to expand this knowledge base for nursing practice and patient benefit.

Symptom Management. Pain, fatigue, anxiety, and depression often accompany an illness such as cancer or heart disease, or a disabling trauma such as a spinal cord injury. In addition to dealing with the specific illness or trauma, nurses also play a major role in the relief of these symptoms, which may hinder recovery and otherwise compromise the patient's quality of life. The Advisory Council regards research and research training in symptom management to be a top NCNR priority.

CONCLUSION

Upon review of the NCNR's activities during 1991 and 1992, the members of the Advisory Council find a pattern of remarkable growth and accomplishment achieved by dedicated NCNR staff and their colleagues in the nursing science community. Information generated through NCNR support, both intramural and extramural, is already beginning to demonstrate the unique and necessary contribution that a research-based approach to nursing practice can make to the health of the American people. We have only the highest praise for the NCNR's strong leadership and creative development of these programs thus far and cannot urge strongly enough that sufficient funds be made available to continue this important mission.

National Advisory Council on Nursing Research (NACNR)
 Budget Recommendations
 FY 1991-FY 1996
 (Dollars in Thousands)

	FY 1991 Actual		FY 1992 Estimate		FY 1993 Pres. Budget		FY 1993 NACNR Level		FY 1994 NACNR Level		FY 1995 NACNR Level		FY 1996 NACNR Level	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
RESEARCH GRANTS														
Research Projects														
Noncompeting	111	\$18,659	118	\$22,962	118	\$24,093	118	\$24,093	121	\$26,355	191	\$43,715	266	\$63,973
Admin. Supp.	(7)	107	(6)	308	(6)	319	(10)	500	(6)	410	(6)	431	(6)	453
Competing	50	9,038	44	8,505	53	10,718	86	20,545	120	27,749	130	31,589	145	37,024
Subtotal	161	27,804	162	31,775	171	35,130	204	45,138	241	54,514	321	75,735	411	101,450
Research Centers	7	1,630	7	1,639	7	1,639	10	2,329	14	5,700	21	6,750	25	9,750
Exploratory Centers	5	513	5	510	5	510	8	1,200	8	1,200	15	2,250	15	2,250
Specialized Centers	2	1,117	2	1,129	2	1,129	2	1,129	6	4,500	6	4,500	10	7,500
Other Research														
Research Careers	12	885	12	1,041	12	1,041	34	3,060	42	3,994	50	4,996	58	6,090
Coop. Clin. Res.									9	3,250	9	3,415	14	6,585
Other Res. Rel.	18	1,046	14	1,031	14	1,031	18	1,300	18	1,365	23	4,059	28	6,890
Subtotal	30	1,931	26	2,072	26	2,072	52	4,360	69	8,609	82	12,470	100	19,565
Total, Res. Grants	198	31,365	195	35,486	204	38,841	266	51,827	324	68,823	424	94,955	536	130,765
TRAINING														
Individual	162	2,036	153	2,122	153	2,122	181	2,762	210	2,780	226	4,475	234	5,097
Institutional	107	2,300	92	2,270	92	2,270	139	3,813	127	4,077	136	4,803	141	5,478
Total, Training	269	4,336	245	4,392	245	4,392	320	6,575	337	6,857	362	9,278	375	10,575
R&D CONTRACTS	1	100	2	150	2	150	4	450	5	1,055	8	1,809	8	1,900
INTRAMURAL RES.	FTEs (5)	550	FTEs (9)	773	FTEs (10)	812	FTEs (12)	1,500	FTEs (16)	3,207	FTEs (20)	3,985	FTEs (23)	4,475
RES. MGMT. & SUPP.	(33)	3,541	(39)	4,169	(41)	4,373	(43)	4,650	(46)	5,815	(50)	6,726	(57)	7,655
TOTAL	0	39,892	0	44,970	0	48,568	0	65,002	0	85,757	0	116,753	0	155,370

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FOGARTY INTERNATIONAL CENTER ADVISORY BOARD

INTRODUCTION

The Advisory Board of the Fogarty International Center (FIC) for Advanced Study in the Health Sciences is pleased to present its fourth biennial report to Congress on the activities of the FIC. The Board wishes to convey to Congress the unique and essential role of FIC among the components of the NIH. The support that FIC provides for internationally based research and training and international policy guidance is an increasingly important contribution to the research missions of the NIH institutes and the well-being of the American scientific enterprise.

