IMPROVING HEALTH THROUGH RESEARCH

Second Annual Report of the Director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

DEPARTMENT OF
HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health

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Preface

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is the Nation's leader for a research program with a formidable task: to elucidate the nature, cause, and progression of a wide spectrum of diseases which heretofore largely have defied the probings of biomedical science. These health problems—afflicting many millions of Americans of all ages, backgrounds, and economic circumstances—are mostly chronic, and many involve an incapacitating downhill course, draining resources and exhausting the spirit of patients, their families, and others who provide care and concern.

Understanding such complex disorders so that they may eventually be controlled, effectively treated, and prevented is the goal of all studies conducted and supported by NIADDK. It is an understanding that must begin at the cellular level, in basic research studies, and be extended by clinical investigations and, ultimately, where needed, by developmental research. This is subsequently followed by transfer of new findings to the health care arena. This process of scientific inquiry, slow and toilsome as it may be, nevertheless has yielded impressive gains which have kept the march of biomedicine inexorably forward.

The Health Programs Extension Act of 1980 (P.L. 96-538) requires that the Director of NIADDK provide to the President and the Congress an annual report on the Institute's progress toward its broad and varied goals in the disease areas within its purview. In this volume, the *Second Annual Report of the Director, NIADDK,* the Institute reports many of its recent gains, the opportunities they present for further research, and the plans developed to meet specific program needs.

Preceding the summary of research advances and program accomplishments is a description of NIADDK's mission, organization, and research strategies, including manpower development, disease prevention, technology assessment and transfer, and program planning, analysis, and evaluation. The fiscal aspects of carrying out these and other Institute activities are described as well.

The volume concludes with the annual evaluation reports of two priority NIADDK programs, the Multipurpose Arthritis Centers and the Diabetes Research and Training Centers. In past years, these reports—which are also congressionally mandated—were transmitted to the Congress as separate documents. They are incorporated here to afford the reader a more inclusive overview of the Institute's progress.

This volume outlines NIADDK's activities and plans for continued contributions to improvements in biomedical knowledge, treatment, and prevention of many chronic and disabling diseases. It would be incomplete without a warm acknowledgment of the tireless and many times unsung work, skills, and dedication of those without whom there would be no progress in the fight of mankind against disease—the biomedical research workers of the past, the present, and the future.

Lester B. Salans, M.D.
Director
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

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The basic laboratory investigations conducted and supported by NIADDK are of potential benefit to every American, as the diseases under study by the Institute affect people of all ages, backgrounds, and economic circumstances.

Chris Cross, UNC-TDRTH

NIADDK Mission and Strategies

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases is 1 of 11 Institutes known collectively as the National Institutes of Health (NIH), the largest biomedical research organization in the world. On its 306 acres of land in Bethesda, Md., NIH incorporates hundreds of sophisticated research laboratories, clinical care facilities, administrative offices, and a national medical library—all dedicated to fulfilling the agency's role as spearhead of the Nation's biomedical research effort.

Over the years, NIH programs and activities have multiplied to meet the ever-growing demand for knowledge about health and disease. To accommodate varying research needs and facilitate progress, each of the 11 NIH Institutes functions as a separate administrative unit within which research activities in one or more disease areas or health problems are planned, coordinated, carried out, and supported.

NIADDK's emphasis on research to uncover the causes of chronic and disabling diseases has earned it recognition as an Institute whose responsibilities are attuned to the pressing health problems of the American public, and whose accomplishments often have a profound impact on the disease interests of other Institutes as well.

The focus on basic research that has guided NIADDK's programs is grounded in the fact that basic understanding of the intrinsic nature of each disease is imperative for the formulation of appropriate, effective strategies for prevention and therapy. Thus, the Institute has an important stake in the pursuit of research using the fundamental sciences, such as biochemistry, biology, physics, chemistry, pathology, genetics, immunology, physiology, and pharmacology, which provide the foundation of knowledge about diseases that can affect many organs or organ systems.

The basic research successes achieved through NIADDK's programs have been impressive, and those laboratory successes are meaningfully applied to improvement of the Nation's health through clinical studies and trials and programs of technology transfer, information dissemination, and coordination with professional and voluntary groups as well as other government agencies.

NIADDK's Mission and History

In 1950, the Omnibus Medical Research Act authorized the National Institute of Arthritis and Metabolic Diseases (NIAMD), incorporating the existing Experimental Biology and Medicine Institute, as a component of the National Institutes of Health. The establishment of NIAMD brought greater priority and impetus to areas of research that previously had been largely unexplored. Chronic diseases (most with unknown causes) were undermining the well-being of the American people, and the need for a federally supported organization to concentrate primarily on fundamental biomedical research in those diseases was obvious.

In its first decade, NIAMD vigorously pursued its mandate by expanding programs and operations to accommodate the growing list of diseases and health problems that came under its charge. In the 1950's, the National Advisory Arthritis and Metabolic Diseases Council was established and approved the Institute's first grants to researchers throughout the country; the NIH Clinical Center (research hospital) was opened, broadening intramural clinical research activities; the Extramural Training Program was established; and Dr. Arthur Kornberg, former chief of the Institute's Enzyme and Metabolism Section, won the Nobel Prize in 1959 for the first successful synthesis of nucleic acids—components of deoxynucleic acid (DNA), the determinants of inheritance.

As the Institute moved into its second decade, increasing research activity and emerging opportunities prompted NIAMD to redefine, expand, and intensify its programs in a number of areas. In the 1960's, the Intramural Research Program established permanent facilities in Phoenix, Ariz., for epidemiological and clinical studies of Southwestern Indian populations, and the National Pituitary Agency was established to increase the availability of human growth hormone for use in clinical research on growth disorders. In 1969 the Nobel Prize was awarded to Dr. Marshall W. Nirenberg, an NIAMD scientist, for his work in partially cracking the genetic code.

The Institute embarked on its third decade with a new name—the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD)—and a renewed commitment to research on the cause, prevention, diagnosis, and treatment of the chronic diseases within its purview. The NIAMDD framework for efficient administration and coordination of research in a growing number of diverse disease areas was a system of "clusters," four separate groupings of research activity:

- Arthritis, musculoskeletal, and skin diseases;
- Diabetes, endocrinology, and metabolic diseases;
- Digestive diseases and nutrition; and
- Kidney, urologic, and hematologic diseases.

The cluster concept permitted individual emphasis for groups of health problems, as appropriate, while fostering the coordination of efforts in closely related areas.

The 1970's were an active period because of the progress in basic research achieved during the previous two decades. During this period, the National Diabetes Mellitus Research and Education Act and the National Arthritis Act were signed; national commissions were appointed to develop long-range plans to combat arthritis, diabetes, and digestive diseases; the establishment of multipurpose arthritis and diabetes research and training centers was authorized; and information clearinghouses for arthritis and diabetes were established. In 1972, Dr. Christian B. Anfinsen, chief of the Institute's Laboratory of Chemical Biology, shared a Nobel Prize with two other American scientists for his work in molecular biology; and three NIAMDD-supported researchers, Drs. Roger C. L. Guillemin, Andrew V. Schally, and Rosalyn S. Yalow, shared a 1977 Nobel Prize for their work in peptide hormones.

With the advent of the 1980's, an education and information clearinghouse for digestive diseases was established, and enactment of P.L. 96-538, the Health Programs Extension Act, authorized a further change in the Institute's name—to the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases—and authorized Institute associate directors and Advisory Council subcommittees for each of the four research clusters. In 1982, the Institute was reorganized and designated a "bureau" of NIH, joining the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Library of Medicine at the bureau level. The reorganization elevated the four research clusters to "divisions," giving them more sharply focused responsibility, greater authority for the national research effort in their areas, and appropriate visibility as national focal points for the biomedical research attack on specific major public health problems.

NIADDK's programs are of profound importance to the American people, since no subgroup of our population is immune to attack by one or more of the diseases or disorders that NIADDK addresses (table 1). The impact of some of these diseases is indicated in table 2, which shows the prevalence, or number of affected individuals in the United States, and the approximate economic costs to the American public. The more profound costs of chronic disease, in terms of human suffering, cannot easily be measured, but they are no less significant. Finding effective methods to prevent, control, and treat these diseases and disorders, through its various research programs and activities, is the mission of NIADDK.

Organization of the Institute

As NIADDK moves forward in pursuit of the knowledge that will lead to more effective methods for improving the health of the American public, its organization must rely on coordinated, interacting mechanisms that will produce responsive and substantive information. The current system under which NIADDK operates is designed to meet these essential requirements.

The organizational structure of NIADDK (see figure 1) reflects its emphasis on basic biomedical and clinical research and research training. Institute efforts are planned and coordinated through both an extramural support program, which provides funding for research at universities, clinical facilities, and research institutions across the country and abroad, and an intramural component, which focuses on research conducted primarily within NIADDK's laboratories and clinical facilities on the NIH campus and in Arizona.

The administrative and advisory activities of the Institute are organized to provide programmatic guidance as well as fiscal, analytical, and review services to facilitate the research efforts. Activities aimed at developing and sustaining linkages to the

Table 1.—NIADDK research areas: some representative examples

DIVISION OF ARTHRITIS, MUSCULOSKELETAL, AND SKIN DISEASES	DIVISION OF DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES	DIVISION OF DIGESTIVE DISEASES AND NUTRITION	DIVISION OF KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES
Arthritis and Related Disorders Rheumatoid arthritis Osteoarthritis Juvenile arthritis Systemic lupus erythematosus Gout Lyme arthritis Epidemic polyarthritis Psoriatic arthritis Inherited connective tissue diseases Systemic sclerosis (scleroderma) Spondyloarthropathies Muscle structure and function Muscle pathophysiology **Musculoskeletal Diseases** Paget's disease Osteoporosis Osteopetrosis Osteogenesis imperfecta Bone metabolism Bone fractures and healing Artificial joints and biomaterials Congenital and acquired skeletal anomalies Low back pain Exercise pathophysiology **Skin Diseases** Psoriasis Acne Bullous diseases Ichthyosis Vitiligo Eczematous and immunologic diseases Allergic dermatoses Cutis laxa Photobiology Heritable skin disorders	**Diabetes** Insulin-dependent diabetes Noninsulin-dependent diabetes Complications of diabetes Etiologic factors in diabetes Immunology and diabetes Insulin receptors Insulin resistance Insulin delivery devices Pancreatic islet cell transplantation Nutrition and diabetes Animal models of diabetes **Endocrine Diseases** Disorders of endocrine glands (thyroid, pituitary, etc.) Hormone synthesis, secretion, action, and interactions Hormonal imbalances Research availability of hormones Growth factors Recombinant DNA production of peptide hormones Neuroendocrinology and brain peptides Hormones and pharmacotherapy **Metabolic Diseases** Inborn errors of metabolism Animal models of inborn metabolic errors Cystic fibrosis Enzyme structure and function Cellular oxidation and biological membranes Cell surface receptors Reye's syndrome Noninvasive instrumentation in metabolic research	**Esophageal, Gastric, and Colonic Diseases** Ulcer disease Functional bowel disorders Gastrointestinal motility dysfunctions Inflammatory bowel diseases Gastrointestinal bleeding Endoscopy in research, diagnosis, and treatment Gastrointestinal growth and regeneration Structure, function, and disease of the esophagus and stomach **Intestinal and Pancreatic Diseases** Gastrointestinal hormones Small intestine structure and function Intestinal absorption Malabsorption syndromes Diarrheal diseases Pancreatitis Pancreas transplantation Salivary gland structure, function, metabolism, and secretion **Liver and Biliary Tract Diseases** Hepatitis Cirrhosis Genetic liver disease Hepatic transport defects Gallstones Cholesterol and bile acid metabolism Liver regeneration Liver transplantation **Nutrition** Nutritional requirements in health and disease Obesity Regulation of fuel mobilization and storage Exercise and energy metabolism Nutritional needs in disease Nutritional status assessment Dietary fiber Essential trace elements and minerals Nutrient transport, utilization, and function Special supportive nutrition in disease	**Renal Physiology and Pathophysiology** Renal metabolism and transport Renin and hemodynamics Hypothalamic regulation of water balance Immunologic basis of renal disease Glomerulonephritis Interstitial nephritis Acute renal failure **Urologic Diseases** Nephrolithiasis and urolithiasis Congenital anomalies of the urinary tract Bladder dysfunction Vesicoureteral reflux Urinary tract infection Prostatic hypertrophy Prostatitis **Chronic Renal Diseases** End-stage renal disease Dialysis therapy Renal dialysis and its complications Kidney transplantation Nutrition and chronic renal disease **Blood Diseases** Anemias of genetic origin Nutritional anemias Metabolic disorders of iron transport and storage Disorders of blood cell production Hematopoietic tissue transplantation immunology Autoimmune hematologic diseases Iron chelation therapy

scientific and health care community also fall within the Institute's realm of administrative and advisory functions.

Table 2.—Prevalence and economic costs of selected disease groups

	Prevalence (in millions)	Economic Cost[1] (in billions)
Arthritis and Related Rheumatic Diseases	30.0	$18.0
Diabetes	10.5	10.0
Digestive Diseases[2]	24.1	11.4
Kidney and Urologic Diseases	7.8	1.8[3]

[1] *Including direct costs for hospital care, professional services, and drugs as well as indirect costs of productivity lost because of death and disability.*

[2] *Excluding malignancies associated with the digestive tract.*

[3] *Direct cost of treatment for 70,000 end-stage renal disease patients only.*

Office of the Director

The focal point for management of NIADDK programs and operations is the Office of the Director. Because this office has ultimate responsibility for the research sponsored and the results disseminated by the Institute, the Director and staff are involved in planning and coordinating the various activities of each of NIADDK's programs.

Specifically, the Director's office oversees the preparation of plans and reports and provides policy direction and staff guidance in such areas as scientific program planning, administrative management, and utilization of resources. In addition, the Office of the Director is directly responsible for developing NIADDK's annual budget, which reflects funding needs and resource priorities for all activities—both program-related and administrative.

The Office of the Director coordinates and prepares information to describe NIADDK's program progress and future plans to the Director of NIH and the Congress. These are ongoing activities that are mandated by the Institute's authorizing legislation so that progress achieved and problems encountered can be continually assessed.

The Office of the Director is assisted in its responsibilities by the following offices and program components:

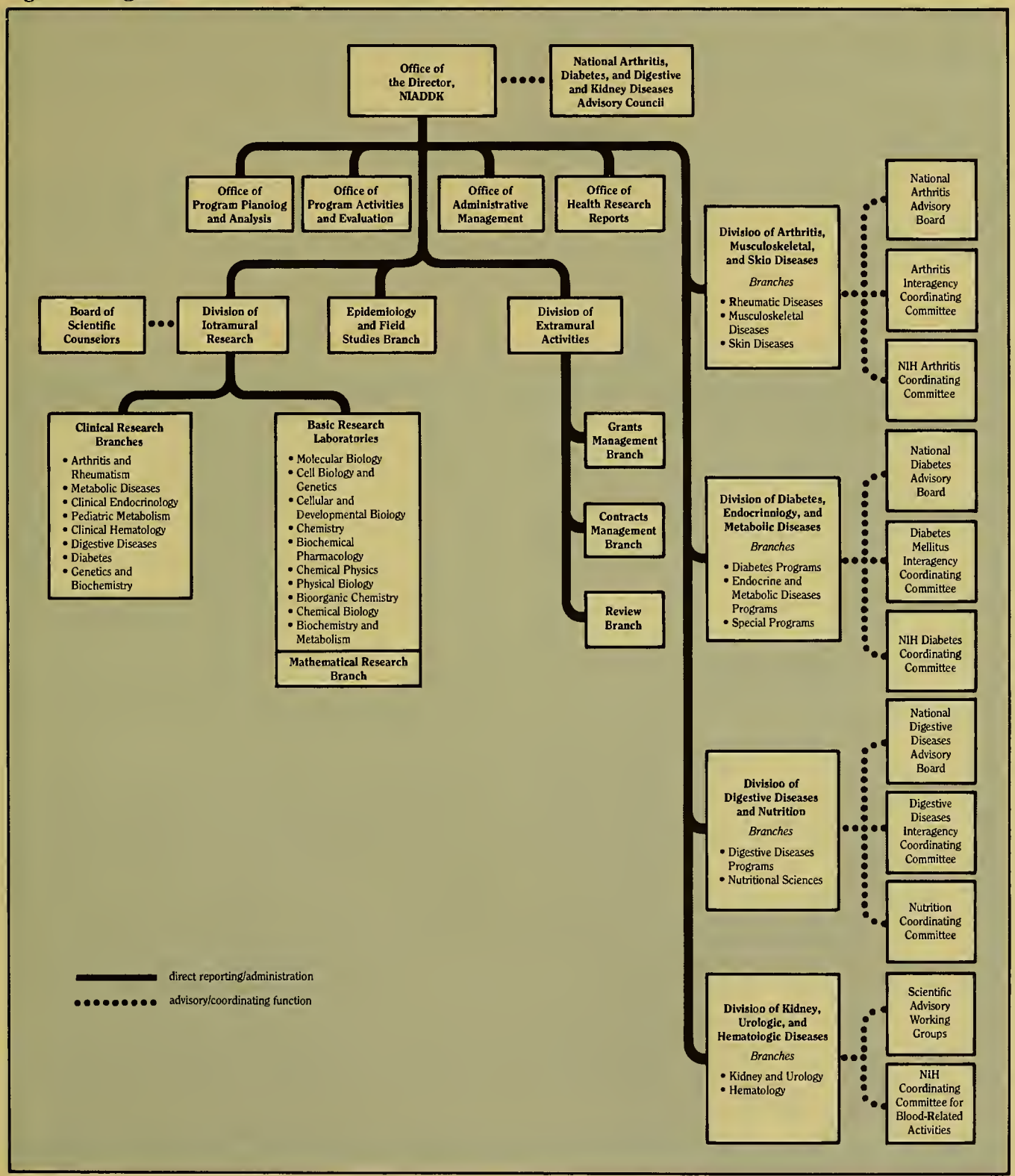
- ***Office of Administrative Management***—responsible for planning and management of day-to-day operations, including budget and financial affairs, contracts, personnel, and office services;
- ***Office of Program Planning and Analysis***—responsible for Institute activities in the areas of planning, program and policy analysis, and legislation; analyzes Institute programs and develops Institute analytic capabilities and data base for planning, policy formulation, and budget justifications; and oversees Institute congressional activities having policy implications;
- ***Office of Program Activities and Evaluation***—responsible for the evaluation of Institute program activities; responsible for coordination, review, and presentation of Institute activities related to disease prevention; and coordinates medical technology assessment and technology transfer;
- ***Office of Health Research Reports***—coordinates preparation and distribution of information and publications on the Institute's programs and activities to a variety of audiences;
- ***Extramural programs***—provide oversight and management of all aspects of research and training programs and projects conducted off-campus as follows:
  - *Directors of the four research extramural divisions* coordinate and direct planning, monitoring, reporting, and review of research and training awards in their respective research areas, in close cooperation with the Office of the Director;
  - The *extramural activities program* manages and administers extramural research awards in conjunction with the Grants Management, Contracts Management, and Review Branches; and
- ***Intramural research program***—through intramural laboratory and branch chiefs, plans, coordinates, and conducts research activities in the Institute's laboratories and clinical facilities.

These offices provide the substantive input that the Office of the Director requires to develop program plans and policies that are responsive to the Institute's long-term goals and objectives as well as to specific requests for information or studies mandated by Congress and the administration. The Director's office also relies heavily on the expertise and advice provided by the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council, a senior consultative body that is essential to the Institute's program organization and operations, and by the national advisory boards and coordinating groups described below.

Extramural Activities

The Division of Extramural Activities comprises investigations that are funded by the Institute but conducted at universities,

Figure 1.—Organization of NIADDK



private and public research facilities, and hospital-based clinical research centers throughout the Nation and, in selected instances, in other countries. NIADDK uses grants, contracts, and other types of awards to generate and administer the extramural project activities of the four research divisions. The various award mechanisms are described in table 3.

Each NIADDK division functions as a distinct administrative unit with responsibility for the allocation and management of research funds through research grants, contracts, fellowships, training grants, and special awards to qualified applicants and institutions. Supported activities range from basic and applied research investigations (including clinical studies) to training programs in fundamental and clinical sciences.

In keeping with the needs, priorities, and research requirements of the disease areas under the purview of the Institute, there is strong emphasis on the support of basic research. This is particularly important since the etiology of many of the major diseases involved is as yet unknown. A significant proportion of extramural research support is aimed at clinical studies to provide an optimal mix for rapid advances in the state of the art of the various disease problems of NIADDK.

The testing for safety and efficacy of an emerging technique, drug, device, or procedure is generally accomplished through clinical studies and trials. Examples of such studies currently or recently supported include the following (grouped by division):

Table 3.—NIADDK extramural program award mechanisms

Research project grants—An institution is awarded a grant on behalf of a principal investigator to facilitate pursuit of a scientific initiative or objective in the area of the investigator's interest and competence. Applications are accepted for health-related research and development in all areas within the scope of the Institute's mission. This is the largest single support mechanism utilized by NIADDK.

Program project grants—Program project grants are awarded to an institution on behalf of a principal investigator for the support of a broad-based, often multidisciplinary, long-term research program with a particular major objective or theme. The type of project supported with this award involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. Each project supported under a program project grant is expected to contribute to the overall program objective.

Center grants—Center grants are awarded to institutions on behalf of a program director and group of collaborating investigators to provide support for long-term, multidisciplinary programs of research and development. However, center grants are more likely to have a clinical orientation than are program project grants and are usually developed in response to announcements of specific program needs and requirements of the Institute.

Resource awards—These awards provide support for research resources such as computer centers or general clinical research centers operating on an institutional, regional, or national basis. While the resources normally serve a wide range of biomedical research, they may be oriented toward specific research needs.

Conference grants—Conferences planned for the purpose of coordinating, exchanging, and disseminating scientific research information related to the Institute's program interests may be supported by conference grants. Generally, the awards are provided for cooperative participation with other organizations in the support of conferences rather than for provision of sole support.

Research contracts—Contracts are offered for specific research problems that have been identified by the Institute and that require central direction, control, and management. Clinical trials of new or established therapies may be funded by this mechanism.

Development contracts—These contracts, which are rarely used, are awarded for projects to produce substances, devices, systems, or other approaches to diagnose, prevent, treat, or control diseases. Examples of such projects include the development of effective vaccines or drugs, surgical techniques or medical devices to assist or replace organ functions, and sophisticated instruments to refine laboratory or clinical procedures.

Demonstration contracts—These contracts are awarded to support projects designed to demonstrate the feasibility of applying biomedical research advances or technologies to individual or community situations to solve certain health problems.

Research and development support—Awards in the research and development category are offered to finance certain resources or services to aid ongoing activities. These include data processing, drug testing, toxicology screening, logistics services, and collection and distribution of materials needed to conduct biomedical research and development.

Scientific communication and evaluation awards—These awards are provided to support special conferences, workshops, and seminars that are planned to analyze the significance of new biomedical research findings and for developing a scientific consensus on those findings.

Manpower training awards—A detailed description of the mechanisms used by the Institute to support manpower development is provided under "Research Manpower Development" in this chapter.

- Division of Arthritis, Musculoskeletal, and Skin Diseases
  - — Total lymphoid irradiation in rheumatoid arthritis
  - — Dimethylsulfoxide in digital ulcers of scleroderma
  - — Fluorides in treatment and prevention of osteoporosis
  - — Psoralen and long-wave ultraviolet light therapy in psoriasis
- Division of Diabetes, Endocrinology, and Metabolic Diseases
  - — Diabetes control and complications trial
  - — Juvenile diabetes mellitus: epidemiology and etiology
  - — Effect of sulfonylurea on glucose tolerance in type II diabetes of young people
  - — Growth stimulation with human growth hormone
  - — Use of azlocillin in cystic fibrosis
- Division of Digestive Diseases and Nutrition
  - — National cooperative Crohn's disease trial
  - — Primary biliary cirrhosis: penicillamine trial
  - — Upper gastrointestinal bleeding—diagnosis and treatment
  - — Human zinc deficiency and zinc requirements in children
- Division of Kidney, Urologic, and Hematologic Diseases
  - — Collaborative study of adult glomerular disease
  - — Plasmapheresis in lupus nephritis
  - — Continuous ambulatory peritoneal dialysis (therapy evaluation)
  - — Ambulatory evaluation and optimal treatment of urinary calculi
  - — Congenital folate malabsorption in megaloblastic anemia.

The Institute's extramural program funds and coordinates each trial over its full course, which may be several years. Population samples for a particular clinical trial may be several thousand people across the Nation or a few hundred residents in a single community. Clinical trial results provide valuable information concerning the advisability of using the subject drug, device, or procedure in the health care setting. A procedure may prove to be very effective but of such high cost that practical application on a large scale would not be feasible; in that case, clinical trials may point up the need for further research to reduce the expense associated with use of the technique.

Intramural Research

The Division of Intramural Research covers investigations within the Institute's laboratory and clinical facilities in Bethesda and Phoenix. Intramural research activities are conducted by eight branches engaged primarily in clinical research on arthritis and rheumatic diseases, metabolism, endocrinology, hematology, digestive diseases, diabetes, and genetics; a ninth branch addresses theoretical mathematical modeling of biological problems. In addition, there are 10 laboratories with component sections organized along scientific disciplines (e.g., molecular biology, chemistry, pathology, pharmacology, physics, and biochemistry). The laboratories are engaged primarily in fundamental research that is related to the Institute's diverse areas of responsibility. The organization of the intramural laboratories and branches is shown in figure 2.

A related intramural group, the Epidemiology and Field Studies Branch, develops and applies epidemiologic methods in field studies among selected populations at risk of developing specific diseases. Investigators in the Epidemiology and Field Studies Branch conduct research throughout the United States and provide assistance to numerous scientific investigators engaged in research on arthritis and metabolic disorders.

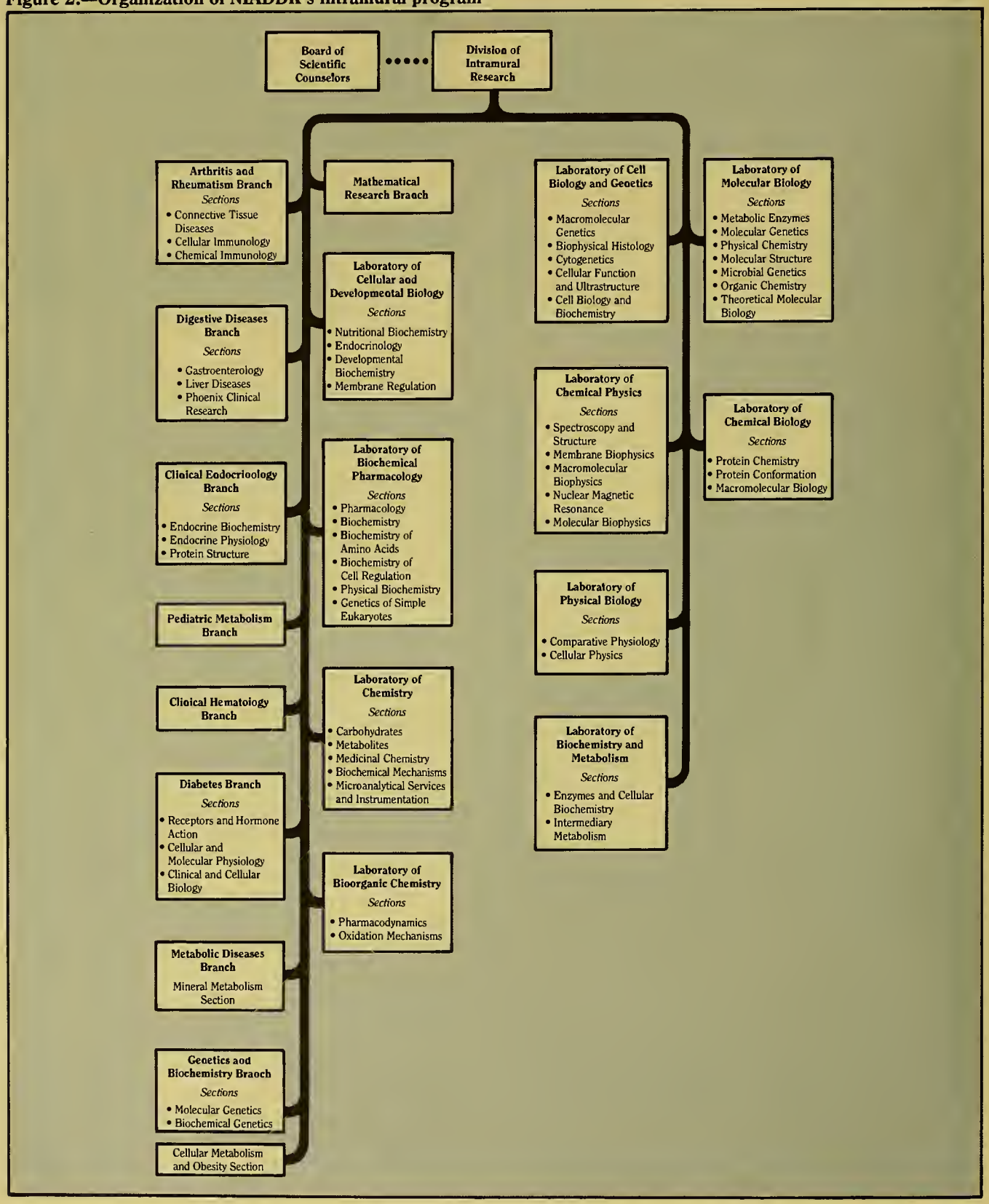
Monitoring and advice on intramural program direction and administrative activities are provided by the Board of Scientific Counselors, an internal review committee. Close collaboration with scientists of other NIH Institutes, other government agencies, and investigators in institutions throughout the United States and abroad ensures an effective approach to research strategy. Moreover, because the intramural program constitutes such an important component of NIADDK's activities and responsibilities, its ongoing and planned research efforts are given strong consideration in program planning by the Institute's other organizational units.

The intramural research staff of NIADDK is generally acknowledged to be a highly productive and innovative group of scientists. The unusual caliber of this program is reflected in the several Nobel prizes and other prestigious awards that have resulted from its work. Also, many scientists who trained in the intramural research program of the Institute are now prominent faculty members at universities throughout the country. The various laboratories and clinical branches are universally sought after for scientific collaboration, while the mathematics branch constitutes a major scientific resource for the intramural efforts of NIADDK and other NIH Institutes alike. NIADDK is justly proud of the achievements and reputation of its intramural research program.

Advisory and Coordinating Groups

Over the years, NIADDK's responsibilities and programs have been greatly influenced by the rapid evolution of biomedical research advances and technology, future research opportunities, and the public's demands for more and better health care services. To keep pace with the rapidly developing biomedical research environment and to ensure that NIADDK's numerous programs continue to address appropriately the Nation's health

Figure 2.—Organization of NIADDK's intramural program



needs, the Institute relies heavily on guidance and recommendations provided by various advisory and coordinating groups. Each of these important bodies contributes to the direction, coordination, and evaluation of research and training activities in major disease areas.

National Advisory Council

The National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council is one of the national advisory councils established legislatively for the NIH, each an important adjunct to its respective Institute. NIADDK's Advisory Council is composed of eminent scientists and experts in selected areas of biomedical research; civic leaders, educators, and laypersons with a specific interest in a particular disease or field of research in that disease; and representatives from the Department of Defense and the Veterans Administration. Current members of the group are listed on the right.

The functions and responsibilities of the National Advisory Council are primarily to assist the Office of the Director in overseeing the activities of the Institute, provide advice and counsel with regard to the Institute's goals and programs, and review and approve or disapprove extramural research grant requests after they have undergone a primary peer review for scientific merit and feasibility. The Council is charged with assuring that the extramural research projects supported by NIADDK have a sound scientific basis, are relevant to the Institute's programs, and show promise of achieving results. The Council's involvement in the planning and coordination of programs within the Institute provides it with an appropriate perspective for judging the merits of grant applications in light of NIADDK's overall priorities for research initiatives.

Members of the National Advisory Council are grouped into four subcommittees, one for each of the four research divisions that constitute the extramural research program; and they are assigned to the subcommittee most appropriate to their special scientific, education, or public affairs expertise in a particular disease area. Each subcommittee is responsible for reviewing the substance of the extramural grant applications for research and training projects related to the diagnosis, prevention, and treatment of the diseases in its assigned area. Its recommendations on these grants and training awards are then presented to the full Advisory Council for further consideration and final approval. The subcommittees also review and evaluate the overall administrative activities of their respective divisions and suggest changes in program structure and operations when they deem such changes necessary.

National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council

Chairman
James B. Wyngaarden, M.D.
Director
National Institutes of Health
Bethesda, Maryland

Chairman Designate
Lester B. Salans, M.D.
Director
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH
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Terrylin G. Neale (1983)
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Nashville, Tennessee

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Milwaukee, Wisconsin

Harold D. Schwartz (1985)
The Capitol Companies
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Johns Hopkins Hospital
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Beth Israel Hospital
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Naval Medical Research Institute
Bethesda, Maryland

Marguerite Hays, M.D.
Veterans Administration Medical Center
Martinez, California

Executive Secretary
George T. Brooks, Ph.D.
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH
Bethesda, Maryland

* *Expiration of term*

National Advisory Boards

Among the many recommendations in the plans submitted by the national commissions on arthritis, diabetes, and digestive diseases was the establishment of national advisory boards for each disease area. When formally designated, each of these

boards was authorized by Federal law to monitor and facilitate the research, training, prevention, and control programs within its particular area of interest.

The National Arthritis Advisory Board, National Diabetes Advisory Board, and National Digestive Diseases Advisory Board are composed of members representing a variety of scientific, educational, health care, and public service disciplines. Current members of the three boards are listed on the following pages.

The primary functions of each board are to review and evaluate progress of the long-range plan developed for its respective disease area; update the plan to assure its continuing relevance to public health needs; provide advice and recommendations on plan implementation to the Directors of NIADDK and NIH, the Secretary of Health and Human Services (HHS), and other Federal agencies; and maintain liaison with advisory bodies related to other Federal agencies involved in carrying out the directives of the plan.

To keep Congress informed of all ongoing activities, issues, and anticipated needs in their disease areas, the advisory boards are required by law to submit annual reports of their activities along with recommendations for changes in the plans, if appropriate.

Interagency Coordinating Committees

NIADDK participates in interagency cooperation through three interagency coordinating committees, which are specifically responsible for fostering and improving research and health care programs in the areas of arthritis, diabetes mellitus, and digestive diseases. The legislatively mandated interagency committees serve to facilitate communication among all Federal agencies directly or indirectly involved in each of the three disease areas. Since their establishment in the mid-1970's, these committees have worked closely with the national commissions and advisory boards to develop improved approaches to information exchange, joint planning, and the identification of areas that hold promise for cooperative undertakings.

The membership of each interagency coordinating committee includes the director of the relevant NIADDK division, who serves as chairman, and representatives from selected Institutes within NIH and from other Federal departments and agencies having programs of related health functions and activities. Through these committees, the Institute is able to determine whether programs of research, health care, and related social services are adequate to meet the needs of those afflicted with arthritic disorders, diabetes, and digestive diseases.

National Arthritis Advisory Board

Chairman
James R. Klinenberg, M.D.
Cedars-Sinai Medical Center
Los Angeles, California

Barbara I. Barrett
Bothell, Washington

Giles G. Boles, Jr., M.D.
University of Michigan
Ann Arbor, Michigan

William R. Felts, Jr., M.D.
George Washington University
Washington, D.C.

Bevra H. Hahn, M.D.
Washington University
St. Louis, Missouri

Edward D. Harris, Jr., M.D.
Dartmouth-Hitchcock Medical Center
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Trans-NIH Coordinating Committees

Certain complex health issues or problems span the program interests of several Institutes, thereby requiring a collaborative, cooperative effort to assure program balance and minimize duplication of activity. For such trans-NIH issues, the Director of NIH has appointed coordinating committees to provide a forum for the exchange of information, a mechanism for the coordination of individual programs, and a focus for policy development. The coordinating committees are composed of representatives of all of the appropriate Bureaus, Institutes, and Divisions (BID's) within NIH. Their activities foster the continuing development of new research approaches in the participating NIH components, and the committee chairman serves as a principal advisor to and representative of the Director, NIH, on all matters relating to that area. The following sections describe coordination efforts in several trans-NIH areas in which NIADDK plays a major role.

Arthritis. In 1977, the NIH Arthritis Coordinating Committee (ACC) was established with representatives from each of the BID's having research interests in one or more aspects of the rheumatic diseases. The activities of the ACC (chaired by the NIADDK representative) are meant to complement those of the Arthritis Interagency Coordinating Committee (AICC) created by the National Arthritis Act. The committee's efforts are directed as follows:

- Strengthening and improving the NIH system for reporting on arthritis and related research and coordinating these efforts with other Federal agencies;
- Identifying opportunities for joint sponsorship of workshops and symposia in selected areas of arthritis research;
- Providing a focus to stimulate productive research in this area and to coordinate it; and
- Exploring opportunities to promote the sharing of facilities and other resources for arthritis research.

National Diabetes Advisory Board

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Planning and emphasis are based on the missions, interests, and research program plans of the participating BID's, as well as on recommendations originally posed by the National Commission on Arthritis and Related Musculoskeletal Diseases. Coordination among the NIH components has been achieved through joint program announcements, workshops, and conferences.

Diabetes. Because diabetes affects so many body systems, research programs in this area fall within the scope of almost all of the BID's. Thus, the trans-NIH Diabetes Research Program was established in 1978 to facilitate cooperation in diabetes-related research programs and activities among all of the relevant Institutes at NIH.

Since its inception, the NIH Diabetes Coordinating Committee has initiated several activities. In 1978, and thereafter, eight Institutes issued an NIH-wide program announcement soliciting applications for research grants in diabetes and diabetes-related areas. These same Institutes, in 1978, solicited applications for research grants on the epidemiology of diabetes mellitus. In 1979, four NIH Institutes, in cooperation with the National Institute of Mental Health (of the Alcohol, Drug Abuse, and Mental Health Administration), published a program announcement to encourage research grant applications dealing with the behavioral and psychosocial aspects of diabetes. The coordinating committee has also fostered research manpower development programs. New awards emphasizing research on diabetes mellitus have been initiated and several others are planned for the near future.

Participants in the trans-NIH diabetes program work closely with the National Diabetes Data Group of NIADDK. The data group serves as the central point within NIH for the collection, analysis, and evaluation of epidemiological data that are fundamental to the development of sound scientific and public health policies related to diabetes and its complications. Members of the trans-NIH diabetes program also collaborate with the staff of the National Diabetes Information Clearinghouse, the national reference source for diabetes information.

Nutrition. NIH is the primary Federal agency that conducts and sponsors research and training in nutrition as it relates to

health maintenance, human development throughout the life cycle, disease prevention, and disease treatment. The NIH Nutrition Research Program involves all of NIH's BID's that support nutrition-related research and is coordinated through its Nutrition Coordinating Committee (NCC). The coordination activity of the NCC not only minimizes duplication of effort among the NIH components, but also identifies areas in which research and research manpower in nutrition require further nurturing. Program announcements and requests for applications developed by the NCC and sponsored by more than one BID encourage activity in areas of perceived need in nutrition.

The NCC has developed a master nutrition plan and prepares an annual report, "Program in Biomedical and Behavioral Nutrition Research and Training," that emphasizes research in four critical areas: clinical nutrition throughout the life cycle, the role of nutrition in disease development, prevention of disease, and treatment of disease. In addition to identifying research priorities, the nutrition plan emphasizes the transfer of modern nutrition technology, nutrition education for professionals and the public, training, and coordination of all these activities.

Cystic fibrosis. Because of the multidisciplinary nature of cystic fibrosis (CF) research, support and management of CF-related investigative efforts are shared among several BID's of NIH. The Cystic Fibrosis Coordinating Committee, chaired by a special assistant to the NIH Director and consisting of representatives from the various NIH components involved in the support of CF-related research activities, coordinates the overall course of investigations to avoid duplication of effort and to identify more readily the specific research and manpower requirements in this field. The coordinating committee has effectively increased researcher awareness of the many challenges and opportunities inherent in the study of cystic fibrosis; as a result of its efforts, the number of applications requesting support of CF investigations has nearly tripled.

Blood-related activities. Support and management of blood-related research activities are shared among several Institutes of NIH. The NIH Coordinating Committee for Blood-Related Activities coordinates the overall course of investigations dealing with blood and the use of blood resources. The membership of the coordinating committee represents six Institutes at NIH, including NIADDK, as well as the Division of Research Resources and the NIH Clinical Center. One of the major goals of the committee is the preparation of a directory of blood-related research projects conducted and supported by NIH, other agencies of the Federal Government, and nongovernment organizations.

Board of Scientific Counselors

NIADDK's Board of Scientific Counselors was initiated in 1956 and currently operates under the statutory authority of P.L. 92-463, serving as an internal review committee responsible for monitoring the activities of the Institute's intramural research program. Establishment of this group was considered essential to ensure that unbiased, extragovernmental expert review of intramural research activities would be provided. In effect, the activities of the board were developed in parallel with the review mechanisms established for the extramural research program.

The board (whose members are listed below) is composed of individuals eminent in research fields and scientific disciplines related to the basic and clinical research activities of the Institute. Board members meet twice a year to visit Institute laboratory facilities, review scientific progress and accomplishments achieved through research activities, and make recommendations for the program to the Director of the Division of Intramural Research, the Director of NIADDK, and the Director of NIH. In addition, the board is required to submit an annual report on its activities and findings to the Secretary of HHS, the Assistant Secretary for Health, and the Director of NIH.

Board of Scientific Counselors

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* *Expiration of term*

Special Programs

Given the Institute's varied responsibilities, the available opportunities for fostering collaboration among scientists across the Nation and around the world to further research and apply new knowledge are numerous. Over the years, NIADDK has implemented special programs to expand research opportunities and services, enabling a reach beyond the realm of the laboratory to the community where those afflicted with disease and those who treat them may benefit more quickly from current progress.

NIADDK's Centers Programs

In addition to providing support for the research and research training programs described in table 3, including traditional research centers, the Institute has responsibility for a program of "multipurpose center" facilities. Through such centers programs, some of which were specifically authorized by legislation in the mid-1970's, institutions have been competitively selected to provide a variety of multidisciplinary approaches to research, education, and community demonstrations in arthritis and related musculoskeletal diseases, and to research and training in diabetes.

NIADDK sponsors 20 Multipurpose Arthritis Centers (MAC's) across the country. The MAC's are engaged in activities that address all phases of the arthritis problem, from basic research in the causes of the disease and pilot and feasibility studies for developing investigators, to education and training and the community application of evolving methods of treatment.

