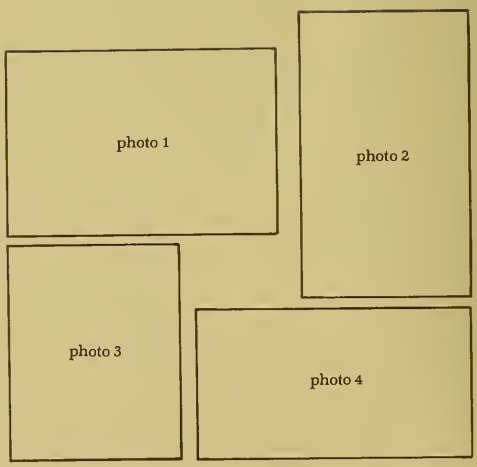
Fourth Annual Report of the Director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

IMPROVING HEALTH THROUGH RESEARCH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service • National Institutes of Health



NIADDK supports the development and refinement of a wide range of therapies. Some of them are high-technology procedures such as kidney dialysis (photo 1) and insulin pump infusion (photo 3). A complex surgical procedure, liver transplantation, has helped this 6-year-old boy (photo 2) to have a normal, active life. Design improvements make splints more effective in treating musculoskeletal problems (photo 4).

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January 1985

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Preface

The Health Programs Extension Act of 1980 mandates that the Director of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) provide the President and the Congress an annual report on the Institute's progress in its research attack on the diseases within its purview. NIADDK is responsible for research on a wide range of diseases—mostly of a serious and chronic nature—including arthritis, bone and skin diseases, diabetes and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and diseases of the kidney, urinary tract, and blood. These diseases afflict many millions of Americans of all ages, backgrounds, and economic circumstances and constitute a tremendous drain, both direct and indirect, on the human and economic resources of the country.

Although these diseases relate to different body systems and organs, many possess common pathogenic mechanisms that can be identified and understood through similar studies in molecular biology, immunology, metabolism, endocrinology, and genetics. Because of the many common threads that run through the fabric of these apparently disparate diseases, new knowledge generated in one group of disorders clarifies and contributes to progress in the fight against the others. It is our hope that the impressive research advances of the past year, chronicled in this report, will contribute substantially to the achievement of our common goal—to create the new knowledge that makes possible improved diagnosis, treatment, and prevention of the diseases within our purview.

Mortimer B. Lipsett, M.D.
Director
National Institute of Arthritis,
Diabetes, and Digestive and Kidney Diseases

Executive Summary

Fiscal Year 1984

Section 434(e) of the Public Health Service Act (as amended by the Health Programs Extension Act of 1980, P.L. 96-538), requires an annual report to the President and to the Congress from the Director of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases on the Institute's progress toward its broad and varied goals in the disease areas under its purview.

In response to this directive, the *Fourth Annual Report of the Director, NIADDK,* highlights the Institute's ongoing programs, recent achievements, and plans for future activities in arthritis, diabetes, digestive diseases, kidney diseases, and the many related diseases for which it bears responsibility. The report is organized by research focus, with chapters II through V presenting the research accomplishments, special programs, and program plans of each of the four major areas of responsibility of the Institute. These chapters are preceded by an overview of the Institute's structure and activities (chapter I) and followed by the annual reports on the evaluation of the Institute's multipurpose centers program (chapter VI).

The first chapter describes briefly the Institute's place within the National Institutes of Health and its role in the health research community. The NIADDK's organization and mission are described in detail, with emphasis on the many diseases within the Institute's purview. Also reviewed and contrasted are the various mechanisms of support used by the NIADDK to foster laboratory and clinical research and research training. Summarized here are the Institute's activities in fundamental and clinical biomedical research, research manpower development, disease prevention, technology assessment and transfer, program planning and analysis, and evaluation. There is a section on financial resources, in historical perspective, which portrays graphically the overwhelming emphasis placed by the Institute on investigator-initiated research grants evaluated by the scientific peers of the applicant. Approximately 85 percent of the extramural obligations of the NIADDK are devoted to this mechanism. Finally, there is a section on awards and honors bestowed during the past year on grantees, Institute consultants, and Institute staff.

Reflected in this initial chapter and in later ones is the sense of excitement generated by recent breakthroughs in science in their application to the endocrine, metabolic, nutritional, digestive, renal, blood, skin, bone, and joint diseases for which the Institute is responsible. Such techniques as cloning and transcription of genetic material, molecular analysis and controlled biosynthesis, applications of monoclonal antibodies, and, especially, the new interdisciplinary convergences seen in immunologic, genetic, and molecular biologic studies of mechanisms of cell function and of disease have led to major new developments in work under NIADDK support. These advances are revolutionizing our understanding of and our clinical approaches to the diseases discussed in this volume.

Chapters II through V are devoted to specific research advances and Institute plans under four broad subject groupings: Arthritis, Musculoskeletal, and Skin Diseases; Diabetes, Endocrinology, and Metabolic Diseases; Digestive Diseases and Nutrition; and Kidney, Urologic, and Hematologic Diseases. In each of these chapters, there is first an overview of the scope of Institute concerns (corresponding to the branch-level programs of each Division, in general), followed by highlights of research advances. Altogether, significant advances are reported in research and development related to more than 70 diseases and medical therapies with a major impact on the national health scene. In addition, these four chapters outline the NIADDK's plans for continued contributions to improvements in biomedical knowledge, treatment and prevention methods, and research skills that, collectively, will make a crucial difference in the outlook for eventual prevention or cure of many chronic and disabling diseases.

The volume concludes with the annual evaluation reports of two important 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 in this overall annual report to afford the reader an all-inclusive overview of the Institute's progress. Each of the two reports in chapter VI provides examples of research and program accomplishments of the centers supported under the two programs. Particular attention is devoted to the educational and community health services projects sponsored by the centers. Center evaluation is discussed, and evidence is provided for the thesis that the sharing of resources, which is fundamental to the concept of these programs, both within centers and among centers, results in significantly enhanced productivity.

Contents

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Exhibits

I. NIADDK Mission and Strategies

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is 1 of 11 Institutes known collectively as the National Institutes of Health (NIH), the largest biomedical research organization in the world. The 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 the spearhead of the Nation's biomedical research effort. 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.

The NIADDK's efforts to uncover the causes of chronic and disabling diseases have earned it widespread recognition as an Institute whose responsibilities are attuned to the pressing health problems of the American public and whose accomplishments often profoundly affect the disease interests of other Institutes as well.

The focus on basic research that has guided the NIADDK's programs is grounded in the fact that an understanding of the intrinsic nature of each disease is imperative for the development 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, molecular biology, physics, chemistry, pathology, genetics, immunology, physiology, and pharmacology that provide the foundation of knowledge about diseases that can affect many organs or organ systems.

The basic research successes achieved through the NIADDK's programs have been impressive, and these 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 places a strong emphasis on basic research because the etiologies of many of the diseases involved are unknown.

Facing page

NIADDK-supported pharmacologic research has led to promising new treatments for conditions such as arthritis, skin disease, diabetic neuropathy, gallstones, and hereditary anemias.

NIADDK's Mission and History

The Institute was established in 1950 through the Omnibus Medical Research Act and started its activities as the National Institute of Arthritis and Metabolic Diseases. Its early history and activities are described extensively in the *First Annual Report of the Director of NIADDK* (NIH Publication No. 82-2375, September 1982). The mission of the Institute and its scope of research have broadened significantly with the passage of time. In 1982, the Institute was designated a Bureau of the NIH, joining the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Library of Medicine at that administrative level. Exhibit 1 lists representative examples of the NIADDK's present areas of research responsibility.

EXHIBIT 1. NIADDK research areas: some representative examples

DIVISION OF ARTHRITIS, MUSCULOSKELETAL, AND SKIN 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

- Scoliosis
- Osteoporosis
- Osteogenesis imperfecta
- Bone transplantation
- Bone metabolism
- Bone fractures and healing
- Artificial joints and biomaterials
- Congenital and acquired skeletal anomalies
- Low back pain
- Exercise pathophysiology
- Osteoarthritis

Skin Diseases

- Psoriasis
- Acne
- Mechanisms of retinoid action on skin
- Bullous diseases
- Ichthyosis
- Vitiligo
- Eczematous and immunologic diseases
- Allergic dermatoses
- Cutis laxa
- Photobiology
- Heritable skin disorders

DIVISION OF DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES

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

DIVISION OF DIGESTIVE DISEASES AND NUTRITION

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
- Anal-rectal diseases and disorders

Intestinal and Pancreatic Diseases

- Gastrointestinal hormones
- Small intestine structure and function
- Intestinal digestion, absorption, and secretion
- Malabsorption syndromes
- Diarrheal diseases, celiac sprue
- Structure and function of the exocrine pancreas
- Pancreatitis
- Small intestine and pancreas transplantation
- Salivary gland structure, function, metabolism, and diseases

Liver and Biliary Tract Diseases

- Hepatitis
- Cirrhosis
- Genetic liver disease
- Hepatic transport defects
- Cholesterol and pigment gallstones
- Cholesterol and bile acid metabolism
- Liver regeneration
- Liver transplantation
- Portal hypertension and varices
- Liver coma

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

DIVISION OF KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

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

Hematologic 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

The Institute's programs are of profound importance to the American people because there is no subgroup of our population immune to attack by one or more of the diseases or disorders addressed by NIADDK.

The impact of some of these diseases is indicated in exhibit 2, which shows the prevalence, or number of affected individuals in the United States, and the estimated economic costs to the American public. The collective economic burden of the diseases addressed by this Institute exceeds $100 billion annually. 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 the NIADDK.

EXHIBIT 2. Prevalence and economic costs of selected disease groups

	Prevalence (in millions)	Economic Cost[1] (in billions)
Arthritis and Related Diseases	$37.0	$18.6[2]
Diabetes	11.0[4]	14.0[2]
Digestive Diseases	38.0	50.0[2]
Kidney and Urologic Diseases	13.0	5.5[3]

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

[2] *As reported by the national commissions on arthritis, diabetes, and digestive diseases, respectively. In the case of digestive diseases, the National Digestive Diseases Advisory Board estimates an economic cost of $50 billion in annual lost wages, taxes, disability, and health care payments, and $17 billion in direct health care costs.*

[3] *Direct medical cost of kidney disease only. (Source: National Kidney Foundation)*

[4] *Includes estimated number of undiagnosed cases in the population as well as the number diagnosed.*

Organization of the Institute

As the NIADDK pursues 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 the NIADDK operates is designed to meet these essential requirements.

The organizational structure of the NIADDK (exhibit 3) 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 the 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 and fiscal, analytical, and review services to facilitate the research effort. Activities aimed at developing and sustaining linkages to the scientific and health-care communities also fall within the Institute's realm of administrative and advisory functions.

Office of the Director

The focal point for managing NIADDK 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 the NIADDK's programs.