The mission of the FIC is to improve the health of the people of the United States and other nations through the promotion of international cooperation and advanced study in the biomedical sciences. To accomplish this mission, FIC is authorized by law to (1) facilitate the assembly of scientists and others in the biomedical, behavioral, and related fields for discussion, study, and research related to the development of health sciences internationally; (2) provide research programs, conferences, and seminars to further international cooperation and collaboration in the life sciences; (3) provide postdoctoral fellowships for research training in the United States and abroad, and promote exchanges of senior scientists between the United States and other countries; (4) coordinate the activities of NIH that are concerned with health sciences internationally; and (5) receive foreign visitors to NIH.

THE ROLE OF INTERNATIONAL ACTIVITIES IN ADVANCING THE NIH MANDATE

FIC has evolved as envisaged by Congress when Representative John Fogarty proposed "a great international center for research in biology and medicine dedicated to international cooperation and collaboration in the interests of the health of mankind." The farsighted importance of this founding vision cannot be underestimated as medicine and biology approach the next century. Biomedical and behavioral research have become inherently international in character. Increasingly, our capacity to capitalize on scientific opportunities and realize the potential of new discoveries will depend on cooperation with our global partners.

This is attributable to global developments that present both new challenges and opportunities. These include the rapid spread of infectious disease across national borders, increasing opportunities to study unique populations and environments in other parts of the world, the growth of centers of excellence abroad, the establishment of global information networks, and the emergence of an international market for research investment and scientific personnel.

Public health priorities such as HIV/AIDS, childhood respiratory diseases, tuberculosis, viral hepatitis, and other infectious diseases require international cooperation to develop effective preventive and treatment interventions. Advances in our understanding of genetically based and acquired diseases are advanced through examination of these diseases in other cultures. In addition, there is a growing need for both financial and human resources to meet the expansive scientific opportunities presented through

advances in molecular biology and new biotechnologies, such as mapping and sequencing the human genome. FIC plays an important role in marshalling critical expertise and resources from around the globe to understand the causes of disease and develop effective interventions that improve the health of citizens worldwide.

FIC PROGRESS IN MEETING ITS OBJECTIVES

The FIC Advisory Board was constituted in 1985 to provide guidance on FIC planning and policy and to conduct second-level reviews of applications for FIC research and training awards. The Board also assesses research priorities and recommends future programmatic directions. To fulfill these responsibilities, the Board convenes three times a year at the NIH. The Board commends the progress achieved by FIC since the last biennial report. Highlights of these achievements follow:

FIC AIDS Institutional Awards. With the guidance and direction provided by Congress, FIC has responded to the global HIV/AIDS emergency by developing an AIDS International Training and Research program to expand the number of highly trained clinical investigators, especially from developing countries. Since the inception of the program, 388 scientists from 49 countries have received training in the United States. In addition, American medical faculty have conducted over 100 in-country training courses that have reached more than 4,500 health care workers and research assistants in developing countries. The program has now expanded to include scientists from Eastern Europe and the Soviet Union and constitutes the largest global research training program for HIV/AIDS.

The Advisory Board notes with enthusiasm the present and potential future contributions of this program in advancing preventive and treatment solutions for HIV/AIDS and strongly encourages its expansion to other public health priorities and to a broader base of U.S. institutions. Advances in recombinant DNA technologies have accelerated the rate of drug and vaccine development and hold promise for the prevention and cure of numerous diseases. Many of these emerging treatments and preventives will require studies in regions of the world where there is a high incidence of a particular disease. The development of an HIV/AIDS vaccine is a notable example, because proof of its efficacy will depend on testing in various regions of the world, including the United States, due to geographic differences in the rates of infection and the genetic characteristics of the virus. International studies will also be required to develop new vaccines against several of the diarrheal, respiratory, sexually transmitted, and parasitic diseases, and viral-based cancers.