The Institute also sponsors seven Diabetes Research and Training Centers (DRTC's), which encompass basic and clinical research as well as the education and training of new investigators and the translation of research results into improved care and management of diabetic patients. For added research incentive, both MAC's and DRTC's provide limited funds for pilot or feasibility studies to encourage young investigators and promote innovation in research concepts.

The Institute is also currently supporting five clinical nutrition research units (CNRU's), which serve as focal points for multidisciplinary research in clinical nutrition as well as provide for the development of programs in clinical nutrition which enhance the education of various health professionals.

Activities of the various types of centers differ according to the local need and support of research, clinical, educational, training, and demonstration projects; however, all centers operate in a core setting of shared, comprehensive facilities, resources, and trained investigators to promote research and the translation of research results into improved patient care.

The geographic distribution of NIADDK-supported centers is shown in figure 3. Details of organization and activities in the various types of centers are presented under "Special Programs" in chapters II through V.

The multipurpose centers program provides important linkages between NIADDK, the scientific community, and the health care delivery system, and continued evaluation is essential to maintaining those linkages. Current evaluation reports for the Multipurpose Arthritis Centers and the Diabetes Research and Training Centers are provided in chapter VI.

A Program for International Cooperation

NIADDK has supported a number of collaborative and individual research efforts that draw upon the talents and investigative expertise of the international scientific community. Continued collaboration with international scientists and the funding of projects that may have worldwide impact is an ongoing priority for the Institute. Through the Bilateral Cooperative Agreements Program, NIADDK has developed collaborative and cooperative activities with Japan, the U.S.S.R., and France in several important fields.

U.S.–Japan Malnutrition Panel. Established in 1966 as part of the U.S.–Japan Cooperative Medical Sciences Program, the Malnutrition Panel is concerned with finding solutions to nutritional problems of importance to Asian people through basic, applied, and clinical research. The program is administered by the Division of Digestive Diseases and Nutrition, NIADDK, with significant support from the National Institute of Child Health and Human Development.

While food availability is no longer a major problem in most countries in Southeast Asia, a number of social, political, and economic forces account for serious inequities in food distribution, and malnutrition and undernutrition continue to be serious problems in many Asian countries. Various disease states (particularly diarrheal infections) may be superimposed on malnutrition and cause further loss or impaired utilization of nutrients. In fact, malnutrition complicated by diarrheal disease is the primary cause of death in children under 5 years of age in these countries. In an effort to combat such complex problems, the Malnutrition Panel has identified five research program objectives:

- Identify the influence of environmental and host factors on nutritional requirements;
- Determine the health significance of iron deficiency and methods to prevent it;
- Elucidate the interaction of nutrition, immune competence, and infection;
- Determine the effects of nutrition on physical and mental development, behavior, physical capability, and work performance; and
- Identify the health consequences of different (or changing) dietary patterns and food habits.

Figure 3.—NIADDK centers grant program

● **Multipurpose Arthritis Centers**

University of Alabama School of Medicine, Birmingham, Ala.
University of Arizona College of Medicine, Tucson, Ariz.
University of California School of Medicine, San Francisco, Calif.
Stanford University School of Medicine, Stanford, Calif.
University of Colorado Health Sciences Center, Denver, Colo.
University of Connecticut School of Medicine, Farmington, Conn.
Indiana University School of Medicine, Indianapolis, Ind.
Johns Hopkins School of Medicine, Baltimore, Md.
Boston University School of Medicine, Boston, Mass.
Brigham and Women's Hospital, Boston, Mass.
University of Michigan Medical School, Ann Arbor, Mich.
University of Missouri Medical Center, Columbia, Mo.
Washington University School of Medicine, St. Louis, Mo.
Dartmouth Medical School, Department of Medicine, Hanover, N.H.
State University of New York, Downstate Medical Center, Brooklyn, N.Y.
University of North Carolina Medical Center, Chapel Hill, N.C.
University of Cincinnati Medical Center, Cincinnati, Ohio
Case Western Reserve University, Cleveland, Ohio
Vanderbilt University Medical Center, Nashville, Tenn.
Medical College of Wisconsin, Milwaukee, Wis.

▲ **Diabetes Research and Training Centers**

University of Chicago, Chicago, Ill.
Indiana University, Indianapolis, Ind.
University of Michigan, Ann Arbor, Mich.
Washington University, St. Louis, Mo.
Albert Einstein College of Medicine, New York, N.Y.
Vanderbilt University, Nashville, Tenn.
University of Virginia, Charlottesville, Va.

△ **Diabetes-Endocrinology Research Centers**

University of Iowa, Iowa City, Iowa
University of Pennsylvania, Philadelphia, Pa.
Baylor College of Medicine, Houston, Tex.
University of Washington, Seattle, Wash.

○ **Other Specialized Centers**

Peptic Ulcer Center—
University of California, Los Angeles, Calif.

Liver Center—
University of California, San Francisco, Calif.

Hepatitis-Cirrhosis Center—
Albert Einstein College of Medicine, New York, N.Y.

Obesity Center—
St. Luke's Hospital Center, New York, N.Y.

Clinical Nutrition Research Units—
Georgia Medical College, Augusta, Ga.
University of Chicago, Chicago, Ill.
Columbia University, New York, N.Y.
Vanderbilt University, Nashville, Tenn.
University of Wisconsin, Madison, Wis.

Through cooperative efforts and the availability of large population groups afflicted with nutrition problems, NIADDK and the other sponsoring members of this program are provided with valuable information and insight about the many aspects of malnutrition and its implications for health and well-being. Despite previous accomplishments, however, malnutrition continues to be a widespread problem in many Asian countries, and NIADDK will continue to make special efforts to increase collaboration with foreign countries in nutrition-related research.

U.S.–U.S.S.R. cooperative program in arthritis. The origins of the U.S.–U.S.S.R. arthritis program can be traced to the Health Exchange Program of 1972, a joint agreement developed to improve collaboration in the field of public health and medical science. In September 1973, arthritis became the fourth major cooperative project in the health sciences under this program. The program is organized into three major areas—clinical studies in rheumatic disease, the basic science of rheumatic disease, and orthopedic surgery for arthritis—with emphasis on clinical studies using commonly agreed-upon protocols for the treatment of rheumatoid arthritis and systemic lupus erythematosus. Twelve major meetings have been held between the members of the cooperating research centers, featuring discussions of preliminary study results and future projects and supplemented by the exchange of reprints and lecture materials. Scientists from both countries have been invited to visit and work in their collaborators' laboratories and to participate in various symposia and professional society meetings as well.

NIH–INSERM agreement. Under an agreement program between NIH and the National Institute of Health and Medical Research of France (INSERM), substantial scientific collaboration has been fostered between the Clinical Endocrinology Branch, NIADDK, and the Unité de Recherche sur la Glande Thyroide et la Régulation Hormonale, INSERM. The exchange of scientists from both groups has provided excellent opportunities for collaborative research and effective use of trained personnel in the study of thyroid hormone synthesis and metabolism. Investigators from both countries had been working on different but related aspects of thyroid physiology and biochemistry, and through a melding of the programs available to each group, the progress of research in these areas has been greatly advanced and new procedures to resolve specific problems in thyroid function have evolved. In addition, many scientific papers have been published jointly by collaborating NIH and INSERM investigators.

Visiting scientists program. The NIADDK intramural research program sponsors researchers from many countries under its visiting scientists program, and, in return, intramural investigators from the Institute visit and collaborate with scientists in laboratories and clinics abroad. During the past year, researchers from Israel, India, Poland, Japan, China, the United Kingdom, France, Germany, and other countries have worked in the intramural laboratories and clinics of NIADDK. The exchange of high-caliber scientists across national boundaries provides vital opportunities for cross-fertilization of ideas and techniques; it has proven mutually beneficial for many years and is expected to provide significant scientific dividends in the future.

Extramural research in other countries. To capitalize on the expertise of investigators in other countries and to further the progress of research in high-priority health problems of international scope, NIADDK continues to support investigator-initiated research by scientists outside the United States as part of its extramural research programs. Support is provided through grants and contracts for highly qualified investigators conducting the following types of studies.

- Action of hormone receptors in the cell membrane;
- Biochemical studies on basement membrane in diabetes;
- Kidney graft rejection;
- Protein, fat, carbohydrate, and salt metabolism during continuous ambulatory peritoneal dialysis for chronic renal failure;
- Medical versus surgical treatment of vesicoureteral reflux in children;
- Steroid receptors in benign prostatic hyperplasia; and
- Thalassemias, hemoglobinopathies, and related problems.

Conferences, seminars, and meetings. Scientific meetings with international audiences play a major role in scientific communication because they provide a forum for the exchange of research information among investigators from different countries, and they often stimulate further scientific collaboration. NIADDK continues to support selected international conferences and symposia as part of its programs; for example, last year NIADDK provided support to 17 such meetings addressing topics such as genetics, nutrition, diabetes, osteoporosis, and many basic science issues.

Research Manpower Development

In the 32 years since its establishment, NIADDK has made impressive strides in biomedical research. Maintaining that momentum requires a complex interplay of factors, including the availability of basic scientific knowledge and technologic

methods, the availability and appropriate utilization of trained investigators, and financial support. While the lack of any single resource may impede scientific progress, the need for trained personnel is particularly critical. The development of research manpower is crucial to the accomplishment of NIADDK's goals and has been a high Institute priority.

Through ongoing analysis and evaluation of research program needs and maintenance of a wide range of training mechanisms, NIADDK continues to seek motivated future investigators to meet critical needs. Recently initiated training mechanisms, such as the new investigator research award, the clinical investigator award, the national research service award senior postdoctoral fellowship, and the special emphasis research career award, contribute markedly to Institute efforts to attract and prepare outstanding investigators for research careers. Table 4 describes the mechanisms utilized by NIADDK to supply talented scientists for each of its categorical disease research programs.

Despite continuing vigorous efforts to avert shortages of personnel in vital areas, there is serious concern about the declining number of physicians who pursue research careers and the shortage of trained epidemiologists in many important fields, but the potential for personnel shortages exists at all levels and in all research specialties. For example, in fiscal year 1980 NIADDK supported 747 training awards of different types in its programs, while in fiscal year 1981 only 632 could be supported. Constraints on NIADDK training resources, payback provisions of the national research service award, and current stipend levels are disincentives to young scientists who have made large investments in their professional training and who may reap greater financial rewards in private practice or industry. NIADDK faces a challenge to overcome the threatened erosion of research manpower resources, and steps are being taken to prevent shortages.

Physician Researchers

In an effort to attract more physicians to academic research careers, NIADDK promotes short-term training programs for students in professional schools. During summer breaks, students are given the opportunity to gain research experience and be exposed to the rewards of a research career at a formative stage of their professional training. Once they have received their professional degrees, such students are eligible for grants in individual or institutional postdoctoral training programs, and those with demonstrated dedication and aptitude in research are eligible for the clinical investigator award, the research career development award, and the special emphasis research career award. By continuing to support physicians throughout the various stages of lengthy research training, NIADDK can help to ensure that adequate numbers of physician researchers will be available to address the Institute's research concerns from both basic and clinical perspectives.

Other Research Professionals

Often, critical manpower needs arise in specific areas or disciplines; for example, progress in epidemiologic studies has been severely restricted because the number of professionals trained in pertinent fields is insufficient. To correct this deficiency, NIADDK encourages the formal training of epidemiologists in field and survey methods through university-based degree programs, nondegree programs in the arthritis and diabetes centers, and epidemiologic projects at the Centers for Disease Control, the National Center for Health Statistics, the Veterans Administration, and NIADDK field studies units. Recognizing the importance of epidemiologic studies to comprehensive national research efforts, NIADDK established an arthritis epidemiology program office in 1978 to encourage research in rheumatic diseases and, with seven other Institutes, solicited applications for diabetes epidemiology research and training. By marshalling all available resources and coordinating them efficiently to fill specific needs for manpower, NIADDK hopes to moderate or avert the severe shortages of trained personnel anticipated in coming years.

Minority Program Support

Traditionally, ethnic and racial minorities and women have been underrepresented in the mainstream of biomedical research, but the Nation cannot afford to allow such human resources to remain untapped. NIADDK therefore vigorously supports programs to strengthen research capabilities and enlarge the potential investigator pool in colleges and universities composed largely of women and minority groups.

In 1977, NIADDK participated in the initiation of the NIH Extramural Associates Program to familiarize minority and women's educational institutions with NIH research activities, thus enhancing their capabilities to participate in NIH-supported health research. Through the Minority Biomedical Support Program, in conjunction with the Division of Research Resources, NIADDK commits funds to projects designed to improve the biomedical science capabilities of minority institutions through support of undergraduate students as well as graduate, postdoctoral, staff, and faculty positions. The Minority Access to Research Careers Program interagency agreement with the National Institute of General Medical Sciences enables NIADDK to increase the number of

Table 4.—NIADDK research manpower development mechanisms

National Research Service Awards—NRSA's provide for the training of biomedical and behavioral scientists in areas of national need. They can be in the form of individual postdoctoral fellowships or institutional training grants. After completing NRSA-supported training, recipients are usually expected to engage in biomedical or behavioral research or teaching for a period equal to the period of support.

- ***Individual postdoctoral fellowships***—Individual NRSA's are made to applicants who have received a Ph.D., M.D., or equivalent degree for postdoctoral research training. The award provides the opportunity to carry out supervised research so that biomedical scientists, clinicians, and others can broaden their scientific backgrounds and expand their potential for research in health-related areas. Each applicant must have arranged to work with a sponsor affiliated with an institution having the staff and facilities needed for the proposed training. Federal laboratories such as those of NIADDK's intramural programs, as well as universities, medical schools, research hospitals, and similar public or private institutions, are among the eligible organizations, and recipients are selected through national competition.
- ***Institutional training grants***—An institutional NRSA may be awarded to a domestic public, nonprofit private, or Federal institution to support a training program in a specific area of research. In most instances, institutions may request support for both pre- and postdoctoral trainees. The applicant institution must have or be able to develop the staff and facilities required for the proposed program and is responsible for selecting trainees. Predoctoral trainees must have received an appropriate baccalaureate degree, and individuals at the postdoctoral level must have received a Ph.D., M.D., D.D.S., D.V.M., or equivalent degree. Institutional grants are for periods of up to 5 years and may be renewed; however, no individual may receive more than 8 years of support (5 years predoctoral, 3 years postdoctoral) unless a waiver is granted by NIADDK.
- ***Short-term training for students in professional schools***—NIH has recently initiated a program to provide research experience for talented students in professional schools. The program is designed to help avert a shortage of clinical investigators by attracting highly qualified professional students to careers in biomedical and behavioral research. Domestic schools of medicine, osteopathy, dentistry, veterinary medicine, optometry, pharmacy, and podiatry may apply for grants to support short-term research training for their students for discrete periods of up to 3 months.
- ***Senior postdoctoral fellowship***—Investigators who have held the doctorate for at least 7 years may apply for a senior postdoctoral fellowship. These awards are intended to provide more established investigators with the opportunity to broaden their scientific background and expertise in health-related research. A senior postdoctoral fellowship is usually awarded for 1 year, is subject to NRSA payback requirements, and may not exceed 3 years' total support unless a waiver is granted.

Clinical Investigator Award—The CIA is directed to clinically trained individuals with demonstrated aptitude in research and provides them the opportunity to develop into independent biomedical investigators. Offering salary support as well as fringe benefits, the CIA program specifically seeks to develop research ability in individuals with clinical background and training. This award is intended to provide research support in the transition between fellowship or trainee experience and a career in independent investigation.

New Investigator Research Award—To help bridge the transition from training status to that of established investigator, the new investigator research award provides funds for relatively inexperienced investigators with meritorious research ideas. The award is designed to encourage the development of research interests and capabilities among both new investigators and those who interrupted their early promising research careers. This special program provides 3 years of nonrenewable research grant support for the initial independent research efforts of new investigators.

Research Career Development Award—The RCDA is a special grant awarded to an institution for support of a named individual. It provides salary and fringe benefits for 5 years, so that the awardee may be relieved of teaching and administrative duties and pursue research interests full time. The program's goal is to provide opportunities for the enhancement of the research capabilities of individuals in the formative stages of their careers who have demonstrated outstanding potential for contributing as independent investigators to health-related research. The awards are available for persons whose research potential is apparent but who need additional experience in a productive scientific environment.

Special Emphasis Research Career Award—SERCA's are sponsored by NIADDK, in conjunction with other Institutes, for three areas of diabetes research, as follows:

- Cardiovascular, endocrinologic, and metabolic aspects (with the National Heart, Lung, and Blood Institute);
- Obstetrical, neonatal, and pediatric aspects (with the National Institute of Child Health and Human Development); and
- Diabetes in the elderly (with the National Institute on Aging).

The SERCA is intended to encourage qualified individuals in the early stages of their postgraduate medical and scientific careers to develop research interests and skills in particular aspects of diabetes mellitus, to provide 5 years of salary support and limited amounts for research expenses to enable individuals to pursue a program of research in various fundamental and clinical research disciplines related to diabetes mellitus and its sequelae, and to create a pool of highly qualified investigators with experience and skills in these selected areas of diabetes research for future roles in related areas of research.

minority biomedical researchers by making funds available for predoctoral faculty fellowships, visiting scientists, and honors undergraduate training.

This year NIADDK scientists began to visit minority institutions, giving scientific lectures and advising students on careers in biomedical sciences. In addition, the Institute's Equal Employment Opportunity Office distributed scientific journals contributed by staff scientists to minority colleges and universities and participated in the Black Colleges Initiative, originated by Executive Order in 1980 to overcome the effects of discriminatory treatment and to strengthen the ability of historically black colleges to provide quality education and participate in federally sponsored programs.

Disease Prevention

As the Nation seeks methods to reduce the toll of disease and accidents and to curb inflation of health care costs, a greater emphasis is being given to disease prevention and health promotion—now a major initiative of the Department of Health and Human Services (DHHS). Modern prevention research has become complex, reflecting a shift in the prevalence of acute and infectious diseases (for example, pneumonia and tuberculosis) compared to chronic diseases (such as arthritis and diabetes) during the past century. The concerns of disease prevention and health promotion in American health care have thus become more challenging to research scientists throughout the country.

NIADDK has long been involved in prevention-related research, although such activities may not always be labeled as such. The primary product of the Institute is knowledge, the ultimate aim of which is prevention, because prevention of disease clearly is the most useful extension of knowledge in the health field. At NIADDK, prevention research has as its objectives both the protection of people from disease and injury and the prevention of the progression of disease to disability or early death.

Focus of NIADDK Prevention Research

NIADDK research is concerned with a variety of diseases with as yet unknown etiologies and, often, with poorly understood paths of progression. Without precise knowledge of causative factors and pathogenic mechanisms, it is difficult to design ways to prevent the onset or progression of a given disease. Therefore, support for basic research in certain disease areas must be emphasized, with the ultimate goal of obtaining the knowledge necessary for development of preventive measures.

Other diseases under study at NIADDK have yielded to basic research, and scientists are now designing means of prevention that will be translated into health care practice if they are shown to be safe, effective, and feasible. Many of the projects described in chapters II through V have important implications for disease prevention and health promotion, and major examples of ongoing prevention research activities for each NIADDK division are highlighted below:

- ***Prevention of osteoporosis***—Osteoporosis is a very common disorder of middle and old age, predominantly among postmenopausal women. It results in a gradual, accentuated loss of bone mass, predisposing patients to fractures of the spine, hip, and wrist. Many researchers are investigating hormonal and other influences on bone formation and resorption to understand more thoroughly the disease's etiology and pathogenesis. Studies are in progress to assess the effects of administering vitamin D, fluoride salts, and/or low-dose estrogen with maintenance of adequate calcium intake and regular programs of weight-bearing exercise in preserving a healthy skeleton and preventing osteoporosis.
- ***Prevention of complications of diabetes***—An unresolved question is whether strict and precise control of blood glucose levels in people with insulin-dependent diabetes can prevent the life-threatening degenerative changes associated with the disease, such as heart attacks, strokes, kidney failure, gangrene, blindness, and damage to the nervous system. Patients' use of new technologies, such as insulin infusion pumps and home blood glucose monitoring, permit scientists to assess for the first time whether tight control of blood glucose can prevent or forestall the secondary complications of diabetes, which account for most of the morbidity, mortality, and economic costs of the disease. A large multicenter collaborative clinical trial to study the relationship between blood glucose control and vascular complications of insulin-dependent diabetes mellitus is now in the final planning phase, and a 2-year feasibility study will soon begin. If it proves feasible and if funds permit, a 7- to 10-year full-scale collaborative trial will follow.
- ***Prevention of obesity and its effects on health***—Obesity, both in young adults and in the mature population, has become a major public health problem in the United States. Aside from the general issue of physical fitness, obesity aggravates cardiovascular disease, osteoarthritis of the weight-bearing joints, hypertension, hernia, and gallbladder disease. It facilitates the emergence of latent noninsulin-dependent diabetes in genetically predisposed individuals, adds to the hazards of surgery, and decreases lifespan. Effective means of preventing or treating obesity would represent

an important tool for disease prevention. NIADDK is engaged in an extensive research effort to develop such means of intervention, ranging from basic metabolic, physiologic, and histologic studies, to research on appetite mechanisms and behavioral approaches, to clinical investigations.

- ***Prevention of initial and recurring kidney stones***—Certain individuals are predisposed to recurrent urolithiasis (development of kidney stones or urinary tract stones). Recent research has demonstrated that selective drug and diet therapy can prevent the formation of new stones in 70 to 91 percent of patients with habitual stone problems. The Institute plans to continue and broaden these studies to develop practical and effective methods for preventing recurrent urolithiasis and, ultimately, for preventing initial stone formation by identifying individuals at risk.

Future Prevention Initiatives

In addition to the continuing studies noted above, several other major areas of investigation offer promise for future accomplishments in prevention, for example:

- Research on prevention of injurious consequences of physical exercise and sports activities, such as jogging;
- Research on prevention of the emergence of noninsulin-dependent diabetes in genetically predisposed individuals through lifelong weight control and physical fitness (80 to 85 percent of such patients are overweight and physically underactive);
- Research on prevention or better control of diverticulosis (protrusion of portions of the inner lining of the gut through weak spots in the circular muscle of the lower intestine) and diverticulitis (infection and inflammation of these intestinal herniations) in the aged through lifelong adequate supply of dietary fiber (bulky roughage); and
- Research on the factors that predispose older men to the development of benign prostatic hyperplasia, with the aim of eventual prevention or amelioration of this widespread disorder.

Prevention Education and Outreach

There are a number of NIADDK programs of relevance to prevention that feature interaction with the scientific and public health community, health providers, and consumers. Major activities are as follows:

- ***Multipurpose arthritis and diabetes centers***—The MAC's and DRTC's have education and demonstration components with information, continuing education, and training programs for medical and allied health professionals and for patients. Of particular importance to prevention are programs of education and dissemination of information for the general public concerning the risk factors associated with disease; the importance of early diagnosis and treatment; and discouragement of the use of unapproved and ineffective treatment measures.
- ***Clearinghouses***—The Institute supports national information clearinghouses on diabetes, arthritis, and digestive diseases, which serve the information/education needs of a broad professional and lay constituency in a number of areas, including disease prevention and health promotion. They act as central resources for information concerning the availability of scientific and popular literature and produce specialized newsletters, bulletins, and other publications.
- ***Clinical nutrition research units***—Supported by NIADDK at selected medical schools, CNRU's are designed to strengthen multidisciplinary research in clinical nutrition; to improve education and training of medical students, house staff, hospital-associated practicing physicians, and paramedical personnel in clinical nutrition; and to enhance improved patient care through better institutional support services. These innovative programs encourage the principles of disease prevention and health promotion by striving to upgrade the use of nutrition knowledge in clinical practice.

As new insights into the cause and development of chronic diseases continue to accrue, new strategies for preventing the onset or destructive progression of these diseases are being devised. However, it is clear that modification of habits and lifestyles—such as avoidance of obesity, dietary changes, and adequate physical exercise—will have an important influence on the degree of success achieved by many of the Institute's prevention initiatives. In light of the man-made risk factors in so many disease categories, successful prevention will depend not only on biomedical advances, but also on concurrent advances in educational, social, and legislative approaches to encouraging behavior change.

Technology Assessment and Transfer

Prior to the scientific revolution of the 1800's, physicians practiced medicine more as an art than a science. With the rapid technologic strides of the last 50 to 75 years, however,

the relative advantages of newer methods, devices, and procedures have been proposed; innovations have been more readily accepted and adopted; and the discipline of medicine has moved toward the practice of technology-based science.

Determining Research Impact on Health Care

Technology assessment, a form of policy research that examines short- and long-term consequences of the use of technology, is an essential safeguard of the public's right to safe and effective health care. Medical technology assessment is concerned not only with the scientific and medical aspects of advances in diagnosis, treatment, and prevention of disease, but also with indirect, delayed, or unintended social impacts of medical innovation; and, in consideration of economic realities, it rigorously examines and determines the optimal balance among the benefits, risks, and costs of health technologies.

The Office of Program Activities and Evaluation is the focal point for assessing medical technologies conceived, tested, and evaluated in NIADDK programs and for advising the Public Health Service and other agencies. NIADDK technology assessment activities include workshops, symposia, and consensus conferences to synthesize expert opinion; state-of-the-art review of issues within NIADDK research purview to assist the Public Health Service in the assessment of health technologies; and evaluation of inventions developed in extramural and intramural research.

NIADDK has participated in approximately 60 national and international scientific conferences, workshops, and seminars in the last year. It has also actively participated in the NIH consensus development program by which various concerned parties are brought together under the umbrella of a technical consensus development conference to seek general agreement on the safety, efficacy, and appropriate conditions for use of various medical technologies.

Last year, NIADDK sponsored/cosponsored two consensus development conferences in conjunction with the NIH Office for Medical Applications of Research (OMAR)—one on Reye's syndrome and the other addressing total hip joint replacement. Consensus conferences on liver transplantation, analgesic abuse-related kidney failure, and prevention and therapy of osteoporosis are now in the preliminary planning stages.

Utilizing advice from Institute experts and other scientific consultants, NIADDK also provides assessment of medical procedures and treatments for communication to the Health Care Financing Administration (HCFA), which administers coverage of health services under Medicare and Medicaid. Examples of technologies that have been assessed include:

- Apheresis for rheumatic diseases and certain types of glomerulonephritis;
- Noninvasive methods for bone mineral analysis;
- Electromagnetic treatment of bone fractures;
- Topical oxygen therapy for decubitus ulcers (bedsores);
- Psoralen and ultraviolet light (PUVA) treatment of psoriasis;
- Insulin infusion pumps and home glucose monitoring to improve control of diabetes mellitus;
- Pancreas transplantation in insulin-dependent diabetes;
- Gastric freezing for peptic ulcer disease; and
- Antigastroesophageal reflux implants.

Medical Technology Information Dissemination

NIADDK recognizes that unless the technologic knowledge gained in basic and clinical research is diffused for application in the health care community, the value of that research is significantly diminished. Therefore, the Institute devotes significant effort to systems that foster the application of scientific knowledge and techniques by those who need and can use them.

The goals of technology transfer are to increase awareness of and interest in new research advances, to promote scrutiny and evaluation of their potential advantages, and to foster their trial and adoption in practice. Technology transfer is first and foremost a communications effort, and effective communication requires the identification of target audiences, development of information products appropriate to audience needs, selection of appropriate means to disseminate information products, and short-term evaluation of feedback on the effectiveness of the communication effort.

NIADDK serves a range of constituency groups that includes basic and clinical researchers, health care practitioners, voluntary and other health agencies, medical educators, and the public. Their individual needs for information are different and may vary at different stages of technologic evolution. Since no single network for information dissemination can satisfy the full spectrum of information needs, the Institute uses varying means to promote the diffusion of information and the transfer of technology:

- ***Information collection and dissemination***—NIADDK's Office of Health Research Reports is the focal point for an

integrated program of information collection and dissemination of research highlights, program achievements, and disease-related materials. The office is responsible for coordinating the production and distribution of publications concerning Institute activities; answering inquiries from Congress, the White House, the media, and the general public on NIADDK activities and disease-related information; providing advice to scientific and program staff engaged in research reporting; and cooperating with voluntary and professional health agencies in the coordination and planning of publications and reports of clinical and research activities.

- ***Clearinghouses***—Important components of the Institute's information dissemination program are the Arthritis Information Clearinghouse, the National Diabetes Information Clearinghouse, and the National Digestive Diseases Education and Information Clearinghouse. Their primary objective is to bridge the communication gaps between those who are developing knowledge through research and those who suffer from the effects of these disorders or who direct their care. To this end, the clearinghouses have evolved as national centers for compiling what is available from various sources of educational materials ranging from technical information manuals for health professionals to audiovisual presentations developed especially for elementary school children. In serving as brokers to facilitate the flow of information, the clearinghouses maintain data bases cataloging thousands of brochures, booklets, reports, journal articles, textbooks, and audiovisual materials, and refer clients to appropriate developers or sources rather than acting as distributors of printed matter.

- ***Scientific conferences***—Members of the scientific and medical community, as potential adopters of new technologies, vary widely in their receptiveness to newly communicated innovations. While some investigators and practitioners make particular use of impersonal sources, such as printed materials, to learn about new information, many tend to rely on personal interchange and the experience of their peer group. Though wider audiences can be reached via the journals and textbooks, the information provided by these means is often not sufficiently comprehensive to change attitudes or behavior or to aid in practice. Recognizing that personal communication with associates is an increasingly important factor in information diffusion and technology transfer, NIADDK continues to support vigorously the conduct of workshops, conferences, and seminars, where representatives of various disciplines can share experiences and discuss different perspectives. The Institute not only provides financial support to such meetings, but sends scientific and program staff representatives to participate in discussions and present reports on NIADDK research advances.

Program Planning and Analysis

The Institute's planning process is designed to cope with the diverse and intricately related issues inherent in biomedical research. In nonresearch planning, contributing factors may be static or at least highly predictable. Research planning takes place in an atmosphere of uncertainty: Conflicting sources of data must be reconciled; knowledge expands; relationships among new findings often are not immediately evident; the timeframe within which new research achievements will occur cannot be predicted; and funding levels are often undetermined. Moreover, decisions regarding research must take into account issues of public health and the public's perception of health needs.

In its planning and analysis activities, then, the Institute complements its expertise by encouraging broad-based contributions from a variety of individuals and groups: the National Advisory Council and the three national advisory boards, other biomedical researchers, and constituent groups. Where societal choices—as opposed to administrative choices—are involved, participation of such outside advisors is especially helpful.

Planning at NIADDK takes two major forms. The first—strategic planning—involves long-term policy development and comprehensive evaluation of opportunities and problems. For NIADDK, this type of planning was most recently performed, with the assistance of program staff, by the national commissions on arthritis, diabetes, and digestive diseases, as well as by a number of evaluation panels. The other type—implementation planning—is an annual process based on the findings of the more comprehensive strategic planning process; it is dynamic and of more immediate impact, focusing on what the Institute intends for the near future, usually the next 1 to 3 years.

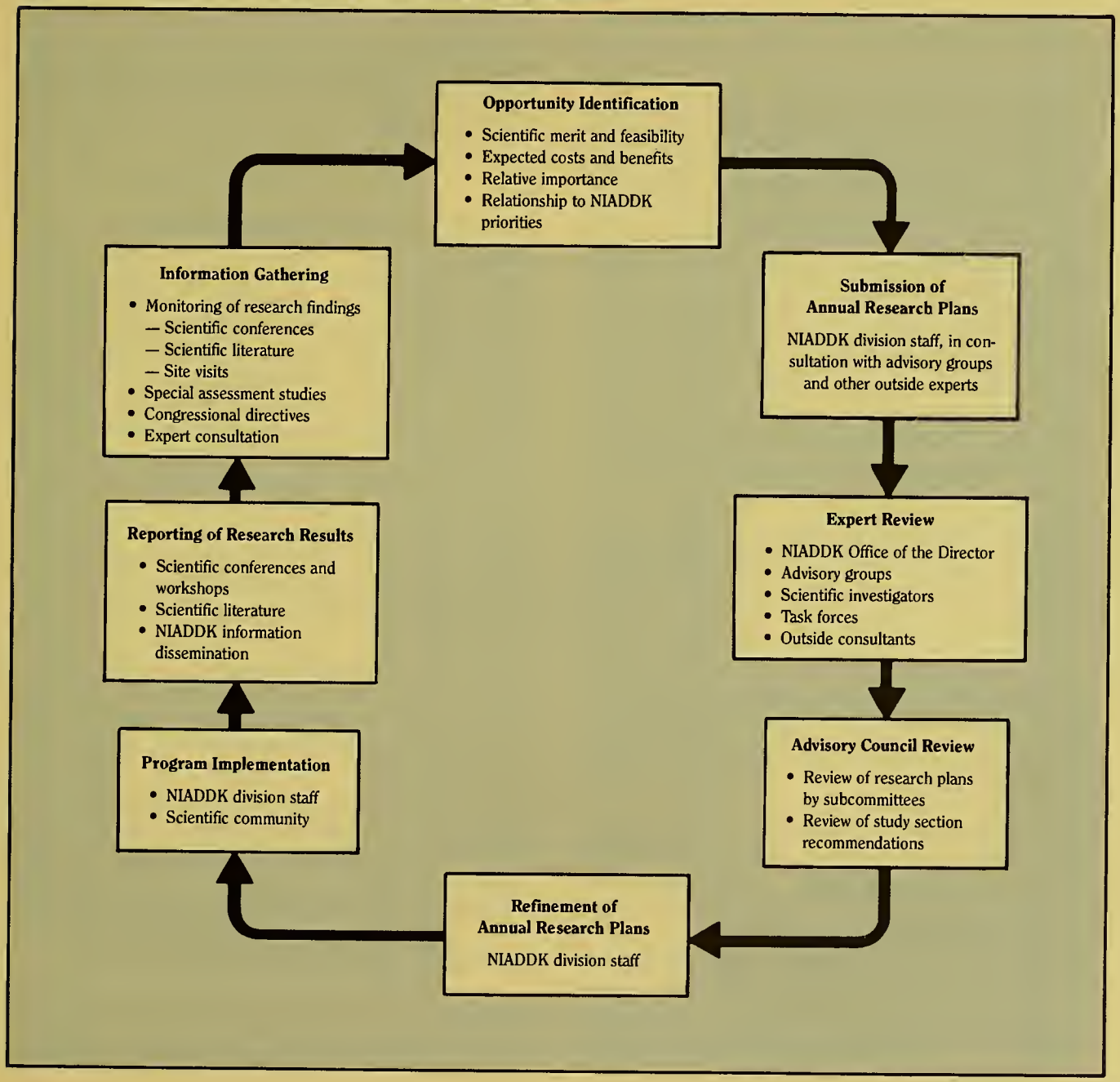
A well-conceived implementation plan enables the Institute to stimulate research activity in selected areas, primarily by guiding the implementation of initiatives by program managers. It guides and justifies long- and short-term internal allocation of funds and provides the basis for program accountability and evaluation. It also guides reporting activities and information dissemination throughout the year.

Since NIADDK relies heavily on investigator-initiated research, new ideas and opportunities explored by the scientific community contribute significantly to the planning process. The

Institute publicizes information about the scientific challenge of new opportunities or emerging research objectives, and these actions usually prompt a positive reaction in the scientific community. Individual investigators contribute to implementation by developing research grant applications that are pertinent to announced high-priority areas.

To determine its research priorities, the Institute uses a planning process based on a series of steps involving information gathering, progress assessment, opportunity identification, and expert review (see figure 4). These steps, which update scientific objectives for use in making decisions on research awards, are as follows:

Figure 4.—Annual NIADDK planning cycle: steps and mechanisms



- Throughout the year, the NIADDK staff regularly monitors the scientific literature, conference proceedings, and progress reports of ongoing research, in addition to visiting the sites of funded research and reviewing investigators' work. Assessment conference task forces and scientific advisory groups are convened in areas of special interest. Congressional directives; plans devised by groups such as the national advisory boards; the advice of professional societies, voluntary health agencies, and consumers; and the results of broad-based evaluation studies organized by the Institute (see below in section on evaluation) are all carefully studied and monitored. These data are then used for assessing progress and identifying scientific advances, opportunities, and Institute initiatives.

- The program staffs of the Institute's four divisions review such data, and each division develops an annual research plan. The plans summarize progress, tentatively revise scientific objectives, and delineate specific new activities that show unusual promise. New opportunities and initiatives are ranked by priority on the basis of their scientific feasibility, expected costs, and expected benefits in terms of the advance of scientific knowledge and, ultimately, improved health care.

- The annual plans submitted by the divisions are then reviewed by experts, including the Office of the Director of NIADDK, advisory groups, National Advisory Council subcommittees, ad hoc task forces, and individual scientific experts. In many instances their comments result in further refinement of the plans.

- Once the overall plan has been approved by the Institute Director, it is presented to the Director of NIH and to the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council.

- In addition to being submitted in a document complete with relevant budgetary information, elements of the Institute's plan are discussed formally with the Director of NIH at an annual research plan review session, at which senior staff members of the Office of the Director, NIH, and of NIADDK participate.

- The National Advisory Council and its subcommittees participate in Institute planning by reviewing the annual research plans of research divisions, making further refinements. In addition, the four subcommittees and the National Advisory Council as a whole review the recommendations of peer review groups (the NIH "study sections") with regard to the funding of individual research applications. Their recommendations on the funding of particular project applications reflect an overall knowledge and support of NIADDK policy and research priorities, as reflected in the annual plan, data on scientific progress, information on related programs outside NIADDK, recommendations resulting from peer review of the projects' scientific merit, and budgetary requirements imposed by available funds.

- Taking the National Advisory Council recommendations into consideration, the NIADDK staff makes awards, giving recognition to the priority scores assigned by the peer review groups, the Institute's financial obligations for ongoing awards made in previous years, and the amount of funds available for new undertakings.

These formal steps in the planning process are specifically designed to ensure that NIADDK supports new research projects of the highest scientific and technical merit, with full consideration of recent scientific progress, health care needs, and the availability of funds.

Evaluation of Institute Activities

Evaluation studies provide a rational basis for managerial decisionmaking, for producing statutorily mandated evaluation reports to the Congress and DHHS, and for responding to public concerns for accountability in government. Through such studies, the Institute is able to determine the extent of its progress toward scientific objectives and determine how to strengthen research and administrative activities, if necessary, to be more efficient and more responsive to perceived needs. Evaluation also provides an effective tool for management to use in maintaining balance between programs and mechanisms of funding. The evaluation process is closely linked with long-term strategic planning and contributes to the annual processes of legislative planning and implementation and budget allocation.

The Institute has often commissioned groups of acknowledged experts in one or more of the diverse biomedical disciplines for evaluation of a particular area. Committees are organized to address individual aspects of the general subject, and by the end of the 1- to 2-year study, the group will have established the current state of the art, assessed the contribution of NIADDK programs, pointed out the most promising directions for future research, and specified particular needs to be met to assure continued research progress. Results of evaluation studies, published as detailed reports and study summaries, have been widely disseminated throughout the scientific community, as well as to the Congress and other interested parties.

The Institute has also benefited greatly from the activities of the national commissions on arthritis, diabetes, and digestive diseases, which conducted thorough evaluations of NIADDK

program activities while developing their comprehensive national plans for combating these diseases. Recommendations presented in the commissions' reports have provided a valuable framework for the Institute's strategic planning and policy decisions concerning new initiatives.

The following are some of NIADDK's recently completed or current evaluation efforts, the results of which are providing impetus for future Institute direction:

- An evaluation of NIADDK's hematology program was conducted to analyze the current state of research in hematology, identify gap areas and the technological advances needed to close them, assess the need for a detailed study of hematology research manpower, and evaluate the extramural hematology program of NIADDK in relation to the identified needs. Recommendations of the study are being incorporated into the hematology program's plans for fiscal year 1983 and beyond.

- A study of the National Diabetes Information Clearinghouse was undertaken for the purpose of reviewing clearinghouse objectives, activities, performance measures, and performance data so that the conditions necessary for conducting a useful evaluation of the program could be determined. A followup evaluation, using a survey questionnaire, is being conducted to assess the utility of materials disseminated by the clearinghouse and the level of user satisfaction. The information obtained from the survey will be useful to the program staff in managing the clearinghouse, including the possible discontinuance and/or addition of certain products and activities.

- The goals, performance, and managerial approaches of the musculoskeletal diseases program are being evaluated to provide a foundation for improving research efforts. This project will also provide an assessment of the health care impact of selected medical technologies that have been developed with program resources. Evaluation groups having broad public and private membership are being used to identify research accomplishments, gaps, and opportunities, and to suggest ways to increase administrative effectiveness.

- A project is under way to investigate the impact of individual fellowships and institutional training grants in preparing young scientists and physician researchers for careers in the fields of diabetes, endocrinology, and metabolic disorders. This evaluation study is intended to be a discrete part of a larger effort to provide a quantitative model of the development of a pool of active biomedical research scientists.

- A study is being conducted to develop suitable methodologies for evaluating the broad spectrum of NIADDK centers programs, which include Specialized Centers of Research (SCOR's), core research centers, and multipurpose centers. Results of the project will aid the programs' staffs in center development and coordination.

- A related project is being conducted to identify appropriate methodologies for assessing the effectiveness of the education and community demonstration activities of the Multipurpose Arthritis Centers. Study information will be used by the NIADDK staff to evaluate the MAC's (as reported in chapter VI) and by center personnel to guide center-based evaluation activities.

Fiscal Resources

As health research and health care have emerged as major domestic policy issues, the responsibilities of NIADDK have expanded and its fiscal obligations have likewise grown. Figure 5, which depicts the 10-year change in the five major categories of Institute expenditures, indicates that the annual obligation for research grants and centers had almost tripled by 1981, then settled to a level of $280.8 million for 1982. However, the appearance of rapid escalation of the NIADDK research budget is deceptive. When adjusted for inflation, as shown in figure 6, the total annual allocation to NIADDK has increased by only $36.4 million—or 25.5 percent—since 1973.

The juxtaposition of growing opportunities in health research and limited resources for use in exploiting those opportunities poses a formidable challenge to Institute administrators. There are difficult choices to be made after careful planning and deliberation aimed at maintaining a judicious balance among public health needs, the immediate and long-range benefits of planned research, and the research community's need to be self-sustaining.