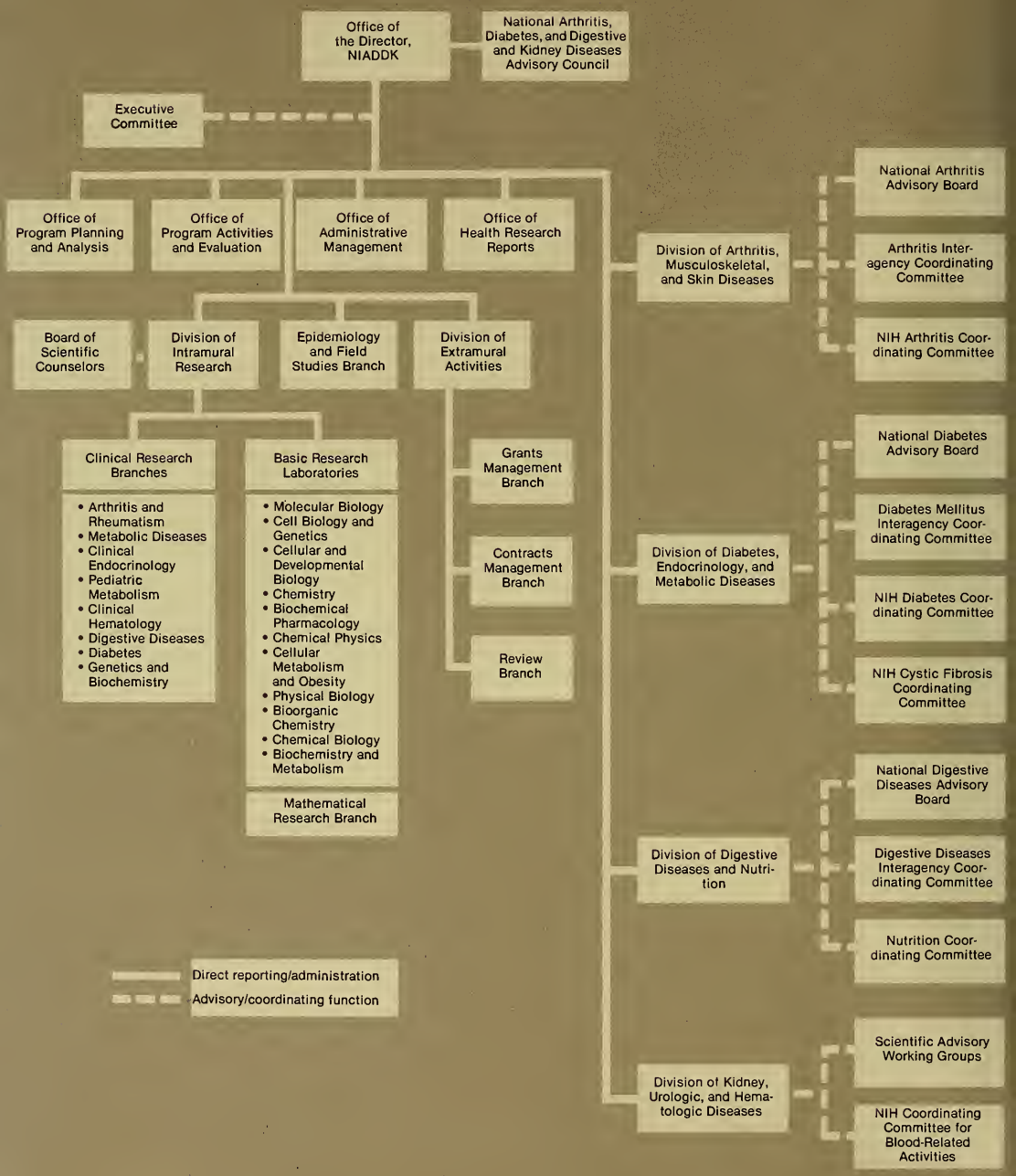
Specifically, the Director's office provides policy direction and staff guidance and oversees the preparation of plans and reports in such areas as scientific program planning, administrative management, and use of resources. In addition, the Office of the Director is responsible directly for developing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

The Office of the Director coordinates and prepares information to describe the NIADDK's program progress and future plans to the Director of NIH and to 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, coordinating, and directing management of day-to-day operations, including budget and financial management, 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 activities of the Institute.

EXHIBIT 3. Organization of the NIADDK



- *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, responds to public inquiries in areas relating to disease categories encompassed by the Institute's mission, and advises Institute staff on matters relating to the Freedom of Information Act.
- *Extramural Divisions*—provide oversight and management of all aspects of research and training programs and projects conducted off-campus as follows:
  - *Four extramural research Divisions* coordinate and direct scientific planning, monitoring, and reporting of research and training programs in their respective research areas, in close cooperation with the Office of the Director.
  - *The Division of Extramural Activities* provides fiscal management of extramural research awards, reviews applications and proposals for specialized research projects, and assures operational coordination among the extramural research programs.
- *Division of Intramural Research*—through intramural laboratory and branch chiefs, plans, coordinates, and conducts research activities in the Institute's laboratories and clinical facilities.

These organizational components 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 and to specific requests for information or studies originating in Congress or elsewhere in the Executive Branch. The Director's office also relies on the expertise and advice provided by the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council, a senior consultative body whose guidance is important to the Institute's program operations and development, by the national advisory boards and coordinating groups described below, and by an executive committee, composed of intramural and extramural senior staff members.

Extramural Activities

The extramural program supports investigations that are funded by the Institute but conducted at universities, private and public research facilities, and hospital-based clinical research centers throughout the Nation and, in certain cases, in other countries. The NIADDK uses grants, contracts, and various other funding mechanisms to generate and administer the extramural project activities of the four research Divisions. The various award mechanisms are described in exhibit 4. Because of its inherent advantages as a means of furthering scientific knowledge, the primary mechanism of research support used by NIADDK is the investigator-initiated research grant.

Each NIADDK Division functions as a distinct administrative unit with responsibility for allocating and managing 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 within the purview of the Institute, there is strong emphasis on the support of basic research. This emphasis is particularly important because the etiologies of many of the major diseases involved are unknown. At the same time, a significant proportion of extramural research support is directed at clinical studies, to provide an optimal mix for rapid advances in treating the various diseases and health problems studied by the 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:

- Total lymphoid irradiation in renal transplantation.
- Fluoride and calcium treatment for osteoporosis.
- Insulin infusion in type 2 diabetics by implanted pump.
- Esophageal variceal hemorrhage—shunt operation versus sclerotherapy.
- Dietary modification of the course of progressive renal disease.
- Psoralen photochemotherapy of psoriasis.
- Radionuclide adrenal imaging in hypertension.
- Studies of human zinc deficiency.

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 include 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 a health-care setting. They may also be useful in comparing the relative efficacy of two or more therapies for the same disease or health problem.

EXHIBIT 4. 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 relatively 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.

- Exploratory grants. These grants support planning for new programs, expansion or modification of existing resources, and feasibility studies to explore various approaches to the development of interdisciplinary programs that offer potential solutions to problems of special significance to the mission of the Institute. Such exploratory studies may lead to specialized or comprehensive centers.

- Small business innovation research grants, phase I. These grants support projects, limited in time and amount, to establish the technical merit and feasibility of research and development ideas that ultimately may lead to commercial products or services. These awards may be made only to small businesses.

Intramural Research

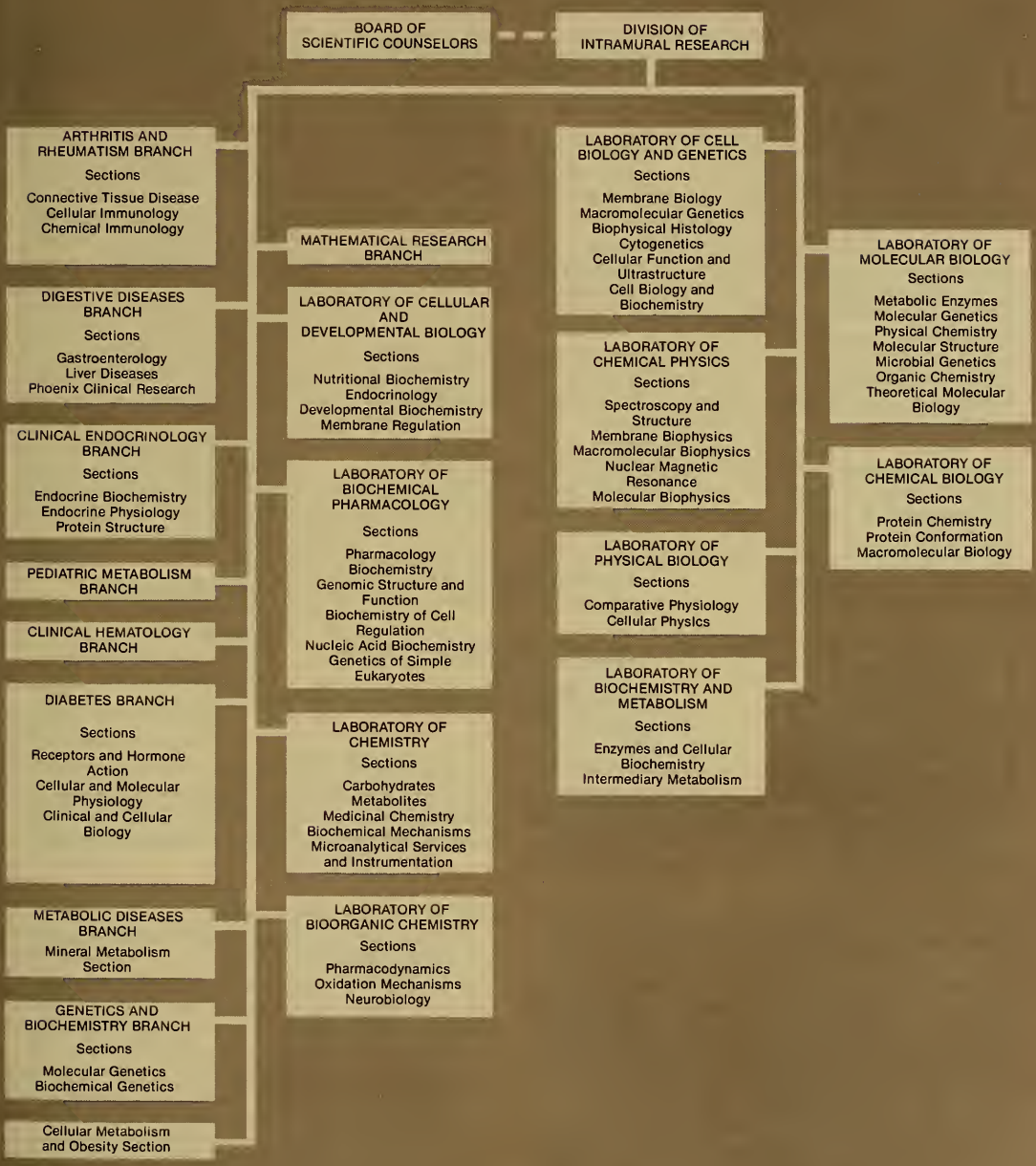
The Division of Intramural Research conducts investigations at the Institute's laboratory and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Intramural research activities are conducted by eight branches engaged primarily in clinical research on arthritis and rheumatic diseases, metabolism, endocrinology, hematology, digestive diseases, diabetes, and genetics; a ninth branch is involved in the theoretical mathematical modeling of biological problems. In addition, there are 10 laboratories with component sections organized by scientific discipline (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 exhibit 5.

A related intramural group, the Epidemiology and Field Studies Branch, develops and applies epidemiologic methods in field studies among selected populations at risk for developing specific diseases. Investigators in the Epidemiology and Field Studies Branch conduct research throughout the United States and provide assistance to numerous 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 external 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 the NIADDK's activities and responsibilities, its ongoing and planned research efforts are given strong consideration in overall program planning by Institute management.

The intramural research staff of the 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

EXHIBIT 5. Organization of the NIADDK's intramural program



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
Pierre F. Renault, M.D.
Acting Director
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Sara S. Austin (1985)*
Greater Cleveland Round Table
Cleveland, Ohio

J. Claude Bennett, M.D. (1984)
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Colonel John Waterman
United States Air Force
Malcolm Grow Medical Center
Andrews Air Force Base
Washington, D.C.

Executive Secretary
Walter S. Stolz, Ph.D.
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH
Bethesda, Maryland

* Expiration of term.

mathematics branch serves as a major resource for the intramural efforts of the NIADDK and other NIH Institutes alike. The NIADDK is justly proud of the achievements and reputation of its intramural research program.

Advisory and Coordinating Groups

Over the years, the 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 demand for more and better health-care services. To keep pace with the rapidly developing biomedical research environment and to ensure that the NIADDK's numerous programs continue to address appropriately the Nation's health 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. The NIADDK's National Advisory Council is composed of eminent experts in relevant areas of biomedical research; civic leaders, educators, and laypersons with 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 above.

The functions and responsibilities of the National Advisory Council are primarily to assist the Office of the Direc-

tor 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 the 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 the NIADDK's overall priorities for new research.

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. 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 research 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 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 area of interest.

The National Arthritis Advisory Board (NAAB), National Diabetes Advisory Board (NDAB), and National Digestive Diseases Advisory Board (NDDAB) are composed of members representing a variety of scientific, educational, health-care, and public-service disciplines. Current members of the 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 the NIADDK and the NIH, the Secretary of Health and Human Services (HHS), and other Federal agencies; and maintain liaison with advisory bodies of other Federal agencies involved in implementing the plans.

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 any appropriate changes in the plans.

National Arthritis Advisory Board

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Medical School
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George Washington University
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Bevra H. Hahn, M.D.
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at Los Angeles
Center for Health Services
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Rutgers Medical School
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School of Medicine
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Maureen E. Reagan
Los Angeles, California

Lawrence C. Rosenberg, M.D.
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Medical Center
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University of Arizona
Tucson, Arizona

Charles Stewart
Chairman of the Board
Arkansas Chapter
Arthritis Foundation
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Francis S. Symms
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Eng M. Tan, M.D.
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National Diabetes Advisory Board

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Houston, Texas

Nina Berlin
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Madison, Wisconsin

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Pittsburgh, Pennsylvania

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University of Texas
Dallas, Texas

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Executive Director
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National Institutes of Health
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National Digestive Diseases Advisory Board

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Telephone Workers' Credit Union
Boston, Massachusetts

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New Brunswick, New Jersey

Irving A. Rubin
Great Lakes Container Corporation
Southfield, Michigan

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Ralph L. Bain, Ph.D.
National Digestive Diseases Advisory Board
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Interagency Coordinating Committees

The NIADDK fulfills the mandate for 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. These committees, which were created as a result of congressional acts, serve to facilitate communication among all Federal agencies directly or indirectly involved in the three disease areas. From their establishment in the mid-1970's, the committees worked closely with the national commissions and advisory boards to develop improved approaches to information exchange, joint planning, and the identification of promising areas for cooperation.