The FIC AIDS institutional awards support these efforts by helping to ensure that a cadre of highly trained U.S.-linked investigators exist in-country to conduct collaborative trials. The program also contributes to the creation of an international sentinel network of basic and clinical investigators to anticipate and prevent new microbial outbreaks before they become global emergencies. It is important to note that, although the HIV/AIDS epidemic exemplifies the difficulties of coping with a new infectious disease, it is but one of more than a dozen new or newly recognized viral diseases that have emerged in recent decades due to rapid and continuing social, demographic, and ecological change.

Special Regional Initiatives. In light of the historic changes affecting all areas of East-West relations that have created unprecedented opportunities for collaborative research,

Congress has called for increased biomedical research cooperation with scientists in Eastern and Central Europe. Within 6 months of major political changes in this region, FIC established a Central and Eastern European Initiative (CEEI) to promote and support cooperation between American scientists and their counterparts in the former Warsaw Pact. The CEEI addresses unique research opportunities in environmental health, neuroscience, pediatric AIDS, and other NIH priorities. In addition to scientific benefits, CEEI contributes broadly to the development of democratic institutions by promoting the values and principles that underpin the U.S. scientific enterprise. Forty-five research projects have been supported to date, involving 13 NIH research institutes and 7 countries in the region.

Also in FY 1990, FIC launched a regional initiative to facilitate biomedical research collaboration between U.S. and Latin American and Caribbean scientists in response to congressional recommendations and Advisory Board guidance. U.S. scientists have gained from unique and untapped scientific opportunities and institutional capabilities in the region. To date, the initiative has supported 28 research projects involving 11 research institutes and 15 countries in the region.

These regional initiatives have been expanded through the establishment of a new small grants program, entitled the Fogarty International Research Collaboration Awards (FIRCA), designed to promote collaborative research between NIH-supported investigators and scientists in the two regions. The response to this program has been overwhelmingly positive. In view of the large number of promising proposals that have been received from NIH grant recipients, the Board is concerned with the limited number of highly meritorious applications that FIC is able to fund due to budgetary constraints. The Advisory Board strongly encourages the Congress to provide additional support to the FIC for the funding of outstanding small grant proposals.

The Board also recommends congressional consideration of a regional program for Africa, which is a leading international health priority of the Secretary of DHHS. Every year 15 million children in the developing world die from infections, malnutrition, and other causes, the highest percentage of deaths occurring in sub-Saharan Africa. In response, FIC has developed an NIH-wide initiative to apply the skills of the U.S. biomedical research community, in cooperation with African scientists, to develop new and improved diagnostics, vaccines, and other means of prevention and treatment. Research benefits would extend to African Americans affected with genetically related diseases prevalent among Black populations worldwide, including sickle cell anemia, familial hypertension, and diabetes mellitus. The program will build on the FIC AIDS institutional awards, expanded to include other determinants of childhood and maternal health in Africa, as well as the FIC small grants and fellowship award programs.

The National Institutes of Health Draft Strategic Plan. The Board enthusiastically endorses the development of the *Draft Strategic Plan*. This plan will identify areas of biomedical research that promise extraordinary dividends for the Nation's future health and address strategic policy issues that affect the implementation of NIH's broad mission. The Board commends FIC for providing leadership in developing the international component of the plan.

Through its award programs, FIC has supported research in each of the promising areas of science to be addressed in the framework. The research supported has ranged from fundamental studies to identify the three-dimensional structure of important proteins to intervention studies to arrest the increasing global spread of tuberculosis. Highlights of selected scientific accomplishments under FIC award programs follow.

Neuroscience and Behavior. Qualitative advances in molecular genetics and imaging technologies over the past decade have resulted in new and unexpected opportunities to identify the causes of neurological disorders and to develop innovative approaches to treatment and management. As a consequence, the U.S. Congress and, subsequently, governments of other nations have designated the 1990s as the "Decade of the Brain." The neurosciences have historically drawn from the talents of a multidisciplinary group of scientists working in laboratories and clinics throughout the world. FIC is working closely with the National Institute of Neurological Diseases and Stroke (NINDS) through the establishment of an FIC-NINDS Standing Committee to develop a program of cooperation to stimulate international cooperation and has established a new neuroscience fellowship program with Central and Eastern Europe.