Table 5 shows the breakdown of NIADDK program funding by research division, and figure 7 demonstrates the relative expenditures for different types of award mechanisms in 1982. Obviously, the greatest portion of NIADDK's budget is invested in research grants. Applications by extramural investigators seeking grants undergo stringent peer review for scientific merit and compete with other applications in the same area for available current-year funds. Although a large number of meritorious applications are approved but not funded, because of limited resources, the Institute was able to support about 635 new and competing individual research projects in 1982. In large measure it is this last category of expenditures—the carefully considered allocation of NIADDK funds among dedicated investigators conducting high-quality basic and clinical research—that has made possible the achievements described in the following chapters.

Figure 5.—NIADDK actual obligations, 1973-1982

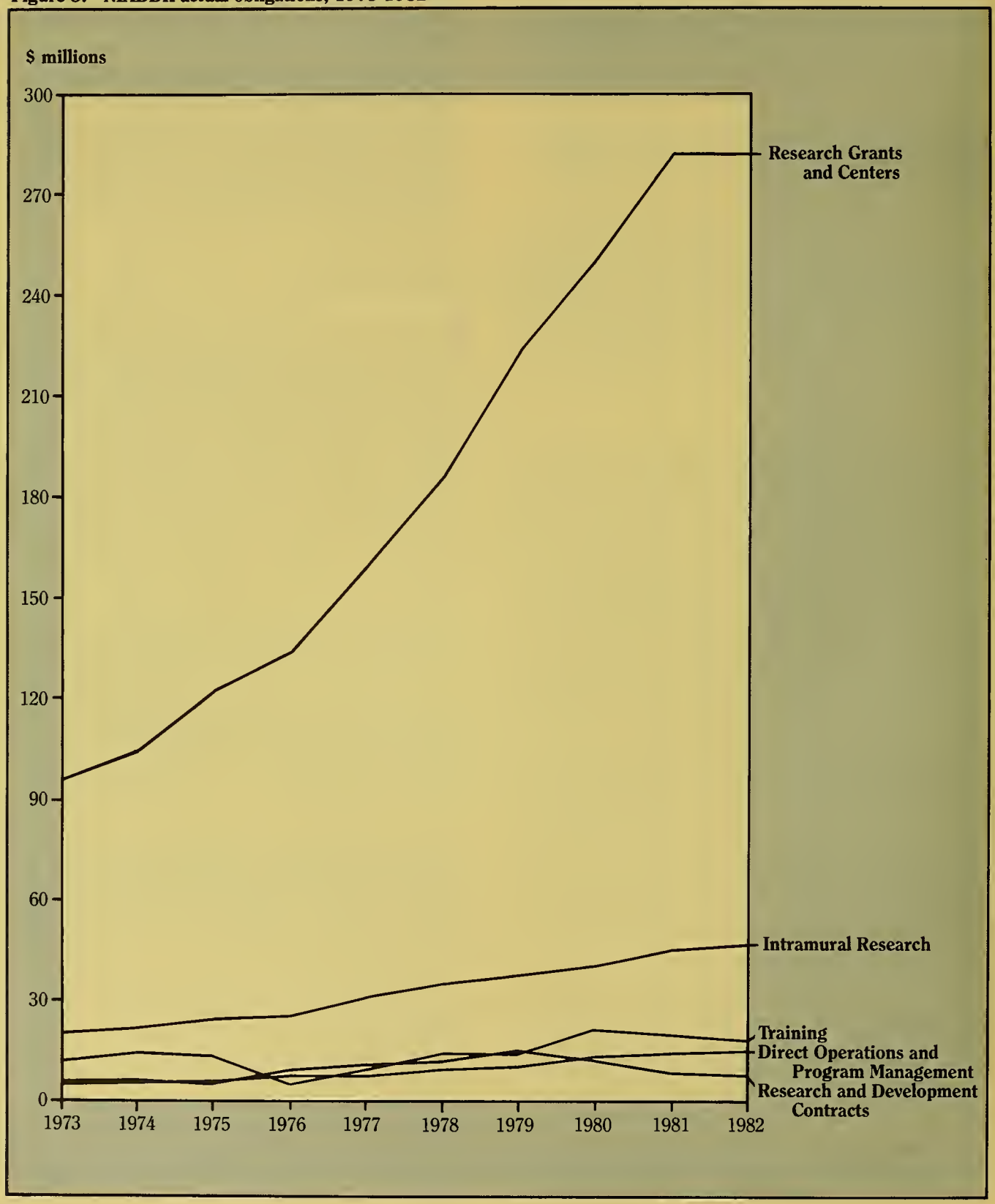


Figure 6.—NIADDK obligations, 1973-1982, adjusted for rate of inflation

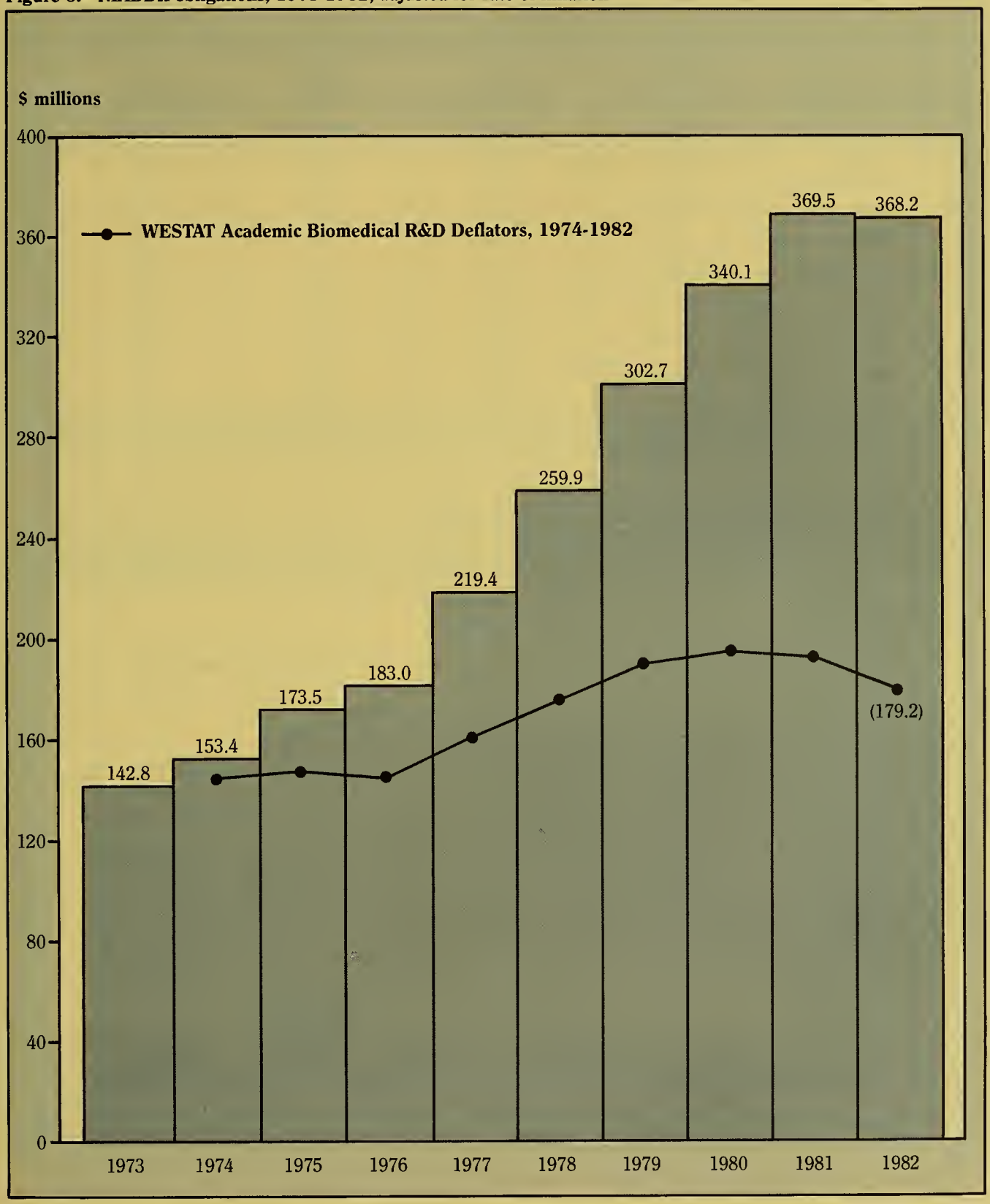
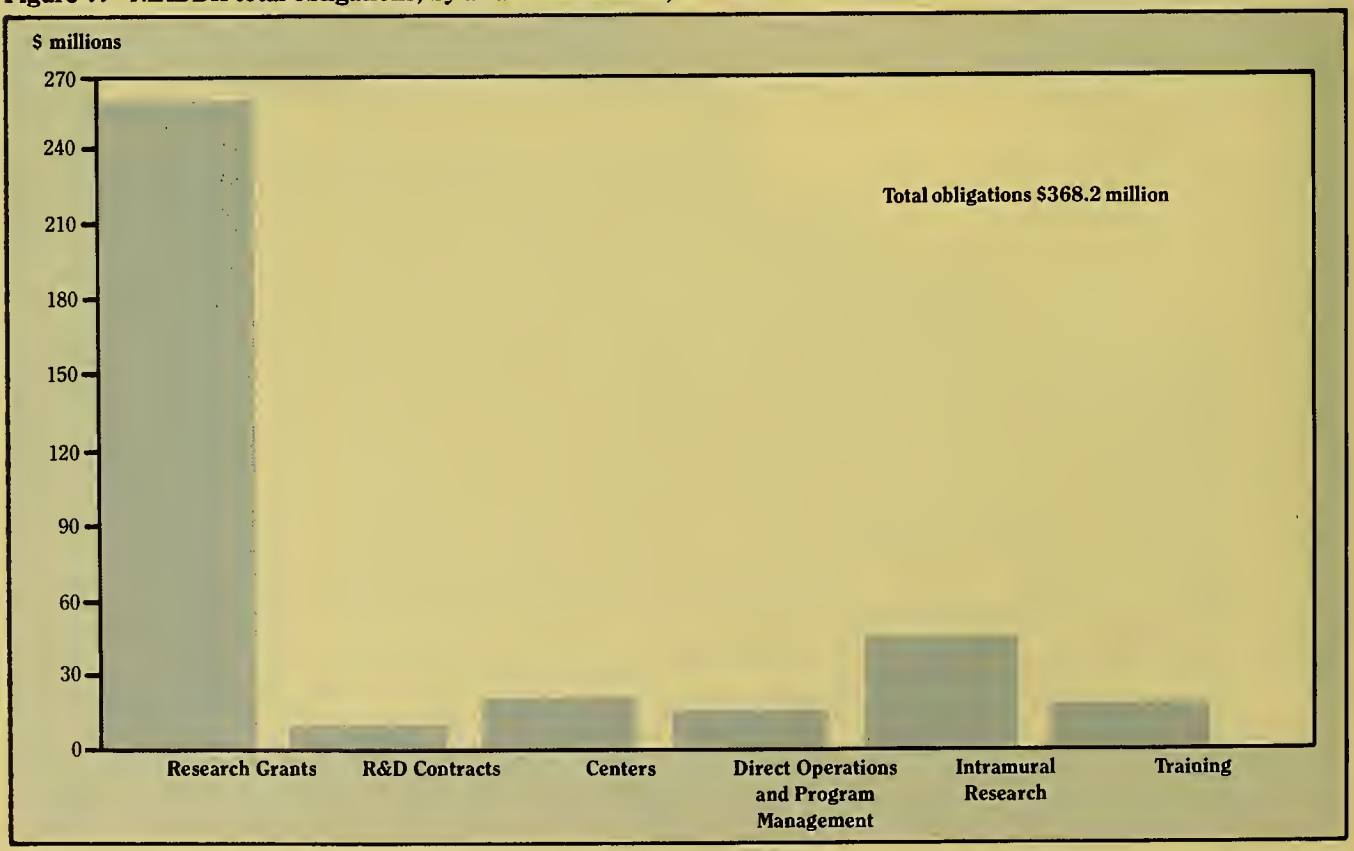


Table 5.—NIADDK program funding, 1973-1982 (dollars in millions)

	Arthritis, Musculoskeletal, and Skin Diseases	Diabetes, Endocrinology, and Metabolic Diseases	Digestive Diseases and Nutrition	Kidney, Urologic, and Hematologic Diseases
1973	$ 24.1	$ 57.8	$ 24.1	$ 28.8
1974	25.1	63.6	28.5	30.7
1975	29.2	70.5	33.7	33.6
1976 adj.	32.1	73.7	36.0	33.3
1977	38.8	96.4	38.1	37.7
1978	45.9	117.7	43.7	42.1
1979	55.2	135.0	50.8	50.3
1980	61.2	154.7	56.0	55.3
1981	69.8	163.8	60.1	62.6
1982	69.3	162.5	59.7	62.4

Figure 7.—NIADDK total obligations, by award mechanism, 1982



Courtesy of Edmund Y. S. Chao, Ph.D., Mayo Clinic

The modern technique of computer-assisted gait analysis now makes possible reliable and efficient measurement of mobility in people with various bone, joint, and skeletal muscle disorders. Such information is valuable to physicians prior to surgery (such as hip joint replacement for advanced osteoarthritis) and to therapists after surgery in their efforts to impart to patients the maximum achievable in freedom of movement.

George Kleiman, UNICEF

Arthritis, Musculoskeletal, and Skin Diseases

Overview

Disorders such as arthritis, diseases of skeletal support structures, and skin diseases, while not usually fatal, are among the most common causes of pain, disability, and disfigurement. In addition to the toll they exact in terms of human suffering, the economic impact of these disorders ranges into billions of dollars each year for medical care and lost productivity. Research efforts of the Division of Arthritis, Musculoskeletal, and Skin Diseases, implemented through extramural grant and contract programs, include investigations at major universities and medical schools throughout the country and abroad. Research in these disease areas is also conducted in NIADDK's Arthritis and Rheumatism Branch at the NIH Clinical Center. Through NIADDK's efforts over the last three decades, these chronic, crippling disorders have yielded significant ground to research. Depending on the severity or degree of progression, many of these diseases can now be partially controlled with medication and/or other types of therapy.

Among the more than 100 different kinds of arthritis and related rheumatic diseases are such disorders as rheumatoid arthritis, degenerative joint disease (osteoarthritis), systemic lupus erythematosus (SLE), gout, and many inherited and acquired connective tissue disorders. The underlying causes of most of these disorders remain unknown, and NIADDK's coordinated program of multidisciplinary basic research in biochemistry, immunology, genetics, virology, and other fields is fundamental to their discovery. While laboratory scientists seek new clues to the causes of arthritis, clinical researchers such as pharmacologists and rheumatologists are applying existing knowledge and methods to the discovery of better drug therapies and other medical technologies to alleviate joint pain and disability and to promote rehabilitation.

The division's musculoskeletal diseases program supports investigations that include basic and clinical studies of normal bone properties, growth, and metabolism; bone and joint diseases, injury, and repair; and disorders of skeletal support structures and functions such as tendons, ligaments, low back pain, and locomotion. The increasingly important areas of exercise pathophysiology and sports medicine are fostered by this program as well. Research advances in joint replacement, bone and cartilage transplantation, and fracture healing have helped to restore mobility and freedom from pain for many of the 40 million people in the United States with orthopedic problems. Investigations in these varied areas are providing the foundation for the eventual prevention or control of these disorders and their resultant disability.

While skin diseases are not usually fatal, they are the cause of considerable physical disability. Their effects—psychologically damaging, unattractive appearance and disfigurement—can be devastating. Diseases of the skin concern almost everyone at some time. Many of them, such as psoriasis, acne and eczematous and immunologic skin diseases, are treatable at present; but the etiology, means of prevention, and cure for most of them are not known. NIADDK's skin diseases program continues to support basic and clinical studies on both normal and diseased skin to obtain a better understanding of disease cause and progression. Past efforts have ushered in significant advances in the treatment of skin diseases, and there is hope for even greater advancement toward alleviating the damaging effects of such disorders.

Highlights of Research Advances

The following are brief highlights of some of the more recent advances in NIADDK-supported basic, applied, and clinical research directed toward the prevention and treatment of arthritis, musculoskeletal, and skin diseases.

- Distinctive features associated with Epstein-Barr virus (EBV) have been found in adults with rheumatoid arthritis, suggesting a possible association between rheumatoid arthritis and an enhanced immune response to EBV. Continued presence of EBV in the immune system after an initial infection, along with a specific T-lymphocyte regulatory defect, may be responsible for at least part of the sustained B-lymphocyte activation in rheumatoid arthritis.

- A randomized, controlled study in patients with rheumatoid arthritis has shown lymphapheresis to provide a definite, though modest, therapeutic benefit, with beneficial effects occurring early in the treatment, after removal of a portion of the patients' lymphocytes.

- In patients with severe rheumatoid arthritis not adequately controlled by conventional therapy, total lymphoid irradiation has been shown to have a definite but temporary beneficial effect. Widespread application of this technology for treatment must await further controlled study.

- Recent studies have confirmed the utility of nailfold capillary microscopy in the diagnosis of scleroderma, dermatomyositis, systemic lupus erythematosus, and other connective tissue diseases. This noninvasive and relatively uncomplicated procedure can serve as an early warning of these diseases.

- Experimental treatment regimens utilizing calcium, estrogen, or vitamin D with sodium fluoride were effective in reducing the bone fracture rate in the majority of women with postmenopausal osteoporosis. The most effective therapy was a combination of sodium fluoride, calcium, and estrogen.

- Significant advances in measuring bone density by noninvasive methods have enhanced our ability to diagnose and monitor many types of bone disease, including osteoporosis and osteopetrosis, without the risks and trauma of surgery for biopsy purposes. The improved methods involve dual photon absorptiometry, computerized tomography, neutron activation, and Compton methods.

- Psoralen ultraviolet A light therapy has been shown to be cost-effective and better than conventional ultraviolet light therapy or other topical agents alone. PUVA has significantly reduced the number and length of costly patient hospitalizations for psoriasis treatment.

Rheumatoid Arthritis

Involvement of Cell-Mediated Immunity and Immune Complexes in Disease Progression

With increasing attention to immunologic studies in rheumatoid arthritis, the importance of cell-mediated immunity and related antigen-antibody complexes in the pathogenesis of rheumatoid synovitis (inflammation of the tissue lining the joint) and the systemic complications of rheumatoid arthritis is becoming clearer. Studies to date have focused on one type of immune complex in particular—immunoglobulin G-rheumatoid factor (IgG-RF)—which appears to be involved in the initiation and progression of these disease processes. Accumulated evidence shows that the serum from certain patients with rheumatoid arthritis contains IgG-RF complexes of an intermediate size. Although these complexes may be found in patients with uncomplicated rheumatoid arthritis, they are found more commonly in patients with systemic complications affecting the blood vessels, lungs, heart, or nerves. Frequently, tissue reactions involving IgG-RF also involve IgM-RF and result in the formation of larger immune complexes which are more difficult for the body to clear from its systems. These complexes, which may be consumed by synovial cells or white blood cells, are associated with the formation and release of lysosomal enzymes. These enzymes are capable of destroying bone and cartilage protein and are currently thought to lead to the articular joint damage characteristic of rheumatoid arthritis.

Whereas many past studies focused primarily on humoral immunity, recent studies have thrown new light on cell-mediated immune mechanisms. The emerging importance of cell-mediated immunity in research in rheumatoid arthritis is illustrated by the following three examples:

Effects of Epstein-Barr virus on T-cell function—The Epstein-Barr virus is a ubiquitous virus that can cause infectious mononucleosis, but infection with the virus often does not produce symptoms, and most people have developed antibodies to EBV by the time they reach young adulthood. Recently, distinctive features associated with EBV have been described in adults with rheumatoid arthritis, suggesting an association between rheumatoid arthritis and an enhanced immune response to EBV. When lymphocytes (white blood cells) from normal immune donors were infected with EBV in culture, they produced increasing numbers of immunoglobulin-secreting cells. This response lasted for approximately 10 days, but it was followed by a marked suppression of the effect, mediated by immunoregulatory T cells. Suppression was nearly complete by the 12th day. When compared with normal donors, patients with rheumatoid arthritis were found to have an increased frequency of elevated

EBV-antibody levels. When lymphocytes from these patients were cultured, they also responded with increased production of immunoglobulin-secreting cells, but the expected suppression of the effect did not occur. Other tests for T-cell functions in these patients were normal, indicating that a restricted defect in suppressor-T-cell function produced by EBV may be present. EBV persists in host B cells of the immune system after the initial infection; thus, there is the potential for perpetual stimulus of immunoglobulin production by these cells. This persistence, coupled with a specific T-cell regulatory defect, may be responsible for at least part of the sustained B-cell activation in rheumatoid arthritis.

Therapeutic benefit achieved with lymphapheresis—Lymphapheresis is a blood purification technique which removes white blood cells (primarily lymphocytes) from the circulation. Apheresis has been used to remove lymphocytes involved in initiating and perpetuating inflammation in rheumatoid joints. Previous use of the technique appeared to bring relief to patients with severe rheumatoid arthritis, but early studies lacked controls, which hindered objective evaluation of efficacy. Recently, however, a randomized clinical trial was conducted to overcome the problems of previous studies and to evaluate the presumed antirheumatic effect of the procedure. Patients who had failed to respond or experienced toxicity with other antirheumatic therapies were assigned randomly to either lymphapheresis or a control protocol involving removal of an equivalent volume of plasma devoid of lymphocytes. Blood was collected from each patient assigned to lymphapheresis from a catheterized vein in the forearm, processed through a device called a continuous-flow cell separator to remove lymphocytes, and returned to the patient's circulation via a second vein. The procedure lasted 3½ to 4 hours and was repeated two or three times a week for 5 weeks.

Antirheumatic effects were measured as degree of reduction of tenderness, swelling, and pain in affected joints. At the end of the course of treatment, it was found that patients in the lymphapheresis group experienced dramatic reductions in the number of circulating lymphocytes, while lymphocyte concentrations in the control group remained stable. Patients undergoing lymphapheresis also experienced significant reduction of tenderness, swelling, and stiffness in their joints; however, there was no correlation between the magnitude of symptomatic relief and the number of lymphocytes removed from the circulation.

The results of this study show a definite, though temporary, beneficial antirheumatic effect of lymphocyte depletion in rheumatoid arthritis that compares favorably with that reported for randomized trials of drug therapies such as gold salts, cyclophosphamide, or penicillamine. Additionally, the favorable response was reported to occur early in the course of treatment, before large numbers of cells had been removed, indicating that cells removed early in lymphapheresis may provide a clue to the mechanisms of rheumatoid arthritis.

New treatment may provide temporary relief—Though the exact origin of rheumatoid arthritis is unknown, it is widely regarded as an autoimmune disorder in which sensitized lymphocytes mediate inflammation in affected joints. The autoimmune features of rheumatoid arthritis are likely attributable to a defect in suppressor T cells which, in healthy subjects, contribute to regulation of the immune system. Previous research has shown that removal of lymphocytes by techniques such as thoracic duct drainage or apheresis produces temporary reduction of joint inflammation in rheumatoid arthritis patients. Building on extensive experience in treating Hodgkin's and non-Hodgkin's lymphomas, NIADDK grantees are now attempting to determine whether total lymphoid irradiation (TLI) will bring relief to patients whose disease is not responsive to conventional therapy. In a small number of severely affected patients, radiation treatments were directed at lymph nodes in the chest and abdominal and pelvic regions on a daily basis for intermittent periods spanning 15 weeks. After the course of treatment, investigators measured immune system parameters as well as objective and subjective indicators of pain, stiffness, and mobility. The majority of patients in this preliminary study reported a significant reduction in the number of swollen or painful joints, reduced morning stiffness, and correspondingly improved mobility. Laboratory tests showed that all patients experienced a prompt decrease in circulating lymphocytes. In contrast, their levels of rheumatoid factors, antinuclear antibodies, and immune complexes were not reduced after treatment. These results demonstrate an anti-inflammatory effect of TLI on patients with severe rheumatoid arthritis not adequately controlled by standard therapy; they do not reveal whether the natural history of the disease is altered. As in other applications of this treatment regimen, very few side effects were noted; however, symptoms of disease appeared to recur in less than 1 year, paralleling the recovery of lymphocyte concentrations. This study further implicates T-cell mediated host responses in the pathogenesis of rheumatoid arthritis. Widespread application of this technology for treatment, however, must await controlled clinical trials.

Role of Collagen Autoimmunity

Earlier research has indicated that rheumatoid arthritis may be the result of the body's antagonistic response to proteins in its own tissues (an autoimmune reaction). Recently, investigators were able to produce arthritis in rats by immunizing them with collagen type II (a protein component of connective tissue), which induced an autoimmune response. This type of

autoimmunity to collagen type II has been demonstrated in patients with rheumatoid arthritis and psoriatic arthritis.

Since these antibodies are found in both rheumatoid and psoriatic arthritis, it may be that the demonstrated reactivity is a late result of inflammatory destruction of joint components. For future research, it will be important to determine whether the reaction observed in the rat arthritis model has applicability to human conditions, and to learn which of the immune or inflammatory mechanisms can be modulated to alleviate the painful, crippling manifestations of chronic arthritis.

Inhibition of Collagenase Production by Retinoic Acid

Collagen is a major component of skin, tendons, bones, cartilage, and connective tissue that provides support to other structures. The enzyme collagenase is a lysosomal enzyme which is thought to be released in the course of rheumatoid arthritis and to damage tissues through destruction of collagenous components. In recent studies, NIADDK investigators have been examining the effects of retinoic acid (a vitamin A derivative) on collagenase production in cultures of synovial lining cells. They have shown that retinoic acid completely inhibits the production of collagenase and moderately inhibits the production of prostaglandin E_2, a fatty acid derivative that fosters inflammation and retards cartilage repair. These preliminary studies demonstrate that retinoic acid may have beneficial properties for the treatment of rheumatoid arthritis. Clinical trials to gauge the efficacy and safety of retinoic acid appear to be indicated.

Milwaukee Shoulder—A Newly Described Syndrome

The shoulder is the most mobile joint in the human body, but its mobility is attained at the expense of joint stability. Stability of the shoulder joint depends on the structural integrity of the fibrous tendons of the surrounding muscles known as the rotator cuff. Recently, NIADDK-supported investigators in Milwaukee, Wis., studied several patients who presented with pain, limitation or loss of motion, weakness, chronic discomfort, instability of the joint, and advanced joint degeneration—features resembling those of rheumatoid arthritis. On further investigation, their problems were found to differ from rheumatoid arthritis in several important aspects. Fluid drained from the shoulder joints of these patients was found to be noninflammatory, containing hydroxyapatite (bone mineral) crystals, activated collagenase, and neutral protease. By contrast, only 1 fluid sample in 10 from patients with rheumatoid arthritis contained active collagenase and none was found in samples from patients with osteoarthritis. This clinical entity involving the chronic presence of particulate matter in synovial fluid, active collagenase, and protease activity had not been described previously, and it has been given the name "Milwaukee shoulder."

Observations obtained from the affected patients suggest that a pathogenetic cycle is established by the enzymatic release of hydroxyapatite crystals from the synovial tissue, altered joint capsule, or degenerative articular cartilage. The crystals are subsequently engulfed by scavenging synovial macrophage-like cells which, in turn, release protein-digesting collagenase and neutral protease into the joint fluid. It is thought that neutral protease provides a means for "activating" collagenase, which subsequently produces destruction of the fibrous components of the joint and leads to the signs observed in these patients. It is uncertain whether Milwaukee shoulder is a discrete syndrome or whether it represents an extreme form of degenerative shoulder joint disease. Further investigation of the apparently unique features of the disorder, however, will shed light on different types of degenerative joint disease.

Systemic Lupus Erythematosus

Role of Humoral Immune Responses

The major cause of death from SLE is nephritis (inflammation of the kidney with kidney failure). Earlier studies strongly implicated a humoral immune response to DNA in the induction of SLE nephritis. Healthy individuals were shown to be capable of producing antibodies to DNA. From new information gained in studies with mice, it now appears that only some subpopulations of anti-DNA antibodies are pathogenic. Several different monoclonal murine antibodies (pure antibodies developed from mouse cells) to single- and double-strand DNA have now been produced successfully. It is now possible to study specific antigenic and pathogenic properties of each antibody subpopulation. If suppression of pathogenic subpopulations with gene-specific sera is successful in preventing nephritis without suppressing normal immune responses, new SLE therapies could result. An additional benefit of these studies is that the development of monoclonal antibodies to DNA may provide probes for further study of RNA (ribonucleic acid) and DNA molecules.

Markers for Predicting SLE Flareups

In the past, studies of systemic lupus erythematosus have correlated abnormal immunologic parameters—complement components, anti-DNA antibodies, and immune complexes—with active disease. These studies also showed that immunologic aberrations returned to normal as flareups of the disease subsided. In studies undertaken recently, researchers have been

carefully monitoring changes in these parameters in SLE patients to obtain reliable indices for predicting flareups of the disease so that appropriate treatment could be given and monitored.

"Complement" includes a complex series of serum protein components which interact with antigen-antibody complexes to generate inflammatory reactions. In current studies it has been found that low levels of complement components CH50, C4, C3, and Clq and high levels of immune complexes and anti-DNA antibodies are associated with flareups of SLE. Patients with kidney involvement alone showed lower levels of CH50 and C3 and higher levels of immune complexes; the lowest levels of CH50, Clq, C4, and C3 occurred in patients with both kidney and other systemic complications; and high levels of anti-DNA antibodies were found in patients with active kidney involvement or systemic involvement alone. C4 depression preceded flareups in many patients who subsequently developed both kidney and systemic involvement. Results of this study now justify serial measurements of C4, CH50, C3, and anti-DNA antibodies in descending order of their value as markers for predicting imminent flareups of SLE.

Development of Animal Models

Animal models are extremely important basic research tools. While a given model may not duplicate every aspect of the human disease, once investigations have been performed in an animal model, it is generally possible to devise indirect means for gauging applicability of the work to the human condition. Two strains of mice with spontaneous autoimmune disease that are easy to raise have been produced and characterized as useful for studying human SLE. NIADDK is now providing support for the establishment and expansion of colonies of Palmerston north (PN) and Swiss Webster antinuclear (SWAN) mice. The expression of autoimmune disease in these mice has been shown to be free of the effects of environmental factors, and SWAN mice have been shown to have rather constant immunopathologic features such as high levels of antinuclear antibodies in the males of the species, lower incidence of anti-DNA antibodies, abnormal skin, and nephritis with immunoglobulin deposition in kidney glomeruli. Although these strains of mice are similar to others that have been developed with regard to the expression of SLE-like autoimmune disease, each differs from the others with respect to underlying immunoregulatory abnormalities, rate of disease expression, and sex and hormone factors. The expression of SLE in humans is variable in terms of severity of disease, pattern and degree of organ involvement, and other factors; thus, the availability of animal models mimicking various aspects of human SLE is a valuable basic research resource.

Gout—Discovery of an Inflammation-Inducing Factor

Many years ago, NIADDK scientists determined that inherited overproduction and/or underexcretion of uric acid were the key flaws in body chemistry responsible for gout. New data are providing additional knowledge about the pathogenesis of the acute, highly inflammatory arthritis of gout. Institute grantees have shown that certain white blood cells—polymorphonuclear leukocytes (PMN's)—ingest urate crystals in gouty arthritic joints and calcium pyrophosphate crystals in pseudogout. After engulfing and ingesting these crystals, the PMN's release a factor called crystal chemotactic factor (CCF). When injected into rabbits, CCF has been shown to induce inflammation like that seen in crystalline-induced acute arthritis. The beneficial result of these studies is twofold: First, a factor has been discovered which appears to initiate an arthritic condition, and further investigation of this factor may provide insight into other arthritic processes; second, application of this factor has aided development of an animal model for continued studies.

Connective Tissue Diseases—Improved Diagnosis with Capillary Microscopy

Previous studies have shown that abnormal patterns of capillaries in the fingertips may have some specificity for certain connective tissue diseases, even though their full clinical expression may not be manifest. Such vascular abnormalities are consistent with disorders of microcirculation in various affected organs. In a more recent study, nailfold areas of patients with scleroderma (hardening and shrinking of connective tissue in any part of the body), dermatomyositis (inflammation and necrosis of skin and muscle fibers), polymyositis (inflammation of multiple muscle groups), Raynaud's syndrome (abnormal cold-sensitivity of fingers and toes, frequently progressing to scleroderma), and SLE were photographed under low-power microscopy. The photographs were interpreted in a blind study by members of the research team. Although normal nailfold capillary patterns were observed in polymyositis and Raynaud's syndrome, characteristically tortuous capillary patterns could be discerned in many cases of SLE, and "bushy" patterns were evident in scleroderma and dermatomyositis. These results confirm the usefulness of nailfold capillary microscopy for diagnosing certain connective tissue disorders. The procedure is noninvasive and relatively uncomplicated.

Bone Fracture and Healing—Electrical Stimulation Promotes Growth

Approximately 5 percent of all bone fractures never reunite and heal normally. Studies in animals and humans have shown that

electrical stimulation by either direct current or pulsing electromagnetic fields is an extremely valuable form of treatment in nonunion fractures resistant to other forms of therapy (such as bone grafts and other surgical fixation procedures). For this therapy, a snug plaster cast is applied to immobilize the affected bone, then Teflon-coated wire electrodes are inserted through the skin into the nonunion area. The wires are connected to an external power source and treatment is applied at home for 10 to 12 hours a day for an average of 6 to 8 months. An alternate technique involves local stimulation through the creation of pulsating electromagnetic fields which are created by electromagnetic coils applied to the outside of the involved limb. Though the precise mechanism of action of local electrical stimulation therapy is unknown, it appears that cell behavior at the fracture site is modified so that, in the cartilage in the nonunion area, the process of calcification, vascularization, and replacement by bone is enhanced and accelerated.

The latest research in this area in laboratory animals involves "capacitive coupling," in which the electric energy is produced by charged plates applied to opposing sides of the area to be stimulated. In animals this method has proven more efficient for delivering stimulation to the nonunion site, and it may permit enhanced bone healing in difficult-access sites such as the hip and spine. Investigators are now pursuing additional studies, applying electrical stimulation techniques to other bone diseases, such as osteoporosis and osteogenesis imperfecta, and are attempting to promote bone growth into porous implant materials to overcome problems of loosening in total joint replacement.

Osteoporosis—Sodium Fluoride Shows Promise in Therapy

Past research has indicated that treatment regimens that include sodium fluoride may be effective in reducing the rate of bone fracture in postmenopausal women with osteoporosis. In a recent clinical investigation, NIADDK grantees systematically studied the effect of this therapy on the rate of vertebral fractures in a large group of postmenopausal women. Patients in the study received sodium fluoride therapy with or without conventional therapeutic agents such as calcium, estrogen, and vitamin D; after 1 year of therapy, vertebral fracture rates in the treated patients were reduced. Overall, 60 percent of patients treated with sodium fluoride showed increased vertebral bone mass on X-ray, and these patients had approximately one-seventh the fracture rate of other patients. The results of this investigation also showed that the most effective therapy was a combination of sodium fluoride, calcium, and estrogen. Researchers believe that patients who did not respond to fluoride treatment may have an intrinsic abnormality of osteoblast function that prevents the stimulation of bone formation above certain levels. Nevertheless, the beneficial outcome for the majority of patients in this study provides a basis for optimism about the effectiveness of fluoride therapy in combination with other available agents for the prevention of fractures in postmenopausal osteoporosis.

Osteopetrosis—Research on Osteoclasts Leads to Improved Treatment

Recent research has established that osteoclasts (cells that resorb and remove bone) are derived from cells in the reticuloendothelial system (RES)—an important body defense system composed of highly phagocytic cells. The derivation of osteoclasts from monocytes, macrophages, and multipotential mesenchymal cells of the RES has been demonstrated in laboratory animals. An important by-product of this research has been a dramatically improved treatment for osteopetrosis (marble bone disease), a previously fatal hereditary disease characterized by abnormally high bone density and thought to be attributable to faulty bone resorption. Once investigators identified osteoclast precursor cells in the bone marrow and peritoneal cavity of laboratory animals, bone marrow transplants were performed in several osteopetrosis patients in an attempt to promote bone-resorbing activity. The transplants produced marked improvement in the patients' condition. Many factors are involved in the resorption of bone, including chemotactic factors (substances that attract cells to the site of resorption), prostaglandins, and osteoclast activating factor. These factors and the interactions of various osteoclast precursor cells in the remodeling of bone are currently the subject of several research studies aimed at advancing our knowledge of bone resorption to provide a basis for better treatment of a variety of bone diseases.

Disease Diagnostics—Noninvasive Measurement of Bone Density

A number of bone diseases such as osteoporosis and osteopetrosis result in alterations of bone density and subsequently affect bone strength. Recent significant advances in measuring bone density noninvasively have eliminated the need for performing bone biopsies to diagnose or monitor the progression of these conditions. A process called dual photon absorptiometry provides accurate measurement of bone mineral content, while computerized tomography (CT), a highly sophisticated X-ray technology, can produce accurate pictures of cross sections of bone. The use of dual energy modes in both of these

techniques enhances the investigator's ability to discriminate between different bone components, such as mineral and marrow fat content, and therefore improves the accuracy of measurements. Other techniques—neutron activation and Compton methods—can be used to measure changes in calcium levels in addition to radiation scattering caused by localized areas of very dense bone. The development of these techniques is a significant advancement in our ability to diagnose and monitor many types of bone disease without exposing patients to the risks and trauma of surgery for biopsy purposes.

Exercise Physiology—Animal Studies in Muscle Tension/Relaxation

Basic research with animals has defined patterns of control occurring when muscles are tense or relaxed. So-called fast or slow muscle fibers respond differently to given training exercises. Physical training programs must include a variety of quick-motion, strength, and endurance exercises to accommodate both muscle types and to derive the benefits of exercise in terms of increased aerobic capacity and energy-producing activity. Studies have shown that fast muscle fibers have poor aerobic capacity and recover slowly from excessive work. Training can produce moderate improvement in these conditions.

In related investigations of muscle activity and joint forces in athletic activity, NIADDK grantees have determined that active muscle force is required to prevent injury from falls during skiing. These results show that, contrary to earlier belief, relaxing during a fall may increase the chance of injury.

Acne—Better Laboratory Method for Research

Acne vulgaris is a chronic inflammatory disorder that is extremely common in the mid- to late-teenage years. It has been postulated that normal bacteria of the skin release enzymes that break down sebaceous gland secretions and liberate fatty acids, causing the development of the inflammatory lesions of acne. Prior attempts at biochemical characterization of the events contributing to the development of acne have been hampered by a continuing inability to isolate human sebaceous gland cells (sebacytes). In new research, NIADDK grantees have reported an improved method for isolating sebacytes from facial skin. Whereas previous attempts to isolate these cells from other skin cells have had a success rate of only 25 percent, viable sebaceous gland cells can now be routinely isolated from skin specimens with a success rate of approximately 90 percent. Use of this improved laboratory method may accelerate studies on the biochemical characterization of the sebaceous gland cell and its secretions and thereby advance our knowledge of the pathogenesis of acne vulgaris.

Psoriasis—Cost-Effective Therapy for Severe Cases

A new treatment for psoriasis, psoralen ultraviolet A light therapy, holds promise as an effective replacement for methotrexate or corticosteroid therapy. Several clinical investigations have confirmed that short-term PUVA therapy, which combines an oral medication with exposure of skin to long-wave ultraviolet light, effectively clears severe psoriasis better than conventional ultraviolet light therapy or other topical agents do alone. Recently reported findings also indicate that PUVA, which can be administered on an outpatient basis, dramatically reduced the number and length of patient hospitalizations for psoriasis treatment—a reduction in health care expenditures that exceeds the cost of the treatment. There are some preliminary indications, however, that long-term use of PUVA may suppress immune system function and indirectly contribute to the increased number of cases of skin cancer that have been noted, particularly in patients with a previous history of cancer or exposure to radiation. Investigations on the long-term use of this effective, less costly alternative for the treatment of severe psoriasis are continuing.

Bullous Skin Diseases—Potential Diagnostic Test Under Study

The bullous skin diseases are both disfiguring and painful, characterized by blistering bullae or papules, which, upon rupture, leave large weeping, denuded areas. Using monoclonal antibody methodology, NIADDK grantees are attempting to produce antibodies to various skin layer components—the cytoplasmic membrane and basement membrane zone—thought to be involved in the development of bullous diseases such as epidermolysis bullosa. In these studies, one antibody that reacts solely with an antigen in the basement membrane zone has already been isolated. Further studies with this antibody are of special interest, since the antigen with which it reacts is thought to be specifically altered in recessive dystrophic epidermolysis bullosa. Continued development of the monoclonal antibody technology, therefore, ultimately could provide the basis for diagnostic tests of bullous skin disorders.

Heritable Skin Disorders—Skin Permeability and Lipid Composition

The stratum corneum is the outermost layer of skin, comprising many layers of dead, flattened cells which are constantly sloughed from the surface. It serves as a relatively impermeable barrier to blunt trauma, corrosive substances, effects of light and other irradiation, and microbial invasion. It also acts to conserve body moisture. Grantees attempting to elucidate the cellular, lipid, biochemical, and pathophysiologic bases of the skin's permeability barrier have demonstrated a unique role for linoleic acid—a fatty acid—in correcting the barrier dysfunction in essential fatty acid deficiency. It has been found that regional differences in permeability can be ascribed to quantitative rather than qualitative differences in skin lipid composition. Stratum corneum lipids from different regions of human skin have been characterized. This type of investigation is now being applied to the study of inherited disorders of keratinization (formation of the scaly protein that constitutes skin, hair, and nails). Specifically, recessive X-linked ichthyosis has been shown to be associated with an absence of the enzyme sulfatase. In the absence of sulfatase, large quantities of cholesterol sulfate accumulate in the skin and probably cause the abnormal scaling that is characteristic of ichthyosis. Thus, lipids have been shown to have a direct control over skin permeability and further research on the manipulation of lipid components may allow control of skin permeability in barrier dysfunction (as seen in burn victims) or correction of specific lipid abnormalities in disorders of keratinization.

Skin Biology—Biochemical Measurement of Skin Viability

Often in plastic and reconstructive surgery, flaps of skin must be raised and/or repositioned to fill in soft tissue defects or reshape body contours. Partially detaching skin flaps from their blood supply decreases the tissues' sources of glucose and oxygen, and in the absence of oxygen, metabolic by-products (primarily lactate) build to as much as five to seven times normal levels and compromise the chances of skin flap survival. In laboratory studies now being conducted, investigators have concluded that improved flap survival and enhanced regeneration of epithelium can be achieved following exposure to high oxygen pressures. These studies also showed that, 24 hours after restoration of blood flow, 60 percent of normal tissue glucose levels had returned in viable skin flaps, and lactate concentrations had decreased to four times normal levels. The ratio of lactate to glucose concentrations correlated well with subsequent survival of the skin flap in these experiments and may be useful in the future as a biochemical indicator of tissue viability.