The membership of each interagency coordinating committee includes the director of the applicable NIADDK Division, who serves as chairman, and representatives from selected Institutes within the NIH and from other Federal departments and agencies with related 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 suffering from arthritic disorders, diabetes, and digestive diseases.

Trans-NIH Coordinating Committees

Certain complex health issues or problems span the program interests of several Institutes, thereby requiring collaborative effort to assure program balance and minimize duplication of activity. For such trans-NIH issues, the Director of the NIH has appointed coordinating committees to provide a forum for 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 the appropriate Bureaus, Institutes, and Divisions (BID's) within the 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 the NIADDK plays a major role.

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 to promote cooperation in diabetes-related programs among all of the relevant Institutes at the NIH. Activities have included joint program announcements and requests for applications as well as cooperation in fostering research manpower development programs.

During the past year, the following activities have been initiated under the auspices of the trans-NIH diabetes program:

- The report of the second national diabetes research conference entitled *Progress and Promise and Diabetes Research*, sponsored by the NDAB, was distributed to every NIH grantee with a diabetes-related project.
- Several NIH Institutes sponsored a trans-NIH diabetes program announcement soliciting new investigator-initiated research grant applications from the scientific community.
- The NIADDK, the National Institute of Allergy and Infectious Diseases, and the National Institute of Child Health and Human Development sponsored a request for applications on the immunobiology of insulin-dependent diabetes mellitus (IDDM).
- Several NIH Institutes collaborated in supporting the development of new mechanisms for the procurement and distribution of human tissues for biomedical research through the National Diabetes Research Interchange.
- Several NIH Institutes collaborated in the planning and implementation of the Diabetes Control and Complications Trial in conjunction with various organizations in the private sector.

Participants in the trans-NIH diabetes program also collaborate with the NIADDK's National Diabetes Data Group. The data group serves as the central point within the 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 utilize the NIADDK's National Diabetes Information Clearinghouse, the national reference source for information on professional and patient education materials and programs related to diabetes and its complications.

Nutrition. The NIH is the primary Federal agency that conducts and sponsors research and training in nutrition related to health maintenance, human development, and disease prevention and treatment. The NIH Nutrition Research Program involves all of the BID's at NIH that support nutrition-related research and is coordinated through the Nutrition Coordinating Committee (NCC). 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 development. Program announcements and requests for grant applications made 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 entitled *National Institutes of Health 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 and nutrition education for professionals and the public.

The NIADDK's involvement in the NCC has included the full range of NCC activities but has focused particularly on several of immediate Institute concern: evaluation of the clinical nutrition research units, with the National Cancer Institute; preparation of a program announcement on overnutrition and obesity, with seven NIH Institutes; participation on a planning committee on problem areas in the support of nutrition work; preparation of data, analyses, and textual information concerning the NIADDK programs in specific areas of nutrition; and the planning of a workshop on nutrition and hypertension.

Cystic fibrosis. The Cystic Fibrosis Coordinating Committee was established to serve as a focus for the coordination of NIH support of research and research training related to cystic fibrosis (CF). The committee is cochaired by representatives of the NIADDK and the National Heart, Lung, and Blood Institute (NHLBI) and includes members from each of those BID's with responsibilities relating to CF. Specific functions of the committee include cataloguing NIH activities and support related to CF, coordinating and facilitating program initiatives in the BID's to address the needs and opportunities in research relevant to CF, encouraging trans-NIH collaboration on activities related to CF, and serving as an information resource and point of contact with other agencies and organizations regarding advances and opportunities in CF research and research training.

Blood-related activities. Support and management of blood-related research activities are shared among several Institutes of the 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 the NIH, including the NIADDK, the Division of Research Resources, and the NIH Clinical Center. One of the major goals of the committee is to exchange information on proposed initiatives related to blood to ensure the best possible focus of activities.

Board of Scientific Counselors

The NIADDK's Board of Scientific Counselors was initiated in 1956 and currently operates under the statutory authority of Section 222 of the Public Health Service Act (P.L. 87-838, Public Health Service Amendments of 1962), serving as an internal review committee responsible for monitoring the activities of the Institute's intramural research program. The operations of the Board are governed by the Federal Advisory Committee Act, P.L. 92-463. The formation of the Board was considered essential to ensure unbiased, extragovernmental expert review of intramural research activities. The activities of the Board developed in parallel with the review mechanisms established for the extramural research program.

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

Board of Scientific Counselors

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Robert E. Canfield, M.D. (1985)*
Columbia University
New York, New York

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Rockefeller University
New York, New York

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Washington University
St. Louis, Missouri

Marian E. Koshland, M.D. (1985)
University of California
Berkeley, California

David B. Sabatini, M.D., Ph.D. (1986)
New York University
New York, New York

Howard K. Schachman, Ph.D. (1987)
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Berkeley, California

Lucille Shapiro, Ph.D. (1984)
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Bronx, New York

Executive Secretary
Jesse Roth, M.D.
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
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Bethesda, Maryland

* Expiration of term.

Special Programs

Because of the NIADDK's varied responsibilities, there are many opportunities for fostering collaboration among scientists across the Nation and around the world. Over the years, the Institute has implemented special programs to expand research opportunities and services, going beyond the laboratory into the community where those affected by disease and those who treat them may benefit more quickly from research progress.

NIADDK's Research Centers Programs

In addition to providing support to institutions and organizations for the traditional research and research training programs, the Institute also has responsibility for a program of center facilities. Through the 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, diabetes, endocrine and metabolic disorders, and digestive diseases and nutrition-related problems.

The NIADDK sponsors 20 multipurpose arthritis centers (MAC's) across the country. The MAC's are engaged in activities that address all aspects of arthritis, 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 Diabetes Centers Program consists of two types of facilities: diabetes-endocrinology research centers (DERC's), which concentrate on basic and clinical investigations conducted in a core setting of shared comprehensive laboratory facilities, and the 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 DERC's and DRTC's provide limited funds for pilot or feasibility studies to encourage young investigators and promote innovation in research concepts.

The Division of Digestive Diseases and Nutrition sponsors centers that support and conduct basic and clinical investigations in a variety of health problems related to its program areas. Two such centers conduct research on liver disease and the effects of drugs and injuries on the liver. Another center is studying diet and eating behavior that contributes to obesity, a model program that is intended to foster multidisciplinary research and exchange of information. Still another focuses on peptic ulcer. The Institute also is supporting five clinical nutrition research units, which serve as focal points for multidisciplinary research in clinical nutrition as well as provide for the development of programs in clinical nutrition that enhance the education of various health professionals.

Activities of the various types of centers differs according to local need and support of research, clinical, educational, training, and demonstration projects. All centers, however, 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 the NIADDK-supported centers is shown in exhibit 6. 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 among the NIADDK, the scientific community, and the health-care delivery system; continued evaluation is essential to maintaining those linkages. The most recent evaluation reports for the multipurpose arthritis centers and the diabetes research and training centers are provided in chapter VI.

A Program for International Cooperation

The NIADDK supports a number of international 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 research projects that may have worldwide impact is an ongoing priority for the Institute. Through the Bilateral Cooperative Agreements Program, the NIADDK has developed collaborative and cooperative activities with Japan, the U.S.S.R., and France in several important fields.

U.S.-Japan cooperative program in malnutrition. Since 1966, the U.S.-Japan Cooperative Medical Sciences Program has been actively engaged in collaborative research efforts to develop greater understanding of the effects of malnutrition on physical growth, mental development, and performance. These activities and projects are carried out through cooperative arrangements developed between the United States and Japan, which share responsibility for the program.

Research continues to be the primary focus of activities supported by the malnutrition program panel. Studies have been developed and conducted abroad among populations with severe nutritional deficiency diseases and are designed to find solutions to complex malnutrition problems. The availability of large population groups afflicted with nutrition disorders provides the NIADDK and other sponsoring members of this program with valuable information and insight into the many aspects of malnutrition and its implications for health and well-being.

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 that use 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, featur-

EXHIBIT 6. The 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, Ia.
University of Pennsylvania, Philadelphia, Pa.
Baylor College of Medicine, Houston, Tex.
University of Washington, Seattle, Wash.
University of Massachusetts, Worcester, Mass.

△ **OTHER SPECIALIZED CENTERS**

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.
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.

ing 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.

NIH-INSERM agreement. Under an agreement program between the 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 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. Through a melding of the programs available to each group, research progress in these areas has been greatly advanced, and new procedures to resolve problems in

thyroid function have evolved. In addition, many scientific papers have been published jointly.

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, Italy, and other countries have worked in the intramural laboratories and clinics of the NIADDK. The exchange of high-caliber scientists across national boundaries promotes 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, the 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 occasionally contracts for highly qualified investigators conducting the following types of studies:

- Mechanism of carbon tetrachloride hepatotoxicity.
- Culture and grafting of fetal pancreatic islets.
- Intrinsic neural control of intestinal motility.
- Diabetes in the Pacific—genetic and environmental interactions.
- Nuclear magnetic resonance (NMR) studies of 57Fe porphyrins.
- Molecular basis of secretion in the exocrine pancreas.
- Study of the expression of the thyroglobulin gene.
- Inborn errors of carbohydrate metabolism.
- Mode of action of thyrotropin: cholera toxin as a model.
- Studies on the mechanism of vascular disease in diabetes.
- Porphyrin ions and radicals in metabolic processes.
- Science and technology of biomaterials.
- Physiology and pathophysiology of somatostatin in diabetes.
- Culture-derived pancreatic islets for transplantation.
- Mechanisms regulating activity of NAK-ATPase.
- Implantable micropump for insulin delivery.
- Islet cell membrane antibodies in diabetes.
- Isolation of islet cell autoantigens.
- The inflammatory response of allograft rejection.
- Clinical trials with transplant aspiration cytology.
- Pathogenesis of reactive arthritis.
- Symposium on urolithiasis and related clinical research.
- Risk factors in glucose intolerance.
- Action of hormone receptors in cell membrane.
- Mechanisms of intracellular protein breakdown.
- Mechanism of insulin resistance in human adipose cells.
- Molecular genetics of steroid hydroxylase systems.
- Autoimmune arthritis: disease protection by T-cell lines.
- Physiology of epithelial monolayers grown in vitro.
- Obesity.
- Diabetes and adipose tissue development.
- Protein/carbohydrate/fat/salt metabolism in continuous ambulatory peritoneal dialysis (CAPD).
- Thalassemias.
- Hemoglobinopathies and related problems.
- Cellular mechanisms of epithelial sodium transport.
- The effects of gut peptides in enteric and central nervous system neurones.
- Microtubules and microfilaments in vasopressin action.
- Improving diabetes control using feedback techniques.

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. The NIADDK continues to support selected international conferences and symposia as part of its programs; for example, last year the NIADDK provided support to seven such meetings that addressed topics such as immunology, hormones, diabetes, hematology, and basic science.

Research Manpower Development

In the 34 years since its establishment, the 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 of 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 the NIADDK's goals and has been a high Institute priority.

Through ongoing analysis and evaluation of program needs and maintenance of a wide range of training mechanisms, the NIADDK continues to seek motivated future investigators to meet critical needs. Recently initiated training mechanisms, such as the Clinical Investigator Award and the National Research Service Award Senior Postdoctoral Fellowship, as well as the New Investigator Research Award, contribute markedly to Institute efforts to attract and prepare outstanding investigators for research careers. The new Physician Scientist Award (see below) is expected to provide one of the most effective mechanisms available to help reach this goal. Exhibit 7 describes the mechanisms used by the NIADDK to supply talented scientists for each of its categorical disease research programs.

Vigorous efforts have been made to avert shortages of personnel in vital areas. However, there are still declining numbers of physicians who pursue research careers and a shortage of trained epidemiologists in many important fields.

Physician Researchers

In an effort to attract more physicians to academic research careers, the 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 newly developed Physician Scientist Award. By continuing to support physicians throughout the various stages of lengthy research training, the 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 restricted severely because the number of professionals trained in pertinent fields is insufficient. To correct this deficiency, the 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 the NIADDK field studies units. Recognizing the importance of epidemiologic studies to comprehensive national research efforts, the 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, the 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. Therefore, the NIADDK vigorously supports programs to strengthen research capabilities and enlarge the potential investigator pool in colleges and universities attended largely by women and minority groups.

In 1977, the 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 Research Support Program of the Division of Research Resources, the NIADDK funds projects designed to improve the biomedical science capabilities of minority institutions through support of undergraduate and postdoctoral students and staff and faculty positions. Currently, the NIADDK is committed to a level of support of approximately $1.35 million each year.