Currently, neuroscientists supported by FIC fellowships are studying changes in the expression and processing of amyloid protein, which is a common pathological process in both Alzheimer's disease and Down syndrome. Identifying the mechanisms of these disorders at the molecular level will provide the basis for future treatment approaches and potential cure.

Molecular Medicine. A leading challenge in biology and medicine is to understand how biological molecules organize into discrete structures and interact through complex, chemically based information and storage transfer systems. FIC-supported scientists are identifying mechanisms that control hormones, neurotransmitters, and growth factors regulating cellular interaction. When these signal systems are disturbed, uncontrolled cell growth, abnormal nerve function, and impaired immune response can result. Fundamental insights that will be gained from these studies have broad implications for the development of treatments for a range of chronic and degenerative diseases.

Vaccine Development. There has been an explosive increase in research on peptides—natural or synthetic compounds of two or more amino acids—and the potential value of synthetic antigens in antibacterial and antiviral vaccines. FIC-supported researchers are studying the role of this important class of compounds in the development of preventives against HIV/AIDS and cancer.

Population-Based Studies. The availability of unique populations and environments in other regions of the world presents important opportunities to expand the scientific knowledge base and conduct studies that could not be undertaken in the United States alone. FIC-supported researchers are conducting studies on the epidemiology and immunology of hepatitis viruses, viral-based cancers such as Kaposi's sarcoma and primary cancer of the liver, and diabetes mellitus.

Biodiversity Initiative. In FY 1991 the FIC, in cooperation with the National Cancer Institute, the U.S. Agency for International Development, and the National Science

Foundation, began to explore mutual interests in international efforts to develop new cancer drugs and antiviral agents from natural products. These discussions have led to development of an interagency program to support research to identify new bioactive natural products from plant and marine extracts and microorganisms and to help preserve the rich natural diversity of our rain forests and oceans. It is hoped that the program will promote both economic growth and ecological conservation by demonstrating the value of biological resources from which natural products are derived.

Policy Activities. The FIC director serves as vice chairman of the Federal Coordinating Council for Science, Engineering, and Technology's Committee on International Science, Engineering, and Technology. This body provides governmentwide policy guidance on scientific and technological issues and serves as a mechanism for interagency planning and coordination. The Board is pleased that FIC assumed lead responsibility for analyses of the effects of European economic integration on cooperative scientific and technological relations with the United States and, more recently, for a study of scientific and technical relations between the United States and countries of Central and Eastern Europe. These analyses provide guidance to the White House Office of Science and Technology Policy and Federal agencies and serve as a framework for scientific and technological relations with these regions.

The Board encourages the FIC to provide further leadership to address current and emerging international policy issues that affect the research environment. With the increasing internationalization of science, the global dimensions of NIH policy issues will require a deepening analysis. FIC should assume a leading role in addressing current and emerging international issues in such areas as new diseases, international competitiveness, and technology transfer. As a first order of priority, the Board encourages FIC to examine whether present opportunities and incentives for American scientists to conduct research abroad are adequate or need to be substantially increased. With the rapid growth of highly innovative research laboratories and centers of excellence in Japan, Western Europe, and other regions, access to overseas laboratories on the frontiers of discovery is essential to continued U.S. leadership in medicine and biology.

RECOMMENDATIONS FOR PROGRAM NEEDS

A wealth of opportunities exist for advancing the NIH mandate through international cooperation. Although these opportunities far exceed available resources, FIC continues to be a catalyst in developing creative and innovative initiatives that augment national programs. The Board expresses its gratitude to Congress, and in particular to the members of the appropriations and authorization committees, for their guidance and their commitment to FIC activities. While recognizing the limitations on Federal resources, the Board strongly encourages congressional consideration of new and expanded activities described in this report. These activities could be implemented with relatively modest additions to the FIC budget.