Research Opportunities

Pathogenetic Mechanisms in Collagen-Induced Arthritis

Significant new information can be provided on the pathogenetic mechanisms of rheumatoid arthritis through continued investigations of an important experimental model. With administration of native type II collagen, arthritis can be induced in rats; further work with this model will determine the immunologic mechanisms involved in its pathogenesis and assess the roles of T-cell and B-cell responses to collagen. Investigators hope to determine whether immune responses to collagen are required to produce arthritis and whether T-cell responses to native and denatured type II collagen are genetically determined in rats as they appear to be in man and mice. Additional studies in this system will attempt to determine the sequence of pathologic events in collagen-induced arthritis, the role of neuroendocrine and stress factors in its control, the cellular responses to other collagen types, the presence of rheumatoid factors, and the timing of immune system sensitivity relative to the onset of collagen-induced arthritis.

Self-Association of Immunoglobulin Molecules

There are continuing needs to explore links between rheumatoid arthritis and one or more defects in immune response mechanisms. Much remains to be learned about various immunoglobulins (complexes made up largely of immune antibodies) by measuring the physical characteristics and biological activity of these complexes. A specific and sensitive assay method has recently been developed for performing these detailed laboratory analyses. Moreover, researchers have discovered a self-association (or self-assembly) phenomenon in certain immunoglobulins, leading to formation of immune complexes that contain only antibody molecules (instead of aggregates of antigen-antibody molecules). Future work will focus on finding determinants of the self-association process which, if found frequently in rheumatoid arthritis patients, may identify an important element that maintains inflammation in joint membranes.

New Anti-Inflammatory Steroids

Scientists are now studying a new class of steroid drugs believed to have significantly fewer systemic side effects while retaining virtually full anti-inflammatory power. This class of steroids was produced through chemical modification of a synthetic

steroid—prednisolone. The modified steroids are fully active when applied to the skin (topical application), but they are quickly excreted after absorption, and supporting data show that they compare favorably with prednisolone in anti-inflammatory activity while exhibiting appreciably fewer side effects. Major objectives of future work in this area will be to evaluate the anti-inflammatory activity of a variety of related steroids and to determine differences in anti-inflammatory potencies. Experiments will also be performed to identify any undesirable systemic side effects.

Immune Regulation in Immunodeficiency and Connective Tissue Diseases

There are ongoing studies of abnormalities of immune regulation and the types of immune system cells and factors that may contribute to them, particularly in patients with immune deficiencies, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue diseases, and chronic active liver disease. Active cells of the immune system comprise various classes of lymphocytes (T cells and B cells) derived from organs including the thymus, lymph nodes, spleen, and tonsils. Investigators are examining subsets of these classes of cells (such as helper T cells and suppressor T cells) and alterations in their function, in addition to the effects of thymic hormones, in patients with immune deficiency and connective tissue disorders. New observations gained from these studies may have application in clinical diagnosis and treatment of patients with these diseases.

Cell Nucleus Antigens in Connective Tissue Diseases

NIADDK researchers are continuing their attempts to determine the structure, function, and immunologic properties of antigen molecules in cell nuclei that are the targets of autoimmune antibodies in connective tissue diseases. Two of these antigens are currently being examined—nuclear RNA-protein complex and chromosomal protein Scl-70. Antibodies to these antigens have been found in patients with mixed connective tissue disease and scleroderma. The central core of these antigens is composed of protein and RNA, but the function of the RNA remains unknown. In continuing studies, the core of these antigens will be analyzed and compared to other classes of nuclear RNA to determine similarities and differences. Scl-70, a protein associated with scleroderma, has been identified and isolated. In future studies, researchers will attempt to gain preliminary information on the molecular structure of Scl-70 and identify its important antigenic features. Investigators will also try to identify substances with which Scl-70 reacts chemically and the subclasses of immunoglobulins that constitute the anti-Scl-70 antibodies in the immune reactions common in these connective tissue diseases.

Etiology of Osteoarthritis

While several theories on the etiology of osteoarthritis have been proposed, there is not yet a clear understanding of the pathogenesis of the disease. In osteoarthritis, the distribution and shape of collagen fibrils in cartilage are significantly altered. A crucial problem appears to be the poor ability of cartilage to repair itself. One possible explanation of this defect is that fibrin (protein formed during clotting) does not appear to adhere to cartilage cells because of a shielding effect of cartilage proteoglycans (carbohydrate-containing proteins).

In an animal model of cartilage defect repair, it has been shown that, during repair processes in osteoarthritis, type I cartilage is formed instead of the type II cartilage produced in normal joints. Investigations such as these on osteoarthritis and cartilage repair can be enhanced in the future through the use of recent improvements in tissue culture technology.

Treatment of Metabolic Bone Disorders

Greater knowledge of the basic mechanisms that regulate bone metabolism has led to improved therapy in metabolic bone diseases such as osteoporosis, Paget's disease, and several osteodystrophies. Basic research on resorption, formation, and the effects of hormones in normal bone turnover led to the finding that fluoride, in combination with calcium and estrogen supplementation, may be an effective therapy in the treatment of osteoporosis. Furthermore, such studies have shown that calcitonin and diphosphonates greatly alleviate the pain and misshapen bones that result from Paget's disease. Metabolic studies on the role of vitamin D in bone formation have also led to the isolation of new metabolites which, in combination with other agents such as phosphate, are being tested in the treatment of various types of osteodystrophy. Building on the knowledge gained from past investigations of basic regulatory mechanisms in normal bone, researchers will be able to pursue new studies, seeking better therapies for bone diseases resulting from altered metabolism.

Improvements in Artificial Joint Replacement

Total joint replacement means replacing damaged joint components with metal and plastic devices which are anchored to surrounding bone by cement; successful results are obtained in a very high percentage of patients. Some problems remain to be solved, however, particularly with regard to long-term use of prosthetic devices. Failure of total joint replacement can usually be traced to postoperative complications, such as deep infection or thromboembolism (blood vessel obstruction), or to mechanical failure, such as loosening of the device from the surrounding bone. While improved bone cement or cementing techniques may alleviate somewhat the problem of loosening, a more permanent attachment permitting ingrowth of bone into the prosthesis may prove more effective. Researchers are now experimenting with porous coatings or special surface finishing that can be applied to existing metallic implants to allow bone ingrowth and strengthen the bond between the bone and the implant. Other investigators are pursuing studies to determine the cause and progression of deep infection and thromboembolitic complications as well. Continued research directed to overcoming these problems, and utilizing recent advances in areas such as gait analysis to evaluate the effects of treatment, will help to ensure maximum functional capacity of artificial joints for use over longer periods of time.

Bone and Cartilage Allotransplantation

Allotransplantation of bone and cartilage is most frequently used in limb-sparing operations for tumors. After removal of a tumor, the resulting bone and cartilage defect is often too large to be replaced by a graft from another site in the same patient. However, the missing bone and joint surfaces can usually be replaced with an allograft from a donor cadaver. Present methods of allograft preservation and immunologic protection allow successful transplantation in most cases, but further research is needed to understand cases of host reaction to the transplanted tissue. In addition, more studies of freezing, thawing, and chemical preservation of tissue are required. A better understanding of immune phenomena in bone and cartilage, improved techniques for handling donor tissue, and advances in microvascular surgical technique will have important clinical applications in the future, not only for reconstruction of limbs, but also for transplantation in growing children with injured or diseased bones and joints.

Control of Bone Mineralization

There are opposing theories about the precise mechanisms that initiate or control bone mineralization—the process by which calcium and phosphate are deposited in cartilage to create bone. Recent investigations have revealed that a chemical substance—glutamic phosphate—is present in all mineralized bone collagen but absent from unmineralized collagen and, thus, may serve as an initiator of mineralization processes. Additionally, preliminary studies show that isolated proteins (such as osteocalcin and osteonectin) in the soft matrix of developing bone may serve as controlling factors in the binding of minerals to the matrix. With the availability of sophisticated laboratory analytical techniques, such as nuclear magnetic resonance, electron microscope element probes, and radial distribution X-ray diffraction, factors that may play a role in the initiation or control of mineralization should be explored further to improve our understanding of bone changes in remodeling and disease.

Regulation of Bone Metabolism

Studies in recent years have led to major improvements in isolating bone cells and bone cell culture systems for the laboratory study of bone metabolism and its regulation. Furthermore, these studies have identified components that may serve as coupling agents, balancing bone resorption and new bone formation at the cellular level. These systems are free of serum and other substances that have complicated the interpretation of previous research results and will permit future studies of local bone growth and regulation in addition to direct examinations of the influence of hormones such as calcitonin, parathyroid hormone, and 1,25 dihydroxyvitamin D_3 on regulatory processes.

Mechanical Stresses and Bone Remodeling

Classically, it has been thought that normal and abnormal bone remodeling (resorption and formation) permit the development of bone structure best suited to resist whatever forces may be acting upon the skeleton. In ongoing studies, however, investigators are seeking more comprehensive theories to explain observed bone growth patterns. A recently developed research model of bone enables scientists to apply various loads to bone to examine the effects of different forces and levels of stress on remodeling. In preliminary studies, it has been shown that low levels of stress are associated with bone resorption, while moderate stress leads to bone formation. At high stress levels, resorption predominates again. Using such models, researchers will be able to modify existing theories of bone remodeling in response to mechanical stresses and to examine the effects of stress during growth.

Enzymes in the Development of Skin Diseases

Several laboratories have demonstrated that psoriatic tissue has an increased content of proteinases (protein-destroying enzymes). A proteinase that results in attraction (chemotaxis) of scavenging white blood cells (PMN's) when injected into laboratory animals has now been purified from human skin. Psoriatic lesions have been found to contain significantly more of this chemotactic proteinase than does uninvolved tissue. Proteinases may be directly involved in the cellular proliferation of psoriatic skin, and if their role can be further clarified, proteinase inhibitors could become a new class of drugs for the treatment of psoriasis.

New Therapies for Psoriasis

Increased proliferation of skin cells and incomplete cellular differentiation are hallmarks of the development of psoriasis. Prior research has shown that psoriatic skin contains decreased levels of cyclic AMP, a biochemical messenger within cells that is normally associated with cellular differentiation. By manipulating the concentration of a cyclic AMP regulatory molecule, researchers may produce new agents for the treatment of psoriasis that are safer than classical antimetabolite drugs. Since the rate of cellular proliferation in psoriatic skin cells often exceeds that of skin cancer, scientists are also attempting to inhibit the synthesis of epidermal DNA with new formulations of topical methotrexate—a drug that has been used internally in the treatment of some cancers. Prior formulations were not sufficiently effective because the drug could not penetrate the skin adequately to inhibit DNA synthesis. In the future, NIADDK grantees will attempt to discover new methods for improving methotrexate penetration. Scientists working in the field of topical chemotherapy will be convened to discuss further development of effective and safe antipsoriasis agents.

New Directions for Epidermolysis Bullosa Research

Diphenylhydantoin, an anticonvulsant drug, has been reported to reduce significantly the blistering of skin and mucous membranes characteristic of recessive dystrophic epidermolysis bullosa. Although the mechanism of action of the drug in this disease remains unclear, there is evidence suggesting that it blocks the production or release of collagenase, an enzyme that breaks down the protein framework of skin. Abnormally high levels of the enzyme have been found in epidermolysis bullosa blisters, reinforcing previous data indicating that the disorder may be attributable to the excessive synthesis and accumulation of collagenase. In response to evolving scientific advances in this area and increased research interest in the disease since last year's state-of-the-art workshop, a program announcement has been issued to stimulate further work in this promising field.

Program Plans

Rheumatic Disease Research

Prior research has indicated that immunogenetic factors or infectious agents may play an important role in the development and progression of diseases such as rheumatoid arthritis, arthritis in children, and ankylosing spondylitis. In rheumatoid arthritis, evidence indicates that immunologic injury may be a factor in joint inflammation. Though great progress has been made in these types of investigations, the roles for cell-mediated immunity and the types of inflammation that occur following immunologic events need to be defined in greater detail. The antigen or antigens involved in these events must be identified and, since the disease is chronic, indications are that exposure to the antigens must be continuous or repeated.

Progress toward understanding the immunological expression of rheumatoid arthritis may be gained from studies comparing the responses of children with arthritis to those of arthritic adults. Many times, children have not been exposed to as many sources of external antigens as adults, their hormonal environment differs, their response to viral illness is different, and, because they are still growing and developing, the destructive effects of inflammation in their joints are different. Continued emphasis on immunologic studies in rheumatoid arthritis and studies comparing the various types of disease expression will yield significant insight regarding its cause and progression.

Increased attention must also be given to posttraumatic arthritis and degenerative joint disease (osteoarthritis). Experimental animal models of osteoarthritic joint injury must be used to identify the primary mechanical and biochemical factors involved in this type of joint damage in addition to identifying the pharmacologic and other aspects of joint repair and rehabilitative treatment.

Rheumatic Disease Workshops

Numerous advances have been made by rheumatologists in the areas of immunogenetics, immune complexes, and immunological expression of rheumatic disease in general. Understanding

of the precise pathogenetic roles of immunological events in these disorders is still incomplete, however. Workshops are needed to bring together people working on various aspects of these phenomena and to relate what is known in basic immunology to the pathophysiology of specific rheumatic diseases. The exchange of ideas will stimulate, promote, and direct future research. Two workshops, one on immunogenetics and the other on immune complexes, are planned for the near future.

Infectious and Immunologic Factors in Rheumatic Disease

To exploit research leads emerging from advances in rheumatic disease and other chronic diseases, high priority should be given to the search for agents involved in the etiology of infectious arthritis, including viruses and other slow-acting microorganisms. Since immunologic factors play a major role in joint inflammation in rheumatoid arthritis, and in kidney and blood vessel inflammation in SLE, methods are needed for selective and specific suppression of immune responses that mediate these conditions but do not destroy the body's defense against infections. The mediators of inflammation and predisposing genetic factors involved in inflammatory rheumatic diseases require specific investigative attention to advance our knowledge of pathogenetic mechanisms.

Systemic Connective Tissue Diseases

Certain systemic rheumatic diseases, such as SLE, polymyositis, scleroderma, and polyarteritis nodosa, may have in common an inflammatory reaction to abnormal immune responses. In each of these diseases, important leads to etiology have been developed, and research activity must now be intensified to identify viruses or other microorganisms from body fluids and tissues of affected patients and to examine antigens and immune complexes that may also be involved. Populations at high risk of developing these diseases should be studied to determine what genetic factors play a role in the development of the inflammatory reaction. More effective forms of therapy and means for evaluating new therapeutic methods should also be pursued.

Studies in Bone Metabolism and Disease

Newly discovered components in bone, markers of bone turnover, and advances in molecular genetics present great opportunities for future research in metabolic and inherited connective tissue disorders. Previous research has led to improvements in tissue culture techniques as well as to studies of new therapeutic approaches to several bone disorders. Outgrowths of these basic studies have been the new clinical trial of fluoride therapy in osteoporosis and the NIADDK-sponsored Conference on Heritable Connective Tissue Disorders. In an effort to increase research attention to important diseases such as osteoporosis and "brittle bone" conditions (e.g., osteogenesis imperfecta), the clinical trial will be monitored closely for results warranting additional studies. Proceedings of the recent conference will be published and distributed to investigators to stimulate research in these areas.

Uses for Electrical Stimulation in Bone Diseases

The dramatic success achieved with direct current and electromagnetic stimulation of bone growth in nonunion fractures, in addition to Food and Drug Administration approval of these devices and techniques, shows promise for application of the therapy to other bone disorders. Furthermore, a recently developed method for applying electrical stimulation, capacitive coupling, may foster new or improved methods of utilization. The basic mechanisms of action of electrical stimulation in promoting bone growth are not known, and further basic studies and additional clinical trials are planned to gain this knowledge and to determine which other bone disorders may be responsive to the treatment.

Improved Artificial Joints

The number of surgical procedures for the placement or revision of artificial joints is increasing rapidly. While the early success rate is high, there is a strong need to improve long-term prognosis. Important areas requiring further research include joint surface replacements, bone ingrowth technology, durable biomaterials, biocompatibility, and reducing the risk of infection. These topics and others were discussed at the NIH Consensus Development Conference on Total Hip Joint Replacement, held in the spring of 1982. In addition to defining the best rationale for when and how to perform such operations, the conference produced suggestions for the future directions of research. It is hoped that recommendations from this conference, a previously held conference on implant retrieval and analysis, and the results of a workshop on implant failure and interface phenomena (in the fall of 1982) will stimulate research in these vital areas and lead to improvements in artificial joint utilization.

Pathogenesis of Low Back Pain

Low back pain is a major source of disability for adults of all ages, yet the etiology of most back pain is unknown. In 1980, a

major workshop sponsored by NIADDK gathered scientists from many research disciplines to discuss the state of the art in back pain research and to explore future opportunities. The results of this workshop were published and widely distributed to concerned investigators. In light of the interest generated by the workshop and a program announcement planned by the Institute, it is hoped that new research projects in this field and advances in knowledge can be stimulated.

Exercise Pathophysiology and Sports Medicine

Increasing numbers of Americans are becoming active in sports and fitness programs, yet few scientific investigations have been initiated to study the positive and negative influences of sports activities on the musculoskeletal system. Moreover, very few studies are addressing mechanisms of injury and repair. Since advances have been made in recent years in determining the properties and function of ligament and muscle in response to training, NIADDK, in collaboration with the American Academy of Orthopaedic Surgery, sponsored a workshop in 1982 dealing with sports activities and injury. Summaries of the workshop proceedings are planned for publication, and research projects applying current knowledge to the area of sports medicine will be encouraged.

General Initiatives in Musculoskeletal Diseases

A full-scale evaluation of the Institute's musculoskeletal diseases program is currently under way. Its purposes are to examine the scientific and administrative goals of the program in the past several years, describe those areas requiring further research, and produce recommendations on the future goals of the program and ways to stimulate needed research. Leading scientists and administrators will examine these issues and, on the basis of their recommendations, program announcements, workshops, interdisciplinary communication, and new research and clinical investigator applications will be encouraged in specified areas of investigation.

Promising Chemotherapeutic Drugs for Psoriasis Treatment

Several years ago, in a national cooperative study, 30 drugs were evaluated for effectiveness in the treatment of psoriasis. The study utilized a double-blind screening program to determine clinical effectiveness of systemic drugs in topical applications. Seven of the drugs tested produced clinical improvement and evidence of clearing without significant toxicity. Systemic administration of such cytotoxic drugs is likely to produce side effects in other organs of the body as well as the skin, so the direct application of these agents to skin lesions is likely to improve the safety of their use. NIADDK plans to foster additional studies to evaluate these promising chemotherapeutic agents further.

Followup Study of PUVA-Treated Patients

Scientists supported by NIADDK are currently in the fourth year of a followup study of 1,300 patients who received PUVA therapy for psoriasis during early testing of the treatment. In the past year, research centers taking part in a cooperative study reported that psoriasis patients previously treated with X-rays are at greater risk of developing squamous cell carcinoma after PUVA therapy. Extended monitoring of these patients is needed to determine more precisely the extent of possible neoplastic alterations, and a request for proposals is to be issued to support such a study.

Second NIH Workshop on Vitiligo

Vitiligo is a disorder of pigmentation in which unexplained destruction of melanocytes (pigment-producing cells) results in striking, irregular, smooth white patches on the skin. The social and psychological handicaps resulting from the disorder are particularly devastating for dark-skinned individuals. In 1978, a workshop on vitiligo was held to review the state of the art in melanocyte-related diseases and new research accomplishments. After the workshop, a consortium grant was awarded to Yale University and five other institutions to study vitiligo. A second conference is tentatively scheduled for 1983 to review advances in the intervening years and to determine future research needs.

Monoclonal Antibodies to Epidermal Antigens

One of the exciting new areas in skin disease research is the recently acquired ability to produce specific monoclonal antibodies to human epithelial (skin) cells. Using this new technique, investigators would be able to study the formation of monoclonal antibodies to human epithelial structural proteins—keratins—and to epithelial cell membranes. Alterations in antigenicity of keratin and cell surface components in genetic skin disorders such as ichthyosis, Darier's disease, psoriasis, and pemphigus could then be examined. Plans for issuing a program announcement to encourage and expand activity in this field are now being made.

Workshop on Heritable Skin Disorders

The ability to diagnose heritable disease during early fetal life has made considerable progress in recent years. Three percent of the newborn population have some type of birth defect considered to be of primary genetic origin. Heritable skin disorders include cutaneous photosensitivity, telangiectasia, hyperpigmentation, atrophy, hyperkeratosis, disturbance of growth, neurological dysfunction, premature senility, and an increased incidence of malignancy. In order to capitalize on the advances made in prenatal diagnosis, a state-of-the-art workshop on birth defects and genetic disorders of the skin is planned for 1983.

Special Programs

Multipurpose Arthritis Centers

In 1974, the National Arthritis Act provided authority for the establishment of Multipurpose Arthritis Centers throughout the country. Each MAC has three components—research, professional and patient education, and community demonstration projects. Center funds are used to support pilot and feasibility studies in rheumatology-related areas that utilize innovative interdisciplinary scientific approaches to arthritis research problems. These projects supplement the traditional investigator-initiated research grants of individual workers associated with the center and may later form the basis of regular research grant applications.

Several MAC's also conduct clinical trials to determine the safety and efficacy of new therapies for the treatment of arthritis. Because of the large number of arthritis patients available for study at the MAC's, they provide an ideal setting for closely monitored evaluation of new treatment regimens before they are disseminated and applied among the general public.

Another important MAC function is the provision of educational services to health care providers and laymen. Through computer- and telephone-based systems, physicians who are not rheumatologists can obtain clinical consultations on arthritis problems in local areas where the necessary expertise is not available. In addition to providing medical student training in the centers, the programs seek to improve rheumatic disease care given by primary care practitioners. Selected centers also sponsor special programs, community projects, and model demonstrations of care in locations outside the center to increase public awareness of arthritis problems and to provide high-quality care. The coordinated approach to arthritis research and clinical care exemplified by the MAC program assures that the highest possible level of care is made available in a timely and effective manner for the benefit of the greatest number of people.

The annual evaluation report on the MAC program and center activities is presented in chapter VI.

Arthritis Information Clearinghouse

In response to recommendations by the National Commission on Arthritis and Related Musculoskeletal Diseases, NIADDK established the Arthritis Information Clearinghouse in 1978. The clearinghouse collects, screens, stores, and disseminates information on arthritis, serving as a nationwide broker of this information for health care providers, medical educators, patients, the families of patients, and the public. The clearinghouse maintains almost 3,000 records of print and audiovisual materials, responds to over 600 information requests each month, and distributes nearly 100,000 pieces of literature every year.

In addition to providing materials-related services, the clearinghouse staff cooperates with and provides technical assistance to the MAC's in conducting needs assessments, identifying gaps in existing materials or services, and designing program and material evaluations. Since many of the Multipurpose Arthritis Centers are emphasizing team care and developing resources to implement education programs, the clearinghouse catalogs MAC efforts in this area and incorporates that information into its data base. The clearinghouse has similar cooperative arrangements with the Arthritis Foundation, the American Pharmaceutical Association, and other government clearinghouses to ensure the appropriate and effective utilization of arthritis information resources.

Future plans for the clearinghouse include further development of patient education materials in recognized gap areas, and an assessment of clearinghouse products and services, by experts outside the Institute, to determine their effectiveness and to improve their utility for a wide range of user audiences.

Arthritis Epidemiology and Data Systems

The Arthritis Epidemiology and Data Systems program serves as the administrative focus of Institute efforts to encourage and support epidemiologic research in arthritis and related musculoskeletal diseases, since this research may provide vital leads to the causative factors in several rheumatic diseases. Epidemiologic studies of rheumatic diseases are particularly compelling

because results of other biomedical research suggest that susceptibility to several of these diseases may be linked to measurable genetic and environmental characteristics. Such studies attempt to assess the community burden that these diseases impose; to investigate risk factors for their development as well as their etiology, mode of transmission, and natural history; to develop bases for programs of prevention through risk factor modification; and to assess the effectiveness of new preventive and therapeutic regimens through clinical trials.

NIADDK support of epidemiologic research studies on arthritis and related diseases in recent years has led to significant advances in knowledge. Among these advances are:

- The report of a strong association between a genetically determined human leukocyte antigen (HLA-DRw4) and a predisposition to the development of rheumatoid arthritis in Caucasian, black, and Oriental racial groups;
- The discovery of significantly increased frequencies of specific genetic markers in patients with scleroderma, Lyme arthritis, and Behcet's syndrome;
- The demonstration, by immunogenetic analyses, that rheumatoid arthritis, ankylosing spondylitis, and other rheumatic diseases may coexist in individuals with dual HLA-associated predispositions; and
- The measurement of age- and sex-specific incidence rates for hip fracture in a U.S. population-based study which indicated that 113,000 women and 34,000 men over age 50 will suffer hip fractures each year at a cost of approximately $1 billion to the Nation's economy.

It has been generally held that there is an important interplay between biomedical research and epidemiology. Building on the advances of recent years in these combined areas, important new research opportunities exist, including:

- Population-based studies to determine the association of certain musculoskeletal diseases with the subsequent development of malignancy;
- Further study of males with SLE to increase understanding of the roles of sex hormones in disease predisposition and progression;
- More studies to determine specific factors influencing the decrease of rheumatoid arthritis incidence rates in certain groups of women; and
- Investigations of genetic, environmental, racial/ethnic, age, and sex determinants of disease expression in patients with ankylosing spondylitis and Reiter's syndrome.

In 1980, NIADDK supported the Arthritis Epidemiology Conference to review the state of the art and identify new research opportunities and directions. Using recommendations from the conferees, NIADDK plans to initiate an ongoing arthritis epidemiology working group within the next year. The working group will provide a forum for further discussion of research advances and formulation of specific approaches to the study of arthritis epidemiology in the future. Further, the published proceedings of the working group meetings will be used to increase interest and to attract more researchers to epidemiologic studies of rheumatic diseases.

Courtesy of Juvenile Diabetes Foundation International

UNEP/WHO

Ongoing NIADDK-supported studies suggest that genetically determined immunologic factors may play a role in the etiology of insulin-dependent ("juvenile") diabetes and that, potentially, this form of the disease might be detected and prevented in the future. Investigations are also being directed at development of new and better methods to control noninsulin-dependent ("maturity-onset") diabetes.

Diabetes, Endocrinology, and Metabolic Diseases

Overview

The human body is composed of a complex, interrelated network of organs that rely, to a certain degree, on products from other components of the body to function normally. When a substance that is required for regulation of an organ or system is inhibited in some way, the resulting imbalance may have far-reaching effects on other related organ systems, to the detriment of vital life processes. It is the responsibility of the Division of Diabetes, Endocrinology, and Metabolic Diseases to direct the NIADDK programs related to the many imbalance-associated disorders, such as diabetes and other endocrine disorders, cystic fibrosis, and various other inborn and acquired errors of metabolism.

Diabetes mellitus, one of the most important research areas supported by NIADDK, is characterized by a deficiency in insulin production or impairment of insulin action. While certain aspects of the disease can be controlled, diabetes has numerous detrimental effects on body systems. The possible complications of diabetes—such as heart, kidney, and blood vessel disease, nervous system impairment, and blindness—are the major source of morbidity and mortality associated with the disease. The long-range objective of NIADDK-supported research in diabetes is to elucidate the means by which the disease and its potentially life-threatening complications can be prevented, better controlled, or cured.

The division also supports investigations of other endocrine disorders, such as thyroid diseases, adrenal and pituitary abnormalities, and growth disorders. Endocrine diseases are among the most common in medicine, and they have an enormous impact on individual well-being and the costs of medical care. Endocrine factors also play an important role in diseases that are attributed primarily to other organ systems, for example, atherosclerosis, cardiovascular disorders, cancer, and psychiatric disorders. For these reasons, NIADDK supports basic and clinical research on the normal and abnormal functioning of the endocrine glands; the structure, function, and mechanism of action of the hormones produced; the effects of the hormones on various processes in the body; and the factors that relate to or modify the effects of the endocrine system.

Since the effects of hormones are manifested through metabolic events within the cell, and because the endocrine system exerts the main regulatory influence on overall metabolism, the disciplines of endocrinology and metabolism have been intertwined, and with them the field of genetically determined metabolic diseases. An important example of an inherited metabolic disorder with devastating effect on its patients is cystic fibrosis—a disease to which NIADDK has traditionally devoted considerable research support.

Although individual genetic disorders are not common, *in toto* they have a profound public health impact. They account for approximately one-third of all infant deaths in the United States, and approximately 30 to 40 percent of all admissions to children's hospitals are attributable to such disorders. In addition, more than one-third of patients in state hospitals for the mentally retarded have genetically determined disorders, incurring costs for care in excess of $1 billion annually.

NIADDK's mission in the area of metabolic diseases is to acquire an understanding of the etiology, pathogenesis, and treatment of acquired or inborn errors of metabolism through support of research into enzymatic mechanisms and their regulation, biological transport, and membrane structure.

Highlights of Research Advances

The following sections describe recent advances achieved in NIADDK research programs addressing diabetes, endocrinology, and metabolic diseases.

- Institution of active diabetes therapy (insulin and antidiabetic drugs or special diets) and the consequent improvement of previously abnormally high blood glucose levels have been shown to improve motor nerve function in patients with noninsulin-dependent diabetes, suggesting that long-term normalization is beneficial for some types of impaired nerve function in certain diabetes patients.
- Studies in which blood glucose levels were effectively controlled demonstrated that strict metabolic control of pregnant diabetic mothers can normalize fetal insulin secretion and infant birth weight and thereby prevent at least some of the infant morbidity and mortality associated with diabetic pregnancies.
- In two separate studies utilizing "open-loop" insulin pumps to bring about improved blood glucose level control, (1) the blood level of somatomedins (growth-promoting factors) in young diabetic patients was raised, and monthly growth rates increased; and (2) blood fat levels and "harmful" types of cholesterol were reduced, while blood levels of certain "protective" types of cholesterol increased.
- Treatment with human growth hormone used for children with normal-variant short stature (height below the third percentile and no apparent organic cause for failure to grow normally) succeeded, in some cases, in increasing their growth rate and raising blood levels of somatomedin C.
- NIADDK grantees have successfully isolated corticotropin releasing factor (CRF), a neurohormone that is an intermediary in the body's production of adrenal steroids. It has been characterized and synthesized, and its synthetic form has been shown to act almost identically to the natural substance.
- A new drug—WR2721—originally developed for other purposes, may be helpful in combating the accumulation of abnormally viscous mucus in the lungs of patients with cystic fibrosis. Definitive establishment of its efficacy awaits more extensive clinical testing.

Diabetes Etiology—Correlation with Obesity, Genetics

A longitudinal study of Pima Indians, begun in 1962, has now produced sufficient data for evaluation of the relative contributions of obesity and genetics to the incidence of noninsulin-dependent diabetes. Previously, such a correlation could be made only with data on prevalence (the number of affected persons at a given time), and researchers found little relationship between diabetes prevalence and concurrent obesity. With further data from the Pima study, though, Institute investigators have demonstrated that the incidence rate of noninsulin-dependent diabetes (the number of new cases arising in a given time) is strongly and directly related to obesity, thus strengthening the hypothesis that obesity is a contributing cause of diabetes. The genetic risk of developing diabetes has also been quantified among the Indians in the current study: Those with one diabetic parent developed the disease 2.3 times as often as those with no diabetic parent, while the incidence of the disease was nearly fourfold for Pimas whose parents were both diabetic. This and other such studies of defined populations aid NIADDK in its efforts to substantiate the suspected risk factors in diabetes and direct research to the causes most amenable to intervention.

Insulin Secretion—Cytotoxic Action Impairs Process

Researchers have made considerable progress in clarifying the specific molecular events and cellular processes by which specialized cells secrete hormones, and currently a number of NIADDK scientists are looking at the reasons for the impairment of insulin secretion that is common in diabetes. It has been proposed that specific circulating antibodies found in many newly diagnosed diabetes patients may have a toxic effect on the insulin-secreting cells of the pancreas (the beta cells), thereby preventing insulin release. To test this hypothesis, investigators observed the reaction of rat pancreatic islet cells exposed to islet cell surface antibodies. The release of radioactive chromium from labeled cells, used as an indicator of cell membrane permeability, was unaffected by antibodies alone but increased dramatically when cells were exposed to both antibodies and complement (a complex series of proteins in normal serum). The complement-dependent cytotoxic reaction appeared to cause cell leakage but not complete destruction. It is anticipated that the technique used for the rat cells can be further applied to test whether antibodies in serum from diabetic patients will affect human beta cells in the same way. A better understanding of this and related processes could lead to the development of procedures to prevent beta cell destruction and consequent impaired insulin secretion.

Hormone Action—Insulin Activity in the Central Nervous System

A considerable amount of research in the last 20 years has contributed to our understanding of the central nervous system's role in the regulation of carbohydrate metabolism, especially CNS influences on secretion of the pancreatic hormones insulin and glucagon. The autonomic nervous system is also directly implicated in carbohydrate metabolism by the liver. Insulin receptors have been identified in the CNS, and in recent studies by NIADDK investigators, minute quantities of insulin were injected into selected areas of the CNS in rats; affected and unaffected areas were differentiated by measured changes in blood glucose levels. Results of the study suggest that there are at least two components to the insulin-sensitive CNS glucoregulator. Whether the observed sensitivity to insulin serves to provide rapid adjustment in the blood glucose level or whether it provides long-term influence on feeding behavior—or both—remains to be determined. Further research to elucidate the role of insulin action in the brain could lead to an understanding of the relationship between obesity and the noninsulin-dependent form of diabetes.

Diabetes Complications

Treatment Related to Nerve Changes

Diffuse impairment of nerve function (polyneuropathy) is one of the many possible neurological complications of diabetes. A group of NIADDK grantees, having previously described a relationship between untreated hyperglycemia and abnormal motor nerve function, recently undertook a study to determine whether institution of diabetes therapy and consequent improvement of blood glucose levels would improve nerve function. The study group was composed of men with noninsulin-dependent diabetes who had not been under treatment and who demonstrated abnormalities of both motor nerves and sensory nerves. Research clinicians evaluated nerve conduction in the men before and after their glucose control therapy—insulin injections, oral drugs, or special diet—and compared those measurements to blood sugar levels at intervals during the 12 months of treatment. It was determined that although motor nerve conduction improved significantly as blood sugar levels decreased during therapy, there was no improvement of sensory nerve conduction. These observations suggest that long-term normalization of blood sugar is beneficial for some types of impaired nerve function in people with noninsulin-dependent diabetes. In addition, the study prompts questions that invite further study of the differences between motor and sensory nerve manifestations and the variant approaches necessary for their treatment.

Strict Diabetes Regimen During Pregnancy Improves Newborns' Status

Often, women whose diabetes is not adequately controlled during pregnancy give birth to abnormally large infants. The newborn's condition, which is known as macrosomia, may be associated with a variety of complications including respiratory distress syndrome, jaundice, low blood calcium, and congenital malformations. Investigators supported by NIADDK undertook a study to determine whether strict metabolic control of diabetic pregnancies would prevent fetal hyperinsulinism (excessive insulin secretion in the fetal pancreas, stimulated by high blood levels of glucose in the mother) and reduce the incidence of abnormalities in the newborns.

The study involved comparison of infants born to insulin-treated diabetic mothers with a similar-size group born to women who had received neither insulin therapy nor intensive blood sugar control for their gestational diabetes. Control subjects were infants delivered of healthy mothers by elective cesarean section. In the treated group, the newborns demonstrated more normal (lower) average birth weight, insulin secretion, and insulin-binding values than did the offspring of the untreated mothers. Further, the latter group of infants had greater numbers of insulin receptor sites than those detected in the treated and control groups. This confirms and extends the findings, reported by other investigators, that strict metabolic control of the pregnant diabetic mother can normalize fetal insulin secretion and infant birth weight and hence prevent at least some of the increased infant morbidity and mortality associated with diabetic pregnancies.

Another group of investigators, seeking better methods of maintaining metabolic control during pregnancy, assessed the efficacy and feasibility of using a portable insulin infusion pump, which introduces adjustable quantities of insulin to the body throughout the day. The women who participated in the study experienced better glucose control (with fewer fluctuations) than they had achieved with standard insulin injections, and their infants, all of normal birth weight, exhibited none of the complications commonly seen in newborns of diabetic mothers. Results of the small-scale study indicate that the portable pump system is a highly efficient way for pregnant women to manage their diabetes and improve their chances for delivering normal babies; but whether the system will prove superior to conventional insulin treatment—and more acceptable—in large groups of patients remains to be established.

Transplantation—Causes Behind Failure of Islet Transplants

The ability to replace destroyed or defective pancreatic islets (cell clusters that contain insulin-secreting beta cells) would be a great advance in the treatment of diabetes, but the use of transplantation in humans has been hindered by the body's tendency to reject grafted materials. Pancreatic islets have been successfully transplanted in inbred diabetic rats—with consequent control of their diabetes—and new techniques not only prolong survival of the grafted tissue, but also reduce the need for immunosuppressive agents, which can have seriously harmful side effects. Before such techniques can be evaluated in humans, however, it is necessary to achieve a better understanding of the mechanisms of immune rejection.

Recent NIADDK-supported studies with rats that had received successful transplants indicated that rejection of grafted tissue could be induced by injection of certain cells from the donor animal; in similar work with mice, a specific antigen (a substance that stimulates immune response and rejection) was identified and successfully combated for more than 6 months. Identification of additional antigens may make it possible to develop antibodies that will avert the body's rejection of transplanted cells, thus prolonging graft survival not only in pancreatic islets but in other types of tissues and organs as well.

In yet another transplantation study, an Institute grantee has presented evidence that it is an autoimmune process, rather than graft rejection, that compromises survival of pancreatic islet transplants. Using a strain of rats with spontaneously occurring diabetes and another group with induced diabetes, the researcher designed a series of experiments to differentiate the influence of graft rejection from that of autoimmunity. He was able to demonstrate that the loss of transplanted islets in the animals with spontaneous diabetes could be curbed by an induced tolerance to bone marrow cells from normal rats, which presumably protected the transplants from a destructive autoimmune process. This study sheds light on the causative mechanism in this particular type of naturally occurring, spontaneous diabetes in an animal—namely an autoimmune process that destroys insulin-secreting beta cells. Further studies with this animal model may provide insight regarding the etiology of insulin-dependent diabetes in man.

Insulin Delivery Systems—Portable Pump Therapy Shows Diverse Benefits

Although the ideal method of providing insulin to diabetic patients has yet to be developed, the new "open-loop" insulin pumps and companion blood glucose monitoring techniques appear to provide an improved method for delivering precise quantities of insulin as needed, without undue restriction of patients' activities. In separate clinical research efforts involving different aspects of using portable insulin infusion pumps, NIADDK-supported scientists have recently observed two distinct, noteworthy phenomena:

- In a study of diabetic patients (aged 13 to 29) receiving insulin by pump for 16 weeks, not only were plasma glucose levels brought under control for the entire study group, but the treatment also raised blood levels of certain growth-promoting factors (somatomedins) such that monthly growth rates of the young adolescents were doubled. These preliminary observations are of potential clinical significance since short stature is a well-documented characteristic of children with poorly controlled insulin-dependent diabetes.
- Another grantee demonstrated that long-term maintenance of near-normal glucose control with portable insulin pumps also served to reduce blood levels of fats and certain "harmful" types of cholesterol in adult men. Conversely, the patients' levels of a "protective" type of cholesterol rose significantly over the course of the study period. These observations indicate the possibility of ameliorating the increased risk of atherosclerosis that faces patients with insulin-dependent diabetes.

Although such studies suggest that a variety of potential benefits may be associated with the use of these new techniques for improving metabolic control, other preliminary reports also raise the possibility of associated risks. Until it is possible to assess these findings further, it is recommended that the use of portable insulin pumps be limited to research settings.

Diabetes Epidemiology—Large-Scale Studies Characterize Diabetic Populations

Since it appears that a number of pathogenic mechanisms may give rise to diabetes, it is important to gain more information both on the number of people affected and on prevalent characteristics in the population that might indicate predisposition to the disease. In major epidemiological studies, investigators measure and examine all of the factors relating to the disease state—genetic markers, susceptibility, environment, lifestyle, and socioeconomic status.

The study of a sample U.S. resident population will contribute to knowledge about diabetes incidence in the country as a whole; therefore, NIADDK has supported a group of investigators who established a patient registry covering a single county

in Pennsylvania from 1965 to the present. The research team has compiled data on all Allegheny County residents who were diagnosed with insulin-dependent diabetes before age 20, and the data through 1976 indicate, contrary to earlier hypotheses, that the annual incidence of insulin-dependent diabetes has not changed since 1965 and that incidence has no relationship to social class. The study reinforces the notion of genetic predisposition, since siblings of known diabetic patients demonstrate a higher prevalence of the disease than that for the remainder of the population. No difference between the incidence rates of males and females has been shown, but the rate in Caucasians is about 30 percent higher than the incidence among blacks.

In another epidemiological study, an Australian research team has uncovered the first genetic (chromosomal) locus to be associated with noninsulin-dependent diabetes, in Fijians descended from North Indian migrants. The group also found that the prevalence of the disease among urban Polynesians in Western Samoa is triple the prevalence for islanders in rural areas, implicating an environmental effect. A sociocultural influence is likewise suggested in the data, since diabetes is rare in both Polynesian and Micronesian populations that have maintained a traditional lifestyle.

Hormone Production and Effects

Many Hormones Not Limited to Single Cell Type

In the past, each hormonal peptide was traditionally considered a unique product of a single cell type which, in turn, was localized in distribution to a specialized region of the body known as an endocrine gland. Recent research by intramural scientists and grantees has shown that these conventional boundaries may be too limited. For some hormones, the particular type of cell that produces them was also found outside of endocrine glands. In addition, it has been found that cancers derived from nonendocrine tissues and diverse neurons can produce peptide hormones. Most recently, it has been demonstrated that *other* cell types (non-neural and nonmalignant) can synthesize certain peptide hormones. Insulin has been detected in the brain, the peripheral nerves, and in cultured cells of diverse origin. ACTH (adrenocorticotrophic hormone) has been found not only in its conventional site—the pituitary gland—but also in the brain, the normal placenta, and other tissues. These recent findings can now explain many diverse phenomena in man and other vertebrate animals, including overlaps of the endocrine and nervous systems, of hormones and tissue factors, of normal and ectopic hormone production, and of endocrine and exocrine mechanisms.