The Minority Access to Research Careers Program intra-agency agreement with the National Institute of General Medical Sciences enables the NIADDK to increase the number of minority biomedical researchers by making funds available for predoctoral faculty fellowships, visiting scientists, and honors undergraduate training.

Scientists from the NIADDK visit minority institutions, giving scientific lectures and advising students on careers in biomedical sciences. In addition, the Institute's Equal Employment Opportunity Office distributes scientific journals and scientific textbooks contributed by staff scientists

EXHIBIT 7. NIADDK research manpower development mechanisms

- **NATIONAL RESEARCH SERVICE AWARDS (NRSA).** These awards provide for the training of biomedical and behavioral scientists in areas of national need. Awards 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 the NIADDK's intramural programs and universities, medical schools, research hospitals, and similar public or private institutions are among the eligible organizations. 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 post doctoral 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 the NIADDK.

  — **Short-term training for students in professional schools.** The 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 (CIA).** 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.

- **RESEARCH CAREER DEVELOPMENT AWARD (RCDA).** 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.

- **PHYSICIAN SCIENTIST AWARD (PSA).** The PSA is a new award intended to encourage newly trained clinicians to develop independent research skills and experience in fundamental science and basic biomedical disciplines. It is a 5-year nonrenewable award based on up to five consecutive full-time 12-month appointments. Eligibility is restricted to those holding health professional degrees in the clinical sciences (M.D., D.D.S., D.V.M., D.O. or equivalent). Physicians also holding the Ph.D. are ineligible. Candidates ordinarily will have completed at least 1 postgraduate year of clinical training by the time the award is made. Each candidate must identify a primary sponsor who is recognized as an accomplished investigator in the basic science research area proposed, and who will provide guidance for the awardee's development and research plan. The awardee's program is designed in two phases. In phase I, there is a basic science learning experience that culminates, in phase II, in an intensive research activity under the general guidance of the sponsor. Both individual PSA's and institutional PSA's are provided for.

- **NEW INVESTIGATOR RESEARCH AWARD.** To help bridge the transition from training status to that of established investigator, this 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.

to minority colleges and universities and participates 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

In recent years, prompted in part by encouraging developments in the science base and in part by the increasing cost of health care, the Nation has placed greater emphasis on finding ways to reduce the toll of disease. One way in which the Department of Health and Human Services participates in this goal is through its initiative on disease prevention and health promotion. Modern prevention research has increased in complexity because of the shift in the relative prevalence of such chronic diseases as arthritis and diabetes when compared with acute infectious diseases such as pneumonia and tuberculosis, which were more common at the beginning of the century. The concerns of disease prevention and health promotion among the American people thus have become more challenging to research scientists throughout the country.

The 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 the NIADDK, prevention research has as its objectives both the protection of people from disease and the prevention of the progression of disease to disability or early death.

Focus of NIADDK Prevention Research

Many diseases under study at the 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 postmenopausal osteoporosis and its sequelae: fractures of the vertebrae, hip, and wrist.
- Prevention of the emergence and progression of type 2 (formerly maturity-onset) diabetes in individuals with an inherited tendency for this disorder.
- Prevention of the appearance and progression of the clinical complications of type 1 (formerly juvenile-onset) diabetes.
- Prevention of dwarfism and normal-variant-extreme short stature.
- Prevention of the recurrence of peptic ulcer in patients with a known history of the disorder.
- Prevention of obesity and its many detrimental effects on health.
- Prevention of the recurrence of kidney stones and their sequelae in known stone-forming patients.

Future Prevention Research

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

- Research on the factors that predispose older men to the development of benign prostatic hyperplasia, with the goal of eventual prevention or amelioration of this widespread disorder.
- Research on prevention and better control of diverticulosis (protrusion of portions of the inner lining of the gut through weak spots in the circular muscles 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).
- Research on prevention of injurious consequences of physical exercise and sports activities such as jogging.

Prevention Education and Outreach

Several NIADDK programs that relate to prevention feature interaction with the scientific and public health communities, health providers, and consumers. These programs are described in other sections of this report. Major activities are as follows:

- Multipurpose arthritis and diabetes centers.
- Clearinghouses.
- Clinical nutrition research units.
- Special activities.

As insights into the causes and development of chronic diseases are made, new strategies for preventing the onset or destructive progression of these diseases are 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 current advances in educational, social, and legislative approaches to encouraging behavior change.

Technology Assessment and Transfer

Before 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 identified; 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 vigorously 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. Technology assessment activities of the NIADDK include workshops, symposia, and consensus conferences to synthesize expert opinion; state-of-the-art reviews of issues within the 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.

Utilizing extensive surveys of the most recent scientific literature and input from Institute experts and other scientific consultants, the NIADDK provides assessment of medical and surgical procedures and treatments and advice to the Health Care Financing Administration concerning Medicare coverage for medical, surgical, and diagnostic technologies. Examples of technologies that have been assessed during the last year include:

- Percutaneous and noninvasive lithotripsy by ultrasound and other modalities in the treatment of kidney stones.
- Photodensitometry (radiographic absorptiometry).
- Dual photon absorptiometry.
- Injection sclerotherapy for the management of bleeding esophageal varices.
- Apheresis in the treatment of scleroderma.
- Apheresis in the treatment of polymyositis.
- Apheresis for acute-stage rejections of renal transplant.
- Apheresis used in preparation for kidney transplant.
- Electrocoagulation for the treatment of gastrointestinal hemorrhage.
- Portable and wearable artificial kidney systems.

Consensus Development Conferences

In addition to participating in approximately 50 national and international scientific conferences, workshops, and seminars each year, the NIADDK takes part in the NIH consensus development program, by which various concerned parties are brought together to seek general agreement on the safety, efficacy, and appropriate conditions for use of a particular medical technology.

During the last year, the NIADDK organized, in conjunction with the NIH Office of Medical Applications of Research, two major consensus development conferences. The first of these conferences was on analgesic-associated kidney disease and its prevention. Experts from throughout the world participated in this conference. The second consensus development conference was on the prevention and treatment of osteoporosis. This conference was a particularly timely one, and the resulting consensus statement attracted considerable attention in the medical literature, lay media, and among medical practitioners. Less than a month after the consensus panel had urged that estrogen supplements "should be considered" for postmenopausal women at risk, the Food and Drug Administration independently announced approval of estrogen for the treatment of osteoporosis. Another consensus development conference on a widespread public health problem, the health implications of obesity, currently is being organized.

Technology Transfer

The NIADDK recognizes that unless the technologic knowledge gained in basic and clinical research is diffused for application in the health-care community, the full value of that research will not be realized. Therefore, the Institute devotes significant effort to systems that foster transmission of the latest scientific knowledge and techniques to this community.

The goals of technology transfer are to increase awareness and interest in new research advances, to promote scrutiny and evaluation of their potential advantages, and to foster their trial and adoption in practice. The 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. Because no single network for information dissemination can satisfy the full spectrum of information needs, the Institute uses various means to promote information diffusion and technology transfer:

- *Information collection and dissemination.* The 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 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, those who suffer from the effects of these disorders, and those who direct their care. To this end, the clearinghouses have evolved as national centers for compiling educational materials and information available from various sources, 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 cataloguing thousands of brochures, booklets, reports, journal articles, textbooks, and audiovisual materials and refer clients to appropriate developers or sources, rather than act as distributors of printed matter.

- *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 are programs of education and information dissemination for the general public concerning new technologies and discouragement of the use of unapproved and ineffective treatment measures.

- *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 experiences of their peer group. Though wider audiences can be reached by 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, the 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 the NIADDK research advances.

Program Planning and Analysis

The long-range goal of the Institute is development of knowledge concerning the diseases under its purview, through conduct and support of biomedical research, that would permit their prompt diagnosis, effective treatment, and, preferably, outright prevention. Shorter term objectives encompass the efficient and productive support and conduct of extramural and intramural programs of basic and clinical research related to individual diseases.

Program planning for research takes place in an atmosphere of uncertainty: conflicting sources of data must be reconciled; knowledge expands; relationships among new findings often are not evident immediately; the time frame within which new research achievements will occur cannot be predicted; and funding levels often are 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, 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, ad hoc scientific advisory groups that counsel the Institute's respective Divisions and programs, 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 the NIADDK takes two major forms. The first—strategic planning—involves long-term policy development and comprehensive evaluation of opportunities and problems. This type of planning was most recently performed for the NIADDK, with the assistance of program staff, by the national commissions on arthritis, diabetes, and digestive diseases and by a number of evaluation panels. The other type of planning, 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.

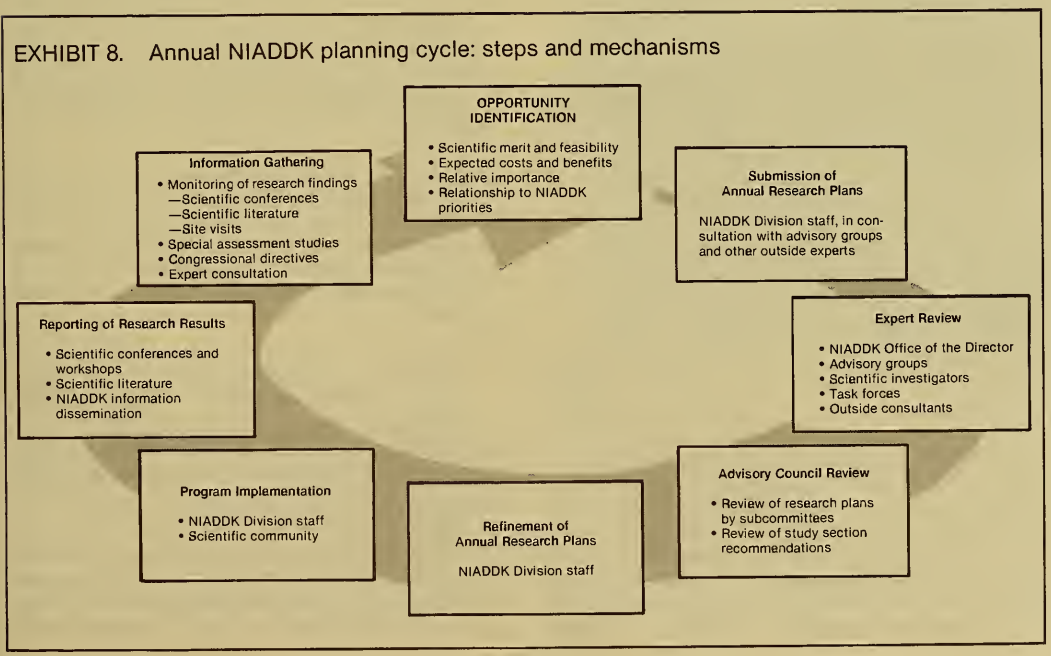
Because the NIADDK relies heavily on investigator-initiated research, new ideas and opportunities explored by the scientific community contribute significantly to the planning process. Also, individual investigators contribute to implementation by developing research grant applications that are pertinent 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 exhibit 8). These steps, which update scientific objectives for use in making decisions on research awards, are as follows:

- 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. Workshops and ad hoc or formal 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, with the assistance of its advisors, 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.

EXHIBIT 8. Annual NIADDK planning cycle: steps and mechanisms



- The annual plans submitted by the Divisions are then reviewed by experts, including the Office of the Director of the NIADDK, advisory groups, National Advisory Council subcommittees, ad hoc task forces, and individual scientific experts. For example, elements of the Institute's plan are discussed formally with the Director of the NIH at an annual research-plan review session, at which senior staff members of the Office of the Director, NIH, and of the NIADDK participate. Comments resulting from further expert review are used to refine the plans.
- Once the overall plan has been approved by the Institute Director, it is presented to the Director of the NIH and to the National Advisory Council.
- The National Advisory Council and its subcommittees participate in Institute planning by reviewing the annual 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.
- 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 designed to ensure that the 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, producing statutorily mandated evaluation reports to the Congress and DHHS, and responding to public concerns for accountability in government. Through such studies, the Institute is able to determine its progress toward scientific objectives and to determine how to strengthen research and administrative activities. Evaluation also provides an effective tool for maintaining balance between programs and mechanisms of funding. The evaluation process is linked closely with long-term strategic planning and contributes to the annual processes of legislative planning and implementation and budget allocation.

The Institute often has 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 examined the 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, are disseminated throughout the scientific community as well as to Congress and other interested groups.