The Board recommends that the Congress appropriate an additional \$5,000,000 to the President's request for FY 1993 of \$20,727,000, for a total of \$25,727,000. This increase will enable FIC to

- initiate an NIH-wide regional program for Africa to save children's lives and improve their health status (\$1,000,000);
- support additional outstanding proposals for collaborative research under FIC's regional initiatives for Eastern Europe, including the former Soviet Union, and Latin America (\$1,000,000);
- increase preparedness for HIV/AIDS vaccine trials through targeted expansion of AIDS International Training and Research Programs (\$2,000,000); and
- establish an international sentinel network of U.S. and developing country institutions to detect and prevent new disease outbreaks before they become global emergencies (\$1,000,000).

GLOBAL LEADERSHIP IN A NEW ERA

The conduct of biomedical and behavioral research has become a global enterprise. NIH has been instrumental in defining its international character through investment in scientific pursuit worldwide. This investment has not only accelerated the development of important drugs, diagnostics, and vaccines, but has advanced broader U.S. economic and foreign policy objectives and significantly influenced the biomedical research agendas of other nations.

Historical changes in Eastern Europe and the Soviet Union over the past biennium will have broad repercussions for science and technology. In a new world order, representing a lessened nuclear threat, research to benefit global health and the environment will be integral to national policy and international diplomacy. It is timely to examine the potential of the FIC to further American global leadership in biology and medicine in response to the demands and opportunities of a new era. Through its unique international mission, FIC can play an instrumental role in fostering cooperation for the benefit of health, economic progress, and global security.

The Advisory Board strongly encourages Congress to support FIC's role as the international arm of the U.S. health research community. We recommend congressional consideration of a major increase in the FIC budget to support innovative, strategic programs that enable NIH to contribute to national objectives through international scientific cooperation. These programs would be designed to capitalize on new opportunities for discovery, explore new realms, and cross interdisciplinary and international boundaries. A unique opportunity exists to help realize the global role of the United States in a new era, and to bring to the American public dividends that derive from medical research wherever it occurs—better health for all.

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EXECUTIVE SUMMARY AND OVERVIEW

The National Center for Research Resources (NCRR) was established in 1990 by the merger of the Division of Research Resources (originally created in 1962 as the Division of Research Facilities and Resources) and the Division of Research Services. The founding of the National Center was based on the recognition that progress in health-related research, and improvements in health care delivery stimulated by that research, demands the presence of an extensive infrastructure. This infrastructure is made up of physical facilities, equipment of ever-increasing technological sophistication, specialized research centers that provide unique materials and research opportunities, and above all, skilled and dedicated biomedical scientists drawn from all segments of the American population. The support given to NCRR and its myriad activities in the past has permitted the country to be at the forefront of biomedical research.

At the present time, however, costs for the maintenance and continued development of the infrastructure undergirding biomedical research are rising while budgetary support is diminishing. This erosion of support is taking its toll. The construction of new and renovated research space took place largely in the 1960s. These facilities are now antiquated, often dilapidated, and hamper the conduct of research using up-to-date techniques. New research technologies are pointing the way to conceptual advances in biomedical knowledge almost undreamed of several decades ago, advances that in turn drive the development of still other kinds of research techniques and instruments needed to explore their implications still further and advance the frontiers of knowledge. But these technical innovations are growing not only in complexity but in cost.

Of equal importance is the need for well-trained biomedical scientists. The generation of men and women who in recent decades have provided the leadership in biomedical research are aging but are not being replaced in like numbers by younger scientists on whom the future depends. Demographic changes in the composition of the Nation, coupled with fewer students electing to pursue research careers, require new efforts to encourage new generations of young men and women from all ethnic groups to aspire to research careers and to develop the support systems that will allow them to do so. The National Advisory Research Resources Council is committed to the view that failure of the NIH budget to keep pace with these very real needs not only deters progress in biomedical science to the detriment of the welfare of the country's citizens, but in tangible terms costs more in the long run to repair.

The primary mission of the NCRR is to support the infrastructure that provides the foundations of biomedical research and is essential to the continued vitality of the research enterprise. This report on the past biennium outlines the kinds of activities undertaken by the various programs under its jurisdiction, some of their needs and accomplishments, and directions for the future.