Recombinant DNA Techniques Aid Growth Hormone Supply

Growth hormone, which is produced by the pituitary gland, is necessary for normal growth in children. Some children lack this hormone and do not grow unless they receive injections of human growth hormone. The only source of the hormone to date has been human pituitary glands collected at autopsy, from which the growth hormone has been extracted. With the advent of recombinant DNA technology, however, the human gene for growth hormone has been isolated and inserted into bacteria which are now producing the hormone. Clinical trials on adults indicate that the artificial hormone has no detectable side effects.

Clinical trials are under way on children lacking natural growth hormone to establish that the bacterially produced hormone will indeed induce growth in the same manner as the hormone extracted from human pituitaries. If these trials establish the efficacy of "bacterial" human growth hormone, more hormone will be available both for therapeutic purposes and for research. While human growth hormone also affects processes other than growth, research on its other effects has been delayed because most of the hormone has been used in clinical research on short stature.

Growth Hormone Shows Unexpected Benefit

Among all children with short stature (defined by a height measurement below the third percentile), about 2 percent are deficient in the pituitary hormone that stimulates growth. A much larger group, 30 to 50 percent of short children, is described as having "normal-variant short stature," the criteria for which are current and projected adult height below the third percentile, birth weight of more than 2.5 kg (about 5.5 pounds), and no apparent organic causes for failure to grow normally. Since such children seem to have normal levels of growth hormone in their blood, they would not be expected to respond to administration of the growth hormone that is used successfully to treat hypopituitary dwarfism. In a recently reported study, however, an NIADDK-supported investigator found that for some types of normal-variant short stature, growth hormone, surprisingly, did increase the children's growth rate. Injection of growth hormone raised the blood level of somatomedin C, a substance that has both growth-promoting and insulin-like properties. One conclusion of the study is that the growth hormone present in the normal-variant children who improved was somehow inhibited in its biological activity; thus, the children profited from the addition of "normal" hormone. The study not only points up the potential to alleviate the problems of short stature; it also raises a number of questions regarding hormonal action and effects that could be resolved in future research efforts.

Studies on the Mechanism of Action of Thyroid Hormone

The mammalian thyroid gland produces three recognized hormones: thyroxine, triiodothyronine, and thyrocalcitonin. The physiologically active form of thyroid hormone is triiodothyronine (T_3). Though there have been many observations of the effects of too much or too little thyroid hormone in clinical conditions, a precise description of the physiologic role of T_3 is not yet available. To elucidate the mechanism of action of this unique hormone, scientists have been conducting investigations on the promotion of glucose degradation by T_3. These studies have focused on the interaction of T_3 with epinephrine and insulin and their effects on cellular uptake of 2-deoxyglucose (2-DG), an analog of glucose. These studies have shown that T_3, when administered alone in relatively large doses, stimulates the uptake of 2-DG at the plasma membrane of cells. When T_3 and epinephrine are administered together, they act synergistically to increase 2-DG uptake, as do combinations of T_3 and insulin, insulin and epinephrine, and all three substances together. These studies are important to define the mechanism of action of thyroid hormone as well as other metabolic reactions affected by it.

Parathyroid Hormones Reproduced

The parathyroid glands are small bits of endocrine tissue found on the back of the thyroid gland in man and most other mammals. The parathyroids produce a hormone that is very important in the control of calcium metabolism—parathormone. Parathormone has now been successfully synthesized by researchers at the National Heart, Lung, and Blood Institute; and NIADDK grantees have cloned the gene for preproparathyroid hormone into *Escherichia coli*. These researchers plan to use the clones for studies on the structure of the hormone as well as on the structure of the gene itself. Since clones are available, the production of large amounts of preproparathyroid hormone should be possible in the near future, enabling expanded research efforts in numerous areas of endocrinology and metabolism.

Isolation and Characterization of Corticotropin Releasing Hormone

It is now well established that the hypothalamic portion of the brain contains cells that act as transducers, receiving neural inputs and generating hormonal outputs. Hypothalamic neurohormones act as either releasing or inhibiting factors for each of the major hormones of the anterior pituitary gland. Adrenocorticotrophic hormone is produced in the pituitary and stimulates the adrenal glands to produce steroids. In turn, the release of ACTH is stimulated by the hypothalamic neurohormone corticotropin releasing factor. Though the existence of CRF has been known for many years, its isolation and chemical characterization have remained elusive until very recently. In the past year, NIADDK grantees have successfully isolated CRF from sheep hypothalami and characterized it as a peptide containing 41 amino acid units. These investigators have also synthesized CRF and shown that the native hormone and the synthetic material have nearly identical effects. Further, it has been shown that regions of the CRF molecule are identical to other physiologically important peptide hormones such as angiotensinogen, sauvagine, and urotensin I. The finding that several of the peptide hormones have similar amino acid structures may account for the similarities in their modes of action and represents a significant advance in our understanding of the control of endocrine gland function.

Cystic Fibrosis— New Drug May Improve Mucus Clearance

A major problem for CF patients is the accumulation of abnormally thick, viscous mucus in the lungs, which complicates breathing and provides an ideal environment for infections to develop. Recently, NIADDK grantees found that a new drug—designated as WR2721—may be helpful in reducing the viscosity of mucus in CF patients' lungs, allowing more effective clearance of the potentially harmful secretions. The medication, which was originally developed for other purposes by researchers at the Walter Reed Army Medical Center, has been effective and well tolerated in tests with both animals and humans. The NIADDK-supported group has embarked on a small-scale clinical trial with CF patients and, although only a few patients have completed the study protocol, the results obtained thus far are encouraging.

Inborn Errors of Metabolism— Early Diagnosis and Treatment

Inborn errors of metabolism are characterized by enzymatic defects that affect metabolic transformations; the insufficient enzyme activity results in interruption of normal metabolism and, many times, in accumulation of unneeded, toxic intermediate substances in the body. Whether the enzymatic defect is caused by structural changes in the enzyme-protein or by the absence of an enzyme-activating factor (for example, a vitamin), current theory holds that the earliest possible correction of the specific enzyme deficiency could repair the faulty metabolic process and prevent clinical manifestations. This is illustrated by a case study recently reported by an NIADDK grantee: After a young child was diagnosed to have an inherited metabolic disorder (multiple carboxylase deficiency), her pregnant mother

underwent amniocentesis to determine whether the unborn child was likewise affected. The test was positive, and biotin—the missing vitamin needed to activate the enzyme—was administered daily to the mother until delivery, thereby preventing manifestation of the metabolic disease in the fetus and newborn infant. After delivery, further clinical manifestations of the inborn error of metbolism could be prevented by daily biotin administration on a permanent maintenance basis.

Research Opportunities

Genetic, Viral, and Immunologic Factors in Diabetes

Clues regarding the various factors that contribute to the cause and progression of diabetes and its complications continue to emerge from investigator-initiated studies, pointing to promising paths for future research. The replication of antibodies by cloning, for example, should advance our understanding of the immune system and help researchers to clarify how changes in the body's immune response relate to the genesis of diabetes. In addition, studies related to the genetic aspects of diabetes will be important in elucidating the interaction between an inborn susceptibility to the disease and the body's response to antigenic challenge.

Unprecedented opportunities have also arisen from the newly developed ability to collect, preserve, and distribute tissues from diabetic patients for use in research by NIADDK grantees and others. The National Diabetes Research Interchange (NDRI) is now providing valuable tissue resources that could bring virologists and immunologists considerably closer to the specific measures that will prevent or interrupt complications in diabetic patients. Although the Institute has provided technical asistance, the NDRI has been developed primarily by the private sector. As the program continues to develop and evolve, there may be an opportunity to expand its scope to ensure the availability of tissues for investigations in other areas of biomedical research.

Assessing the Obesity-Diabetes Relationship

It has been established that the majority of patients with noninsulin-dependent diabetes are obese, and obesity may precede the development of abnormal carbohydrate tolerance. Recent research indicates that some patients with noninsulin-dependent diabetes may have abnormalities in the perception of satiety and that there is some type of a regulatory feedback mechanism between energy expenditure and food intake, with insulin acting as the key feedback signal to the central nervous system. Continued advances in these areas of research will increase our understanding of human obesity and aid in the development of improved therapeutic approaches to the prevention and management of both obesity and noninsulin-dependent diabetes.

Biologically Active Analogs of Insulin

Although it is well established that insulin has enormous significance in determining the clinical manifestations of diabetes, its mode of action has not been fully defined. Recent studies involving various analogs of insulin have yielded some intriguing results: One synthetic analog displayed a disparity between receptor binding and biological activity; another showed increased biological potency with respect to bovine insulin. The use of analogs differing from native insulin by single amino acids has permitted direct assessment of the participation of key functional groups in the action of insulin. Continued chemical and physical-chemical studies should lead to a better understanding of the relationships between the chemical structure and biological activity of insulin. They could also lead to the development of biocompatible analogs with increased potency or tighter affinity for insulin receptors and thus could be useful in tailoring desirable properties for more specific function in diabetic patients.

Exploring Complications of Diabetes

The microvascular complications of diabetes mellitus in the kidney represent a major public health problem. It appears that metabolic derangements that are a consequence of diabetes, including hyperglycemia, may be the primary cause for diabetic nephropathy. The resumption of attempts at pancreas transplantation in patients with renal transplants could address whether reversal of the metabolic consequence will prevent or reverse the development of nephropathy. NIADDK, hoping to stimulate research in this area, issued a request for applications in fiscal year 1981 for the study of the pathogenic mechanisms underlying the development of diabetic nephropathy.

There is also a need to apply increased knowledge in neurology to the field of diabetes more quickly than in the past. Expansion of research is essential in the areas of nervous and humoral control of pancreatic islet secretion so that investigators can identify and characterize the CNS pathways relevant to the metabolic state in diabetes. The recent demonstration of the relationship between metabolic control and peripheral nerve function should stimulate further application of methods to assess diabetic neuropathy.

Improving Prospects for Transplantation

Although conventional insulin therapy prolongs the lives of patients with diabetes, it does not prevent the long-term complications of the disease. The transplantation of pancreatic islets may be a viable alternative therapy once the major problems of human transplants, especially rejection, are resolved. Recent exciting developments in research with animal models have shown that certain immune barriers can be overcome and the likelihood of graft rejection minimized. Further studies to address development of an optimal allograft preparation and determination of the most effective site for islet transplantation may lead to refinement of a procedure that will be as effective in human diabetes patients as it has been in laboratory animals.

Bioengineering for Diabetes Monitoring and Therapy

Efforts to develop insulin infusion devices are under way in both the academic and private sectors; however, at present all delivery devices, whether implantable or extracorporeal, are "open loop" devices in that they do not have the ability to adjust insulin doses automatically in response to measured blood glucose levels. Independent efforts to develop an accurate, compact, and reliable glucose sensor continue. The coupling of a noninvasive or implantable glucose monitoring system with an insulin delivery device would provide a long-sought, portable, "closed loop" system to ensure the automatic normalization of blood glucose and other metabolites that may prevent or ameliorate many of the complications of diabetes.

Behavior/Psychology in Diabetes Research

Research related to the behavioral and psychosocial aspects of diabetes has been enhanced through the application of statistical procedures that permit complex analyses of multiple interactive effects. The use of advanced social science research techniques will permit investigations such as the following:

- Assessment of the potential stress associated with long-term use of insulin infusion devices;
- Development and evaluation of methods to predict the likelihood of a patient's complying with his or her prescribed regimen;
- Determination of approaches to assure optimum self-care for the elderly; and
- Assessment of cultural variables that affect self-care procedures.

The results of these types of studies will aid clinicians in their efforts to develop optimal treatment strategies for diabetic patients.

Studies on Growth Hormone Variations

Like many other hormones in the body, growth hormone has been shown to have a variety of physiologic effects in addition to the stimulation of cell and tissue growth. It has been suggested that these various effects may be caused by different types of growth hormone. Such heterogeneity may occur either because several genes produce growth hormone products that vary slightly from each other, or because growth hormone as it is known now is converted into different biologically active fragments when it is utilized by various organs and tissues. With the availability of pure growth hormone from recombinant DNA synthesis, the causes and effects of hormone heterogeneity may be studied more easily in the future.

Hormone Effects in Spinal Injury

Thyrotropin releasing hormone (TRH) is produced in the hypothalamus of the brain and causes release of thyroid stimulating hormone (TSH) from the pituitary. TSH then causes the thyroid gland to release thyroid hormone. Recently, studies involving spine-injured laboratory animals suggest that administration of TRH, in contrast to other treatments, improves local blood flow to the site of injury but does not interfere with the pain-relief action of the body's natural opiate-like substances. Future studies in these and related areas are important, not only for their potential therapeutic value, but also to define the many physiologic effects that hormones may produce in the body.

Biosynthesis and Metabolism of Hormones

NIADDK has supported research to elucidate the pathways by which various hormones are synthesized and produced in the body, as well as studies on the degradation of hormones, presumably after they have exerted their effects. It has been determined that various peptide hormones are usually synthesized in a precursor (or prohormone) form which may be cleaved into one or more active forms at the secretion site or at the target site. Furthermore, prohormones have been detected in relatively large quantities by radioimmunoassays where tumors of endocrine organs are present. Additional research is needed in areas related to hormone synthesis and metabolism for exploring the possibility of developing techniques for tumor diagnosis and therapy through interventions directed at pathologically altered biochemical processes.

Further Investigations of Cell Surface Receptors

In order to exert their biologic actions, hormones must first combine with specific molecular sites. Many of these sites, or receptors, appear to be composed of proteins or glycoproteins and are found on the cell surface membrane. Cells that are responsive to a particular hormone have receptors with very specific molecular configurations that match the structural features of the hormone much like a lock and key. Specific hormone-receptor interactions at the cell membrane then are coupled with complex secondary biochemical reactions within the cell to facilitate the hormone's effects, leading to subsequent biologic responses in a particular cell or tissue. A broad range of studies related specifically to receptors, receptor structure, and postreceptor events are needed if we are to understand further the molecular mechanisms of hormone actions.

Cell and Tissue Responses to Hormones

The determinants of any hormone-regulated process include not only the nature and strength of the hormonal signal, but also factors within the target cell that influence the nature and intensity of its response. A single hormone may have different effects in different tissues, and a single tissue may respond to very similar hormones in divergent ways. There already is evidence that innate responsiveness to hormones is altered in various ways by aging, disease, and nutritional state. Studies are needed now to investigate the intrinsic state of the target cell if disorders such as postmenopausal osteoporosis are to be understood and controlled.

Further Research on Multihormone Regulatory Roles

Few, if any, hormone-sensitive processes are regulated by a single hormone. Rather, hormones from a variety of endocrine glands work concurrently to achieve physiologic control of vital processes. Interactions among hormones, whether they are cooperative or antagonistic, provide flexibility and sensitivity in controlling these processes, yet very little is known about such interactions. Studies to define these important regulatory interrelationships must be encouraged in the future.

Studies Related to Brain Peptides

About 30 peptides (poly-amino acid constituents of proteins) have been found in the central nervous system, many of which appear to have hormone-like effects. Other hormonal peptides, originally discovered in various parts of the body and thought to have actions on peripheral target tissues, are thought also to affect the CNS. Unanswered questions about these peptides, including their mechanisms of biosynthesis, release, and interaction with receptors, provide numerous and exciting opportunities for future research.

Treatment Modalities for Inborn Metabolic Diseases

Effective treatments of many endocrine and other disorders have been developed through delivery of hormones or other active factors from outside the body to their intended sites of action in the body without loss of their biological activity. Similar methods for the replacement of missing or defective enzymes are now being developed through advances in enzyme purification techniques and imaginative techniques for delivery within the body. Successful replacement of such enzymes promises to effectively control some metabolic diseases.

Program Plans

Major Prevention Initiative in Diabetes

NIADDK has selected 21 medical centers to participate in a nationwide clinical trial that will examine whether tight control of blood glucose levels in diabetic patients can prevent, delay, or decrease the early vascular complications of insulin-dependent diabetes. The relationship between blood glucose control and complications, which can include stroke, blindness, heart disease, kidney failure, gangrene, and nerve damage, has been the single most important and controversial clinical question in diabetes.

The study, which may take 10 to 15 years to complete, will consist of four phases. In the first (planning) phase, NIADDK and medical center staffs will establish specific protocols and uniform guidelines for conducting the clinical trial. Phase II will consist of limited (pilot) clinical studies of approximately 200 volunteers with insulin-dependent diabetes and will focus on four key issues:

- Whether diabetic patients on a tight control program can maintain better blood glucose control than those on conventional treatment;
- Whether it is possible to assign patients to different treatment programs in a randomized manner;

- Whether a high rate of patient compliance can be achieved in both the tight control and conventional groups; and
- Whether the effects of the two methods of management on the development or progression of diabetic complications can be reliably assessed.

If the phase II results indicate that a long-term trial will produce meaningful conclusions, the full-scale trial will be undertaken in phase III with 400 to 600 volunteers.

The primary complication to be assessed in the full trial is diabetic retinopathy, and two categories of patients will be recruited: those with no evidence of retinopathy, and others with early signs of this complication. This will make it possible to determine simultaneously whether tight control can prevent the development of eye complications and whether tight control can halt or reverse eye damage at an early stage. Study participants will be followed carefully to determine if one method of management is superior to the other in preventing, delaying, reversing, or alleviating the early vascular complications of diabetes.

Phase IV, analysis and reporting of data generated in the trial, will conclude the study. The information learned from the clinical trial will be published in the medical literature to assist physicians in choosing the best treatment for their diabetic patients.

Program Announcements To Stimulate Needed Diabetes Research

In the coming fiscal year, NIADDK plans to join other relevant NIH Institutes in issuing the following series of program announcements related to research on diabetes and its complications:

- A trans-NIH announcement to stimulate the development of investigator-initiated projects in the area of diabetes etiology will help to expand our understanding by addressing the endocrinologic, metabolic, nutritional, genetic, immunologic, and viral aspects of the disease.

- Another announcement, to be coordinated with the National Institute of Allergy and Infectious Diseases, will specifically solicit grant applications for cooperative efforts between diabetologists and immunologists. This type of collaborative effort should facilitate the application of recent research advances in immunology and immunogenetics to the etiology, pathogenesis, and epidemiology of diabetes and its complications.

- NIADDK will cooperate with a number of other Institutes in promoting research on the complications of diabetes. A planned program announcement will be designed to encourage scientists examining the same phenomenon (for example, microangiopathy) in different organ systems to exchange, adapt, and apply each other's methods. The anticipated benefit is a better understanding of the processes underlying diabetic complications, to be achieved through identification of similarities and differences among the various organs affected by such complications.

Efforts To Develop/Disseminate Animal Models

Trans-NIH cooperative efforts are needed to develop, characterize, and disseminate animal models for use in studies of diabetes mellitus and its complications. An NIH workshop held in 1981 identified a number of problems and needs with respect to the availability of support for such an activity. To assist in overcoming the major obstacles, NIADDK plans to cooperate fully with other NIH components in establishing a committee to investigate the feasibility of a centralized NIH program to coordinate and support the characterization and dissemination of useful animal models. Institute advisory group members and consultants, as necessary, will be involved in this effort.

Providing Hormones for Research and Treatment

The development of new recombinant DNA techniques capable of replicating both growth hormone and insulin on a large scale provides the potential for producing other peptide hormones by these techniques. The anterior pituitary hormones, such as prolactin, gonadotropic hormones, and thyroid stimulating hormone, as well as parathyroid hormone and various growth factors, are potential candidates. Commercial interest in the production of some of the peptides will ensure that sufficient quantities will be produced for basic research and clinical treatment. However, other crucial peptides may not be produced in the quantities needed without NIADDK support. In those cases, the Institute will issue requests for proposals to develop such hormones, and the products will be distributed to researchers and physicians by the National Hormone and Pituitary Program. Once a hormone is being produced by recombinant DNA techniques, it will be available in quantities sufficient for investigators to conduct expanded studies of its mechanism of action and effects.

Workshop on Hormone Analogs

A workshop is proposed by NIADDK to review the development and possible uses of hormone analogs in diabetes research. Recent developments in hormone research have led to

the synthesis of several insulin, glucagon, and proinsulin analogs, which have been instrumental in increasing our understanding of the relationships between chemical structure and biologic activity. Future studies could lead to biocompatible analogs with increased potency or tighter affinity for receptors, which would allow for useful tailoring of desirable properties for better function in diabetes. The workshop should produce observations and recommendations that will guide future work in this field.

Cystic Fibrosis Tissue and Materials Repository

A planning conference will be held to examine prospects for initiating a tissue bank for CF-related materials. It is anticipated that the experience of the National Diabetes Research Interchange, which was developed with support from the private sector, will aid planners in designing the proposed CF repository.

Workshops/Program Announcements Address Enzymes in Metabolic Diseases

A series of workshops has been planned by the Institute to assess the state of the art in specific areas of enzyme research. Many of the most exciting research opportunities in the study of metabolic processes focus on enzymes and their actions, and the purpose of this initiative is to ensure that NIADDK's scope and priorities remain fully current with these developments. The following interdisciplinary workshop topics are planned:

- Isozymes and mutant enzymes in metabolic diseases;
- Enzyme inhibitors and their role in treatment of metabolic diseases;
- Translational and posttranslational modifications during protein synthesis.

Program announcements emphasizing each of these research areas will be considered following each workshop; if warranted, collaboration with other Institutes will be explored.

Animal Models for Study of Inborn Errors of Metabolism

Plans for the future include the issuance of a request for proposals to initiate identification of animal models for the study of hereditary metabolic diseases. This initiative should provide for a concerted effort to test, diagnose, and characterize enzyme defects in small animals so that animal forms of human inborn errors of metabolism can be identified. The first stage of the planned contract will concentrate on establishment of a central unit at a school of veterinary medicine to organize and maintain contact with other schools or with veterinarians so that acquisition of diseased animals is assured. In the second phase, the established unit will test, diagnose, and characterize the afflicted animals. If it appears that study of the identified disease will provide insight into the etiology and pathogenesis of metabolic disorders in humans, NIADDK will use a small grants mechanism for the breeding of small animal colonies to provide models for the numerous research opportunities emerging in the field of inherited metabolic defects.

Special Programs

Diabetes Centers

Both Diabetes Research and Training Centers and Diabetes-Endocrinology Research Centers (DERC's) must meet NIADDK's primary requirement for center programs: a strong base of high-quality, ongoing biomedical research. The center grants provide for core facilities (shared resources), pilot and feasibility studies, and program enrichment.

While biomedical research is the singular focus in each of the four DERC's, the DRTC's, numbering seven in 1982, also include training of medical and allied health professionals, continuing education, and model demonstration and outreach activities. Limited funding is available in the DRTC's for research related to training and information transfer. The current-year activities and accomplishments of the DRTC program are described in detail in chapter VI.

Diabetes Data Group

Concerns of the National Diabetes Data Group include defining data needs, coordinating the collection of data from multiple sources, standardizing collection procedures and terminology, making reliable data available to users, and measuring the medical and socioeconomic impact of diabetes. The data group, which was authorized by Congress in 1980, consists of epidemiologists, representatives of Federal and voluntary-sector organizations, and experts in the research, nutritional, and socioeconomic aspects of diabetes. It is the data group's mission to establish, in concert with the National Diabetes Information Clearinghouse (NDIC), "a system for the collection, storage, analysis, retrieval, and dissemination of data concerning diabetes, including, where possible, data involving general populations for the purpose of detecting individuals with a risk of developing diabetes." Through its data collection and analysis activities, the data group serves as a

central source for the accurate statistics that are essential to rational development of scientific priorities and public health program plans.

National Diabetes Information Clearinghouse

The NDIC was established in September 1978 to serve as the central resource for the collection and dissemination of information about educational and scientific materials, programs, and other resources relevant to diabetes. Since its inception, the clearinghouse has abstracted, indexed, and incorporated in its data base more than 3,000 educational brochures, booklets, and other materials on diabetes for health care professionals, people with diabetes, and the general public. Requests for information and/or publications from NDIC average about 700 to 800 a month.

The clearinghouse not only serves to provide information but also identifies areas needing more educational materials and assists in developing such materials. For example, to address the severe shortage of diabetes information for adults with limited reading ability, the NDIC has plans to work with the Diabetes Mellitus Interagency Coordinating Committee, the Centers for Disease Control, other Federal agencies, voluntary associations, and industry to develop and distribute easily understandable messages about diabetes for use in all the media. Such an effort exemplifies the clearinghouse's commitment to developing strategies that will increase community awareness and understanding of diabetes as a major health problem and encourage effective patient, family, and community educational programs.

National Hormone and Pituitary Program

In 1963 NIADDK, with support from the College of American Pathologists, instituted the National Pituitary Agency, now known as the National Hormone and Pituitary Program. Since then, the program has provided supplies of human growth hormone for research related to treatment of hypopituitary dwarfism and other growth disorders. With research advances over the years, it was found that other anterior pituitary hormones could be extracted from the same glands, and the scope of the program was therefore expanded to provide for the distribution of follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, adrenocorticotrophic hormone, and lipotropin. Today, the program produces and distributes a wide range of not only pituitary hormones, but also analogous hormones from sheep, rats, and cattle—animals commonly used in basic endocrine research. The program also develops and distributes many antisera to the various pituitary hormones. The availability of these rare substances, through the activities of NIADDK's distribution program, has proven invaluable in many extensive programs of basic and clinical investigation.

Under NIADDK's digestive diseases and nutrition research program, improved diagnostic techniques and drug therapies have been developed for a wide range of gastrointestinal diseases, including peptic ulcer (arrow). Research is also aimed at defining more specifically the role of diet in disease prevention and health promotion.

Michael J. Pettyes-I, UNIPHOTO

RESEARCH FOCUS

Digestive Diseases and Nutrition

Overview

More than 20 million Americans are afflicted with diseases of the digestive system, disorders that exact a high toll in terms of disability, suffering, and economic costs. Digestive diseases are responsible for $52 billion in losses to the Nation's economy each year. But the greater cost is the number of lives lost—approximately 200,000 deaths each year (including those associated with malignancies).

NIADDK's mission, addressed through its Division of Digestive Diseases and Nutrition, is twofold—to reduce the suffering associated with these diseases and to reduce their economic impact. The Institute's program in digestive diseases supports basic scientific investigations of the structure, function, and diseases of the digestive system organs as well as clinical studies to develop and evaluate new pharmacological agents and noninvasive diagnostic and therapeutic methods for the clinical management of these diseases.

Investigations sponsored by the division's esophageal, gastric, and colonic diseases program and intestinal and pancreatic diseases program areas are directed at the structure, function, and diseases of the esophagus, stomach, small and large intestines, pancreas, and salivary glands. Of particular concern are heartburn and esophagitis, peptic ulcer disease, diverticulitis, ulcerative colitis and Crohn's disease, intestinal malabsorption syndrome, sprue, diarrhea, acute and chronic pancreatitis, and Zollinger-Ellison syndrome. Also included are general studies of the gastrointestinal hormones.

Through its liver and biliary diseases program, NIADDK supports studies of the structure, function, and diseases of the liver, biliary tract, and gallbladder. Included are inflammatory, metabolic, and genetic diseases of the liver, such as hepatitis, cirrhosis, Wilson's disease, primary biliary cirrhosis, fatty liver, hepatic encephalopathy, Dubin-Johnson syndrome, and Gilbert's disease. Other investigations focus on liver regeneration, liver assist ("artificial liver") devices, and liver transplantation, as well as liver ischemia, portal hypertension, and toxic liver disorders. Biliary and gallbladder studies are directed at cholestasis, pigment and cholesterol gallstones, and the metabolism of bile and bile salts. Results of this research have been wide-ranging clinical applications such as the dissolution of long-standing cholesterol gallstones; a practical, sensitive test for screening blood donors and blood products for serum hepatitis virus; and an improvement in the outlook for patients with liver transplants.

Diet is believed to play a significant role in 6 of the Nation's 10 leading causes of death: heart disease, stroke, cancer, diabetes, atherosclerosis, and cirrhosis of the liver. Nutrition research has traditionally been an important area of interest for NIH in general, and especially for NIADDK. Obesity and borderline malnutrition command increasing attention as serious pervasive problems, especially because of the role they may play in exacerbating other diseases. NIADDK supports basic, clinical, and behavioral research in the study of nutrition. Priority areas of investigation in this program include obesity, nutritional requirements in health and disease, nutritional support of hospitalized patients, the roles of fiber and trace elements in the diet, and basic studies of nutrient function.

Highlights of Research Advances

The following sections briefly describe a number of areas in which the Division of Digestive Diseases and Nutrition has reported recent progress in its research programs.

- There is recently developed evidence that the effectiveness of sucralfate in healing duodenal and gastric ulcers and in reducing the recurrence of peptic ulcers is attributable to a selective physical-chemical binding of the drug to tissue proteins at the ulcer site, which creates a protective mechanical barrier. Sucralfate has been found as effective as cimetidine, the most prescribed anti-ulcer drug in the United States.
- A newly applied combination of cyclosporin A and low-dose prednisone as immunosuppressive agents has resulted in an enhanced survival rate for liver transplant patients. The combination may be particularly effective when given in low and tapered doses to avoid untoward effects that, in the past, had been attributed to cyclosporin A.
- Recent studies show that in long-term carriers of hepatitis B virus, the hepatitis-causing organism integrates into a genetic apparatus of host liver cells. Patients with liver cancer who had previously been long-term hepatitis carriers showed the same incorporation of the virus into the genetic apparatus of host cells. Such studies may show the way to identifying hepatitis B carriers at high risk of developing liver cancer.
- Recent findings have suggested that the hormone cholecystokinin (CCK) may control satiety in regions of the brain controlling appetite. Preliminary studies have shown that intravenous infusions of a variant of CCK shorten meal duration and thus lead to the consumption of less food in one sitting.
- High-carbohydrate, high-fiber diets have permitted a reduction of insulin doses in patients with noninsulin-dependent diabetes who require exogenous insulin. Discontinuation of insulin therapy is possible in the majority of lean patients, and most patients on such a diet exhibit reduced serum cholesterol and triglyceride levels.

Esophagitis—Clues for Possible Drug Interventions

Heartburn and reflux esophagitis can be caused by the entry of acidic stomach contents into the lower end of the esophagus, leading to irritation and inflammation. One reason that reflux occurs is the inability of the lower esophageal sphincter (LES)—a "gate" between the esophagus and stomach—to remain closed when the stomach is full.

Recently, two teams of NIADDK grantees have found that two distinct classes of chemical compounds cause relaxation of the LES. One substance, a peptide hormone known as vasoactive intestinal peptide, is released in the LES area when the vagus nerve is stimulated. The other compound, morphine, reduces LES pressure by acting on the central nervous system. It is possible, therefore, that naturally occurring morphine-like compounds in the CNS (endorphins) are involved in the physiological control of pressure on the LES.

These findings may contribute to the improved management of critically ill patients, who are prone to suffer from vomiting and reflex esophagitis, especially when confined to bed for long periods, by eventually leading to pharmacologic methods of inhibiting relaxation of the LES and thus preventing gastric reflux. Further research may also result in the preparation of new drugs for relief of the more common forms of esophagitis.

Peptic Ulcer

Gastrin-Inhibiting Compound May Offer Protection

Some cases of peptic ulcer are associated with abnormally high levels of gastrin, the hormone that stimulates secretion of digestive juices in the stomach. Initial studies on sheep were undertaken by NIADDK-supported scientists to determine if high levels of maternal gastrin would cross the ewe's placenta and cause harm to the growth and development of the fetal lamb.

Preparing the animals so that blood samples could be taken from both ewe and fetal lamb, the investigators injected gastrin until the maternal blood levels of the hormone were four times the normal level. They observed that not only did the maternal gastrin not cross the placenta, but also the fetal gastrin level became depressed. Conversely, creating artificially high levels of gastrin in the fetus caused levels in the ewe to decrease, an effect that is consistent with clinical observations over the years that women with peptic ulcers who become pregnant find that their ulcers tend to heal.

Experiments now are under way to determine the nature of the hypothetical gastrin inhibitor involved. If the agent can be identified, therapeutic measures may be developed for patients who suffer from ulcers caused by excessive secretions of gastrin.

Specific Mechanisms of Sucralfate Activity Shown in Humans

Sucralfate is a basic aluminum salt of sucrose sulfate, with sustained protective effects against pepsin, acid, and bile at the site of a peptic ulcer. Recent studies have shown that the compound is effective in reducing the recurrence rate of peptic ulcers and is more effective than low-dose antacid in healing

gastric and duodenal ulcers and as effective as cimetidine, the most prescribed anti-ulcer medication in the United States. One mechanism of this protective activity appears to be selective binding of the drug to proteins at the ulcer site, but most of these investigations have been carried out in test tubes or in rats with experimentally induced ulcers.

An NIADDK grantee has now provided evidence for this selective binding activity in humans. Patients with gastric ulcer were given multiple oral doses of sucralfate prior to partial gastrectomy, and binding of the drug to both ulcerated and healthy stomach tissue (mucosa) was estimated by chemical determination of aluminum and sucrose sulfate. The ulcerated mucosa was found to contain six to seven times more sucralfate than the control mucosa. These and other data suggest that the ability of sucralfate to accelerate the healing of ulcer disease is attributable to several mechanisms, one of which is the formation of a protective barrier at the ulcer site through complex formation between sucrose sulfate and proteins.

Acute Liver Failure—Liver Cell Transplantation Succeeds in Dogs

Because the liver has a natural ability to regenerate itself, patients with acute liver failure could, in theory, recover and survive if sufficient metabolic support were provided during the critical period of regeneration of new, functional liver tissue. However, most of the numerous support methods attempted have failed to provide an adequate substitute for the vast array of functions normally performed by the liver, and most patients die before their liver has a chance to recover. Liver transplantation, which has shown some success, is an extremely risky procedure in ill patients and is associated with complications that can lead to graft failure and death. An alternative approach is to transplant liver cells as a free graft to function until the patient's own liver recovers.

NIADDK-supported scientists now report preliminary success of the transplant procedure in dogs. After inducing liver failure in the animals, the investigators injected some of the dogs' own liver cells directly into the spleen and tied off that organ's main artery to prevent the transplanted liver cells from migrating to the liver or lung. The 10-day survival for dogs undergoing this procedure was 70 percent, compared to 20 percent for the control group lacking transplanted liver cells. Liver cells were readily identifiable in the spleen 2 and 4 weeks after transplantation.

Not only do these findings demonstrate the therapeutic potential of implanted liver cells, but the experimental design also parallels the clinical situation in which treatment would begin after injury to the liver. The cell transplant approach may lead to an improved outcome for patients with potentially reversible but otherwise lethal acute liver damage. It also redirects the thrust of research—away from blood-cleansing columns and other devices outside the body, to a living graft.

Liver Transplants—New Immunosuppressive Drug Combination Improves Prospects

Cyclosporin A is a protein-like substance of fungal origin which prevents or delays transplant rejection by suppressing activity of special white blood cells (T-lymphocytes) involved in immune system activities. Previous studies showed cyclosporin A to be highly effective in promoting survival of transplanted organs including the kidney, liver, and heart. In this respect, cyclosporin A surpasses conventional immunosuppressive drugs (such as azathioprine and prednisone), which are toxic to the bone marrow, heighten the risk of infection, or have other undesirable side effects.

Recently, an NIADDK grantee has reported success with cyclosporin A and low doses of prednisone in prolonging survival of liver transplants. Transplant surgeons removed diseased livers from 14 patients, aged 8 to 41, and replaced the organs with healthy transplants from compatible donors. On the same day, they began daily oral or intramuscular administration of 17.5 milligrams of cyclosporin A per kilogram of body weight. After 6 to 8 weeks, the dose was tapered to 10 mg/kg/day or less. Among the adults, each patient received an initial dose of 200 mg prednisone on the day of the operation, reduced by 40 mg daily for 4 days, and further decreased by 20 mg on the fifth day. In other patients, prednisone either was given in low doses on the day of the operation or, in a few cases, was not administered until threatened rejection of the transplant.

Ten of twelve patients (83 percent) who survived the operation were still living after more than 15 months. Two of the original fourteen patients died during surgery, making a real survival rate of 71 percent—a rate higher than the 30 to 50 percent survival among 170 patients from a previous series treated with conventional immunosuppression. Transplant rejection phenomena in the recent study were common but controllable with small doses of cyclosporin A and prednisone. Six patients had postoperative complications, including cardiac arrest, abdominal abscesses, and respiratory distress. Surviving patients were maintained on low doses of the immunosuppressive drugs.

Although followup was for a relatively short period, these results nonetheless demonstrate the impressive clinical utility of cyclosporin A paired with prednisone in prolonging survival of

patients bearing successfully transplanted livers. In the past, cyclosporin A, when given in larger doses, manifested liver and kidney toxicity and a tendency to stimulate cancers of the lymph system, but researchers hope that such side effects will be less likely when the drug is given in lower, tapered doses.

Hepatitis

Serum Enzymes Predict Type B Remission

The presence of "hepatitis B e antigen" (HBeAg) in the serum is recognized as a marker of chronic active liver disease. Use of this marker to trace the natural disease history is important for evaluating treatment of chronic type B hepatitis. Persistence of HBeAg correlated with elevated levels of hepatitis B-specific enzymes in the serum reflects progression of the underlying disease. On the other hand, spontaneous reduction of these serodiagnostic factors usually signifies remission.

NIADDK scientists have recently shown that conversion of serum findings from circulating HBeAg to its corresponding antibody (anti-HBe) is accompanied by disappearance of viral-specific enzymes, thus heralding remission of chronic type B hepatitis. In a study population of 25 patients (24 men), aged 21 to 60, who were followed for 1 to 6 years, 13 patients experienced conversion of serum findings from HBeAg to anti-HBe. This change occurred during the first year in seven individuals, during the second year in three, and during the third to sixth years in three more. Abnormal serum enzyme levels fell to normal in all three cases. Patients who remained HBeAg-positive had persistently elevated enzyme levels and evidence of chronic liver disease. Withdrawal of corticosteroids was followed by appearance of anti-HBe in two of seven patients. The results confirm the hypothesis that detection of serum conversion from HBeAg to its corresponding antibody is accompanied by a fall in viral-related serum enzymes, and is of value in predicting spontaneous remission from chronic type B hepatitis. Thus, patients with persistent stable levels of antigen and enzymes are suitable candidates for testing the therapeutic efficacy of either experimental antiviral drugs or hepatitis B vaccine.

Molecular Studies of Viral Infection and Liver Cancer

It is now known that years after a person is infected with hepatitis B virus, a chronic carrier state can develop, leading to chronic active hepatitis and, as epidemiologic and other evidence suggests, an increased risk of liver cancer. There are about 180 million carriers of the virus worldwide (some 750,000 in the United States). Because chronic active hepatitis occurs in 1 to 5 percent of the carrier population, and there is a current controversy about the treatment of the disease, it is important to learn whether unresolved hepatitis may become malignant.

With advances in recombinant DNA and other techniques of modern molecular biology, scientists have now been able to investigate at the molecular level—using small amounts of tissue from liver biopsy samples—genetic changes from one stage of infection to another. Once hepatitis B virus affects liver cells, the viral DNA may genetically reprogram the invaded host cells; this process is called "integration" of DNA into the genetic apparatus of the host cell. In studies supported by NIADDK, viral DNA was found in the liver cell nucleus, but was not integrated into the liver cell DNA, in five patients who had evidence of the carrier state and liver disease for less than 2 years. In two patients who had been carriers for more than 8 years, however, DNA of the virus was integrated into the DNA of the host cell. Moreover, in patients with primary liver cancer who were also hepatitis carriers, DNA extracts from all tumors showed the same change: integration of hepatitis viral DNA into the patient's genetic apparatus.

Future research that sequentially follows all stages in viral hepatitis B infection, from onset of acute hepatitis to chronic liver disease and possibly to liver cancer, is now feasible. Such studies may be useful in identifying viral hepatitis carriers at high risk of developing primary liver cancer and may lead to an understanding of when therapy will be most beneficial.

Ascites—Levels of Special Defense Cells Indicate Infection

In the study and treatment of ascites (the accumulation of serous fluid in the abdomen), the protein and white blood cell concentrations of the ascitic fluid have been considered to be indicative of the etiology of the condition. High concentrations have been thought to indicate an "exudative" type of ascites, such as results from tuberculosis or cancer, and low concentrations to indicate a "transudative" type, such as results from cirrhosis with high portal pressure. There are several problems with this etiological approach, however, and research has been under way to solve them.

Recently, an NIADDK grantee, making serial observations in the same patients during diuresis (an induced increase in the secretion of urine), has shown that the finding of a transudate may be progressively converted to that of an exudate, apparently as an effect of the diuresis. Moreover, the grantee showed that this shift is caused by a reduction in the total volume of ascitic fluid achieved by selective condensation of the ascites, and that the concentrations of two different types of white blood

cells (lymphocytes and polymorphonuclear leukocytes) do not change in the same direction. Lymphocytes, which are long-lived, increase in relative number as the ascitic volume decreases, whereas PMN's, with very short lifespans, do not increase but may even decrease unless stimulated by an infection or other host-defense process.

The clinical importance of this research is the observation that the finding of large numbers of lymphocytes reflects the normal response to successful diuresis and that the diagnosis of bacterial peritonitis (inflammation of the abdominal lining) should not be based on the concentration of lymphocytes in a patient who has had diuresis. This observation may prevent an inappropriate diagnosis of peritonitis and exposure to potentially toxic antibiotic treatment on the basis of elevated lymphocyte levels during diuresis.

Gallstones

Clinical Trial of Chenodiol Shows Modest Benefit

The first demonstration that chenodeoxycholic acid (chenodiol) could result in the dissolution of cholesterol gallstones met with an immediate wave of enthusiasm that led to the therapeutic use of the drug in Europe before its long-term safety and effectiveness were established. The National Cooperative Gallstone Study, supported for the past several years by NIADDK, was initiated in 1973 (following animal toxicity testing) to provide these critical data. This well-controlled, double-blind clinical trial compared chenodiol at two doses with a placebo over 2 years of treatment for each of 916 patients at 10 clinical centers across the country. Results showed that the drug administered orally at 750 mg/day (high dose) completely dissolved gallstones in 14 percent of patients within the 2-year period, and partially or completely dissolved them in 41 percent of patients. Low-dose administration of chenodiol (375 mg/day) led to complete stone dissolution in 5 percent of patients and partial or complete dissolution in 24 percent. Significant side effects included reversible liver damage, usually mild diarrhea, and slightly elevated serum cholesterol.

The study data suggest that chenodiol appears to have a more limited role in gallstone therapy than originally envisioned; high-dose administration may be appropriate for dissolution of gallstones in a small number of patients who are fully informed of the potential risks and for whom medical therapy is appropriate. These findings will help prevent misuse of the drug, an important consideration in view of the fact that 16 million to 20 million people in the United States have cholesterol gallstones. Moreover, by helping to define the mechanism of action of chenodiol, this study will add further insight in the design of more effective agents.