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

- As the NIH lead Institute in endocrinology and in conjunction with the National Institute of Child Health and Human Development, the NIADDK has prepared an evaluation and report on endocrinology research supported and conducted by all NIH Institutes since 1980. This was a followup of a previous evaluation (and its recommendations) of research needs in endocrinology and metabolic diseases conducted for the Institute in 1978-79 by a group of outside experts in this field.
- The results of a recently completed evaluation of the NIADDK's Hematology Program were published and distributed in the form of a 600-page book entitled *Research Needs in Hematology*. It will be invaluable as a reliable guide in formulating plans of the program for allocation of resources according to realistic research priorities.
- The results of a recently completed evaluation of the NIADDK's Musculoskeletal Diseases Program (including an assessment of the health-care impact of selected medical technologies developed with program funds) have been published and widely distributed in the form of a 220-page book. Recommendations from this evaluation are being incorporated into the Musculoskeletal Diseases Program's plans.
- A new evaluation project will survey the existing portfolios of research of the NIADDK and other relevant NIH Institutes in obesity-related areas. It will compare these portfolios with recommendations for

research directions and specific areas that require further development to be made by a group of experts in the field convened for a Consensus Development Conference on the Health Implications of Obesity. The goal will be to assess the coverage and scope of the existing research program in obesity and to identify areas in particular need of further exploration.

Fiscal Resources

As health research and health care have emerged as major domestic policy issues, the responsibilities of the NIADDK have expanded, and its fiscal obligations likewise have grown. Exhibit 9, which depicts the 5-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 and has reached $364.935 million in 1984. When adjusted for inflation, as shown in exhibit 10, the total annual allocation to the NIADDK has increased by only $63.7 million—or 45 percent—since 1973.

The NIADDK supports research primarily through the mechanism of investigator-initiated research project grants. There has been a steady increase in emphasis on this mechanism over the years. At the same time, the Institute must maintain 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; therefore, several types of funding mechanisms must be used.

Exhibit 11 demonstrates the relative expenditures for different types of award mechanisms in 1984. Obviously, the greatest portion of the 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. The Institute was able to support 785 new and competing individual research projects in 1984. In large measure, it is this last category of expenditures—the carefully considered allocation of the NIADDK funds among dedicated investigators conducting high-quality basic and clinical research—that has made possible the achievements described in the following chapters.

Honors and Awards

Many of the outstanding individuals associated with the Institute receive awards or are appointed to organizations and societies reflecting their significant accomplishments. In recognition of outstanding work, grantee scientists around the Nation, intramural scientists at the NIH, Advisory Council and board members, and the NIADDK staff have been honored in the past year. The following is but a sample of individuals who have received honors or recognition in the past fiscal year for their work.

EXHIBIT 9.
NIADDK actual obligations, 1980-1984

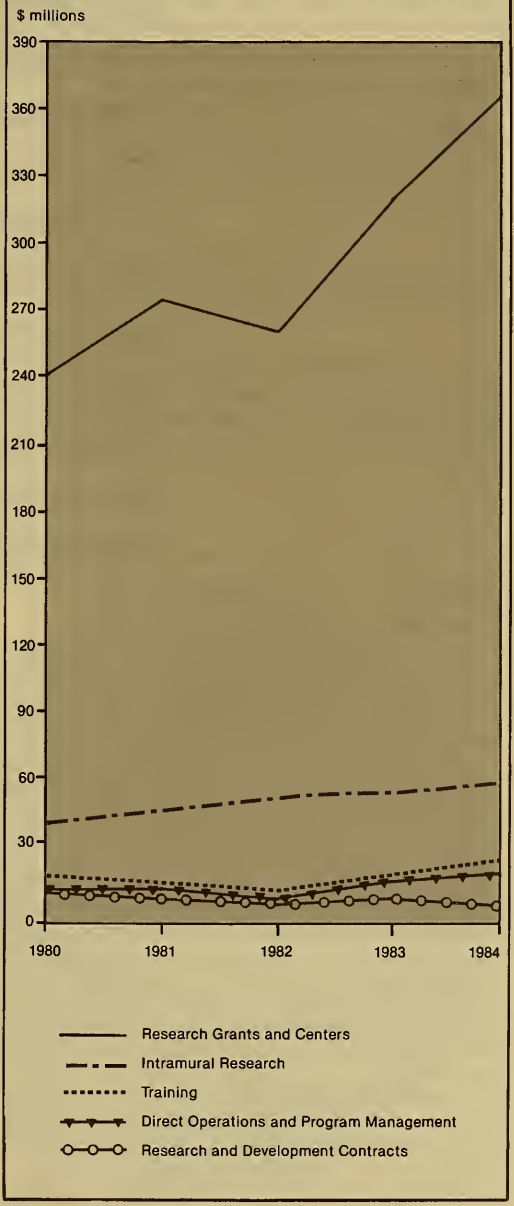
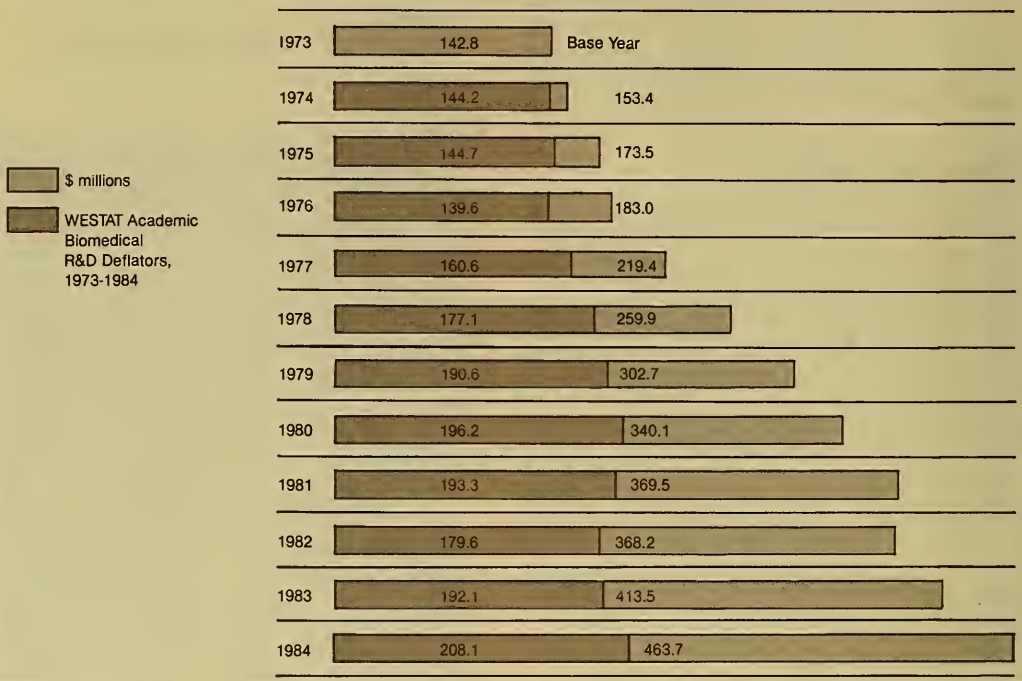


EXHIBIT 10. NIADDK obligations, 1973-1984, adjusted for rate of inflation



Grantees

Dr. Klaus Beyenbach, associate professor of physiology, Cornell University, has been awarded a Fogarty International Center Senior International Fellowship in West Germany to study the renal transport of magnesium.

Dr. Neal Bricker, professor of medicine, University of California at Los Angeles Medical School, presided over the IX International Congress of Nephrology in Los Angeles in 1984. This was only the second time that an American researcher has served in such a capacity.

Dr. Alan Cherrington, professor of physiology, Vanderbilt University, received the Eli Lilly Award for his studies in the regulation of glucose production at the 1984 American Diabetes Association (ADA) meeting in Las Vegas.

Dr. Donald Coffey, professor of urology, oncology, and pharmacology and experimental therapeutics, Johns Hopkins University, gave the Ramon Gutierrez Lecture at the 1984 meeting of the American Urological Association in New Orleans.

Dr. Michael Czech, professor and chairman, department of biochemistry, University of Massachusetts Medical Center, gave the Edwin D. Astwood Lecture at the 1984 International Endocrine Congress in Quebec City, Canada. He spoke on his work on insulin and somatomedin receptors.

Dr. George Eisenbarth, associate professor of medicine, Harvard Medical School and head of the section on immunology at Joslin Diabetes Center, received the Richard E. Weitzman Memorial Award of the Endocrine Society. The award was established in 1982 to honor outstanding research achievements in the field of endocrinology and metabolism by a young investigator.

Dr. Marilyn G. Farquhar, professor, department of cell biology and pathology, Yale University School of Medicine, has been elected to the National Academy of Sciences.

Dr. Michael Field, professor, department of medicine and pharmacology and physiological sciences, University of Chicago, received the Distinguished Achievement Award from the American Gastroenterological Association for research achievements in "the cell biology of diarrheal disease."

Mr. Robert Fishel, chief of technology transfer and assistant head of the space department, Applied Physics Laboratory, Johns Hopkins University, received the 11th Inventor of the Year Award from the Intellectual Property Owners, for his work on the implantable insulin pump.

Dr. Yuet Wai Kan, a geneticist whose work has been supported for many years by NIADDK, is the first occupant of the Louis K. Diamond chair in hematology at the University of California at San Francisco School of Medicine. The

Diamond chair is named for Dr. Louis K. Diamond, eminent researcher and clinician and former NIADDK grantee.

Dr. Juha Kokko, chief of nephrology, University of Texas Southwestern Medical School, has been elected president of the American Society of Nephrology, to serve from December 1984 until November 1985.

Dr. Daniel E. Koshland, Jr., professor, department of biochemistry, University of California at Berkeley, shared the Rosenstiel Award from Brandeis University for research in biochemistry, in the area of cell surface and membrane interactions. He also received an honorary doctorate from the Weizmann Institute, Rehovoth, Israel.

Dr. Gerald Lazarus, professor and chairman, department of dermatology, University of Pennsylvania School of Medicine, was the Montagna Lectureship awardee of the Society of Investigatory Dermatology at their 1984 annual meeting in Washington.

Dr. Alton Meister, professor and chairman of the department of biochemistry, Cornell University Medical College, received the William C. Rose Award in biochemistry from the American Society of Biological Chemists for his research on amino acids and glutathione.

Dr. Robert Schrier, chairman, department of medicine, University of Colorado School of Medicine, has been elected president of the National Kidney Foundation for 1985-86.

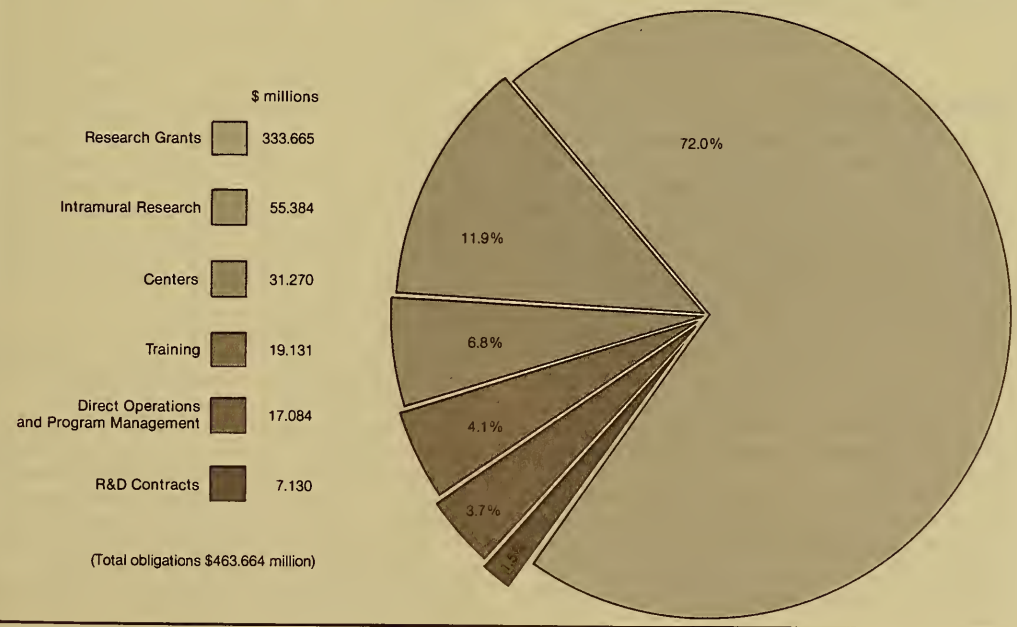
The following grantees received Kappa Delta awards at the annual meeting of the Orthopaedic Research Society and American Academy of Orthopaedic Surgeons:

- Drs. Kai-Nan An, Edmund Y. S. Chao, William P. Cooney, and Ronald L. Lindscheid of the Mayo Clinic were honored for Biomechanics of the Hand—A Basic Research Study.
- Dr. Michael G. Ehrlich, Massachusetts General Hospital, Boston, received the Elizabeth Lanier Award for work on Degradative Enzyme System in Cartilage.
- Drs. Raymond T. Morrissy and Darrel W. Haynes were recognized for their work on Acute Hematogenous Osteomyelitis: A Model With Trauma as an Etiologic Agent.
- Dr. William Petty, University of Florida, received a Young Investigators Award for work on the Influence of Skeletal Implant Materials on Infection.