BIOLOGICAL MODELS AND MATERIALS RESOURCES PROGRAM (BMMRP)

The Biological Models and Materials Resources Program (BMMRP) has a major goal of identifying and characterizing nonmammalian models for biomedical research, thereby responding to the congressional mandate to reduce the use of mammals in biomedical research, where scientifically possible. The program is also responsive to the desire of the biomedical community to maximize the intertaxonomic transfer of information. The program is thus concerned with developing model systems of invertebrates, nonmammalian vertebrates, and cell cultures, as well as with developing data-driven mathematical and computer models. The last biennium is the first full term of the program. At present, a lack of resource growth is severely restricting the program's ability to respond to initiatives proposed by investigators in this area.

The program currently supports centers to acquire, authenticate, and maintain a variety of nonmammalian organisms and other biological materials for the scientific community. It also supports a diversity of investigator-initiated studies covering a range of plants and vertebrate and invertebrate organisms. Of particular focus recently has been the support of freshwater and marine models, which represent a major opportunity for biomedical research. The program has also continued to support mathematical and computer models with an emphasis on the Matrix of Biological Information.

Illustrative of the program's operation is support of the *Caenorhabditis* Genetics Center (CGC), a repository for over 1550 mutant strains of the nematode *Caenorhabditis elegans*, a small roundworm that has been adopted as a model proving ground for sequencing by the Human Genome Project and has a variety of biomedical research applications. For example, investigator-users of CGC strains reported on *C. elegans* as a potential model system for the study of aging. They discovered that a mutation in one of the genes controlling aging in *C. elegans* resulted in a 65 percent increase in the roundworm's mean lifespan and a 110 percent increase in its maximum lifespan. These and related studies are expected to give geneticists clues about the contribution of individual genes to the normal and pathologic aging of humans.

BIOMEDICAL RESEARCH SUPPORT PROGRAM (BRSP)

A major mission of the Biomedical Research Support Program (BRSP) is to enhance the biomedical research enterprise through several mechanisms not otherwise available through NIH.

Biomedical Research Support Grants (BRSG) provide support to individual investigators for short-term, small-scale research projects in a manner that allows rapid response to unanticipated needs and opportunities. BRSGs have been a highly cost-effective device for funding high-risk pilot studies in which promising innovative ideas can be tested; for stimulating the research of young investigators, by helping them to set up their laboratories, and to initiate projects that may provide the basis for subsequent competitive research applications; and for providing interim support for established investigators who need to keep their laboratories in operation when there is a gap between the end of one grant and the beginning of another. Although BRSG funds have suffered an 89 percent

reduction since 1990, the need for this highly effective and unique program remains at least as strong as in earlier years.

BRSP funds also go to support the Shared Instrumentation Grant Program (SIGP). SIGP provides sophisticated, state-of-the-art instruments to groups of NIH grantees to enhance the goals of their ongoing research efforts. Examples of these instruments include NMR imagers, coupled hybrid mass spectrometers, scanning laser confocal microscopes, and gene sequencing equipment. Over 1,000 NIH-funded investigators have been major users of instruments awarded through the SIGP. If these users had each acquired these instruments on their individual research grants instead of using shared instruments, the costs to NIH would have been approximately eight times greater. Investigators would also have been deprived of interdisciplinary interactions that occur at the institutional level. Budget cuts in SIGP funds, however, have resulted in fewer instruments being acquired through this mechanism of shared use, despite continuing demands. In 1991, with a budget of approximately \$32.5 million, 401 SIGP applications were received, with requests totaling \$118 million; of these applications, 139 were awarded. During 1992, 440 applications were received requesting a total of \$95.1 million, while only 38 awards, totaling \$8.7 million, could be made.

The Minority High School Student Research Apprentice Program (MHSSRAP) also falls within the purview of BRSP. A key objective of MHSSRAP is to interest minority students in pursuing careers in health-related research or in health care. MHSSRAP provides minority high school students with up to 8 weeks of hands-on experience in clinical or basic research laboratories. In 1991, the program was expanded to include high school science teachers who are either minority group members or who teach a significant number of minority students. The teachers are provided in-depth laboratory experience in biomedical sciences such as physiology, genetics, developmental biology, microbiology, and immunology during a summer internship at a local university, professional school, or research organization. The long-range goal is to establish year-round linkages between biomedical scientists and high school science teachers that will foster continued mentoring and encouragement of young students to seek careers in bioscience. Allocations to MHSSRAP increased in 1991 and 1992. In 1992, the program provided for almost 3,000 student positions and almost 500 teacher positions.