Technique Distinguishes Cholesterol Stones from Pigment Stones

The choice between medical and surgical management of patients with gallstones often depends on the composition of the stones. For patients with pigment gallstones, the only available treatment is surgery. Failures of chenodiol treatment may be attributable to the inadvertent inclusion of patients with pigment gallstones in the medical treatment protocol; therefore, reliable prediction of gallstone composition is essential to the selection of appropriate therapy.

Recently, NIADDK research workers have demonstrated the value of the statistical method of discriminant analysis in predicting accurately the composition of gallstones from physical characteristics revealed through oral cholecystography. Discriminant analysis maximizes separation of two or more groups by combining multiple features and ranking them along a linear scale. In this study, higher values for gallstone diameter, smoothness, number, rim calcification, and buoyancy collectively supported the probability of high cholesterol content. Conversely, lower values for these characteristics strongly suggested pigment stones. Thus, a finding of less than 50 percent probability of "cholesterol stone" resulted in a classification of "pigment stone."

For 39 patients with cholesterol gallstones and 17 with pigment stones, the predictive value of the discriminant score was 93 percent (stones falling between the scores of -1.0 and 0.2 were of indeterminate composition). Thus, the probabilities calculated in this study permit selection of appropriate therapeutic modalities. Patients with high probability of cholesterol stones could be considered suitable candidates for medical management with drugs, such as chenodiol, whereas those with low cholesterol probability are best treated surgically.

Obesity—Diet Affects Number and Size of Fat Cells

The problem of abnormal increase in the number of fat cells (hyperplasia) in severe obesity continues to be a focus of nutrition research since hyperplasia may be the basis for the obstinacy of the disorder. Fat cells, once formed, tend to persist indefinitely.

Studies by NIADDK-supported scientists now have shown that different degrees of hyperplasia in rats experimentally induced

to overeat are caused by differences in diet composition even when the animals gain equal weight. Rats fed a milk diet developed *more* fat cells than did chow-fed controls. High fat feeding was shown to induce hypertrophy (an increase in fat cell size) in all fat depots and hyperplasia in some. Starved rats or rats exposed to cold had reduced fat cell size, but showed no reduction in number of fat cells. Diet restriction in early life resulted in both less fat mass and fewer fat cells, characteristics sustained in later life when diet was no longer restricted. Thus, the composition of the diet and levels of energy intake in early life appear to be important factors in obesity.

In other studies, the amount of food eaten by rats during the day appeared to be closely related to both the size and number of fat cells. Whether the fat cells generate specific signals, such as hormones, or exert their effect on appetite through some indirect effect on substrate concentration, is not known. However, these studies justify the search for such signals.

Satiety—Possible Regulation by Hormonal Interaction in Brain

Cholecystokinin is the parent molecule of a family of polypeptide hormones, some of which are secreted into the circulation from the small intestine after eating. This compound stimulates both secretion of the exocrine pancreas and contraction of the gallbladder, and CCK-like molecules have also been identified in the central and peripheral nervous systems. The biological significance of CCK in the brain, however, has yet to be determined.

Recent work by NIADDK grantees has provided new evidence for a specific central nervous system role for CCK. The investigators prepared a special complex of CCK that binds to specific receptors in the brain and pancreas of laboratory animals, and undertook a study to determine whether CCK receptors in mouse brain were influenced by fasting. In a comparison of fed mice and 42-hour-fasted mice, fasting significantly increased CCK binding to its receptors in the olfactory bulb (by 46 percent) and hypothalamus (by 42 percent), but not in other brain regions. The increase was shown to be a result of an increase in the number of receptor sites.

The discovery that fasting leads to an increase in CCK receptors in the hypothalamus—which has been shown in several species to regulate appetite—supports the concept that CCK may control satiety through interaction with that region of the brain. Continued research may have implications for weight control and weight reduction in obese persons. Recently, other NIADDK grantees have reported that the intravenous infusion of another CCK-like molecule will shorten the duration of the meal period in both lean and obese human subjects and thus result in the consumption of considerably less food during meal sittings.

Therapeutic Diets—Practical Diets Lower Insulin Requirement

It has been demonstrated that the addition of plant fibers (pectin and guar gum) to the diet of patients with diabetes is accompanied by significant reductions in blood sugar levels. With hydration, these fibers form gels in the small intestine and colon. Such a gel system may delay the rate of absorption of carbohydrates and largely prevent the peaks and valleys in blood glucose concentration. Intestinal transit time, which is shortened by dietary fibers, also may influence the rate of absorption.

An NIADDK investigator has studied the use of high-carbohydrate, high-fiber diets in which the dietary fiber is supplied by conventional foods in adults with noninsulin-dependent diabetes. The diets provide 55 to 60 percent of calories as carbohydrate (approximately 75 percent in the nonrefined, "complex" form), 15 to 20 percent as protein, and 20 to 25 percent as fat, with about 50 grams of dietary fiber. Such practical diets permitted reduction of insulin dosage after 16 days, from an average of 27 units per day to 7 units per day. Insulin therapy was discontinued eventually in 15 of 20 lean subjects, even though the same lean weight was maintained. In addition, most of the patients on the test diets had substantially reduced serum cholesterol and triglyceride values.

Since low intake of dietary fiber is a characteristic of societies with a relatively high incidence of obesity, diabetes, and heart disease, these findings suggest a potential impact on the emergence and course of noninsulin-dependent diabetes, and the need for increased research in this area is clear.

Nutrition—Oat-Bran Lowers Cholesterol Levels

Eating of certain plant fibers, the indigestible portions of plant foods, has been found to lower serum cholesterol levels in humans. Several water-soluble fibers, such as pectin, guar, and Bengal gram, demonstrate this effect, whereas most water-insoluble fibers, such as cellulose and cellulose-rich wheat bran, do not. To determine the cholesterol-lowering effects of oat-bran, a palatable and inexpensive cereal rich in water-soluble fiber, investigators supported by NIADDK and the Veterans Administration recently examined the benefit of adding oat-bran to the diet.

Eight men with previously documented hypercholesterolemia (high serum cholesterol levels) were fed two solid diets for 10 days each. The diets were composed of common foods and were identical in calories, carbohydrates, protein, and fat content. The test diet, however, included 100 grams of oat-bran per day provided in muffins and hot cereal. Blood samples were taken daily during each 10-day diet period; and total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, fats, and sugars were measured. Stool specimens were analyzed as well.

The investigators found that seven of the eight men on the oat-bran diet had significantly lower total serum cholesterol levels and concentrations of low density lipoproteins. No changes in cholesterol levels were observed when the men were on the diet without oat-bran. Additionally, the high density lipoprotein cholesterol concentrations were not changed by the oat-bran diet. This is important in light of the recent discovery that not all cholesterol is unfavorably implicated in heart disease: While low density lipoprotein cholesterol seems to promote atherosclerosis (hardening of the arteries), the high density fraction seems to protect against the disease.

These results indicate that the fiber contained in oat-bran may have substantial benefit for selected patients with hypercholesterolemia. Although the food is not yet commercially available, 300 grams of whole oats will provide about 100 grams of oat-bran. Further studies are required to determine the long-term benefits of oat-bran intake on serum cholesterol concentrations.

Research Opportunities

Role of Gut-Neural Peptides

A number of new biologically active peptides have been found in the brain, the central nervous system, and the gastrointestinal tract. In the gut most of these peptides have been classified as hormones related to the control of the digestive tract and its function; there is considerable speculation about the role of these same or structurally similar peptides in the brain. With the recent availability of many peptides or hormones and assay methodologies, studies can now be initiated with the long-term goal of characterizing the actions of gut and brain peptides on the central neural control of the gastrointestinal tract, identifying their mechanism of action, and determining their physiological role in the regulation of gastrointestinal function. Emphasis should also be placed on isolating and characterizing neural peptides from human gastrointestinal tissue to compare and correlate more correctly the results obtained from studies using peptides obtained from animal sources.

Expansion of Endoscopy Research and Development

Endoscopy has become established over the past 20 years as valuable in the diagnosis and treatment of various disorders of the gastrointestinal tract, such as bleeding, polyps, and gallstones lodged in the bile duct. There is also potential for its use in basic and applied studies related to the functions and activities of the digestive tract, such as circulation, motility, and secretion. New biomedical engineering technology should be exploited and used in conjunction with currently available or newly developed endoscopic instrumentation to enhance research, diagnosis, and therapy of digestive diseases. To realize this opportunity, programs and facilities with specific research as well as training missions in endoscopy should be established and staffed by gastroenterologists, endoscopists, biomedical engineers, physiologists, and biostatisticians.

Investigations of Pancreatitis Development

Although the clinical presentations of pancreatitis (inflammation of the pancreas) have been well described, virtually nothing is known about its origin and development. Knowledge of the pathogenesis of the condition is critical for developing effective approaches for therapy and precise, convenient techniques for diagnosis. The following two areas of investigation offer particular promise for increasing our understanding of pancreatitis:

- ***Development of techniques to obtain pancreatic tissue from patients***—Biopsy of the pancreas has long been regarded as a dangerous procedure because of the risk of producing a pancreatic fistula (abnormal passage or opening to another organ or the body surface). The ability to obtain biopsy samples more safely should thus be a high-priority aim of research efforts; analysis of such samples would allow scientists to characterize changes in the pancreas that accompany the onset and progression of pancreatitis and other pancreatic diseases.

- ***Studies of models of pancreatitis***—A large number of animal models of pancreatitis have been reported; however, the usefulness of data derived from studies of the animal models has been limited by our lack of evidence that the models reflect the disease process in humans. Development of meaningful animal models and studies using pancreatic tissue maintained in tissue or organ culture are key research opportunities, and they should be facilitated by a better understanding of the pathogenesis of human pancreatitis.

Phospholipase Inhibitors in the Treatment of Acute Pancreatitis

The human pancreas is rich in the enzyme phospholipase A_2, which is stored in an inactive state until activated by trypsin, another enzyme found in pancreatic juice. Phospholipase A_2 then acts to split lecithin into fatty acid and a toxic by-product of lecithin. In acute pancreatitis, the amount of lecithin decreases in pancreatic tissue while levels of its toxic by-product increase; this and other evidence indicates that phospholipase A_2 may play an important role in the pathogenesis of the disease. Preliminary clinical studies have shown that certain compounds that inhibit the activity of this enzyme are effective in treating patients with acute pancreatitis. It is still unknown whether phospholipase A_2 activity is elevated early in all patients with the disease, and whether increased serum levels of the enzyme are reliable predictors of pancreatitis. To address these questions and determine the efficacy, safety, and optimal delivery of phospholipase A_2 inhibitors, a multicenter controlled clinical trial of these agents in the treatment of acute pancreatitis is indicated as an important research opportunity.

Clinical Trial of Somatostatin for Acute Pancreatitis

The peptide hormone somatostatin, a known inhibitor of stimulated pancreatic secretion, recently has been shown to improve the course of acute pancreatitis in the dog and the rat during the early onset of symptoms, possibly by inhibiting digestive enzyme secretion from still-intact exocrine cells. In a recent German clinical pilot study involving 30 patients with acute pancreatitis, somatostatin treatment led to quick loss of pain and improvement of all clinical and biochemical findings. An opportunity now exists for a multicenter controlled clinical trial of the hormone to determine its safety, how soon to initiate treatment, and the optimal dose schedule. Results from such a study would complement those from the German investigators, who are conducting a 2-year, 19-center trial of somatostatin in the treatment of acute pancreatitis.

"Uncoupling" of Secretion Processes in the Liver

Recent scientific and technologic advances have reestablished the role of the liver as a key organ for the regulation of cholesterol balance. It is the liver that largely compensates for changes in cholesterol input to the body from the diet, that synthesizes various lipoproteins which combine with and deliver cholesterol to certain peripheral tissues, that takes up other lipoprotein complexes carrying cholesterol from peripheral tissues back to the liver, and that secretes cholesterol and bile acids from the body. In spite of all the points at which the process could break down, cholesterol secretion seems to remain very well coupled with the secretion of phospholipids and bile salts so that cholesterol remains soluble in bile. However, it appears to become "uncoupled" when cholesterol gallstones form, and study of this derangement is a highly promising research opportunity.

Progression of Viral DNA in Hepatitis

As described in the section on research advances, integration of the DNA of hepatitis B virus into the genetic apparatus of liver cells of the human host—thereby genetically "reprogramming" the invaded cells—is suspected to precede the development of manifest liver cancer. Advances in genetic engineering technologies now have provided tests sensitive enough to detect viral DNA sequences in minute liver specimens which can be obtained by simple needle biopsy, with results 1,000 times as sensitive as those from conventional radioimmune assay. Thus, through determination of the presence and "integration state" of hepatitis B viral DNA in liver specimens, there is the potential to identify carriers of the virus who are at increased risk of developing liver cancer. Using the integration state as an endpoint, scientists also have the opportunity to assess the ability of drugs such as corticosteroids to prevent the progression from the unintegrated to the integrated state in patients with chronic active hepatitis of viral origin.

Diagnostic Advances Permit New Studies in Liver Disease

Recent studies of the natural history of primary biliary cirrhosis (a rare form of cirrhosis of the liver) have shown that, like chronic active hepatitis, the disease is more heterogeneous than earlier suspected. Further defining the natural history of this and other cholestatic liver diseases (those marked by the obstruction of bile flow), thereby allowing attempts to intervene in their progression, depends on earlier and more accurate diagnosis. Dramatic advances in a number of diagnostic techniques—ultrasonography, endoscopy, immunology, and nuclear magnetic resonance—have made such studies feasible. Thus there is an opportunity to begin long-term (10- to 20-year) research aimed ultimately at treating and preventing these chronic diseases.

Improved Nutritional Support of Hospital Patients

Recent studies underscore the importance of adequate nutritional support for patients hospitalized with chronic or acute diseases or for surgery. There are opportunities for the development of improved methods to assess nutritional status and the acquisition of more complete information about the effects of

disease states on the nutritional needs of patients. Additional attention also should be given to nutritional support of the patient and to the effect of overall nutritional status of the individual and the effect of nutrient intake on the course of specific diseases or conditions. In addition, studies are needed to examine the metabolic consequences of bypassing the intestinal tract and liver in total parenteral nutrition, especially as it relates to the synthesis of "nonessential" nutrients and the combined nutrient-drug management of patients. Such research should be facilitated by the existence of the NIADDK-supported clinical nutrition research units, which have served to focus investigator attention on the nutritional needs of hospital patients.

Program Plans

Clinical Trial for Endoscopic Control of Upper Gastrointestinal Bleeding

Effective control of upper gastrointestinal hemorrhage, such as occurs in bleeding ulcer, is a major problem. During the past 5 years, research and development efforts have resulted in a number of methods other than surgery that can be used in conjunction with the fiberoptic flexible endoscope to arrest such bleeding; they include laser photocoagulation, tissue adhesives, thermal probes, and several different modes of electrocautery. To provide adequate data on the efficacy and safety of the procedures, a multicenter, controlled clinical trial is planned. Preliminary evidence suggests that laser therapy may be impractical when other factors such as cost, installation and maintenance requirements, and mobility are considered; electrocautery probes appear to hold the greatest promise for therapy of the condition.

Establishment of Endoscopy Research Units

To exploit fully the potential for advancing the state of the art of endoscopy and its potential for research on the cause and cure, diagnosis, and treatment of disease, facilities are needed that bring together the technological expertise of engineers, the practical experience of endoscopists, and the support of the private sector, which stands to profit from the innovations that these facilities will foster. Plans are being considered to establish two or three such endoscopy research units to be jointly sponsored by NIH and either individual companies or groups of companies which would contribute to the programs. Each unit would contain a "core" clinical research facility with adequate support to provide for the continuity of key staff. In-depth research emanating from pilot projects or initiated *de novo* will be supported as individual research grants or contracts through the NIH competitive review process.

Interrelationships Between Pancreatic Endocrine and Exocrine Regions

In the pancreas of mammals, birds, and reptiles, islets of endocrine (internally secreting) tissue are scattered among the exocrine (outwardly secreting) acini. Studies reveal both cell-to-cell contact between these two types of tissue and direct connections between the capillaries of the islets and the acini. Scientists have suggested that these structural arrangements reflect a regulatory role of the islet hormones in the function of the exocrine pancreas. Recent evidence indicates that, of these hormones, insulin directly and indirectly influences the function of pancreatic acinar cells. For additional research on these and other observed interactions between the exocrine and endocrine regions of the pancreas under both normal and diseased conditions, a program announcement is planned to encourage applications for funding of relevant research projects.

Targeted Multidisciplinary Studies in Pancreatitis

To capitalize on the research opportunity related to the study of the pathogenesis of pancreatitis, a program announcement is planned for support of multidisciplinary investigations on the development of techniques to obtain pancreatic tissue from patients with pancreatitis, and development of meaningful experimental models of the various diseases constituting human pancreatitis. Either two specialized centers of research or two research program projects would be funded.

Core Centers for Clinical Research in Chronic Liver Disease

Plans are under way to establish a number of core centers directed at specific chronic liver problems such as primary biliary cirrhosis, chronic active hepatitis, and liver transplantation and regeneration. Such centers would serve as a stable, long-term resource for coordinating basic and clinical studies of well-defined groups of patients. The core group of investigators—such as biostatisticians, epidemiologists, molecular biologists, and immunologists—could also attract practitioners and their patients from other specialties. For example, in chronic cholestatic liver disease, orthopedists might focus on osteopenia (reduced bone mass) associated with the disease; neurologists could study the progressive neurologic syndrome of children with the disease; and dermatologists could investigate the

accompanying pruritis (itching). The centers approach also offers a model environment for the training of specialists in the study of the liver.

Methods for Individualized Characterizations of Obesity

Most clinical studies of obesity fail to differentiate one type of obesity from another, since no physiologically valid and clinically acceptable classification scheme exists. Clinical studies of heterogeneous groups of obese subjects thus yield little precise information about the cause of the disorder, and the interpretation of results from therapeutic or preventive interventions is severely limited. Using the outcome of a scientific workshop, NIADDK plans to test, in a cooperative pilot study, a proposed classification system to resolve such problems. Those methods found to be important and clinically suitable will be described for publication in a manual of methodologies for characterizing obesity. If results are positive, it is proposed that a 3-year multicenter intervention trial be initiated to evaluate the usefulness of the classification scheme for individualizing therapy in obesity research.

Role of Dietary Fiber

Research findings have shown that diets high in fiber and complex carbohydrates may be valuable in the prevention and control of certain types of obesity, diabetes, coronary artery disease, diverticulosis, and possibly colon cancer. Progress in methods of analysis of different dietary fiber components now makes it feasible to conduct more reliable studies in this area. To capitalize on this research opportunity, NIADDK plans to issue a program announcement for support of research on methods for the further chemical characterization of dietary fibers and basic studies on the effects of dietary fiber components on food transit time, water-holding capacity, bioavailability of nutrients, intestinal microflora, and digestion, and for studies on their rate of absorption and their interactions with bile acids, drugs, and other substances.

Expansion of the CNRU Program

Currently seven clinical nutrition research units are supported by NIH (five of them by NIADDK). To establish additional units during the next several years, a program announcement and guidelines for CNRU applications are planned. The new awards will expand current efforts to stimulate progress in multidisciplinary research in clinical nutrition, strengthen training environments, improve patient care, and make nutrition information available to the public.

Special Programs

National Digestive Diseases Education and Information Clearinghouse

As a major information service of NIADDK, the National Digestive Diseases Education and Information Clearinghouse coordinates the national effort to educate the public, patients, patients' families, physicians, and other health care providers about the prevention and management of digestive diseases. The program is specially designed to reach neglected population groups, such as the elderly, minority groups, rural Americans, and children.

The clearinghouse provides a central point for the exchange of information among professional organizations, foundations, and voluntary health organizations involved with digestive health and disease. In working with these groups, the clearinghouse aids in the distribution of information products, determines what additional materials are needed, and encourages production of such materials.

Fact sheets produced by the clearinghouse describe specific disease areas and are prepared by professionals in the field at the request of the clearinghouse advisory committee. Recent meetings of the advisory subgroups resulted in the development of new fact sheets on cirrhosis of the liver and diarrhea from infections and other causes. Manuscripts in progress include the topics of milk intolerance, stomach ulcers, gallstones, bleeding in the gut, and inflammatory bowel disease. Another clearinghouse publication, "Letter from the Clearinghouse," discusses current research and the activities of various government and private-sector organizations.

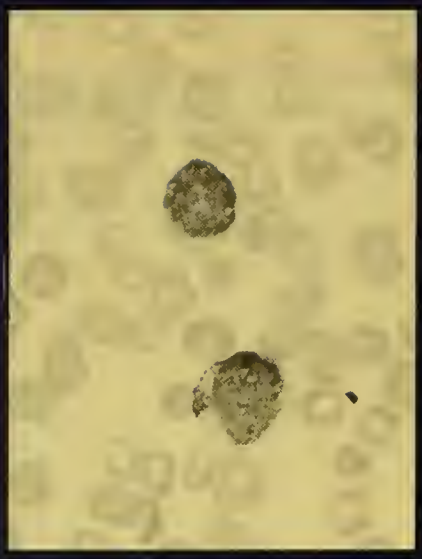
Recently, the clearinghouse collaborated with organizations of laymen in distributing to their chapters nationwide the fact sheets, a flyer describing the clearinghouse, and a directory of organizations concerned with digestive diseases. The clearinghouse has also designed a plan for evaluating currently available educational materials for medical accuracy and clarity.

Clinical Nutrition Research Units

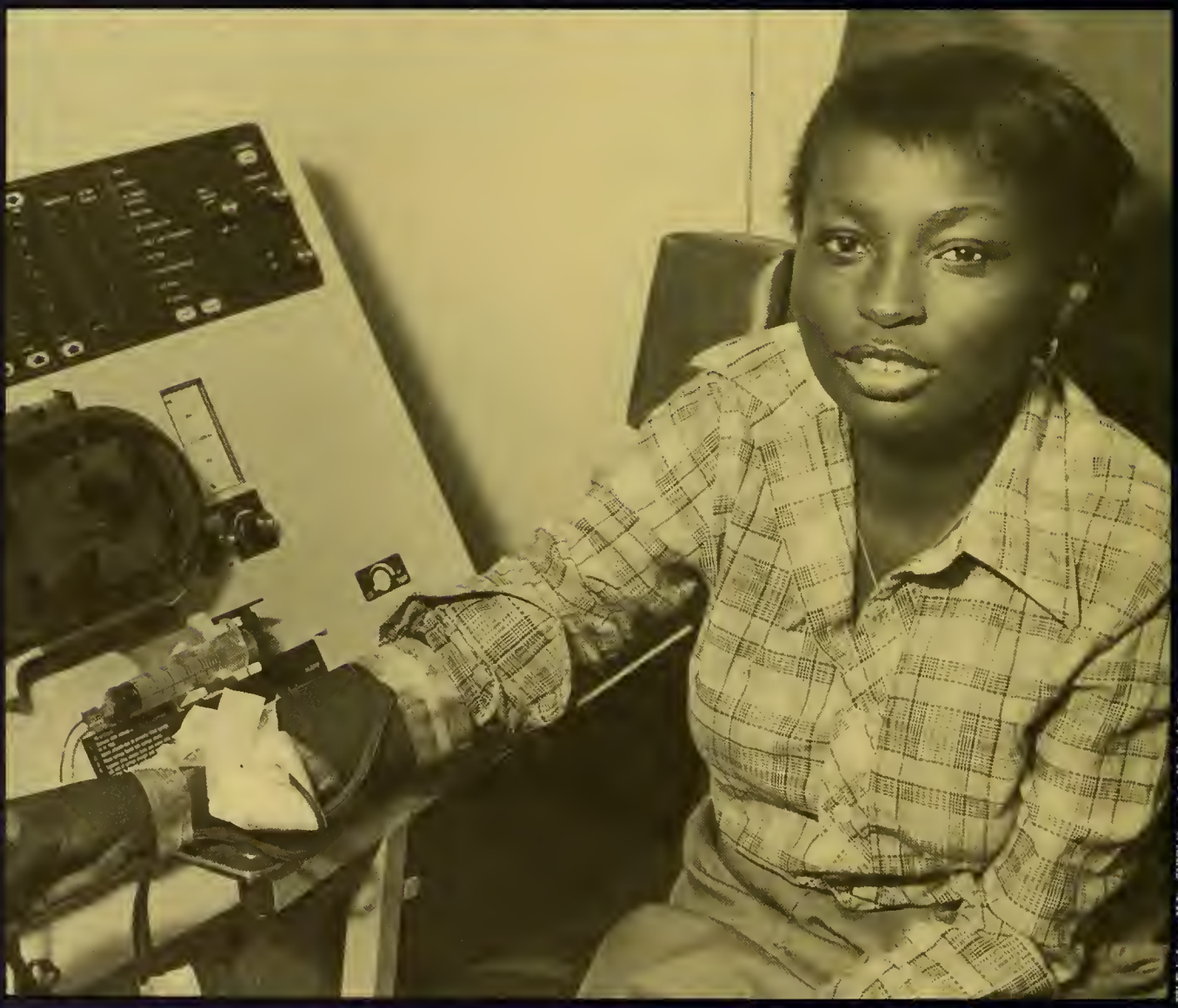
As a joint effort with the National Cancer Institute and the National Institute on Aging, NIADDK has fostered the development and operation of clinical nutrition research units to encourage a multidisciplinary approach to clinical nutrition research opportunities and problems. Core grants awarded

through the program are designed to provide support for common laboratories and a focus for clinical nutrition research and related educational and service activities in biomedical institutions and to complement ongoing research project grants and training awards. In addition to enhancing an environment for the education of medical students, residents, practicing physicians, and trainees and fellows in nutrition, each CNRU also provides support for a new investigator in clinical nutrition.

Currently there are seven CNRU's in operation, five of which are funded by NIADDK. During the past year, progress continued at these institutions in such areas as nutritional health maintenance, improved nutritional support of the acutely and chronically ill, nutritional support of hospitalized patients, assessment of nutritional status, effects of disease states on nutritional needs, effects of changes in nutritional status on disease, and resolution of controversies in clinical nutrition.



Research scientists in hematology are examining such areas as blood cell formation, cell membrane characteristics, and immune system mechanisms to provide insight into the causes of various blood diseases and the development of new methods for treating them. Scientific investigations are also improving knowledge of many forms of kidney disease and have resulted in the development of lifesaving measures such as dialysis.



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Kidney, Urologic, and Hematologic Diseases

Overview

Research efforts supported by the Division of Kidney, Urologic, and Hematologic Diseases are concentrated on the development of new methods of preventive therapy, early diagnosis, and more effective treatment through understanding of the basic mechanisms and causes of these disorders.

The kidneys are vital organs, critical to maintenance of the body's internal environment, particularly the composition, volume, and pressure of the body fluids. Under the renal physiology/pathophysiology program, studies address not only the normal structure and function of the kidney, but also the pathogenesis of renal diseases, such as glomerulonephritis, interstitial nephritis, and acute renal failure. In past years, such research has increased our knowledge of renal metabolism and the immunological causes of renal disease and has resulted in the development of several life-saving measures.

In the chronic renal disease program, studies focus on the metabolic and systemic abnormalities of uremia, a toxic condition that develops once renal failure is sufficiently advanced; it affects more than 10 per 100,000 persons annually. Other research projects are devoted to improving methods of kidney transplantation and maintenance therapies for end-stage renal disease (ESRD) patients and reducing the associated complications. Advances that have resulted from these investigations make useful lives possible for many patients who otherwise would have died after loss of kidney function. Hemodialysis (use of an artificial kidney machine to remove poisonous wastes directly from the blood) has been improved through new techniques; peritoneal dialysis (a procedure for clearing toxic waste across the peritoneal membrane) has become a clinically effective alternative to hemodialysis in the treatment of ESRD; and kidney transplantation has evolved from a method of last resort to the treatment of choice for certain patients.

Inseparable from the function of the kidneys is the function of the lower urinary tract, the primary concern of the urologic diseases program. Urinary tract infection, neuromuscular disorders of bladder function, obstruction, and kidney stone disease (urolithiasis) account for about 20 percent of deaths from kidney disease, and together these interrelated conditions account for a major portion of all disability caused by disorders of the urinary tract. They affect an estimated 8 million people in the United States each year. To provide insight into the causes and development of these multiple diseases, NIADDK supports many basic science investigations in both normal and abnormal lower urinary tract physiology as well as clinical studies of techniques to control resulting disorders. As products of this research, new drugs that permit effective treatment of serious infections have been developed, and advances in urologic surgery have led to the ability to repair congenital anomalies and surgically reconstruct diseased organs.

The division also supports a program of hematologic research in normal blood cell function and the pathogenesis of various diseases affecting the blood cells. Five major disease categories are of particular interest: anemias of genetic origin, nutritional anemias, metabolic disorders, disorders of blood cell production, and autoimmune hematologic disease. These studies, which are coordinated closely with other NIH blood disease programs, range from determination of the molecular structure of abnormal types of hemoglobin (the protein that enables blood cells to act as oxygen carriers) to clinical application and evaluation of new treatment methods of certain blood diseases such as aplastic anemia, Cooley's anemia, and sickle cell disease. This research has increased both fundamental and applied knowledge about blood and has led to improved management of many specific diseases.

Highlights of Research Advances

The following sections summarize recent accomplishments in research supported by the Division of Kidney, Urologic, and Hematologic Diseases.

- A new technique—percutaneous transluminal renal angioplasty—which involves the insertion of a special catheter into an abnormally narrowed renal artery and its forcible expansion, has been successfully used in the treatment of high blood pressure resulting from renovascular stenosis.

- High-dose intravenous methylprednisolone therapy can result in improved kidney function in a responsive subset of patients with renal complications of systemic lupus erythematosus.

- Hollow-fiber hemodialyzers can be reused safely and effectively in hemodialysis up to five times, after appropriate reprocessing and resterilizing. This can provide significant savings in a relatively costly maintenance therapy for end-stage renal disease.

- Continuous ambulatory peritoneal dialysis (CAPD), a technique for treating end-stage renal disease, developed under NIADDK sponsorship, has been shown to be a therapy particularly well suited to treatment of diabetic patients with chronic renal failure.

- The recurrence of upper urinary tract stone formation can be prevented by selective treatments tailored to underlying abnormalities of individual patients, involving restricted diets, ingestion of a minimum daily quantity of fluid, and specific drug protocols. Successful prevention of urolithiasis in up to four-fifths of known stone-formers represents a significant advance in dealing with a problem affecting at least 2 million to 3 million Americans and millions more throughout the world.

- A new, quicker, and more sensitive test for prenatal diagnosis of sickle cell anemia has been developed which does not involve the relatively risky procedure of acquiring samples of fetal blood. The complexity and cost of the new test are so reduced that it is feasible for many laboratories worldwide, rather than just the few specialized laboratories capable of performing such tests heretofore.

Kidney Cell Physiology—Analysis of Ion Concentration by Electron Microprobe

The powerful technique of electron probe microanalysis has been applied to the study of kidney physiology since the early 1970's. It has been adopted for analyzing the ionic composition (sodium, potassium, calcium, magnesium, chloride, phosphorus, and sulfate) of the filtered liquid from the glomeruli (the filtering units of the kidney) and the fluid in the proximal and distal tubules. This method of analysis is especially valuable in that it is specific for many ions that otherwise are difficult to identify, it requires only minute samples, and it preserves the sample following analysis.

With electron probe microanalysis, understanding of kidney transport mechanisms is being gained through comparison of the ionic content of tubular cells and tubular fluids. The handling and location of drugs within the kidney are also being explored. Recently, NIADDK grantees have used this method to develop techniques for determining the chemical composition of the contents of isolated kidney epithelial cells grown in culture. They have found that the compound ouabain, used as a tonic for heart muscle, causes a marked increase in sodium within these cells. This and other findings resulting from the continued refinement and application of electron probe microanalysis promise to provide new insight into the processes associated with transport, metabolism, and volume regulation in epithelial cells in both the healthy and the diseased kidney.

Nephropathy

Analgesic Abuse Highlighted at Conference

A habitual, excessive intake of analgesic drugs may emerge as another cause of kidney disease in the United States. Recently, one team of investigators has produced evidence that about one-fifth of a group of 101 patients with interstitial nephritis had a history of consumption of large quantities of analgesics. Another study suggests that 13 percent of 362 patients with chronic renal failure and 10 percent of 140 patients with end-stage renal disease exhibited symptoms of analgesic nephropathy (kidney damage attributed to long-term analgesic abuse).

Recently, NIADDK cosponsored a conference on nephrotoxic mechanisms of drugs and the environment, at which preliminary epidemiological data were presented. These included indications, derived from a study of 520 dialysis patients and 1,016 matched hospital patient controls, that the relative risk for end-stage renal disease is greater when associated with large doses of *combined* analgesics as compared to ingestion of only one analgesic. The most frequently implicated analgesics are

phenacetin, its principal metabolite, acetaminophen, and aspirin. There is evidence that large doses of aspirin and phenacetin combined are more consistent nephrotoxins but that even lower doses, cumulative over longer periods of time, also may be damaging.

Clinical features of most cases of analgesic nephropathy include abnormal renovascular X-rays, markedly contracted kidneys, urinary tract infections, and upper gastrointestinal tract disease. Anemia is also frequently present in patients with analgesic nephropathy.

The group that appears to be at greatest risk for analgesic nephropathy is women over age 45 who chronically have ingested large quantities of combinations of analgesics (six or more tablets daily for 3 years or longer). In one study, patients gave a number of nonmedical reasons for their use of analgesics, including the desire to increase productivity at work or relieve tedium, as a general stimulant (since many combinations of analgesics also contain caffeine), or as a "habit." Fortunately, data show that early discontinuation of analgesic abuse can result in a measurable reduction in risk for nephropathy as well as stabilization or improvement of kidney function.

Rapidly Progressive Form of Silicon Nephropathy

Chronic exposure to silica in the workplace has been associated with mild malfunctioning of the kidneys and minor changes in their microscopic structure (histology). NIADDK grantees recently reported on four patients with silicon nephropathy who, unlike other patients identified with this disorder, had rapidly progressive renal failure much more severe than would be indicated by the histologic damage to their kidneys. Despite vigorous treatment, two patients died of the systemic illness and one continued on hemodialysis. The fourth improved after aggressive "pulse" therapy with the drug methylprednisolone.

From their findings, the investigators propose that silica induces this multisystem disease in two stages. The first is activation of the immune system with resulting complications similar to those seen in systemic lupus erythematosus, such as aches, joint pains, arthritis, and other musculoskeletal symptoms. The second is a direct, dose-dependent toxic effect on kidney tissue. The occurrence of this silicon nephropathy in four patients from similar locales suggests that geographic factors may be important in the ultimate kidney toxicity associated with silicon exposure. Although the mechanism of the beneficial effect of pulsed methylprednisolone therapy in the one improved patient is not known, the scientists recommend that this therapy receive serious consideration as part of the treatment regimen for any patient with this syndrome.

Polycystic Kidney Disease—Insights on Tubule Abnormalities

Polycystic kidney disease (PKD) is an inherited, slowly progressive condition that causes the diameter of renal tubules to expand to such a degree that some eventually balloon out to create cysts, and the expanded tubules eventually choke off the normal surrounding nephrons (blood filtering units). PKD is estimated to be responsible for 9 to 10 percent of all cases of end-stage renal disease. The specific pathogenic mechanism of PKD is unknown, and no effective treatment or preventive measures are at hand. However, there is mounting evidence that the basement membrane of the affected tubules is abnormally "stretchable." Studies to provide such data have been limited until recently by lack of a good animal model of the disease.

NIADDK-supported research workers currently are studying three chemically induced animal models of PKD (in rats and mice) and have developed a strain of mice with a genetic form of PKD for use as a comparison model. The scientists have observed a number of significant differences between normal and chemically altered animals. Kidneys from the latter group are much larger and have an abnormal texture upon dissection (possibly because of their cysts' being filled with fluid). Tubules in the polycystic animals also tend to lose their cells to a greater degree than those in controls, and they have a 10 percent increase in amino acid content, a level characteristic of the fibrous protein collagen. Careful chemical and physical analysis of cell and tissue samples from normal and polycystic animals will continue; results will help to characterize further the nature of the observed differences in the basement membranes of tubules, adding to our understanding of the onset and progression of PKD.

Renovascular Disease—New Nonsurgical Technique Appears Promising

Percutaneous transluminal renal angioplasty (PTRA) has recently emerged as a potential alternative to open surgery in the treatment of high blood pressure resulting from renovascular stenosis, a narrowing of the renal artery. The new technique involves a special catheter with a tiny built-in balloon at its tip. The tip of the catheter is advanced into the obstructed renal artery, and the balloon is momentarily inflated at high pressure, causing a forcible expansion and opening of the narrowed blood vessel. The balloon is then quickly deflated and the catheter withdrawn. Although early experience with the application of this novel approach has been quite encouraging, the studies have been limited and uncontrolled, and they included only short-term followup.

Investigators supported by NIADDK recently have extended this clinical experience by reporting on their use of PTRA in 12 patients with critical renovascular stenoses, marked functional impairment of their kidneys, and severe high blood pressure. The procedure, primarily performed in an attempt to preserve kidney function, led to at least partial expansion of 11 of the 13 stenoses treated, and stabilization or modest improvement in kidney function in 7 of the 11 patients in whom some technical success was achieved. Moreover, the patients' blood pressure appeared to be improved after PTRA. Complications encountered in the study were of only modest severity. Long-term observations are required to assess the duration of improvements from PTRA as well as any possible problems such as recurrent stenosis. However, the relatively less invasive nature and reasonably easy repeatability of the procedure are features that make PTRA particularly attractive in the treatment of selected high-risk patients with renovascular disease.

Lupus Nephritis—Therapy Shown Effective in Selected Patients

A few studies have shown that high-dose intravenous methylprednisolone (IV-MP) therapy may be effective in controlling rejection of kidney transplants as well as in ameliorating renal complications of systemic lupus erythematosus. Recently, NIADDK grantees undertook a study to identify factors that may predict a positive therapeutic response to this treatment among SLE patients with advanced loss of renal function.

The study population consisted of 34 patients with SLE-related nephritis, all of whom exhibited advanced renal deterioration. Therapy consisted of 1 gram of IV-MP administered over 30 minutes on 3 consecutive days. Kidney function was assessed through certain key measures—serum creatinine, creatinine clearance, and urinary protein—during the first 4 weeks following therapy and intermittently during the next 6 months. Twelve patients responded within 2 months of the beginning of therapy with evidence of at least a 20 percent improvement in kidney function. This improvement lasted about 6 weeks in 60 percent of responders. Those most likely to respond had developed renal deterioration within 3 months prior to treatment. These results suggest that high-dose IV-MP "pulse" therapy can result in improved kidney function—at times dramatically and of long duration—in a responsive subset of patients with SLE nephritis.

Chronic Renal Failure—Damaging Effects of Phosphate

Animal studies of chronic renal failure have demonstrated that high intake of phosphate accelerates kidney damage and the rate of loss of kidney function. Conversely, studies of patients with chronic renal disease receiving low-protein diets (which also tend to be low in phosphate) prior to dialysis show examples of slowing the loss of kidney function. An understanding of the mechanisms potentially responsible for the kidney-damaging effects of phosphate is thus of considerable practical importance.

NIADDK grantees, using a rat model of chronic renal failure, have studied changes in kidney tissue structure and function in animals maintained on diets of varying phosphate content. Rats fed higher phosphate food were found to have higher serum calcium, more calcification (hardening of tissue by deposits of calcium salts) in the kidney, and other adverse changes. The scientists also observed that kidneys removed from patients with chronic renal failure had a calcium content nine times greater than normal. These findings lend support to the hypothesis that diets high in phosphate may speed the loss of kidney function in these patients through calcification of the kidney's supporting tissue—the cortical tubular cells, basement membrane, and interstitium. Additional studies to develop practical means to slow or reverse this process are indicated.

Kidney Transplantation

Virus Particles Jeopardize Graft Survival

Cytomegalovirus (CMV) infection frequently occurs in renal transplant recipients, but an unresolved question is whether the infection is of sufficient gravity to impair graft survival significantly. Since previous studies had suggested that the presence of CMV particles in the blood (viremia) is a critical determinant of clinically important disease, clinicians supported by NIADDK and other NIH Institutes decided to investigate the effects of this state on the integrity of glomeruli (blood-filtering tufts of capillaries) in transplanted kidneys.

The investigation focused on 14 patients, all of whom were receiving some form of therapy to suppress their natural immune responses (immunosuppression) to their transplants; 11 suffered from CMV infection, and 7 of those had viremia. Biopsy specimens from the viremic patients showed severe *glomerular* damage and irregular deposits of immune proteins. By contrast, specimens from nonviremic patients had kidney *tubule* changes typical of graft rejection. The graft from one patient exhibited rejection pathology within 2 weeks after transplantation, which disappeared with increasing dosage of immunosuppressive steroid. However, 7 weeks after transplantation, CMV infection became manifest and the same kidney graft displayed glomerular lesions similar to those accompanying viremia. These lesions resolved when immunosuppressive therapy was decreased.

Results show that CMV infection and concomitant viremia compromise kidney transplant survival by causing acute glomerular injury, which is essentially distinct from the typical graft rejection phenomena. To preserve graft function in patients with CMV manifestations, the investigators recommend that clinicians perform renal biopsies and decrease immunosuppressive therapy whenever findings indicate CMV infection rather than immunologic rejection of the graft.

Prior Blood Transfusions Improve Graft Survival

Because of the limited supply of donor kidneys from compatible, living, related donors, the majority of kidney recipient patients receive cadaver kidney grafts. The overall rate of functional cadaver graft survival remains substantially below that for transplants from closely related, living donors, where a 5- to 8-year graft survival can be expected in about 60 to 70 percent of cases. In an effort to improve success of renal transplantation, scientists have studied the effect of various factors, including pretransplant blood transfusions, on graft survival.

NIADDK-supported investigators now report that the 3-year graft survival in patients pretransfused with one or more units of blood is 50 percent or higher, compared to 30 percent for nontransfused recipients. The benefit was shown to increase with the number of transfusions (up to 20) administered prior to the transplant procedure and was more manifest with the less well-matched grafts. These and similar studies add further support to the recommendation that candidates for eventual cadaver kidney transplants receive multiple blood transfusions during the period of maintenance dialysis preceding transplantation.