Advisory Council and Boards

Dr. Allan Drash, member of the NDAB, as well as past president of the American Diabetes Association, received the Banting Medal for Service at the 1984 ADA meeting in

EXHIBIT 11. NIADDK total obligations, by award mechanism, 1984



Las Vegas. Dr. Drash is a professor of pediatrics at the University of Pittsburgh.

Dr. Daniel Foster, member of the NDAB, received the Banting Medal for Scientific Achievement at the 1984 ADA meeting. Dr. Foster is a professor in the department of internal medicine, University of Texas Health Science Center at Dallas.

Dr. Howard Polley, member of the NAAB, spoke on the "Discovery of Anti-Inflammatory Effects of Cortisone and Corticotropin" as part of a Special Scientific Symposium on Landmark Advances in Rheumatology at the 1984 Annual Meeting of the American Rheumatism Association (ARA), on the occasion of its 50th anniversary. Dr. Polley is a professor of medicine at Indiana University.

Drs. Paul Sherlock and James Boyer, chairman and deputy chairman, respectively, of the NDDAB, received an award from the Coalition of Digestive Disease Organizations for "distinguished and effective leadership of the NDDAB" at the 1984 session of Digestive Disease Week in New Orleans. Dr. Sherlock is chairman of the department of medicine, Memorial-Sloan Kettering Cancer Center, New York, and Dr. Boyer is a professor of medicine at Yale University Medical School.

Dr. Eng Tan, member of the NAAB, was named president-elect of the ARA at the 1984 meeting, held in Minneapolis. Dr. Tan is head of the W. M. Keck Autoimmune Disease Center of the Scripps Clinic and Research Foundation.

Ms. Thelma Thiel, member of the NDDAB, has been named to the board of directors of the newly formed American Council on Transplantation.

Institute Staff

Dr. Gilbert Ashwell, formerly chief, Laboratory of Biochemistry and Metabolism, was given the Merck Award of the American Society of Biologic Chemists "for his outstanding contributions to the advancement of biomedical research." Dr. Ashwell has been promoted to the rank of Institute scholar, a rank established at NIH in 1984. It is intended to provide a suitable honor for investigators of outstanding achievement while freeing them from administrative burdens and providing an environment in which to further pursue their biomedical research activities. Dr. Ashwell is the first individual at NIH to hold this rank.

Dr. Arnold Brossi, chief, Medicinal Chemistry Section, Laboratory of Chemistry, received an honorary doctorate at Bowdoin College's 179th commencement exercises in Brunswick, Maine.

Dr. Samuel Cushman, chief, Cellular Metabolism and Obesity Section, received the PHS Special Recognition Award "for significant contributions to the study of insulin action that contributed to the understanding of obesity and diabetes, diseases of profound importance in today's society."

Mr. James Fordham, writer/editor in the Office of Health Research Reports, won a second prize from the National Association of Government Communicators for his pamphlet on the prevention and treatment of kidney stones.

Dr. Robert Levine, PRAT (pharmacology research associate training) fellow in the Laboratory of Cell Biology and Genetics, received one of six Outstanding Young Investigator in Neurochemistry awards from Vector Laboratories for his studies on the effects of a chemical neurotoxin, kainic acid, on the central nervous system of the rat.

Drs. Daniel Malone and Thomas Santoro of the Arthritis and Rheumatism Branch received the American Rheumatism Association Senior Fellowship Award.

Dr. Henry Metzger, chief, Arthritis and Rheumatism Branch, was given the Joseph Mather Smith Prize by the College of Physicians and Surgeons of Columbia University for the most meritorious research by an alumnus.

Dr. Elizabeth Neufeld, chief, Genetics and Biochemistry Branch, was awarded the Elliott Cresson Medal of the Franklin Institute "in recognition of her many contributions to our knowledge of the molecular basis of genetic diseases that form the basis of ultimate treatment."

Dr. Elizabeth Raveche, Laboratory of Cell Biology and Genetics, was awarded the Scientific Achievement Award of the Washington Academy of Sciences "for her contributions toward the understanding of modes of inheritance and autoimmunity."

Dr. Griffin Platt Rodgers of the Laboratory of Chemical Biology received a fellowship from the Robert Wood Johnson Foundation's Minority Medical Faculty Development Program.

Dr. Phil Skolnick, chief, Neurobiology Section, Laboratory of Bioorganic Chemistry, received two awards: the PHS Special Recognition Award "for providing key new insights into the behavioral roles of recognition (receptors) for drugs and neurotransmitters in the central nervous system," and the Scientific Achievement Award of the Washington Academy of Sciences for his "contribution towards the characterization of the neurochemical basis of anxiety." Dr. Skolnick also was given an Inventor's Award by the Department of Commerce for his work in developing a rapid, sensitive, and specific radioreceptor assay for measuring benzodiazepines in plasma.

Dr. Joe-Hin Tjio, chief, Cytogenetics Section, Laboratory of Cell Biology and Genetics, was awarded a fellowship by the Japanese Society for the Promotion of Science, which can be used in Japan for a period of up to 31 days.

Dr. Harold Roth, director of the Division of Digestive Diseases and Nutrition, received an award of special recognition from the American Gastroenterological Association "for his wise, dedicated, and courageous championing of support for research and training in Digestive Diseases."

Dr. Lester Salans, former director of NIADDK, received the first Richard Schweiker Award for Excellence in Government from the Juvenile Diabetes Foundation at its 1984 meeting in Washington.

Ms. Barbara Weldon, writer/editor in the Office of Health Research Reports, was recently voted a special recognition award by the American Lupus Society "in appreciation of creating and perpetuating lupus awareness in 1983."

The following staff members received NIH Merit Awards, the second highest honor presented by NIH to Civil Service employees, in the past year:

- Ms. Keturah Blom, staffing assistant (typing), Office of Administrative Management, "for exceptional services in providing staffing support for the NIADDK intramural visiting scientists program."
- Ms. Rose Lee Claggett, copier-duplication equipment operator, Division of Intramural Research, "for consistently superior performance in the Division of Intramural Research, NIADDK."
- Ms. Helen Jenerick, secretary (stenography), "for superlative performance as a secretary for the Laboratory of Biochemical Pharmacology, NIADDK."
- Dr. Keatha Krueger, director, Diabetes Centers Program, Division of Diabetes, Endocrinology, and Metabolic Diseases, "in recognition of exceptional resourcefulness as Diabetes Centers Program director and executive secretary of the Diabetes Mellitus Interagency Coordinating Committee."
- Dr. Alan Moshell, director, Skin Diseases Program, Division of Arthritis, Musculoskeletal, and Skin Diseases, "for superior performance in directing and developing the skin diseases research and research training programs."
- Dr. Richard Pledger, health scientist administrator, Review Branch, Division of Extramural Activities, NIADDK, "for excellence of leadership and service in the review of grant and contract mechanisms."
- Dr. Martin Rodbell, chief, Section on Membrane Regulation, Laboratory of Cellular and Developmental Biology, "for creative achievements in molecular endocrinological research."
- Ms. Elizabeth Singer, director, Office of Health Research Reports, "in recognition of her superlative and creative leadership and management of the public information program of NIADDK."
- Mr. Charles Zellers, budget analyst, Office of Administrative Management, "for consistently superior performance in planning and formulating extramural budget requirements."

II. Research Focus—Arthritis, Musculoskeletal, and Skin Diseases

Overview

Disorders such as arthritis, diseases of skeletal support structures, and diseases of the skin, 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. Arthritis and related diseases afflict nearly 37 million Americans.* Arthritis is the Nation's primary crippler, causing an increasing number of persons to leave the work force before normal retirement age. The resultant loss of earnings has been estimated at $25 billion a year. Arthritis is reported to affect more than 40 percent of people over age 65. An estimated 250,000 children have arthritis or a related joint disease; some 100,000 of these children will carry serious handicaps into adulthood. In addition to crippling of limbs, some forms of juvenile arthritis can cause kidney disease, blindness, and even premature death. 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 also is conducted in the NIADDK's Arthritis and Rheumatism Branch at the NIH Clinical Center. Through the 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 other types of therapy.

The term "arthritis" encompasses more than 100 different disorders of the joints and connective tissues, including osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis (spinal arthritis), and gout. Investigation into the area of arthritis was the original mandate of the NIADDK and continues to receive research and program emphasis. While the underlying causes of most types of arthritis remain elusive, considerable progress has been made in some of them.

The content of the research effort in arthritis can be considered in four general areas that consume roughly equal portions of the program budget. The first of these areas includes the projects associated with immune disturbances, autoimmune diseases, rheumatoid factor, antigen-antibody reactions, and immune complex formation. The second area consists of research concerned with collagen, connective tissue, basement membranes, synovial fluid, and articular cartilage. The third area consists of research projects in several specific rheumatic diseases (rheumatoid arthritis, degenerative joint diseases, systemic lupus erythematosus, gout, and heritable disorders). The fourth area concerns research associated with the structure, function, contraction, and metabolism

Osteoarthritis is a leading cause of pain and disability for older Americans, but technological improvements have set the stage for major advances in the next decade.

Facing page

An estimated 250,000 children have arthritis or joint disease. Many will carry serious handicaps into adulthood.

* Source: National Commission on Arthritis and Related Musculoskeletal Diseases.

of skeletal muscle. The program continues to give visibility to rheumatic disease activity and skeletal muscle research as distinct entities.

The Division's Musculoskeletal Diseases Program supports basic and clinical studies on the various components of the musculoskeletal system in normal and diseased conditions. This support includes studies of properties, growth and metabolism of normal bone, bone and joint diseases, musculoskeletal injury and repair, disorders of skeletal support structures such as tendons and ligaments, and specialized studies in areas such as low back pain and locomotion. The increasingly important areas of exercise pathophysiology and sports medicine are other foci of this program. Research in joint replacement, bone and cartilage transplantation, and fracture healing has helped to restore mobility and freedom from pain for many Americans with orthopedic problems, and preventive approaches promise the eventual control of many of these disorders.

It is estimated that more than 40 million people are affected by these diseases, mainly from bone and joint disorders, fractures, and injuries of tendons and ligaments.* The resultant economic loss is enormous.

Significant advances in measuring bone density by noninvasive methods have enhanced our ability to diagnose and monitor many types of bone disease such as osteoporosis (reduction in skeletal bone quantity). These improved methods, which obviate the risk and trauma of surgery for biopsy purposes, involve dual-photon absorptiometry, computerized tomography, neutron activation, and Compton methods.

The NIADDK's Skin Diseases Program continues to support studies of both normal and diseased skin to obtain a better understanding of cutaneous diseases. The vast group of skin diseases causes a great deal of human suffering through discomfort, disfigurement, or chronic disability. Indeed, skin diseases are a leading cause of industrial disability. The medical, psychosocial, and economic costs of cutaneous disease justify an extensive and diverse research effort.

Areas of emphasis in the Skin Diseases Program include psoriasis and disorders of keratinizing tissues; vitiligo and other disorders of pigmentation; photobiology, photoallergy, and phototoxic reactions; metabolic studies of skin, including effects of hormones and interaction with enzymes; immunologically mediated cutaneous disorders, including atopic dermatitis, eczema, contact dermatitis, and vasculitis; bullous diseases of the skin, including pemphigus, pemphigoid, dermatitis herpetiformis, and epidermolysis bullosa; acne and physiologic activity of the sebaceous gland; disorders of hair growth, including alopecia areata; and cutaneous manifestations of connective tissue disease disorders, including lupus erythematosus, scleroderma, and pseudoxanthoma elasticum.

Skin diseases concern almost all persons in every age group. Many of these diseases such as acne, psoriasis, and eczematous and immunologic skin diseases are treatable in varying degrees at present; however, the etiology, means of prevention, and cure for most of them are unknown. Past efforts have resulted in significant advances in the treatment of selected skin diseases, and there is hope for even greater advancement toward alleviating the damaging effects of such disorders.

Highlights of Research Advances

The following section briefly highlights a number of areas in which the Division of Arthritis, Musculoskeletal, and Skin Diseases has reported recent progress in its research programs.