BIOMEDICAL RESEARCH TECHNOLOGY PROGRAM (BRTP)

The Biomedical Research Technology Program (BRTP) has the mission of providing crucial technological underpinnings for the entire enterprise of biomedical research, including essentially all of the promising areas of science targeted in the *National Institutes of Health Draft Strategic Plan*. About three-quarters of the BRTP budget supports 58 resource centers that both develop and make available a very diverse set of technologies ranging from synchrotrons and supercomputers, to medical imaging and isotope preparation, to biomedical data bases and calculational methods, and to specialized versions of instrumentation used for research in structural biology, cell biology, biochemistry, etc. The facilities of these centers are used in a large fraction of the basic and clinical research supported by NIH. In some cases they provide capabilities available nowhere else in the world, and in all cases they provide a cost-effective sharing of needed infrastructure among many laboratories. Other major components of BRTP activity are the support of related

research projects at the research centers, and the support of technological innovation through pilot grants to individuals and small businesses.

Although budgets have been very tight, BRTP has maintained a high level of excellence in its centers and research. Particularly noteworthy recent research results to emerge from work at BRTP centers include identification by high-voltage electron microscopy of the specific lesions produced inside nerve cells by the amyloid fibers in Alzheimer's disease, and the development and application of magnetic resonance technology for in vivo studies of metabolic events accompanying disease and recovery from disease. Important recent developments of enabling technologies include better computer simulation methods in areas as diverse as blood flow in vascular networks, population behavior in AIDS transmission, and the addition of real-time force calculations to interactive molecular modeling; and the enhancement of structural biology by work with synchrotrons.

Synchrotron crystallography is an especially appropriate technology for NIH research. The speed and extremely high resolution possible with synchrotron sources are essential, for example, for drug design. It is a very significant accomplishment of BRTP, therefore, to have taken a lead in the interagency alliance to fund this crucial but expensive development. BRTP is also taking an active part in the initiative for High-Performance Computing and Communication, which is a natural extension of its ongoing activities.

COMPARATIVE MEDICINE PROGRAM (CMP)

The broad mission of the Comparative Medicine Program (CMP) is to support the biomedical and health research community in its efforts to conduct humane animal research and to support laboratory animal scientists in their quest to improve and assure the health, quality, and usefulness of laboratory animals; to determine environmental and welfare requirements of research animals; to identify, develop, and characterize animal models; and to establish and maintain special animal colonies for research. The mission is accomplished by supporting research, animal resources, and training, through its three sub-programs. The Laboratory Animal Sciences Program (LASP) supports research on animal model development and on animal resources such as colonies of unique genetic stocks and models and reference centers, and improves animal facilities and the health status of laboratory animals. This program also supports postdoctoral fellowship programs providing specialized research and clinical training in Laboratory Animal/Comparative Medicine and Pathology. The Regional Primate Research Centers Program supports a national network of seven regional primate research centers. These centers provide the Nation's biomedical research community with specialized facilities for nonhuman primate research of critical importance to understanding human health problems and disease processes, including AIDS, Alzheimer's disease, Parkinson's disease, cancer, and cardiovascular diseases. Finally, the AIDS Models Program supports the development and use of animal models for AIDS-related research. The program coordinates these efforts with NIH categorical institutes.

In the last 2 years, CMP programs have made significant advancements in spite of limited support. To highlight a few examples: the development of transgenic mouse models of serious infant immunologic and metabolic disease; the development of rodent models for Lyme Disease; the development of SPF rhesus monkey breeding colonies; the identification

and development of a nonhuman primate model for investigations on human AIDS; and the training of comparative medicine scientists.

The opportunities and challenges for the CMP are great. Given its broad and vital mission, funding for CMP must keep pace with that provided to NIH overall. Research animals are required to support nearly half of all NIH-sponsored programs. CMP activities affect almost all animal research conducted in the United States and, therefore, are a vital component of the infrastructure of the Nation's biomedical and health research effort.