Dialysis Therapy

Repeat Use of Hemodialyzers Can Reduce Costs

Patients with irreversible kidney failure must be kept alive either with the aid of successful kidney transplantation or through maintenance dialysis treatment administered thrice weekly. Maintenance dialysis is very costly, partly because the blood filtering and purifying device (the hemodialyzer cartridge) is usually considered a disposable item of equipment, used only once and thrown away after a dialysis treatment.

In a laboratory study commissioned by NIADDK, investigators at the National Nephrology Foundation now report that reprocessing of the hollow-fiber hemodialyzers is both feasible and clinically effective for a total of five uses of the device. The researchers have found that with adherence to a specific procedure of washing and sterilizing and with suitable process and quality controls, reprocessed hemodialyzers have functional properties similar to those of new dialyzers. The data also demonstrate adequate cleanliness and sterility of reprocessed dialyzers. In fact, the scientists report, in 1979 about 18 percent of dialysis centers were routinely reprocessing and reusing part or all of their dialyzers, making possible additional cost savings in maintenance dialysis of patients with end-stage renal disease.

Ambulatory Treatment for Diabetic Patients with ESRD

End-stage renal disease in diabetes continues to be a serious medical and socioeconomic problem. Good results have been obtained with transplantation of kidneys from closely related donors, but the results of conventional dialysis therapy or of transplants from cadaver donors are not as good as those observed in nondiabetic ESRD patients. NIADDK investigators now report the successful treatment of diabetic ESRD patients by a method known as continuous ambulatory peritoneal dialysis. With this technique, metabolic waste products in the blood are removed through use of the patients' abdominal cavity lining (the peritoneum) as the filtering membrane. A patient on CAPD therapy maintains about 2 quarts of dialysis solution in the abdomen, exchanging it several times a day through a tube leading out of the abdominal cavity. This innovative and portable therapy enables patients to remain mobile and perform everyday tasks while their blood is being cleansed.

In this study, 20 patients with diabetic nephropathy who had received no previous dialysis treatment were treated with CAPD for periods of 2 months to 36 months. CAPD therapy resulted in satisfactory steady-state control of uremia, control of high blood pressure, a steady cardiovascular status without rapid fluid shifts, improvement of anemia, and good control of blood sugar (achieved by intraperitoneal administration of insulin, which eliminates the need for multiple insulin injections under the skin). The calculated 1- and 2-year survival rates (92 and 81 percent, respectively) and rates for control patients on maintenance hemodialysis (87 and 76 percent) were comparable to those reported by centers with the best success rates in hemodialysis. The investigators concluded that CAPD appears to be a good alternative treatment for many diabetic ESRD patients.

Essential Amino Acids and Reduction of Treatment Frequency

When patients with failing kidneys undergo chronic hemodialysis, they require a relatively substantial amount of dietary protein to maintain acceptable nitrogen balance. Unfortunately, however, the large quantity of nitrogen supplied by the ingested protein from mixed natural sources is metabolized to urea and a range of other potentially toxic nitrogenous waste products

which accumulate and must be removed by relatively frequent dialysis. In recent studies supported by NIADDK, investigators have sought to avoid the physiologic and economic burden of frequent dialysis treatment by lowering the protein content of some patients' diets and supplementing them with highly concentrated essential amino acids.

The study group consisted of five men and two women who had begun maintenance dialysis treatment 2 to 6 months earlier. The patients were dialyzed once weekly and participated in two different protocols: protocol 1, involving intake of 0.96 gram of protein per kilogram of body weight per day, and protocol 2, in which dietary protein was decreased to 0.40 gram and supplemented with capsules containing nine essential amino acids (e.g., valine or leucine). Comparison of protocol results demonstrated that a low-protein diet supplemented with essential amino acids (protocol 2) improves nitrogen balance and protein nutrition, and increases lean tissue mass, while reducing nitrogen waste accumulation in patients with kidney failure. These findings could justify less frequent dialysis, at least temporarily, for patients who have been admitted relatively recently to maintenance dialysis and still have a modicum of residual natural kidney function.

Aerobic Exercise Training Improves Patient Health

About 70,000 people in the United States are now being kept alive by some form of maintenance dialysis therapy. Such patients often have numerous other health problems that interfere with their normal activities. They also have numerous risk factors that predispose them to heart disease and stroke. In recent studies supported by NIADDK, scientists have found that an aerobic exercise program for patients on dialysis can reduce blood pressure, improve anemia, correct abnormalities in fat and carbohydrate metabolism, improve capacity to do physical work, and improve psychological and social adjustment.

A major finding of research in this patient population is that aerobic (endurance) exercise performed regularly results in a progressive lowering of serum triglycerides, which are linked with atherosclerosis, and an increase in the level of high density lipoproteins, considered protective against atherosclerosis. The investigators also found that endurance training improves glucose tolerance and insulin sensitivity, a potentially desirable change from a diabetes-like metabolic aberration that can occur in some kidney failure patients. Moreover, psychological tests demonstrated an association between aerobic training and improvement in signs of depression, hostility, anxiety, social interaction, and a patient's outlook on the future. While more research is necessary to determine fully the benefits of exercise training for patients on kidney dialysis, this evidence indicates that such exercise may improve markedly both the length and quality of their lives.

Urolithiasis

Prevention of Recurrent Kidney Stones

Urinary tract stone disease (urolithiasis) is one of the most common renal-urologic diseases and represents a significant world health problem. In the United States, at least 1 percent of the population will develop urinary tract stones, primarily in the kidneys. Moreover, in many patients, even if stones are passed or surgically removed, new stones tend to develop. To meet the need for a planned and coordinated program of basic and clinical research on urolithiasis, five NIADDK Specialized Centers of Research are conducting multidisciplinary investigations aimed at improving the diagnosis and treatment of this problem and attempting to develop ways to prevent it.

Recent advances have enabled scientists to characterize the underlying problems leading to kidney stone formation in the majority of patients, permitting definitive diagnosis through simpler and more accurate clinical evaluation protocols. Moreover, by recognizing these specific chemical, physical, and anatomic abnormalities, research workers are developing selective therapies for individual patients.

At one SCOR, scientists now report that they have successfully prevented recurrence of upper urinary tract stone formation by such selective treatments. The study population consisted of 128 patients with a history of recurrent kidney stones containing calcium oxalate and/or calcium phosphate. Patients were placed on diets restricted in oxalate, calcium, sodium, and purine, and were urged to drink at least 3 liters of fluid per day to ensure a minimum urine output of 2 liters per day. Seven specific drug and dietary protocols were instituted to correct the suspected causes of stone formation, such as excessive intestinal absorption of dietary calcium or supersaturation of urine by uric acid salts. In the 4-month evaluations collected over the 3.4-year treatment period, most of the patients showed significantly reduced stone formation; the observed number of stones formed was only 9 to 26 percent of those expected. Moreover, 70 to 91 percent of the patients remained in complete remission. These results overwhelmingly support the thesis that selective treatment of underlying physiologic derangements can effectively prevent formation of kidney stones. The safety and efficacy of these and other treatment modalities continue to be evaluated at all five urolithiasis SCOR's.

Advances in Measuring Oxalate in Urine

All stones formed within the urinary tract contain an organic skeleton (matrix) and various types of mineral salt crystals. The major crystal type found in urolithiasis patients in the Western Hemisphere is calcium oxalate; thus, measurement of calcium and oxalate is necessary for study of excretion rates and other processes related to stone formation. However, although many urinary stones are high in oxalate content, few patients with stones have a significant increase in urinary excretion of this substance. A major deficiency in the study of oxalate metabolism is the lack of a simple, reliable method of measuring oxalate in biological fluids that can be adapted to microanalysis by renal physiologists.

With NIADDK support, two research groups are in the final stage of developing new techniques for the accurate determination of oxalate in urine. One method involves high-pressure liquid chromatography that separates from the urine a certain derivative of oxalate; the second technique measures another derivative of oxalate by electron capture detection. The NIADDK-supported scientists, joined by a third laboratory that uses an older, recognized method of oxalate measurement (which is both cumbersome and time-consuming), are now testing and comparing these new techniques. If results are favorable, investigators will have an improved means for evaluating stone-forming patients, which will assist in the development of more effective approaches to preventive therapy.

Cooley's Anemia

Improved Drug Delivery for Control of Iron Overload

In Cooley's anemia, a serious inherited red blood cell disease, patients are unable to produce sufficient new red blood cells to replace those that age prematurely and die. The only treatment currently available is repeated transfusion of normal blood; however, the therapy has the side effect of increasing the iron load in the patient's tissues through accumulation of the additional iron derived from repeated blood transfusions. The iron overload causes functional failure of various organs, particularly the heart, and will eventually lead to death. Removal of excess iron by iron-chelating (iron-binding) agents is the only known therapy, and the only practical and approved chelating drug to date is desferrioxamine (DF). The efficacy of DF remains limited, however, by rapid excretion in the urine, low uptake by iron storge organs such as the liver and spleen, and the cost and pain involved in administration of the required high doses.

NIADDK-supported investigators have now found that several types of man-made "liposomes"—tiny spheres of fat-like material used to encapsulate other substances—can act as biological carriers for the "packaging" and delivery, in the body, of iron chelators. In studies with mice, such liposome-encapsulated drug preparations have been shown to be more effective than the injection of nonencapsulated DF in reducing liver iron content and increasing urinary excretion of iron. They also offer the potential of reducing effective drug dosages (and thus cost) and toxic side effects of the chelator. This technique of using liposome-encapsulated chelators may improve markedly the current therapy for iron overload in patients with Cooley's anemia and may allow effective delivery of new chelating agents currently under development.

Anemia of Renal Failure

Erythropoietin Therapy Shown Feasible

Nearly all of the 70,000 patients undergoing dialysis for chronic renal failure suffer from anemia, largely due to decreased production of erythropoietin (EP) by their diseased kidneys. EP is a hormone-like substance which stimulates the development and maturation of new red blood cells in the bone marrow. Theoretically, one could enhance blood cell production by adding EP from exogenous sources, but this theory has not been supported experimentally. To resolve the controversy, an NIADDK-supported investigator has established a sheep model of chronic renal failure. The sheep, some of which must be maintained on hemodialysis, are being studied for their response to infused EP. The investigator has shown clearly that the anemia of chronic renal failure in the sheep can be corrected entirely with daily EP infusions. No inhibitors of erythropoiesis (the production of red blood cells) have been demonstrated in the uremic sera of sheep. Although these studies must be extended, they are the first to show the feasibility of this therapeutic approach.

Injectable Androgens Indicated for Dialysis Patients

Earlier studies have shown certain male sex hormones (androgens) are moderately effective in treating the anemia of chronic renal failure. Such studies have been largely uncontrolled and have not assessed comparative drug efficacy or the patients' responsiveness. NIADDK grantees have now completed a randomized clinical trial to compare the effects of injected and of orally administered androgens in increasing the number and mass of red blood cells (hematocrit) in anemic patients on maintenance hemodialysis.

One hundred and forty-three patients (103 men, 40 women), including 15 patients whose kidneys had been surgically removed, were enrolled in the study protocol, which involved administration of four androgens: nandrolone decanoate and testosterone

enanthate by intramuscular injection, and fluoxymesterone and oxymetholone by mouth. Men were divided into groups receiving all four androgens; women did not receive testosterone enanthate.

Significant hematocrit increases occurred in more than 50 percent of the patients, and were related to the injected drugs—nandrolone and testosterone (men), and nandrolone alone (women). Almost 25 percent of the subjects withdrew from the study, primarily because they were concerned about reported androgen side effects, such as liver damage, acne, and the appearance of secondary male sex characteristics in women. Patients without kidneys did not respond, possibly because they lacked the kidney-derived hormone that controls red cell production.

The study results demonstrate that the injectable androgens surpass oral androgens in correcting the anemia of hemodialysis patients. The problem of significant potential side effects of the androgens remains a concern that must be addressed.

Elliptocytosis—Reduced Cell Membrane Protein Linked with Defect

Elliptocytosis is an inherited disorder in which 25 to 75 percent of a person's red blood cells are elliptical rather than spherical in shape, and which is marked by varying degrees of increased red cell destruction and anemia. Using a new cellular analysis technique called ektacytometry, NIADDK-supported investigators have found that a specific red blood cell membrane protein ("band 4.1") is present in reduced amounts in patients from North Africa who have the disease. This is the first significant defect that has been characterized for a membrane structure disorder in man. It is now known that band 4.1 plays a central role in maintaining the stability of normal cell membranes, a finding that promises to have a significant impact on the study of cell membranes and membrane-related disorders of blood cells and cells of other tissues.

Sickle Cell Anemia

Red Cell Flexibility May Have Primary Role

Sickle cell anemia, an inherited disease affecting about 50,000 black Americans, is caused by the presence of an abnormal hemoglobin molecule in patients with the disorder. Sickle hemoglobin (hemoglobin S) aggregates (clumps) upon deoxygenation into elongated crystals and distorts the ordinarily disk-shaped red blood cells into a "sickled" form. Many scientists believe that log-jam-like blockage of capillaries by elongated, sickled cells leads to the tissue damage and destruction of red cells that is characteristic of this severe and even fatal disease.

Using novel methods, scientists at NIADDK and the National Institute of Dental Research have been able to detect aggregated hemoglobin S inside red cells under conditions similar to those existing in *arterial* blood. This was surprising since such aggregation was expected only under conditions similar to those occurring in capillary or *venous* blood.

These results, confirmed by a newly developed theoretical analysis, have significant implications for understanding sickle cell disease. It appears now that sickled red cells may have difficulty passing through arteriolar parts of the circulation even when the cells appear normal or unsickled under the microscope. Apparently, red cell flexibility is the important determinant of red cell survival, and tissue damage ensues from inflexibility, i.e., resistance to distortion of cell shape with narrow passages, rather than from the sickling process alone.

The experimental results of the NIH investigators indicate new possibilities for the treatment of sickle cell anemia. Drugs that change the amount or properties of the aggregated polymer within the red cell appear to be more important than agents that change the outer appearance of the sickled cells. As a result of these findings, investigators are now examining the possibility of using different drugs to modify the red blood cells' environment.

Improved Prenatal Test Developed

NIADDK-supported investigators have devised a new and sensitive assay for the prenatal diagnosis of sickle cell anemia. The assay improves on previous techniques which required sampling of fetal blood, a risky procedure. The new assay has extreme sensitivity, allowing the use of uncultured amniotic fluid cells withdrawn from the mother by relatively simple and safe procedures.

The assay is based on the recent development of a broad spectrum of enzymes that cleave DNA where specific nucleotide sequences (structural units of the DNA) occur. One of these enzymes, identified as MstII, cleaves DNA of the normal human beta-globin gene at a site which results in two fragments of differing lengths. However, the sickle mutation alters this recognition site so that the enzyme activity results in a single fragment of an intermediate length. This difference is easily detected by autoradiography and reduces the time required for the test from 5 weeks to 2 weeks. The complexity and cost of the test are so reduced that the assay is feasible for many laboratories around

the world, rather than just the few specialized laboratories that have been able to perform it until now.

Research Opportunities

Action of Drugs on Kidney Transport Systems

Development of plasma membrane vesicles from portions of specific kidney tubular cells has allowed the direct study of various transport processes in the kidney. Using this innovation, scientists can now gain a better understanding of the function, limitations, and regulation of the transport system in the intact kidney. This approach is particularly applicable to renal pharmacology, in which drugs and diuretics can be used to define and separate different transport processes. Conversely, the mode of action of many drugs can be understood only when the specific transport system upon which they act has been determined.

Mechanisms of Calcification in Renal Failure

As reported in the section on research advances, new evidence lends further support to the idea that diets high in phosphate may hasten the deterioration of kidney function in patients with renal failure by calcifying certain structural components of the kidney. The opportunity now exists to study the detailed molecular mechanisms responsible for this rapid calcification and the mechanisms involved in slowing the loss of kidney function by phosphate restriction.

Mechanisms of Transfusion-Improved Graft Survival

New data show that the 1-year graft survival rate in kidney transplant recipients with up to 20 previous blood transfusions is more than 30 percent greater than the survival rate in patients not receiving transfusions. Studies of the mechanisms underlying this improvement of graft survival, such as enhancement of the patient's immune system, should now be pursued.

Development of New Noninvasive Techniques

Clinical management of urinary tract stone disease has progressed significantly during the past decade. Despite numerous unresolved questions, there are now therapeutic methods to prevent, in many cases, the development of new stones. However, because kidney stones requiring surgical removal to preserve kidney functions will continue to occur, there remains a pressing need to develop new noninvasive techniques to dissolve, disrupt, or remove such stones. Several technical approaches, such as the use of ultrasound disintegration and shock wave disruption, are in the developmental or initial clinical testing stages.

Study of Genetic System with New DNA Techniques

In recent years, the rapidly emerging field of recombinant DNA technology has produced an explosion of knowledge of the genetics and synthesis of proteins (such as hemoglobin, the oxygen-carrying protein of red blood cells) at the molecular level. For example, the entire DNA sequence of several globin genes has been obtained by cloning and mapping, and the fine details of the process of globin chain synthesis have been elucidated with the use of special protein synthesizing systems. There are opportunities for extending these techniques to the study of any genetic system, such as that controlling the production of normal red blood cels, which becomes deranged in such diseases as hereditary spherocytosis, a congenital form of anemia.

Hybridomas As a Research Tool

Hybridomas are artificially created cells that produce pure or "monoclonal" antibodies. Newly developed technology now allows large numbers of these antibody-producing cells to be grown and relatively large amounts of pure antibody to be harvested. The hybridoma technique represents a powerful new way to investigate the differentiation process in general, and to obtain information specific to diseases of the blood-forming system. Using the technique, investigators will be able to learn how factors that determine the antigenic and surface properties of the red blood cell precursors are expressed, and to study changes that occur as the cells mature. They also will be able to purify populations of differentiating stem cells, permitting the study of normal stem cell function and of abnormal function in such blood diseases as leukemia and aplastic anemia.

Studies of Membrane Structure and Function

Techniques and methods have been improved sufficiently to elucidate the membrane structure of red blood cells and other, more complex cells, and pioneering studies have been performed

to relate structure and function in both normal and abnormal red cell membranes. Further investigation is a pressing need, particularly with regard to the following problems: abnormal red cell shape caused by foreign substances; disturbances of the fluidity of membrane lipids in processes such as cellular transport, enzyme function, and maintenance of membrane integrity; red cell hemolysis (liberation of hemoglobin) often associated with oxidant damage to red cell membrane lipids and proteins in a variety of disorders such as vitamin E deficiency and Cooley's anemia; and fragility of membranes in the inherited anemia called hereditary spherocytosis.

Program Plans

Investigations into Mechanisms and Mediators of Immunologic Kidney Disease

Three major forms of kidney disease—glomerulonephritis (inflammation of the glomeruli), nephrosis (damage to the renal tubules), and renal vascular disease—are responsible for the loss of kidney function in one-third to two-thirds of patients treated by dialysis or kidney transplantation. To obtain better definition of the problem of immunological kidney damage as seen in these disorders, and ultimately to understand any benefits of therapeutic or preventive measures, NIADDK plans to issue a request for applications inviting investigator-initiated research projects directed to immune mechanisms of the kidney. Additional information is needed regarding the identification, classification, clinical-pathologic correlation, familial features, and natural history of such kidney damage, as well as the mediators of immunologically induced glomerular injury. Institute advisors hope that a better understanding of mediator systems and their regulation will lead to advances in treatment.

Greater Cross-Disciplinary Training Orientation

A consensus among NIADDK advisors is that research training of future specialists in the study of the kidney should be reoriented to provide trainees with greater cross-disciplinary exposure to basic sciences such as biochemistry, pharmacology, immunology, genetics, and microbiology. To effect such a shift in training, the Institute has recommended to the program directors of the existing 32 institutional national research service awards that the breadth of basic sciences be expanded in their programs.

Announcement for Multidisciplinary Projects

Polycystic kidney disease is a serious problem, often leading to end-stage renal failure; however, only two or three laboratories are currently focusing active research attention on the disorder. In light of this fact—and because there are now sufficient models of PKD, both chemically induced and inherited, available for study—a request for applications is planned to encourage multidisciplinary investigator-initiated studies of PKD. Successful applicants will be required to represent two or more areas of research such as cellular biology, biochemistry, histochemistry, organ culture, immunology, nephrology, renal physiology and pathology, epidemiology, and genetics.

Prevention Monographs for Investigators, Clinicians

Through comprehensive literature searches by staff, contractors, and/or consultants, NIADDK plans to publish two prevention-related monographs. The first will define and describe areas of research that offer leads for development of additional data to enhance our ability to prevent kidney disease; it will be designed to stimulate investigator-initiated projects in those areas. The second monograph will summarize research or clinical experience that has been associated with either preventing or slowing the progression of disease; it will be directed toward enhancing the capability of primary physicians and kidney specialists.

Natural History of Chronic Renal Disease

NIADDK advisors have noted the lack of reliable epidemiological data on the various diseases leading to end-stage renal disease, the lack of broad-based data on the normal course of many of these diseases, and the scarcity of information on the effects of intervention. To address these needs, the Institute plans to establish a registry of patients with intermediate levels of chronic renal disease—that is, patients not yet close to terminal renal failure. Development of the registry will require the participation of consultants in such fields as epidemiology and statistics and of other appropriate Institutes (such as the National Heart, Lung, and Blood Institute), agencies (such as the Centers for Disease Control), and societies (such as the National Kidney Foundation). The project will be funded as a research grant or contract.

Effects of Nutrition Therapy on the Progression of Renal Failure

In April 1982, NIADDK organized a conference on nutrition therapy in chronic renal failure. One of the recommendations emanating from the conference was for a study on the effects of

nutrition therapy on the progression of renal failure. NIADDK will pursue this direction as part of a broader study on the natural history and mechanisms of renal diseases leading to end-stage renal disease, since many factors in addition to nutrition affect the progression of renal disease. The Institute intends to publish a request for applications for prospective, controlled studies in this area. Though provision will be made for sufficient breadth and flexibility to encourage innovative approaches, a major goal will be to identify and monitor nutritional, biochemical, and other factors that affect progression of kidney function toward renal failure. The studies would include nutritional/metabolic parameters and would consider the effects of variations in intake of nutrients on renal function. The announcement will emphasize the need to focus on nutrition and kidney disease.

Parameters for Initiating Dialysis Therapy

Currently 8,000 to 10,000 new patients are placed on dialysis therapy each year. However, practice on initiating dialysis varies widely among kidney specialists; some use extensive conservative therapy with strict dietary control, while others may initiate dialysis even when considerable kidney function still remains. To provide essential data on patient parameters (such as levels of residual kidney function) for initiating dialysis, a multicenter prospective study is planned. Such an investigation also promises to provide needed information about the relative outcomes of patients maintained for a period with careful dietary control.

Focus on Pathogenesis of Urinary Tract Infection

It is estimated that one-fifth of all women will develop urinary tract infection sometime in their lives. Even though most illness associated with this condition (ranging in severity from the simple appearance of bacteria in the urine to severe kidney infection and loss of kidney function) is actually attributable to infection of the lower urinary tract, pyelonephritis (infection and inflammation of the kidney and its pelvis) still accounts for 16 percent of the total deaths related to kidney-urinary tract disorders. Understanding of the factors involved in the onset and continuation of infection, however, remains relatively nonspecific, and knowledge is lacking with regard to specific details such as host-parasite interactions, the ability of bacteria to adhere to urinary tract lining, and the role of the mucin layer of the bladder as an antibacterial defense mechanism. To stimulate investigator-initiated research in these and other areas, NIADDK plans to cosponsor a conference with the National Institute of Allergy and Infectious Diseases that will focus multidisciplinary attention on research in progress. Following the conference, a request for applications or a program announcement will be issued.

State-of-the-Art Conference on Benign Prostatic Hyperplasia

The challenge to improve our understanding of benign prostatic hyperplasia has met with increased interest from scientists in disciplines beyond urology and endocrinology. As a result, NIADDK will encourage exploration of new avenues in prostate cell biology and cell receptors, biochemistry, hormonal influences, and disease treatment and prevention. Before issuing a request for applications or a program announcement for multidisciplinary projects related to benign prostatic hyperplasia, the Institute plans to conduct a state-of-the-art conference to focus on progress in prostate research and other related disciplines. A similar conference was held in 1975, and the next 5 years saw development of an animal model for this widespread disorder and several other major advances.

Refinement of Culture Systems for Stem Cell Differentiation

A number of systems are now available which have the potential for elucidating the mechanisms that control the early differentiation of stem cells (cells in the bone marrow that eventually produce different types of blood cells). However, the complexity and impurity of these recently developed test-tube culture systems and the general inadequacy of most of the techniques to separate different cell types are critical limitations. NIADDK therefore plans to issue a program announcement for projects to refine these systems and separation techniques and to characterize further the early events in the differentiation of bone marrow stem cells.

Multidisciplinary Conference on Metal Chelation

Since the first Symposium on Development of Iron Chelators for Clinical Use, held in 1975, interest in chelating agents (which bind to specific metals and prompt their elimination) has widened dramatically. Progress in this field has demonstrated the importance of applying information gained from seemingly unrelated studies by investigators in such disciplines as metal coordination chemistry, biochemistry, and pharmacology. Moreover, application of information gained from the now common use of iron-chelating drugs in the treatment of patients with Cooley's anemia would help advance research on chelation

therapy for disorders related to other metals such as lead and aluminum, and for cases of accidental poisoning with radioactive isotopes. To expedite such information exchange for improving our understanding of chelation in medicine, NIADDK is planning a conference to bring together a group of investigators interested in chelation of various metals, along with experts in relevant medical fields.

Special Programs—Urolithiasis SCOR's

Urinary tract stone disease is one of the most common renal-urologic diseases worldwide. In the United States, at least 1 percent of the population will develop urinary tract stones, primarily in the kidneys. The condition, while not usually fatal, causes considerable suffering, morbidity, and loss of work. Moreover, it is recurrent in many cases, new stones being formed in certain individuals repeatedly. Prior to the initiation of the Specialized Centers of Research in urolithiasis, there was relatively little support for research on the disease. Five SCOR's in urolithiasis were awarded for the first time in 1977 on the recommendation of NIADDK's National Advisory Council and Congress. The SCOR's were established to meet the need for a planned and coordinated program of basic and clinical research specifically directed at diagnosis, treatment, and prevention of the disease.

Each SCOR is an identifiable organizational unit within an academic institution and has the central theme of urolithiasis research. The SCOR pools resources from multiple disciplines and departments in both basic and clinical sciences, allowing those with in-depth knowledge and common research interests to work together toward specific objectives. Thus the divergent resources, facilities, and expertise of many disciplines can be utilized to meet scientific goals that would be difficult to accomplish through traditional research grants.

During the past year, investigators at the urolithiasis SCOR's continued their progress in a wide range of research areas, including the following:

- Development of a rational treatment program for urolithiasis in which therapy is selected on the basis of its appropriate physicochemical effects on stone formation in urine, the correction of the underlying physiologic derangements, and minimal potential complications.
- Prospective identification of the factors influencing the risk of kidney stone recurrence.
- Examination of the role of urinary macromolecules in inhibiting the growth of calcium oxalate crystals in the urinary tract.
- Investigation of the pathophysiology of hypercalciuria (an excess of calcium in the urine) and kidney stone formation, and possible hormonal influences on the relationship between calcium, oxalate, urate, and phosphate transport across epithelial tissue in the kidneys and intestines.
- Systematic exploration of the physicochemical mechanisms governing calcium-oxalate-seeded crystal growth, such as the nature and concentration of inhibitors, degree of supersaturation, and presence of surface-active agents.

Based on the program to date and projected research needs, an evaluation of the SCOR's is being sponsored by NIADDK to compare their effectiveness with that of other support mechanisms for stimulating research in urolithiasis.

Stephen McCarr-II, UNIPHOTO

Through NIADDK's centers program, specialized multidisciplinary environments are fostered to expand and improve research, patient and professional education, and clinical care and rehabilitation in arthritis and diabetes.

Stephen McCarr-II, UNIPHOTO

William A. Kelley, UNIPHOTO

Sixth Annual Report on Evaluation of Multipurpose Arthritis Centers*

Introduction

In fiscal year 1977 NIADDK initiated the Multipurpose Arthritis Centers program in response to the National Arthritis Act of 1974, which first authorized a new, national program of comprehensive arthritis centers. The MAC's are designed (1) to demonstrate and stimulate the prompt and effective application of available knowledge for the treatment of patients with arthritis and related musculoskeletal diseases and (2) to develop new knowledge essential for the control of these disorders. To this end, the centers are expected to develop and effect programs in basic and/or clinical research; professional, patient, and public education; and community-related activities and health services research.

A major goal of NIADDK is to encourage each center to achieve an optimal balance among the three essential operational components while developing special competence in one or more fields. This report, the FY 1982 submission, concentrates primarily on examples of studies conducted during the past year that reflect the diversity and value of the centers program. These highlights are indicative of activities of all centers but should not be considered comprehensive for 1982.

Center Research Projects

Inherent in the concept of a Multipurpose Arthritis Center is a strong component of research. Center grant support is intended to complement traditional research grant support in a given institution to establish related special projects and stimulate the development of new research projects. Consequently, each candidate Multipurpose Arthritis Center is required to be receiving research grant support for basic and/or clinical biomedical research related to rheumatic diseases if it is to be eligible for a center grant award. Each center, therefore, possesses a substantial research base to examine the cause of rheumatic diseases and to study the means of improving their diagnosis and treatment.

Research projects supported by center grant funds are almost exclusively developmental and feasibility studies. These studies are designed to encourage investigators to explore interdisciplinary and highly innovative scientific approaches which may later form the basis of applications for traditional research grant awards from NIH or other agencies. The activities described in this evaluation report are funded primarily with center grant support. Figure 3 in chapter I lists all current active Multipurpose Arthritis Centers and their locations.

MAC investigators at the University of Connecticut in Farmington are studying the role of zinc in rheumatoid arthritis. This substance has been shown to influence immune function and the inflammatory response—key factors in the etiology of rheumatoid arthritis. They are studying the zinc profiles of patients with rheumatoid arthritis and comparing the results with those obtained from age- and sex-matched controls. The first phase of the study is a survey of a large group with rheumatoid arthritis, regardless of their current therapy for the disease, to determine whether there is a difference between zinc profiles in these persons and those in disease-free and nontreated control individuals. So far, 27 patients with rheumatoid arthritis and 20 controls have been studied. Initial results indicate that plasma zinc levels for patients with rheumatoid arthritis are significantly lower than those of healthy controls, and that zinc levels in red cells were significantly higher in patients with severe rheumatoid arthritis than in healthy controls. It is next planned that more patients will be added to the study population. In addition, future studies will include the effect of various drug therapies, such as treatment with aspirin and penicillamine, on zinc levels,

* *The Public Health Service Act, which mandates a program of Multipurpose Arthritis Centers and Diabetes Research and Training Centers at NIADDK, also directs that the activities of these centers be evaluated each year and be reported to the Congress. The center evaluation reports for fiscal year 1982 are presented in this chapter.*

and will also include patients with osteoarthritis and systemic lupus erythematosus.

During the past several years, the Johns Hopkins center in Baltimore has been involved in a long-term investigation of the genetics of inbred populations with regard to susceptibility to rheumatic disease. The primary group being studied is the Old Order Amish of Lancaster County, Penn., a highly inbred population of 17,000 people descended from a limited number of European Caucasian ancestors. These individuals have not only well-documented genealogies, but also large families: factors that make this group an ideal one in which to study the genetics of rheumatic disease. So far, center investigators have found that two specific diseases, sacroiliitis and ankylosing spondylitis, are associated in large numbers in this population with the major histocompatibility antigen known as B27.

The Johns Hopkins study is also beginning to show that the prevalence of other rheumatic diseases, including both adult and juvenile rheumatoid arthritis and SLE, is also greater than would be expected in other populations. Analysis of the data associated with individuals who have SLE has shown, however, that the distribution of histocompatibility antigens in this case is not greater than would be expected in a normal population. Further work has suggested that there may be at least one non-histocompatibility gene that is common to several autoimmune diseases. Studies are under way to determine how this gene might influence the expression of these diseases, and, using a larger study population, if this hypothesis is valid.

Investigators at the University of Missouri MAC in Columbia are examining a phenomenon closely associated with some rheumatic diseases: the production of autoantibodies that recognize a number of antigens associated with the cell nucleus. The reason for the production of these antibodies, the types of antigens recognized by the antibodies, and the nature of the immune response itself remain to be explained.

Utilizing the mouse as an experimental system, investigators are developing a series of hybridomas (artificially produced immunocompetent cells that each manufacture a single type of antibody to a specific antigen) that produce antibodies to a number of nuclear antigens. These antibodies will be of use in measuring the heterogeneity of the host immune response to the nuclear antigens and will provide information on the biochemical nature of the antigenic determinants recognized by the individual autoantibodies. So far, researchers at the center have discovered that most of the monoclonal hybridoma-derived antibodies produced have been of the immunoglobulin M class. In addition, one of the mouse monoclonal antibodies recognizes a small protein that is similar to nuclear antigens recognized by human antibodies. This is significant because it shows that the mouse system may be an appropriate one in which to examine human rheumatic disease. In the coming year, the researchers expect to develop more such monoclonal antibodies for further study of the antibody system concerned with the recognition of nuclear antigens.

Boston University's Multipurpose Arthritis Center is conducting a project to explore the possible role of hypersensitivity or antigenic mechanisms in the pathogenesis of the arthritis caused by disseminated gonococcal infection. During the past year, investigators at the center have shown that injection of gonorrhea-causing bacteria into the knee joints of rabbits causes synovitis (inflammation of the joint membrane). This is similar to, and histologically indistinguishable from, the arthritis that occurs following the injection of *E. coli* (intestinal) bacteria. Viable *E. coli*, however, can be recovered for long periods of time after injection into the knee joints, while the gonorrhea-causing bacteria cannot be recovered alive beyond 48 hours after injection. Therefore, utilizing the hypothesis that nonviable bacterial components may be involved in the etiology of gonococcal synovitis, arthritis center personnel found that synovitis could be caused merely by the injection of killed gonococci into the rabbits' knees.

The next step of this study involves being able to detect the persistence of bacterial components in the rabbit's synovial fluid and synovial membrane following the development of chronic arthritis. A monoclonal antibody is prepared for this purpose. In addition, for study of the role of complement in the disease process, a colony of complement-deficient rabbits is being bred. The rabbits will be injected with bacteria to determine if disease development in them differs from that in normal animals.

The center at the University of Michigan in Ann Arbor is investigating whether rheumatic diseases might be caused by viruses. Specifically, scientists there are examining reovirus-induced arthritis, a disease that occurs naturally in chickens and has a close histological resemblance to human rheumatoid arthritis. This provides an ideal model of viral-induced arthritis, which can be used not only to characterize in general terms the role of these viruses, but also to identify the detailed pathogenetic mechanism by which individual viral proteins induce the disease process. During the past year, a number of different strains of avian reovirus have been isolated. All virus isolates produced were found to induce arthritis, but the severity of the lesions varied among the different isolates. Comparison of these isolates showed that they could be distinguished from one another by unique electrophoretic patterns of migration of their genetic material (RNA). This ability to identify individual isolates will be important in planned studies designed to study the epidemiology of avian reovirus-induced arthritis in nature.

The MAC at Brigham and Women's Hospital in Boston is conducting a study of the ways that sleep patterns are altered in patients with arthritis and the reasons for such alterations. So far, 227 ambulatory patients have completed questionnaires about their sleep habits. Their medical records have been examined to determine the precise clinical diagnoses and the medications being used. Substantial sleep problems have been reported: 36.6 percent of the patients awaken every night; 20.4 percent get less than 6 hours' sleep a night; and 41.6 percent feel tired in the morning. Most of those who answered the questionnaire (57 percent) have rheumatoid arthritis, while a lesser number (13 percent) have osteoarthritis. In the next stage of the study, 15 patients will be selected for intensive analysis, including EEG sleep monitoring and psychological testing. Since sleep disturbances are a common problem in patients with arthritis, it is hoped that this study will lead to better understanding and, possibly, a remedy for the problem.

Center Education Projects

Another integral aspect of the Multipurpose Arthritis Centers program involves educational activities designed to facilitate and increase the education of all types of health professionals. The MAC at the University of Connecticut in Farmington is typical in utilizing its educational resources to teach health professionals in the community, including nurses, physical therapists, social workers, occupational therapists, and physicians, about rheumatic diseases. For example, a curriculum and course have been developed for allied health professionals. The objectives are to teach students to (1) recognize signs and symptoms of the various rheumatic diseases; (2) understand when referral to a physician is indicated; (3) identify the patient's need for physical therapy, use of adaptive equipment, rest, exercise, and joint protection; (4) be aware of common psychological problems associated with these conditions and how to deal with them; and (5) be aware of the community resources available to patients with these conditions and how to utilize these resources. Teaching is done both by lecture and by group discussion. This educational intervention will be evaluated by assessment of knowledge gains using a pre- and a post-test with a control and an experimental group. Similarly, the staffs of three visiting nurse associations are being trained in the use of computer-based lessons designed by the center. It is hoped that, through use of this latter method, education about the rheumatic diseases can be more easily disseminated throughout the community.

In addition, the Connecticut center has, for a number of years, been concerned with developing computer-based education methodologies for patients and physicians. A recent project was initiated to evaluate the efficacy of a 1½- to 2-hour patient education lesson on rheumatoid arthritis. After the lesson was constructed with the aid of center rheumatologists, an examination was devised through use of the center's statistical and evaluation core. The data that have been gathered so far indicate that the lesson increases the patients' knowledge of their disease, patients increased the length of their rest periods and took increased care to protect their joints, and they had an improved general outlook on life. Elements of this lesson are being expanded for use in teaching about other joint diseases, such as osteoarthritis.

This project is significant in that it shows that a relatively short period of computer-assisted instruction can be used to modify patient behavior. The center plans to develop a library of lessons for patients about different rheumatic diseases which can be used throughout the country to improve knowledge of patient care and also improve patient social support structure through the use of the lessons by the family and friends of the patient.

A national study, reported in 1979 in *Arthritis and Rheumatism*, concluded that educational opportunities in the area of rehabilitation were minimal for physicians studying to be rheumatologists. The Dartmouth center has attempted to rectify this deficiency by developing a curriculum in rehabilitation specifically designed and organized to meet the needs of the practicing rheumatologist. Educators who are specialists in curriculum design formulated a 20-hour course with three goals in mind: (1) to demonstrate how a rehabilitation consultation should be utilized; (2) to show how rehabilitation specialists could be used as patient care providers; and (3) to describe how a rehabilitation program could be successfully monitored. During the first phases of this project, sample curricula were evaluated not only by rheumatologists, but also by physical and occupational therapists.

Packaged as an instructional unit with a teacher's manual and audiovisual support materials, including videotape and slide/tape shows, the sample curriculum has been sent to nine other arthritis centers for testing among their physician populations. The pilot testing of the curriculum is now almost complete. Preliminary results indicate that this type of instruction has been received very favorably by all of the participating centers. During the next year, the curriculum will undergo a final revision to incorporate the suggestions received from the various users, then the instructional package will be made available and distributed to training centers throughout the country.

Center Community/Health Services Research Projects

The MAC located at the Brigham and Women's Hospital in Boston is evaluating the efficacy and efficiency of providing specialty outreach and physical and occupational therapy to the homebound elderly who are disabled by musculoskeletal disease. The intervention consists of 8 weeks of treatment in all activities of daily living and safety, which will be compared to the provision of usual services by home care programs. Outcomes measured by an independent assessor include functional ability, contentment, hospitalizations, and support services usage. Preliminary data analysis indicates that, while there has been no change in the number of hospitalizations or number of services used, there was a significant increase in the patients' ability to conduct daily activities. The findings suggest that reversible functional deficits exist in elderly homebound patients for whom physical therapy has not been prescribed. This is especially important in a population with an increasing average age, since 5 percent of Americans of age 65 and over are homebound at present, and 29 percent of these have arthritis.

The arthritis center at the University of California in San Francisco is conducting a study to evaluate the long-term social and medical outcomes of total hip joint replacement, an exceptionally costly operation. The 90,000 hip joint replacements performed each year are estimated to cost at least $1 billion, and though the procedure has been shown to be successful in relieving pain and restoring physical function in a large proportion of recipients, it has not been evaluated in terms of how it improves the quality of life and reduces disability—areas that this study is designed to explore.

The study initially examined 1,389 total hip replacement operations to determine if adequate data were available for an intensive survey of costs of care, social and medical outcomes of treatment, and the relationship among medical, functional, and disability outcomes. One hundred and eighty-one persons have been entered into the study and assessed for previous work history, work disability, and occupational characteristics, as well as joint pain, physical function, and health status. A preliminary finding is that, among interviewed patients, the proportion of those who were employed did experience a reduction in work limitations after surgery. It was also discovered that the measurement of hip function up to 1 year after surgery was not a predictor of the ability to work. The investigators have concluded that, although total hip replacement results in reduced pain and increased range of motion, it has very little net effect on employment.

In the area of pediatric rheumatology, researchers at the University of Missouri's MAC in Columbia have developed a comprehensive model care demonstration unit dealing with arthritis in children, which has been integrated into the entire training program at the medical school. For example, during the past year, 80 third-year medical students have attended one afternoon pediatric rheumatology clinic, and 3 fourth-year students have taken a block of work which includes four to six afternoons in the clinic. In addition, residents in physical medicine, rehabilitation, child health, and rheumatology spend a significant amount of time in the clinic as part of their training. The center has also developed a number of lectures which have been presented throughout Missouri. The subjects addressed during the past year include pediatric spondyloarthropathies, Kawasaki syndrome, plasmapheresis in children, Reiter's syndrome, and rheumatic fever. There are also regularly scheduled conferences for family practice residents. In addition to the social worker, nurse, dietitian, and physical and occupational therapist, who are already members of the pediatric rheumatology team in the clinic, an ophthalmologist who has a specific interest in the inflammatory eye conditions that afflict children with rheumatic diseases has been added.

The Missouri center is also making progress toward developing an evaluation of outcome in the demonstration unit through analysis of referral patterns of physicians both before and after they have had training in pediatric rheumatology at the MAC. A telephone log is being developed as an outcome measure, since it reflects unsolicited requests for information and assistance. The hypothesis being tested is that general knowledge of the availability of a pediatric rheumatologist at the center will increase the volume of calls over time, but this increase will be much more rapid among those with direct training by the pediatric rheumatology unit than among those with no prior contact.

Core Units

During the past year, a number of core units were in operation at several of the Multipurpose Arthritis Centers. These shared-use facilities are designed to increase the effectiveness and efficiency of each center's activities. For biomedical research, there are core units for tissue culture, connective tissue metabolism, immunology, histocompatibility testing, and research involving hybridomas, among others. Core units in other areas are concerned with biostatistics, evaluation methodologies, educational activities, and epidemiology.