- An analogue of vitamin A, 13-*cis* retinoic acid, successfully reduced the inflammation and joint destruction associated with experimental arthritis.
- In a controlled short-term clinical trial, an orally administered gold complex, auranofin, proved almost as effective as injected gold preparations in reducing joint pain, tenderness, and signs of disease activity in rheumatoid arthritis and was somewhat less toxic.
- Evidence has been obtained supporting the involvement of viruses in causing rheumatoid arthritis (the Epstein-Barr virus and a parvovirus) and dermatomyositis (the coxsackievirus B).
- Advances in understanding the joint cartilage changes in osteoarthritis were made in the areas of biomechanics (reproducible induction of the disease by experimental trauma) and biochemistry (detection of abnormalities in collagen metabolism and cartilage matrix).
- Early treatment of Lyme disease, an infection due to a spirochete transmitted by a tick bite, with high doses of antibiotics can prevent its progression to arthritis and other late complications. Antibiotics can also cure established Lyme arthritis.
- Experimental evidence shows that supplementing the diet with fluoride added to the combination of calcium and estrogen can significantly decrease the occurrence of spinal fractures.
- Risk factors associated with spinal fractures due to osteoporosis in men have been identified. The major factors are advanced age, abnormal calcium or bone metabolism, smoking, and alcohol consumption.
- Paget's disease of bone may be caused by the long-term effects of a virus (the respiratory syncytial virus); abnormal breakdown of bone tissue in the disease shows similarities to neoplastic transformation.

* American Academy of Orthopaedic Surgeons.

- The nature of the collagen defect in several forms of brittle bone disease, osteogenesis imperfecta, is now better understood and may be the basis for future approaches to treatment of the disease.
- The blistering observed in epidermolysis bullosa is associated with increased collagenase activity, which causes collagen breakdown. The drug diphenylhydantoin can suppress the increased collagenase activity and is now being tested clinically.
- The abnormal behavior of the skin protein keratin seen in psoriasis and acne has been characterized more fully. Acne and one form of psoriasis respond favorably to treatment with oral 13-*cis* retinoic acid.
- Lupus erythematosus of the newborn is associated with certain histocompatibility antigens in the mother, who passes autoantibodies to the fetus. Antibodies to a soluble tissue ribonucleic acid, RNA, protein antigen (SSA/Ro antibodies) are closely correlated with disease activity in the skin and heart. These findings may help in development of screening and prevention efforts.
- Vitiligo may be the result of abnormal autoimmunity. Patches of skin pigment loss characteristic of the disease may be due to specific autoantibodies that act on the surface skin pigment cells; these antibodies bind to cell surface antigens and can kill the cells.

Arthritis Research

Retinoic Acids Reduce Inflammation and Destructive Activity in Experimental Arthritis

Prior Findings

A major characteristic of rheumatoid arthritis is the breakdown of collagen in cartilage, bone, and other tissues that leads to progressive proliferative and destructive joint changes. Central to the destruction of collagen in arthritis is the activity of the enzyme synovial, or joint lining, collagenase. Collagenase is synthesized and secreted in large quantities by rheumatoid synovial cells, and this and other substances, especially prostaglandin E^2, are active in the joint destruction seen in rheumatoid disease.

Two analogues of vitamin A are being tested for their ability to modify the types of disease processes seen in rheumatoid arthritis. Naturally occurring all-*trans* retinoic acid and the synthetic retinoid 13-*cis* retinoic acid have been evaluated previously as potential therapeutic agents in a variety of disorders. They have been found effective in the prevention of experimental neoplasms, the management of human tumors, and especially in the treatment of a number of proliferative dermatologic diseases—acne, ichthyosis, and other keratinizing disorders.

Recent Advances

Investigators have developed an animal model, "adjuvant arthritis" in the rat, for studying the underlying basis of joint changes. This animal model shares a number of features with rheumatoid arthritis in humans. Treatment of animals with 13-*cis* retinoic acid suppressed the development of adjuvant arthritis in both the initial and later manifestations of the disease. 13-*cis* retinoic acid also was effective in the treatment of *established* adjuvant arthritis as indicated by reduced inflammation. The production of collagenase and prostaglandin E^2 by cells taken from inflamed ankle joints of these animals was suppressed. Oral administration of 40 or 160 mg/kg significantly reduced the inflammation associated with developing and established adjuvant arthritis. The amount of collagenase secreted in tissue culture by adherent cells isolated from the inflamed joints also was decreased.

Research Directions

The successful use of retinoids in the treatment of this proliferative disorder demonstrates a new application of these compounds and the potential for 13-*cis* retinoic acid or other related retinoids to be helpful in treating some forms of arthritis in humans.

Gold for the Treatment of Rheumatoid Arthritis: A Controlled Clinical Trial of Auranofin

Prior Findings

In previous controlled studies, intramuscular injection of gold salts such as gold sodium thiomalate has been shown to improve both clinical and laboratory findings in rheumatoid arthritis. No one fully understands the basis for the effects of chrysotherapy (from chrysos, the Greek word for gold). Debate continues on the role of gold in rheumatoid arthritis, although this form of therapy has regained some of its former popularity in recent years. Of particular interest is the appearance of an orally administered gold complex known as auranofin.

Recent Advances

Ten university-based clinics, along with the intramural NIADDK staff, participated in a carefully controlled 21-week clinical trial, supported by the Institute, that compared treatment of rheumatoid arthritis using auranofin orally, a conventional gold preparation (gold sodium thiomalate, or GST) by injection, and a placebo (a dummy medication). Although none of the preparations produced

remission, both auranofin and GST were effective in reducing painful and tender joints and disease activity as judged by the physician. Injected GST proved slightly superior to oral auranofin; the difference was statistically significant only by certain laboratory measures of drug efficacy (increased hemoglobin concentration, decreased platelet count). However, GST also produced more adverse skin, gastrointestinal, and other side effects and withdrawals from treatment. The results indicate that both forms of gold are effective in the short-term treatment of rheumatoid arthritis.

Research Directions

The questions of long-term benefits, tolerability, and safety of the newer compound cannot be answered yet, but the answers are necessary, and the questions should now be addressed. In addition, a key issue is how to identify patients who will benefit from gold therapy, something that the data from the present study did not resolve. Further analysis of subsets of patients who respond well to treatment should be pursued, with a view to development of guidelines for starting chrysotherapy. A trial of gold therapy at an earlier stage than is usually done would provide additional information about patient responsiveness in early rheumatoid arthritis.

Evidence for Viral Involvement in Two Rheumatic Diseases

Prior Findings

Many of the rheumatic diseases are generalized diseases of connective tissue. While the evidence for immunologic processes in the major rheumatic diseases is very strong, including evidence for genetically determined abnormal immune regulation, it has not been possible to find specific causes that trigger the disease process in the vast majority of them. In rheumatoid arthritis and dermatomyositis, attention has turned to findings suggesting a viral role in initiation of the disease process.

Recent Advances

Antibodies to the Epstein-Barr virus (EBV), known to cause infectious mononucleosis, are found in higher titer in rheumatoid arthritis than in normal control subjects, and there appear to be abnormalities in immune regulation associated with the presence of EBV in patients with the disease. These abnormalities may contribute to joint damage.

For the first time, a specific viral agent has been isolated from the synovial tissue of patients with severe rheumatoid arthritis. Work supported in part by the NIADDK identified the agent as a small DNA-type virus in the family of parvoviruses, once thought to occur only in animals but now associated with human aplastic anemia and thought to be widespread. Extracts of cultured synovial cells containing the virus caused bone and nerve disorders and other abnormalities in newborn mice. Antibodies against the virus detected the antigen in the synovial cells of rheumatoid arthritis patients but not in those of osteoarthritis patients.

Individual case studies suggested coxsackievirus B as a possible cause of juvenile dermatomyositis (JDMS), a connective tissue disorder characterized by muscle weakness and skin, vascular, and joint involvement. Serological investigation of 26 children with definite JDMS recently revealed an increased frequency, shortly after disease onset, of antibody to coxsackievirus B but not to other viruses. A significant proportion of the sera from the 26 JDMS patients had detectable titers of coxsackievirus B antibody as compared to the sera obtained from children with juvenile rheumatoid arthritis attending the same pediatric rheumatology clinic. Subsequent serological surveillance further substantiated the findings. These data have advanced the concept that infection by coxsackievirus B may be of importance in the pathogenesis of JDMS.

An experimental model of this disease in its polymyositis, or muscular, form was produced in mice by inoculation with coxsackievirus. The coxsackievirus B family has been associated with respiratory, pleural, meningitic, pericardial, and myocardial infections in humans.

Research Directions

The hope with identifiable virus infections is that weakened strains or their associated antigens can be used to create a vaccine. Current recombinant DNA methodology makes this process more likely, once the necessary research information is available. It remains to be demonstrated that parvoviruses can cause rheumatoid arthritis or that coxsackievirus B can cause dermatomyositis and polymyositis.

Parvoviruses can persist at the molecular level as integrated inserts in chromosomal DNA, but the relevance of this fact to human connective tissue disease must be established by further research.

Joint Cartilage Changes in Osteoarthritis

Prior Findings

Osteoarthritis is the most prevalent of the rheumatic diseases. Its etiology is not understood; however, mechanical factors often are linked to its development. In osteoarthritis, the cartilage seems reluctant to repair itself. In several animal models, with increased impulsive loading and walking on hard surfaces, bone microfractures and subsequent stiffening have been shown to precede damage to the cartilage. An in vitro experiment has shown that stiffening of the bone with methyl methacrylate (bone cement) significantly increased articular cartilage wear.

Recent Advances

Research advances have been made in understanding the biomechanics and biochemistry of normal and degenerative cartilage. Techniques for preserving tissue explants and culturing and reproducibly inducing osteoarthritis in traumatic injury models have been improved.

Osteoarthritis is associated with changes in the synthesis of collagen and in the regulation of cartilage matrix formation. The proteoglycans (protein-polysaccharide polymers) of the matrix become depleted, and the matrix itself is degraded. An enzyme, protease, that breaks down cartilage has been identified. Metabolism of sulfate by cartilage cells is abnormal.

In a canine model, osteoarthritic changes in cartilage can be simulated with a tear of the anterior cruciate ligament. Dogs fed aspirin showed a significant reduction in proteoglycan synthesis but not an increased degradation when compared with controls. Injured knee joints show greater susceptibility to the effects of aspirin than normal knees, possibly related to changes in permeability, when the matrix is depleted of proteoglycans.

Research Directions

Research on this condition requires a multidisciplinary effort. The biomechanical and biochemical technologies related to cartilage are at a high level of sophistication that should foster further successful research efforts. Advances in this area could have a major impact on management of millions of patients with osteoarthritis.

Successful Treatment and Prevention of Lyme Arthritis With Antibiotics

Prior Findings

The infectious agent responsible for Lyme disease, originally reported as Lyme arthritis, was discussed in last year's report: in 1982, a previously unrecognized spirochete was isolated from ticks (*Ixodes dammini*) in an area known to be endemic for Lyme disease. Nine patients with Lyme disease were shown to have high antibody levels against this organism. Recently, researchers have isolated this spirochete from the blood, skin lesions, or cerebrospinal fluid of 3 of 56 patients with Lyme disease as well as from the tick associated with the disease. The isolation of the disease agent and its immunologic characterization are important steps toward treatment and prevention. Specific patterns of antibody formation accompany the disease in its early stage of skin lesions (elevated immune globulin M) and in its later stage of arthritis, nervous system, and/or heart involvement (elevated immune globulin G). The later manifestations of Lyme disease may mimic other immune-mediated rheumatic disorders, including rheumatoid arthritis or rheumatic fever. Unlike other spirochetal infections, the late manifestations of Lyme disease consist primarily of arthritis, although meningoencephalitis and myocarditis are other manifestations.

Recent Advances

Lyme disease usually begins in summer with a unique skin lesion, erythema chronicum migrans, accompanied by headache, stiff neck, fever, myalgias, arthralgias, malaise, fatigue, or lymphadenopathy. Patients with this skin lesion took part in treatment trials conducted by NIADDK grantees. These trials established that early antibiotic therapy can prevent the late complications of the disorder, prominent among which is joint disease. A 10- to 20-day course of tetracycline was found to work best for adults; penicillin or erythromycin was recommended for children.

Results from these trials showed that antibiotic treatment can prevent the progression of the disease to the late stage of Lyme arthritis. A new finding is that treatment of established arthritis in this disease is possible. Intramuscular penicillin in high doses was given to 16 patients with Lyme arthritis, preventing any further arthritis attacks in 7 of the 16. Intravenous penicillin in high doses was subsequently given to 20 patients with Lyme disease, and 14 of the 20 remained well many months later. By contrast, similar patients in control groups continued to show signs of Lyme disease. In another study, these same investigators treated 12 patients who had neurologic problems such as meningitis from the Lyme disease by using high doses of intravenous penicillin. This approach proved successful; there were no relapses.

Research Directions

Further research is needed to determine whether the manifestations of Lyme disease are due to continuing infection with the spirochete or to immunopathologic reactions secondary to spirochetal infection.