GENERAL CLINICAL RESEARCH CENTER PROGRAM (GCRCP)

The principal mission of the GCRCP is to provide clinical research infrastructure to extramural clinical scientists who receive research funding from the categorical institutes of NIH and other government and private sources. The program comprises a national network of 74 centers, each representing a dynamic "human laboratory" where patients can be investigated under a carefully controlled environment. The GCRCP has continued to make notable strides in understanding the causes of human ailments, in detecting and treating human diseases, and in training physicians and paramedical personnel how to do research involving human beings.

The GCRCP has recently faced the challenges of rising costs of hospitalization, escalating nursing salaries, and the need for accommodating AIDS research. These challenges have been met by streamlining the program and making innovative initiatives, such as promotion of outpatient research, use of satellite beds, reimbursement for industry-sponsored research, adoption of cost-accounting practices, a more rigorous review process, encouragement of collaborative research, replacement of weak centers by strong ones, and upgrading of remaining ones. The GCRCP can now rightly boast that it offers one of the most efficient and cost-effective settings for performing research with human subjects. Moreover, it now supports broad-based research involving many investigative groups.

However, new challenges await the GCRCP. Exciting advances in the laboratory, particularly in molecular medicine, demand translation into clinical practice. The GCRCP must be prepared to meet such needs by supporting or implementing application of emerging technologies, testing new products, and gene therapy. Moreover, the alarming continued attrition of young clinical investigators is seriously threatening the very viability of clinical research, at a time when more clinical researchers are needed to exploit the rapid advances in basic sciences. The settings of the GCRCs is ideal for training of clinical investigators. The Clinical Associate Physician Program is a model for training young physicians to become independent clinical investigators. The GCRCP is intensifying its efforts to further stimulate and assist individual centers to expand and broaden their training activities. The GCRCP is dedicated to work towards training and retaining a cadre of well-trained physicians who can meet the challenge of molecular medicine, maintain research programs across the full spectrum of clinical research, and become tomorrow's teachers and academic leaders.

RESEARCH CENTERS IN MINORITY INSTITUTIONS PROGRAMS (RCMIP)

The primary mission of the Research Centers in Minority Institutions Program (RCMIP) is to expand the Nation's capacity for biomedical research by providing grant support to eligible minority institutions to expand their research infrastructure for biomedical and behavioral research. Support is provided to enhance faculty expansion and development, physical facility improvement, and other research-related activities such as purchase of laboratory equipment, computers, and the renovation of facilities for state-of-the-art biomedical investigations.

The RCMIP was developed and initiated in response to a congressional mandate in FY 1985. Seven doctorate-granting minority institutions received awards in 1985. Presently, 17 eligible institutions are participants in the program. The scope of the program was expanded in 1989 in order to involve the RCMIP grantee community in addressing AIDS, a disease that current statistics show has a disproportionate effect on African-American, Hispanic, and other ethnic minority populations. Through collaborative support with the National Institute of Allergy and Infectious Diseases (NIAID), RCMIP grantees are now developing the capacity to conduct AIDS clinical trials. Since the scope of the RCMIP was expanded, 12 of the 17 RCMIP grantees are now involved in AIDS and AIDS-related research. A spinoff benefit of this initiative has been the formation of a consortium by three RCMIP grantee institutions to develop behavioral modification strategies to intervene in the fight against AIDS. The ethnic focus of this initiative is African Americans, Hispanic Americans, Native Americans, and Native Hawaiians.

It is anticipated that the number of RCMIP grantee institutions, along with the scope of the activities supported collaboratively by the ICDs with the RCMIP, will increase. With this expanding research capacity, the lack of adequate research space is increasingly becoming a limiting factor. Major support for alterations and renovations or new construction is a critical requirement for the continued success of the RCMIP. FY 1992 projected capital needs are approximately \$25 million, with continuing needs through FY 1993 and 1994.

Additional funds are also required to facilitate the participation of the RCMIP grantees in clinical trials and research, especially for those diseases that have a disproportionate effect on the populations served by the RCMIP grantee institutions. These diseases include a variety of cancers, diabetes, cerebrovascular and cardiovascular disease, homicide and suicide, infant mortality, and AIDS.

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