The center at the University of Alabama in Birmingham has developed a hybridoma core unit to enable investigators associated with the center to utilize this new technology to produce highly specific antibodies as research tools. Initially, the

hybridoma core was able only to produce limited numbers of hybridomas from animals immunized by the investigator and to freeze them for later use. Core unit personnel are now able to supply the necessary equipment for scientists who wish to produce their own hybridomas but lack the facilities; assist in planning and performing immunizations and screening assays; and immunochemically analyze the monoclonal antibodies that have been produced.

A related core, dealing with immunology, has been established at Indiana University's arthritis center in Indianapolis. It serves as a central facility for measurement of circulating immune complexes and *in vitro* antibody formation by human peripheral blood lymphocytes. The core is used by several members of the center in projects dealing with immune function in polymyositis, the role of complement in immune function, and the pathogenesis of hypogammaglobulinemia.

The MAC at Boston University has two active core units. The first, dealing with amyloid, supports essential personnel, animal resources, and other research needs, and the core staff coordinates a variety of amyloid studies including biophysical, immunologic, electron-microscopic, clinical, and therapeutic projects. For example, center investigators have evaluated the soft tissue uptake of bone-scanning radionuclides in patients with amyloidosis in an effort to find a diagnostic test that would not require tissue biopsy. In another study, it was observed that a specific strain of mice, the A/J strain, was highly resistant to amyloid induction, a finding that led to a series of experiments designed to elucidate the genetic basis of amyloid resistance or susceptibility.

The other Boston core, concerned primarily with evaluation, has focused on the measurement of health status in arthritis patients. Investigators have developed the Arthritis Impact Measurement Scales (AIMS), a self-administered questionnaire designed to measure the effect of various interventions on rheumatic diseases. The AIMS instrument has had a major impact on the ways in which the results of clinical drug trials and other interventions are defined and measured, and it is currently being used by a number of investigators throughout the country. The staff of the evaluation core unit has also worked closely with the amyloid core staff to develop a computerized data set on amyloid patients, which, when completed, will be a unique resource for the study of the disease, since the director of the Boston center has collected one of the largest clinical series of amyloid patients in the world.

Another evaluation core unit is in operation at the Multipurpose Arthritis Center at the University of Michigan in Ann Arbor. This core unit is designed to provide center investigators with assistance related to all aspects of statistics, computer programming, design of questionnaires and other instruments, and data collection for ongoing projects. These include studies of arthritis in children, development of training modules for occupational and physical therapists, and a project measuring how social work referrals are implemented for arthritis clinic patients.

The statistical core unit at the Johns Hopkins MAC has provided a means of data storage and analysis for many projects, including those dealing with epidemiology of rheumatic diseases, nervous system manifestations of Sjögren's syndrome, and the early detection of ischemic necrosis of bone, and a study to define better the course and outcome of lung disease associated with scleroderma. This core has also made it possible for the center to carry out projects involving a large number of survey data, such as a manpower study for the entire state, and, by providing resources to center members in different departments (i.e., orthopedics, pediatric rheumatology, and dermatology), has facilitated the collaborative efforts of the entire center.

A statistics and evaluation core unit located at the University of Connecticut center has provided support services to a variety of projects requiring data base management, computer access and programming, aid in the design and evaluation of projects, statistical analyses, and formal evaluation techniques. Specific projects in which the core has been active include patient education using computers, research involving the role of zinc in rheumatoid arthritis (described above), and study design and data analysis for an investigation of the regulation of the immune response.

Coordination and Collaboration Among Centers

A special emphasis of NIADDK program management is to foster and effect intercenter activity to make the Multipurpose Arthritis Centers program more efficient. One way of approaching this goal has been NIADDK's sponsorship of annual meetings of center directors, center personnel, and the Institute staff responsible for administering the program. Such meetings, at which ongoing activities and plans are thoroughly discussed, provide an important opportunity for closer coordination among centers. In addition, the NIADDK centers program office annually compiles and updates a directory of center personnel as well as a listing of instructional materials produced by the centers, and is in contact with each center by means of periodic letters and phone calls. The centers have also been encouraged to utilize the services of the Arthritis Information Clearinghouse, which is funded by

NIADDK contract as a repository for educational and other materials. This enables health professionals around the country to have access to literature produced by the centers during the course of their investigations.

An example of intercenter collaboration is found at the Multipurpose Arthritis Center located at Dartmouth, which has been testing, along with nine other MAC's, a rehabilitation-oriented curriculum for rheumatology fellows. So far, the curriculum has been distributed and implemented. In the next step, the program will be evaluated by both the instructors and the fellows, and appropriate modifications will be made before the teaching program is finalized for publication and dissemination to other locations.

The arthritis center at Stanford University has developed a program training manual on using self-help groups in the care of arthritis. The program has been tested in a middle-class community and is currently available in both English and Spanish. The University of Connecticut MAC is cooperating with Stanford by testing the Spanish-language materials in a low-income community.

The Multipurpose Arthritis Center at Boston University has been active with other centers in a number of areas. The evaluation core unit at Boston has worked with Stanford's center to develop a direct comparison between the AIMS instrument, described above, and various disability-measuring instruments that Stanford has developed; has collaborated with investigators at the University of Wisconsin's MAC in Milwaukee to examine the psychological aspects of arthritis; and is conducting a study with the Johns Hopkins center on the benefits of multifaceted treatment (drug therapy, exercise, psychological support) for the functional and health status of patients with rheumatoid arthritis. The Boston center is also working with the Indiana arthritis center on a study on the hyaluronic acid content of deep and subcutaneous bursae.

Center Evaluation

To ensure that the goals addressed by each center in its original grant application are being fully and successfully implemented, there are several types of ongoing evaluation activities. First, the MAC's evaluate continually both the quality and the effectiveness of their endeavors. The evaluation mechanisms vary according to the activity being studied, such as pre- and post-testing of students, chart audits of physicians who have received training, and process evaluation based on numbers of attendees at courses and lectures. A number of these measures, which may involve special evaluation core units, are described in preceding sections of this chapter. Many of the centers also have groups of outside consultants visit their institutions for several days at a time each year to determine the quality of the ongoing activities.

In addition, the centers program office of NIADDK monitors carefully the work of the various MAC's through staff site visits, analysis of yearly progress reports, letters and telephone calls, and the annual meeting of the center directors.

On a more formal basis, NIADDK recently awarded a contract to develop methodology to evaluate the education and community components of the Multipurpose Arthritis Centers. During the course of the project, the contractor first gained a familiarity with the activities of the various centers and then, after close consultation with the NIADDK program staff, formulated a number of specific evaluation questions to be addressed. The results of this effort have been a description of each evaluation question along with an assessment of the best way to perform the evaluation, the resources required by both NIADDK and each center, and the optimal time for evaluation. In addition, the contractor has produced an "evaluation guide" to be distributed to all MAC's to ensure that they will maintain high evaluation standards.

Conclusion

The Department of Health and Human Services finds that the Multipurpose Arthritis Centers are continuing to progress significantly toward achieving their congressionally mandated objectives. This progress has been particularly evident during the past year with notable maturation of the program, involving high-quality research developments, prompt application of research findings in patient care, professional and lay education, broad collaboration with care providers, and productive demonstration activities.

Fifth Annual Report on Evaluation of Diabetes Research and Training Centers

Introduction

In 1974, Congress authorized the Secretary of Health, Education, and Welfare (now HHS) to establish the Diabetes Research and Training Center program within the National Institutes of Health. This authority was subsequently delegated to the National Institute of Arthritis, Metabolism, and Digestive Diseases (now NIADDK), which initiated the DRTC program in October 1976. The law mandates that the DRTC's conduct

"(A) research in the diagnosis and the treatment of diabetes mellitus and related endocrine and metabolic disorders and the complications resulting from such disease or disorders,

(B) training programs for physicians and allied health personnel in current methods of diagnosis and treatment of such disease, disorders, and complications, and

(C) information programs for physicians and allied health personnel who provide primary care for patients with such disease, disorders, or complications."

Section 435(b) of the Public Health Service Act states:

> "The Secretary shall evaluate on an annual basis the activities of the centers developed or expanded under this section and shall report to the Congress (on or before November 30 of each year) the results of his evaluation."

At the present time there are seven centers, with $7.9 million funding in fiscal year 1982. This report provides Congress with an evaluation of the DRTC program in general for fiscal year 1982, and it includes current evaluation information on selected program activities.

The establishment and development of the DRTC's has followed closely the recommendations of the National Commission on Diabetes (*Long-Range Plan to Combat Diabetes*, DHEW Publication No. [NIH] 76-1018). Toward this end, the centers have been established at institutions where a substantial base of high-quality, independently supported research in diabetes and related endocrine and metabolic disorders already existed. Within this environment, key participating investigators in each of the DRTC's hold individually funded support in diabetes-related research and training, and the additional support from the center funding provides for shared resources (cores), pilot and feasibility studies for young investigators or investigators new to the field of diabetes, training and information transfer activities, and enrichment of the total research environment.

This interdisciplinary approach has led to enhanced cooperative and collaborative efforts to address the problems associated with diabetes mellitus and has provided a unique national resource. Outreach activities have provided prompt and effective transfer of new knowledge to health professionals. While each DRTC has developed its own independent program in accordance with local needs, interests, and resources, each is also responsive to national needs and works cooperatively with NIADDK and other federally supported diabetes programs. The DRTC's also collaborate with relevant municipal, county, and state health agencies and coordinate their various activities with local and regional medical associations and appropriate voluntary agencies.

The most recent report of the National Diabetes Advisory Board (NIH Publication No. 82-2143, May 1982) has a chapter entitled "Barriers to Widespread Application of Treatment Advances," which points out that widespread dissemination of present knowledge and its incorporation into clinical practice could have a significant impact on both the quality of care for diabetic patients and the cost of that care. Further, it was stated that, since such dissemination is dependent on a diverse health care

system, the circumstances cited have impeded effective dissemination. The DRTC program was one of several congressionally mandated programs established to improve this situation. In the past 5 years, the DRTC's have developed and evaluated a variety of approaches to professional education and training for use in other settings. These approaches include the most recent advances and are designed for training of the broad spectrum of health care professionals responsible for the management and care of the diabetic patient.

The DRTC's have joined with Federal, state, and voluntary agencies in an effort to make the availability of materials developed by all of the centers as widely known as possible. Much more needs to be done and will require the cooperation of all segments of the health care system. The DRTC's actively collaborate with other programs and health groups; for lack of space, this report presents only selected examples. The significant progress in program development will be underused if there are not greater efforts toward dissemination of current knowledge of treatment and care for diabetic patients.

The DRTC's will continue to pursue all avenues open to them within their mandate for the dissemination of current knowledge to as many health care professionals as possible. The fact that there are only seven DRTC's would confine the program to very limited impact in this regard, were it not for the effort to design programs to encourage individuals receiving training in one center to teach these programs to others who, in turn, will be able to pass on the information. Under this strategy, the centers are always available for needed consultation but can devote their major efforts to development of needed approaches or modifications.

Table 6 lists the seven active DRTC's, the date each was established, and the total amount awarded to each in fiscal year 1982. All have undergone at least one competitive renewal review and have received continued funding. A renewal application from one center will undergo review during FY 1983.

Of NIADDK's total Diabetes Extramural Program budget for fiscal year 1982, approximately 9.5 percent was allocated for the support of Diabetes Research and Training Centers. Since the centers foster interdisciplinary activities, and the research, training, and information transfer activities are interrelated, the fraction of total center funds supporting each component can be only approximated; however, 60 to 75 percent is primarily associated with the research component.

Types of Evaluation

The evaluation of the DRTC's is accomplished by four independent mechanisms: (1) the NIH peer review system, (2) organizations external to the NIADDK, (3) NIADDK staff, and (4) individual, center-based, in-house evaluations. In-house evaluations concentrate primarily on activities in and materials produced by center training and information transfer components in order to demonstrate effectiveness, and on preparation of progress reports and applications which intrinsically involve evaluation. Because all aspects of the local review process at centers are fully evaluated by the peer review process, no further consideration of the center-based evaluation will be included in this report. The other three approaches are addressed below.

Table 6.—Start dates and fiscal year 1982 support for active Diabetes Research and Training Centers

	Project Start Date	FY 1982 Support (Total Cost)
Albert Einstein College of Medicine Bronx, N.Y.	9/1/77	$1,077,185
University of Chicago Chicago, Ill.	9/1/77	1,674,602
Indiana University Indianapolis, Ind.	9/1/77	911,370
University of Michigan Ann Arbor, Mich.	9/1/78	1,783,052
Vanderbilt University Nashville, Tenn.	9/1/78	1,027,593
University of Virginia Charlottesville, Va.	9/30/78	1,034,138
Washington University St. Louis, Mo.	9/1/77	414,246*
Total:		$7,922,186

* *3 months' funding*

Evaluation by NIH Peer Review

The peer review system of the National Institutes of Health provides a rigorous, thorough, and effective evaluation of the DRTC's. This form of evaluation comprises an initial review group site visit to the proposed center and a subsequent independent review of the initial review group's report by the

National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council. This evaluation serves as the primary basis for determining whether a center will be funded and for how long (usually 3 years or 5 years). At the end of the funding period, a renewal application may be submitted, the review of which includes a consideration of the center's progress toward achieving its goals and objectives during the previous period of support. Although conducted only every 3 to 5 years, the close scrutiny accorded this aspect of center evaluation makes it an extremely valuable, and indeed critical, part of the overall evaluation process. All of the eight centers originally funded have undergone competitive renewal review. One of these, although approved in principle, was judged not to have made sufficient progress toward program objectives to merit continued funding.

Evaluation by Outside Organizations

National Diabetes Advisory Board

The National Diabetes Advisory Board (NDAB) has a mandate to oversee progress and make recommendations regarding the efforts by all relevant Federal agencies in implementing the long-range plan originally proposed by the National Commission on Diabetes. Within this comprehensive framework, and after careful consideration of center activities, each report of the NDAB has addressed the progress of the DRTC program toward achieving its goals. In addition, the Board's advice and suggestions provide an ongoing external source of valuable guidance to the program. The NDAB's latest report stated,

> "Multidisciplinary centers, specialized research facilities, and major research programs related to diabetes and its complications are important components of the Long-Range Plan to Combat Diabetes. These programs provide opportunities distinct from individual research grant support by facilitating interdisciplinary collaboration and provision of core facilities in a cost-effective and efficient manner. In addition, productive interactions have developed between these centers and other Federal, State, and local components of the diabetes program which have resulted in improved training of professional and paraprofessional personnel providing care to the diabetic population."

Contract Evaluation

To provide more in-depth evaluation of the centers program, NIADDK has contracted with an outside group for a study to identify appropriate methods for evaluating the various center programs of the Institute, including the DRTC's. Because NIADDK-supported centers programs are new and highly innovative programs that are still developing and maturing, the Institute is particularly interested in methods appropriate to formative evaluation, an evaluative approach designed to aid in the development of a program in its early phases. Formative evaluation is expected to provide the Institute with useful information concerning ways in which the programs can be guided and strengthened. Since the contract was awarded, the contractor has been acquiring an operational knowledge of the program origins, objectives, organization, and operations, as well as reviewing and assessing existing methodologies for evaluating centers and programs of similar nature to identify precedents relevant to the current study. The contractor is refining the key issues for further development and matching them to available evaluation methods and measures to determine which issues can be most usefully and feasibly addressed. It is expected that a report of the results of this phase will be available in 1983. After appropriate review of the report, a decision will be made concerning a full-scale comprehensive evaluation.

Evaluation by NIADDK Staff

Each year, different aspects or activities of the DRTC's are selected for evaluation, and over a period of several years the major components of the centers have been addressed. For example, after 3 years of centers operation, a study of the pilot and feasibility studies was made which indicated that most new investigators receiving this funding went on to obtain individual research grants from NIH or other sources; thus this mechanism was an effective way of introducing and enticing investigators into research in the diabetes area. Next year this study will be repeated to see what has happened to these investigators in the meantime and how effective the mechanism remains in terms of recruitment to diabetes research. The results of the study will appear in next year's report.

Biomedical Research Cores

A biomedical core at a DRTC is a facility that provides a service needed by and available to a number of center research investigators to enable them to conduct biomedical research more efficiently. A core is usually directed by an acknowledged expert or has a consultant expert with particular capabilities relating to the function of the core. Cores differ from traditional clinical laboratories in that they (1) serve the *research* needs of a special group of funded investigators; (2) offer, in addition to a particular service or function, consultation and collaboration; (3) are often involved in experimental design; and (4) provide services which are generally not routine and are near the cutting edge of science. In addition, they may often involve equipment or procedures that are not easily developed, applied, or acquired by one individual investigator.

Another important feature of the cores is the training of individuals in new techniques and procedures. In general, the presence of cores makes unique resources, techniques, and capabilities available economically to a wide variety of new and established investigators who are involved in both basic and clinical research. In any given DRTC, the cores are based on ongoing research programs and thus reflect the focus of those programs. While centers do have cores with similar foci, the uses of these cores are very individualistic from one center to another. Centers have an average of four cores in the biomedical component. Typical cores serve as resources for performing radioimmune assays, preparing tissue cultures and/or media, and performing electron and light microscopy. All cores provide quality control consultation and perform limited developmental work.

The core director is a key element in the core's success. Although presently a subjective measurement, the consensus is that, ideally, the director should be a relatively senior scientist with an established research program, so that the core that he or she directs is in many respects an outgrowth of his or her research interests. This is the case in most of the DRTC cores. Excellence of performance and the core training function are believed to be highly dependent on the core director.

Cores expand primarily because of consumer demand. New scientific developments and techniques also contribute to expansion but may also be the cause for eliminating a service. It has been suggested that charges for core services would permit them to be self-sufficient. Experience at three DRTC's that have experimented with this concept in varying degrees shows that the added administrative costs for bookkeeping consumes most of the derived income and thus nullifies the potential cost-savings. For services performed in volume, centers are able to document cost-savings, greater efficiency, and increased quality control, when compared to the situation in which individual investigators perform their own analyses. Measures of cost-effectiveness for consultative services, increased collaboration, training, developmental research, and support to pilot and feasibility studies are very difficult to assess objectively, and no rigorous attempt has been made to show cost-savings in these areas.

Recently, considerable interest has been expressed with regard to the possibilities of sharing core resources among the centers. A "Diabetes Centers Core Inventory" has been prepared by NIADDK and distributed to the centers. A copy is also being deposited with the National Diabetes Information Clearinghouse so that these specialized resources will become more widely known. Considerable collaboration already exists among the centers and between centers and other institutions. While the center cores could not, within their budgetary constraints, perform large numbers of analyses or measurements for other institutions, the knowledge of these special resources should promote further collaboration and cooperation among research scientists. Further, under appropriate conditions, the DRTC cores may be available for training other scientists in specialized techniques, such as those associated with the use of a special animal model in the Vanderbilt DRTC animal resources core (described in the "Fourth Annual Report on Evaluation of Diabetes Research and Training Centers").

Further discussion of technology transfer among centers took place at one of the workshops associated with the diabetes centers annual meeting in June 1982. Though there were concerns that any given core could be overwhelmed with outside requests, it was also believed that judicious exploration and expansion of this concept was in everyone's best interests. Two proposals, which will be explored further, emerged from this meeting: (1) that a brief newsletter concerning new advances, availability of materials, etc., be coordinated by the NIADDK program staff for distribution among other centers; and (2) that glucagon and insulin radioimmunoassays be upgraded by exchange of reagents and samples for assaying and subsequent comparison.

That DRTC cores are very valuable adjuncts to research progress can be illustrated by selected highlights of recent research that involved utilization of the cores. Investigators at the University of Virginia DRTC have made a major contribution to understanding how insulin works by demonstrating the existence of and determining some of the characteristics of "mediators," a family of small molecules inside cells, which carry messages from insulin in the extracellular fluid into intracellular organelles. These mediators appear to be part of the cell membrane, and when insulin comes in contact with the membrane, the mediators are released and travel to various parts of the cell, carrying information that action is required. The discovery and characterization of these mediators is of major importance in understanding why insulin does not seem to be effective in certain kinds of diabetes and in developing new drugs for treating this disorder. The radioimmunoassay and tissue culture cores contributed significantly in the performance of these studies.

Studies at the Vanderbilt University DRTC that have significantly used core support from the animal model, instrumentation, and clinical research cores relate to an understanding of how glucose is transported in tissues and of its importance in unraveling abnormalities in diabetes. We know that insulin facilitates the entry of glucose into the cell. This is the principal mechanism by which insulin accelerates the metabolism of glucose. It is important that the glucose molecule is transported across the outer membrane of the cell by a specific molecule referred to as the "glucose carrier." For a number of years, a perplexing question has been whether the existing number of carriers simply shuttle back and forth across the membrane at a

more rapid pace or whether increased numbers of glucose carriers are made available for the transport function when the overall process is accelerated by insulin. These investigations have demonstrated that there is a reservoir of glucose transporters that reside in the Golgi apparatus of the adipose cell and are relocated into the plasma membrane when their action is needed to accelerate the transport process. In other words, the addition of insulin to the cell system brings about the recruitment of new glucose transporters from a reservoir within the cell to the surrounding cell membrane so that they can actively transport glucose from the exterior to the interior of the cell.

Cores containing special equipment that can be used by a number of investigators often provide unique resources, such as the cell sorter in the tissue culture core at the University of Virginia DRTC. Insulin is normally produced by beta cells of the pancreas. The beta cells constitute only a small fraction of all the cells in the pancreas; therefore, to understand the metabolism of beta cells completely, it will be necessary to isolate them from the other cells of the pancreas and study them independently. Using the pituitary gland as a model, a team of investigators at the Virginia DRTC has recently developed a method for separating hormone-secreting cells. The cell sorter, using a laser beam, can separate a mixture of cell types into its component cell types. The method provides a powerful new technique to aid investigation of the properties of beta cells and what goes wrong when they fail to secrete insulin in diabetes mellitus.

Collaborative efforts of research investigators at the University of Chicago DRTC, involving the radioimmunoassay and clinical studies, peptide and protein analysis, and cellular and molecular biology cores, have extended recent work on variant products of the human insulin gene. They (1) have demonstrated that the mutation resulting in an amino acid replacement in the insulin from one patient results in deletion of a restriction enzyme cleavage site in the patient's insulin gene, with the resulting product having no insulin activity; (2) have shown that the cause of familial hyperproinsulinemia (a higher than normal level of proinsulin in the blood) is an insulin gene mutation resulting in an amino acid replacement at one of the prohormone conversion sites; and (3) have identified a patient who secretes an insulin with lower than normal biological activity, but who responds normally when treated with porcine insulin. These studies document the causes of one class of diabetes and provide important information on the structure and function of the human insulin gene in health and disease.

Diabetic patients develop dilated areas called microaneurysms in the capillary vessels of the eye that can be visualized with an ophthalmoscope. This lesion occurs almost exclusively in people with diabetes and exemplifies the unique changes in small blood vessels that are associated with diabetes. An investigator at the Albert Einstein College of Medicine DRTC has recently described similar changes in the capillary vessels of the heart in diabetic animals, suggesting similarities in the vascular disease process in both the eye and the heart in diabetes. The chemistry core was useful in this study.

Investigators at the University of Indiana DRTC, utilizing the immunoassay core, have shown that there are an increased number of areas in fetal liver cells which bind insulin (insulin receptors) during the period just prior to birth. Unlike the process in adults, fetal binding does not decrease with high insulin levels. Thus, unborn children of diabetic mothers would be especially liable to have problems with high insulin levels because their cells cannot protect themselves by decreasing insulin binding.

Investigators at the Washington University DRTC, in continuing their studies on prevention of immune rejection of transplanted islet cells among different species, have developed a unique and important method for separating the islets from collagen. The large amount of collagen present in bovine, porcine, and human pancreas has been a barrier to successful isolation of sufficient numbers of islets by the previously used method of digestion with a specific enzyme, collagenase. The new process—a physical separation step—involves the use of Velcro; its fishhook-like structure retains the partially digested collagen and allows the islets to pass through. The technique now allows isolation of large numbers of islets in the purer form needed for further islet cell transplantion studies.

Patient Registries

The DRTC guidelines allow for the establishment of a patient registry but restrict its size to only the number of patients that can be justified for ongoing research and training and information transfer needs. Recently there has been interest in exploring the possibility of sharing data and of examining other uses of the registries and their value to the center activities. Such interest was evidenced by a workshop on this subject during the most recent annual diabetes centers meeting.

All but one of the seven DRTC's maintain patient registries. The number of patients entered varies from 65 to 1,500 (an average of 727). All registries have entered both insulin-dependent and noninsulin-dependent diabetic patients, with a slight preponderance of the latter. The collected data on each patient vary widely from center to center, reflecting the needs of the projects using each registry. The primary use for the registries at the DRTC's is in identying candidate patients for clinical research. Secondary uses include assessing the impact of professional

education, collecting longitudinal data, and training and teaching.

Educational Programs and Dissemination of Materials Developed for Professionals

The primary mandate of the DRTC training and information transfer component is the education and training of health professionals involved in the management of diabetes. More specifically, these activities encompass translation of the latest knowledge from research into general practice. At the time DRTC's were established, there was a relative paucity of tested or evaluated programs or materials addressing the current state of the art for training health professionals. Therefore, the centers initially had to develop and test new approaches, incorporating the best available information. Generally, as new materials have been developed, the DRTC's have utilized them in local programs to assess their effectiveness.

Ultimately, the centers are expected to promote training and education outreach programs designed to reach the largest possible number of health professionals responsible for the management of the diabetic patient. Not only must the programs be developed for use in a variety of settings, but also they must be adaptable for use by a wide variety of health professionals with, at most, consultation from the DRTC. When materials are ready for wide dissemination, the centers must also have enlisted the cooperation of Federal, state, and local agencies and voluntary health groups to undertake the task of wide dissemination of the programs and materials.

Most DRTC's are just beginning this phase of outreach. Some liaisons have been established, but more effort is needed to accomplish successfully the greatest possible dissemination. Coordination with other groups involved in various aspects of addressing the overall diabetes problem—the Centers for Disease Control State Diabetes Demonstration Projects, the Indian Health Service Model Diabetes Care Program, American Diabetes Association, Juvenile Diabetes Foundation, American Association of Diabetes Educators, and others—has been initiated by the DRTC's. Currently limited resources for this expansion of coordination has sharply restricted dissemination efforts.

NDIC Project

One approach that NIADDK has initiated to promote wider knowledge of available materials has been a cooperative venture of the centers with the National Diabetes Information Clearinghouse. The DRTC's, through their representation on the NDIC Advisory Committee, have begun to create a network for appropriate distribution of materials relating to education of patients and professionals and programs for training health professionals in diabetes. The collected materials will be collated by the NDIC into subject groupings, descriptive annotations will be prepared, and a composite listing will be developed. The accomplishments of the DRTC's will constitute the nucleus of the listings, which will be disseminated by the NDIC to all interested groups. This effort will provide nationwide access to information about a large proportion of available material in this area. It will also bring the most current methodology into more widespread usage and help prevent duplication of effort.

DRTC Programs and Materials

The DRTC's have almost eliminated overlap and/or duplication of effort in training and information transfer because of the varied interests and focus of each center and the close cooperation among centers during the developmental phase of the program. This can be illustrated by short descriptions of some selected activities in continuing medical education, new technology transfer, the team concept for the care and treatment of the diabetic patient, and interventions. In almost all cases, these programs are presented through DRTC cooperation with a local voluntary health agency or other health-oriented group.

Continuing Medical Education

The University of Michigan DRTC presents a semiannual symposium and preceptorships for practicing health professionals (nurses, dietitians, social workers, etc.). The trainees as a group first attend the symposium, during which they receive basic knowledge in the metabolic derangements, complications, special problems, diagnosis, and treatment of diabetes. Following the symposium, trainees in groups of four obtain a 2-day hands-on experience at the DRTC model demonstration unit, where they learn teaching and management skills. The preceptorship program is tailored to each participant's need. The effect of this program is being evaluated through formal testing of each participant before and after the symposium and following the preceptorships. In addition, skills are evaluated during the preceptorship. Six months after the preceptorship, the impact of this combined program on the participants' practice is assessed. This program will serve as a model for similar programs in other geographic areas. Thus far the program has been very popular in Michigan, with 75 or more in attendance at each presentation, and there is a waiting list for future offerings.

The Indiana DRTC has completed an intensive education program for internal medicine residents in the ambulatory care of

diabetic patients. The program consisted of seven components: (1) "Problem-Oriented Protocols" (POP's), a handbook of DRTC recommendations for diabetes management; (2) a day-long seminar to teach residents the skills necessary to use the POP's; (3) three weekly followup conferences to identify barriers to following the recommendations; (4) a retrospective chart audit; (5) use of patient record reminders generated by the clinic computer; (6) a special consultation service; and (7) a review conference 5 months after initial instruction. The most effective aspects of the program are being identified for use with future trainees.

More intensive training programs have been developed for nurses and dietitians. The University of Chicago DRTC curricula, "Becoming an Effective Educator: A Program for Staff Nurses" and "Diabetes and Nutrition: A Curriculum for the Practicing Dietitian," are complete training programs. Each contains a written monograph syllabus, handout materials, and professionally prepared slides illustrating numerous aspects of curriculum content. In addition, videotape simulations are provided for the nutritionist curricula; instructors' guides are provided for both. Evaluation of these curricula during developmental stages permitted many improvements in both format and content over the past few years. The curricula are continually examined for correctness and audience acceptability. Dissemination of curricula and training methodologies has occurred during formal presentation of these programs and through answers to direct requests from others for curriculum use.

The Washington University DRTC also has well-developed programs (described in last year's evaluation report) for nurses and for dietitians, which involve two unique aspects: an experience of "living as a diabetic" and a practicum in the model demonstration unit.

A self-instructional module on diabetes mellitus was developed at the University of Indiana DRTC for graduate nursing students enrolled in a clinical specialist (primary health care) program. The objectives of the module are to provide a brief overview of the pathophysiology of diabetes mellitus, provide up-to-date information on detection and management of diabetes, and assist in identifying components of nursing management in an ambulatory diabetic population. The students are given 3 weeks to learn the material and then are tested on their mastery of the content.

The University of Indiana DRTC also has developed a dietitian-diabetes referral network (in conjunction with the Indiana Dietetic Association) within the state. The purpose of the network is to provide more continuity of care and followup nutritional guidance for persons with diabetes. Ten percent of the registered dietitians in Indiana have volunteered to be members of the network. There are plans for evaluation of the network after 1 year, to include measures of both usage and patient outcomes. Not only does the network serve as an outreach resource for Indiana, but, if effective, it may serve as a prototype for many other states as well.

The Vanderbilt DRTC has addressed training for home health nurses who provide ongoing care through the nursing service of the local health department for individuals who are confined to home. Similarly, the Washington University DRTC has prepared a guide for home health aides. Both the Vanderbilt and the University of Chicago DRTC's have developed training programs for diabetes educators.

Two other programs that have been developed are "Consumer Problems in Management of Patients with Diabetes Mellitus" for medical practitioners (by the Vanderbilt University DRTC) and a diabetes seminar for the Scientific Assembly of the Virginia Academy of Family Physicians (by the University of Virginia DRTC). In addition, primary care physicians and their professional colleagues from a number of neighboring states have participated in regularly scheduled (every 3 months) 3-day courses at the Washington University DRTC. Participating physicians are instructed in the practicality, complexity, potential hazard, and resources required for implementation of diabetes treatment programs that include insulin infusion devices.

New Technology Transfer

One of the most important clinical questions today relating to diabetes is whether normalization of glucose metabolism will prevent the development of complications. Significant technological advances have occurred during the past few years through the development of insulin infusion devices (pumps) and home blood glucose monitoring systems. The DRTC's are making valuable contributions in facilitating transfer of these new technologies into general practice.

The Washington University DRTC has developed a physicians' seminar on new technology in diabetes care, which offers health professionals an intensive orientation and training program. The center is also preparing a guide to enable other professionals to give similar seminars.

A seminar on home blood glucose monitoring has also been presented by the University of Virginia DRTC. A manual for physicians who have attended the seminar is being developed to assist in their continuing management of diabetic patients. The Albert Einstein DRTC presented a symposium, "New

Technology in Diabetes Control," for nurses, dietitians, and physicians, which covered use of insulin infusion pumps, home blood glucose monitoring, and dietary approaches for home monitoring programs. The Indiana DRTC has developed a 15-minute didactic presentation on home blood glucose monitoring for interdisciplinary staff rotating through the diabetic outpatient clinic. This presentation compares urine and blood monitoring for glucose and gives an overview of the needed supplies and instruments, their availability and cost, and how they are used. The emphasis is on how to choose the most appropriate method for an individual patient with the goal of achieving glycemic control.

The Washington University DRTC has prepared materials for use with patients, including three videotapes on intensive diabetes control: "Auto Pump and Blood Glucose Monitoring," "Diabetes and the Pump," and "Blood Glucose Monitoring for Kids by Kids." Among various patient education booklets prepared by the Michigan DRTC is one entitled "Insulin Pump Therapy."

Team Concept for Care and Treatment

The use of the team concept by DRTC's for care and treatment of the diabetic patient was presented in detail in the "Fourth Annual Report on Evaluation of DRTC's." Extensions of the use of the team for diabetic care have occurred during the past year. The Albert Einstein DRTC has made the team concept the focus of its training and information transfer activities in training other teams, in the continuing education programs presented for physicians and other health professionals, and in training in its newly developed model demonstration unit.

One team training effort was at a long-term care facility for the chronically ill. (Approximately 15 percent of patients in such facilities suffer from diabetes mellitus.) By virtue of the prevalence of diabetes among the residents, team staff of the Albert Einstein DRTC were invited to evaluate the quality of care at this 1,000-bed institution. Based on the results of their initial evaluation, retraining of professional staff by the DRTC resulted in widespread changes in the quality and system of care. Through its program development approach, the DRTC was able to create a multidisciplinary team who, in turn, served as both consultants and teachers for other hospital staff members.

The University of Chicago DRTC also uses the team approach in its model demonstration unit, and it is developing a patient-oriented course entitled "Diabetes Survival—Pathways to Self-Management." The course utilizes a team of health care professional teachers (including nutritionists, nurses, pharmacists, and psychologists, as well as physicians) and consists of eight modules that can be given separately or in sequence. Active audience participation is encouraged through workshops, take-home assignments, and discussion. The thrust of the course, which has been pilot tested and subjected to formative evaluation, concerns the importance of group interactions in dealing with the multifaceted clinical and emotional problems of diabetes. The program thus represents an evolving training intervention involving the patient as an active member of the health care team.

The model demonstration unit at the Vanderbilt DRTC provides an opportunity for nursing, medical, dietary, and behavioral science students to work together and to develop a greater appreciation of these closely related disciplines. This training laboratory for health professionals is in an ambulatory setting, as most health care services for patients with diabetes can be provided on an ambulatory basis. The program has been thoroughly evaluated, and the results uniformly indicate that this is an excellent opportunity for students at Vanderbilt to observe and participate in the team care concept during their student years.

The University of Virginia DRTC has extended the team concept to include physicians in its outreach program in nearby communities (described in the fourth annual DRTC evaluation report) and has introduced the team concept in its new facility for training, continuing education, and patient care.

Interventions

The DRTC at the University of Chicago, in collaboration with the Centers for Disease Control-supported Illinois Diabetes Demonstration Project, has initiated an impact evaluation study of its diabetes physician education curriculum, which was developed over the first years of the DRTC program. The evaluation involves two groups of physicians in two similar suburban communities in a controlled study. Results indicate that the control group of physicians showed no significant changes in practice, whereas physicians taught by the physician education curriculum show significant positive changes in diabetes patient care management practices (involving making the diagnosis of diabetes, classifying the types of diabetes, having patients use home blood glucose monitoring, and providing patients with appropriate patient education through local hospital diabetes teaching services). The results of the study (which is still in progress) document the utility and value of the physician education curriculum and show that continuing physician education plays a major role in translating current clinical care modalities into optimal management of diabetic patients.

In a preliminary feasibility study on outreach activities, the Michigan DRTC selected six large and six small Michigan

communities for analysis. In four of the large and four of the small communities, an intensive study of all facets of diabetes care is nearly complete. The eight communities originally were randomly selected, and participating primary care physicians in each community were also randomly selected, as well as representative numbers of their diabetic patients. The study has involved an analysis of the diabetic care delivery system (services available, educational system, patient-professional interaction dynamics, etc.) and the outcome of this care for the diabetic patient. Eighty physicians and nearly 500 patients were involved. In large communities, 83 percent of patients had received formal education in diabetes during the course of their illness, but only 65 percent of patients in small communities had received such education. In communities of both sizes, the average time since the last formal patient education regarding diabetes management was 3 years, suggesting that there is considerable room for improvement in providing up-to-date diabetes education. Home glucose monitoring was being used by less than 5 percent of all patients, suggesting that increased health professional and patient education may have the potential of significantly improving patient management. The design of this study will permit an accurate portrayal of the current state of care for people with diabetes, including both care components and outcomes. This information should have considerable utility for others involved in planning and conducting community-based diabetes education programs, and there is evidence that this activity has generated a new interest about diabetes-related activities within these communities.

The selected DRTC programs and materials described above illustrate that considerable progress has been made in the areas of education and training. Many of these programs are now being disseminated, and efforts are under way to facilitate their distribution and use beyond the local areas where they were developed.

Collaborative Activities

An often-stated objective of multipurpose centers is to "increase collaboration." The DRTC's exhibit a wide variety of types of collaboration, some of which are presented here briefly.

Much collaboration occurs among individual research investigators. Such interactions are almost taken for granted, for they represent a fundamental aspect of the creative research process. Center investigators have expressed the opinion that the existence of their center has increased these collaborative efforts for the following reasons: (1) availability of the core resources, particularly the consultative services; (2) availability of funding for pilot and feasibility research projects; (3) seminars that are more frequent and more multidisciplinary; (4) more outside speakers coming to the center; and (5) greater opportunity for clinical collaboration because of the presence of the model demonstration units and patient registries.

Collaboration takes place not only among investigators in a single center, but, as often, with investigators in other centers or in other institutions. The latter type of collaboration often occurs as a result of availability of unique services from the center cores, and it supports the concept of the centers as a national resource.

Frequently, collaborative activities involve cores from one DRTC serving personnel at other DRTC's. Examples include the distribution of an animal model, consultation regarding specialized techniques, or providing training in new and/or highly specialized methodologies.

Collaboration also exists with cores or facilities in centers or large programs in other disciplines at the same institution, such as two administratively independent tissue culture cores sharing space, personnel, and equipment, or contributing to an already existing instrument core rather than setting up a separate one. Not only may this foster further collaboration with investigators in other disciplines, it also represents an economy for both types of centers involved. The DRTC's have been encouraged to explore additional opportunities for collaboration in areas that offer the potential for further economies.

Documentation exists for a significant increase in clinical research due to the availability of model demonstration units and patient registries supported by the centers. Clinical research is by nature interdisciplinary; thus, creating an environment conducive to collaboration can naturally be expected to increase the opportunities for clinical studies. Illustrative of this type of collaboration are the new training programs relating to insulin pumps and home blood glucose monitoring described previously.

NIADDK's initiation of its multicenter clinical trial on the relation of blood glucose control to development of diabetic complications (Diabetes Control and Complications Trial) has also provided opportunities for use of expertise and programs developed by the DRTC's. Phase I of the trial, which is now in progress, involves preparation of the protocols for phase II (which will test the feasibility of maintaining two groups of patients with different blood glucose levels). Two of the DRTC institutions are participating clinical centers in the trial, with DRTC personnel in active roles. In addition, the principal

investigator from one of the DRTC's is serving as chairman of the clinical trial steering committee. Many other DRTC staff members are serving as ad hoc consultants to the many work groups necessary to prepare the study protocol. There are indications, as the clinical trial develops, of other potentially significant activities in which the DRTC's may play key collaborative roles, particularly in the area of professional education and the psychosocial aspects of diabetes.

There is also considerable collaboration among the centers in relation to training and information transfer activities. An annual meeting of key participants in this area is held in early winter each year, hosted by one of the centers. This is not only a valuable opportunity for exchange of information and ideas, but also allows individuals from one center to observe firsthand the facilities and capabilities of another center. This interchange has resulted in exchanges of materials among centers, in adoption of methodologies across centers, and in invaluable review and critique of each center's program by peers from the other centers and invited outside speakers/consultants. In one example, the University of Chicago DRTC staff conducted its dietitian program in Grand Rapids, Mich., and at the same time trained members of the University of Michigan DRTC staff so that they will be able to replicate the symposium. Another symposium of this type is scheduled to be conducted by the University of Michigan DRTC staff in October.

The participation of the DRTC's as a group in the NDIC project (described above) will result in even greater collaboration, not only with other Federal and private agencies involved, but also with groups or individuals contemplating or engaged in the use of materials and programs developed at a center. This activity will contribute significantly to the role of the DRTC's as a national resource.

Collaboration of DRTC's with other Federal programs in diabetes has been strongly urged from the inception of the centers program. There are and have been many collaborations between the DRTC's and the Centers for Disease Control State Diabetes Demonstration Projects. Many instances have been described in previous reports; they may be characterized generally as (1) training by DRTC's of Centers for Disease Control state personnel about diabetes, (2) cooperating actively or as consultants relative to interventions being carried out by the state projects, and (3) exchange of data and other information. As described previously in this report, one current example of such collaboration involves the Illinois Diabetes Demonstration Project and the University of Chicago DRTC, regarding an intervention comparing the value of additional training and education of physicians to "business as usual" in two matched Chicago suburbs.

The DRTC's have also been collaborating with the Indian Health Service Model Diabetes Care Program in a feasibility study to develop and evaluate culturally acceptable and effective methods to reduce the severity and costs of diabetes and its complications in the Indian population. Several DRTC's have been actively cooperating with this program in terms of providing consultants, providing training for Indian Health Service professional staff, and modifying materials to make them appropriate for use with specific Indian populations.

When all of the types of collaboration are considered together, the benefits of center activities that accrue to programs and activities outside the center institution are impressive. This maturation of the centers in progressing toward a fulfillment of the mandate originally posed is very gratifying and provides significant justification for continued support of the centers program.

Conclusion

The Department of Health and Human Services finds that the Diabetes Research and Training Centers are continuing to progress significantly toward achieving their congressionally mandated objectives. This progress has been particularly evident during this past year with the notable progress toward maturation of the training and information transfer programs and activities, the breadth and diversity of collaborations that have been developed, and the high quality of research developments involving the core resources.

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