Musculoskeletal Diseases

Advances in Osteoporosis Prevention and Treatment

Prior Findings

As summarized by an Institute-sponsored consensus development conference in 1984 (see report under "Program Accomplishments"), accepted clinical measures for osteoporosis prevention and treatment include estrogen replacement therapy in postmenopausal women, increased calcium intake in both women and men, maintenance of normal vitamin D levels, and moderate weight-bearing-joint exercise such as walking. While not yet approved for clinical use, several other treatment and prevention

approaches were reported at the conference as having promise for future clinical use.

The amount of bone is the result of a balance between its formation and its breakdown, resorption, which are tightly coupled in normal metabolism. In osteoporosis, there is an absolute decrease in the amount of bone to a level at which fractures occur after minimal or no trauma. Most available therapeutic agents for osteoporosis, such as estrogen, calcium, and the calcium-regulating hormone calcitonin (from the thyroid gland), act by reducing bone resorption rather than by increasing bone formation. This action is partially negated by a compensatory decrease in bone formation to balance the decreased resorption.

Recent Advances

The ideal therapeutic program for osteoporosis would increase the amount of bone by increasing bone formation to a level greater than the bone loss by resorption. Four approaches appear to have this capability: combined use of oral phosphate and calcitonin, use of a synthetic fragment of the calcium-regulating hormone of the parathyroid gland in low doses, use of a proposed system of pulsing to synchronize the timing of bone-cell populations while depressing resorption, and combined fluoride and calcium therapy. Only the last of these has been studied in detail.

Sodium fluoride increases bone formation by stimulating bone cells. Preliminary trial results show that it significantly decreases the occurrence of spinal fractures when accompanied by supplemental calcium to ensure adequate mineralization of the new bone. If estrogen is added to this combination, some early results show a fracture rate less than one-third that of the best available current therapy, calcium plus estrogen.

Research Directions

Questions of long-term safety of the fluoride-based therapies remain to be answered by further studies, as does the question of whether the beneficial effect of fluoride is limited to the vertebral column. Fracture rates in the arms and legs with fluoride use need to be checked. The reasons for individual differences in response or lack of response to its use need to be examined. Two clinical trials are now under way with NIADDK support to clarify these issues.

Research should continue on the other treatment programs discussed above as well as on other possible therapies such as steroids and growth substances that promote tissue growth, hormones of calcium balance like calcitriol, and drugs such as thiazides. Much more information is needed on the development and maintenance of bone as a tissue, including both mineral and matrix formation and remodeling.

Areas of study recommended by the consensus conference include population-based studies that focus on demographic and behavioral correlates of bone mass and fracture rate; studies on types of osteoporosis by age, sex, and distribution of affected bone; studies on methodologies for determining risk, diagnosis, and clinical status; studies of optimal regimens for existing therapeutic agents; and studies of the mechanics of bone and osteoporotic fractures.

NIADDK's Musculoskeletal Diseases Program supports studies of properties and growth of normal bone, bone and joint diseases, and musculoskeletal injury and repair.

The Action of Fluoride on Bone-Forming Cells

Prior Findings

Fluoride is essential in the diet, at levels of 1 mg to 4 mg a day, and seems to be required for normal dental and skeletal growth and development. Sodium fluoride (NaF) was found to be the most potent agent for increasing bone volume in patients with osteoporosis. It has been shown to increase the number of osteoblasts, or bone-forming cells, the rate of bone formation, and the activity of a key osteoblast enzyme, alkaline phosphatase (ALP). Experiments were undertaken with NIADDK support to determine the basis for these actions of NaF and to examine its relationship to other bone growth factors.

Recent Advances

Fluoride was able to increase the proliferation rate of bone cells, as measured by isotope incorporation into cell DNA, by direct action on these cells. It also increased the ALP content of bone cells and embryonic bone and enhanced the growth and mineralization of embryonic bone. Two other direct-acting bone-cell stimulators, parathyroid hormone and human skeletal growth factors,

both increased the effects of NaF. These actions were unique to bone cells and occurred at concentrations comparable to those effective in vivo.

Research Directions

The clinical role of fluoride in the prevention and treatment of osteoporosis requires that its mechanism of action and full range of effects be fully understood. Further research of this type is essential to ensure maximal clinical usefulness and safety.

Spinal Osteoporosis in Men

Prior Findings

Although men do not have a distinct, age-related change in hormonal status comparable to the menopause, they can develop spinal osteoporosis clinically similar to postmenopausal osteoporosis, at comparable ages. It seems likely that apart from the hormonal change in women the risk factors for the disease would be common in men and women and that the lower incidence in men represents the underlying level of risk common to both sexes.

Recent Advances

In 105 male patients with vertebral fractures due to spinal osteoporosis, four main risk factors were evaluated and compared to their prevalence in the control group, patients with an unrelated vertebral disease (Paget's disease). Patients with a significant underlying disease known to affect calcium or bone metabolism had a relative risk of osteoporosis and fracture of 5.5. Patients who smoked cigarettes had a relative risk of 2.3, and those who drank alcoholic beverages had a relative risk of 2.3. Obese patients were protected, with a relative risk of 0.3. All of these results represented statistically significant differences. The effects showed a linear relationship to amount of smoking and drinking. An inverse linear relationship was seen for the degree of obesity, although loss of height due to compression fractures, without loss of weight, complicated the interpretation, based on standard height-weight tables. A mathematical model showed an effect for age of the patient, and it was found that the effects of smoking and drinking were not apparent in the under-60 age group and were greatest in the 70-or-over age group. The risks for underlying disease and obesity were independent of age.

Research Directions

The risk factors identified in this study show a pattern of multiple causes for spinal osteoporosis fractures in men. These risks need to be evaluated similarly in women, with a view to ascertaining whether they are additive to the effect of menopause. The search for other risk factors should continue.

Collagen Defects of Brittle Bone Disease

Prior Findings

Osteogenesis imperfecta (OI) is a heterogeneous genetic disorder producing various forms and degrees of fragile bone. Four clinical types of OI have been loosely defined. Type I is mild and of dominant inheritance; it is based on contribution of a specific gene from *both* parents. Type II is the lethal variant, fatal at or near birth. Type III involves progressive skeletal deformation, is severe, and is recessively inherited (it involves the inheritance of a specific gene from *one* parent). Type IV refers to a mixture of cases showing disease of moderate severity.

At present, the rare but severely disabling conditions of OI have only nonspecific treatments based on symptomatic relief from fracturing. Underlying defects are becoming better understood. Defects in collagen underlie several connective tissue diseases. The collagens are a family of extracellular proteins that are the major component of connective tissue. Of the five major types of collagen, type I is the principal collagen of bone, tendon, and skin. The defect in some types of OI appears to be a lesion in type I collagen synthesis.

The collagens are similar in that each is composed of three polypeptide chains (alpha chains) intertwined in a triple helix structure. Type I collagen is made up of two identical a_1 chains and one dissimilar a_2 chain. These are called a_1(I) and a_2(I), respectively.

Recent Advances

Using cloned probes for specific genes, the location of the collagen chain gene on chromosomes was determined, and it was found that in the perinatal lethal form of OI, type II, there is a deletion of about 500 bases from the DNA molecule making up the gene for the procollagen a_2(I) chain in one of the paired chromosome locations, or alleles. There is a failure to secrete type I collagen into the extracellular matrix. Deletions of amino acids from both the a_1(I) and a_2(I) chains have been observed as has the substitution of one amino acid, cysteine, for another, glycine. Types IIA and IIB have been defined for lethal forms of OI. In both type IIA and type IIB, defective regulation appears to occur. The pathogenesis of IIA seems to be based on insufficient accumulation of osteoid for normal bone formation; whereas IIB may be caused by incorporation, and later proteolytic removal, of a defective collagen, leading to a "moth-eaten" defective osteoid.

In a genetically dominant form of OI of moderate severity, type IV, there was an abnormal ratio of a_1 to a_2 collagen chains, with accumulated collagenous material in the rough endoplasmic reticulum. The excess material probably is related to degraded products of incompletely formed type I collagen.

In one mild form of the disease, type I OI, there appears to be a low content of a_1(I) messenger RNA, suggesting the presence of a nonfunctional allele of the a_2(I) gene. In two cases, there was a direct relationship between the gene function and decrease in total collagen synthesis.

Research Directions

Looking to the future, patient management may be based on replacing specific defective biochemical components or genes responsible for collagen and bone formation.

The research base is strong in these areas of biochemical analysis and cell culturing. The modern technology for molecular genetic studies is very powerful. Extensive characterization has progressed on three large clonal DNA's to the a_1 and a_2(I) collagen messenger RNA. There is considerable optimism for further identification of specific defects in the various forms of OI.

Paget's Disease of Bone: A Slow Virus Infection?

Prior Findings

First described by Sir James Paget in 1876, this crippling bone disease affects as many as 3 million Americans over age 40. Its main features are abnormal resorption of bone tissue, which can cause severe pain, and abnormal regrowth of replacement bone, often causing bowing of long bones or fractures. The breakdown of the collagen matrix of bone by osteoclast cells releases the amino acid hydroxyproline; the regrowth is due to osteoblast cells, which produce the enzyme ALP. Measurement of the levels of these two substances, together with bone scans and the irregular x-ray appearance of the bones of the limbs and skull, confirms the clinical diagnosis.

Effective treatment of Paget's disease will depend on finding its cause—although presently used inhibitors of bone resorption such as calcitonin, the synthetic diphosphonate drugs, and the anticancer antibiotic mithramycin provide clinical relief. Research on its cause has found evidence for a viral particle in the characteristic nuclear inclusions of the cells. A relationship to "slow-virus" diseases was suggested by the long period of disease development prior to symptoms, by the absence of acute inflammation, and by the restriction to a single organ, bone. An example of a slow-virus infection is subacute sclerosing panencephalitis, a fatal disease of children caused by a measles-related virus.

Recent Advances

Particles that resemble the respiratory syncytial virus (RSV) have been discovered in samples of osteoclast cells from nearly 200 patients with Paget's disease. The virus itself has not been isolated to date. RSV antigens were detected in mononuclear blood cells from patients with Paget's disease. These antigens have been passed into tissue culture cells exposed to the patients' blood cells. This cell culture line, HEp-2, may be readily infected by RSV.

The same investigators were able to produce an experimental model of osteogenic sarcoma that sometimes develops in Paget's disease by infecting the skeletal tissue of immune-deficient mice with mononuclear cells from patients with Paget's disease. The disease itself, therefore, is considered by some to be a type of neoplastic transformation.

Research Directions

It is possible that the various features of Paget's disease are different types of expression of viral "information" from an earlier slow-virus infection, but further work on disease mechanisms is essential to clarify this possibility. Isolation of the virus and its identification using new techniques of monoclonal antibodies and recombination genetic analysis would be a major step forward.

Skin Diseases

Increased Collagen Breakdown in Epidermolysis Bullosa

Prior Findings

It was reported last year that workers at NIH, using monoclonal antibody and other techniques, have demonstrated the presence of a protein called laminin in the basement membrane zone and have shown that its size, shape, and binding sites indicate that it may be important in binding the basal cells of the overlying epidermis (outer layer of the skin) to the collagen of the underlying dermis (inner layer of the skin).

Investigators at NIH also have isolated a monoclonal antibody that binds to a noncollagenous constituent of a layer, the lamina densa, of the basement membrane and have demonstrated that binding of this antibody is absent or faint in recessive dystrophic epidermolysis bullosa and reduced in dominant dystrophic epidermolysis bullosa. Binding was normal in epidermolysis bullosa simplex, a dominant form without later scarring in contrast to the dystrophic form, in parents of recessive dystrophic epidermolysis bullosa and in normal subjects.

Recent Advances

Institute grantees have demonstrated that a specific (monoclonal antibody to human fibrils anchoring the epidermis to the dermis reacts with these structures in the skin of normal individuals. By contrast, there is deficient

binding in the skin of patients with the dystrophic form of epidermolysis bullosa.

At an NIADDK workshop, research findings were presented that indicate the activity of the enzyme collagenase is increased in recessive dystrophic epidermolysis bullosa. The resulting increase in collagen breakdown would be expected to contribute to the blistering process. Further, it was found that the drug diphenylhydantoin, dilantin, which is known to stimulate collagen production, suppresses the increased collagenase activity in this disease. This finding offers hope that a clinical therapy may be developed.

A carefully controlled clinical trial of diphenylhydantoin in epidermolysis bullosa is now in progress, with several centers cooperating in the evaluation of the drug.

Research Directions

The NIADDK is working to expand the already significant interest among the academic research community on research into the causes, treatment, and prevention of epidermolysis bullosa. Specific areas of interest include the basic pathogenetic mechanisms of blister formation; the abnormal immune process, involving specific autoantibodies to proteins located in the boundary layer between the epidermis and the dermis; epidermal-dermal interactions, including the structural components that hold the epidermis to the dermis; and enzymes involved both in the normal formation and destruction of collagen, such as in wound healing and in such abnormal processes as occur in blistering diseases. Support of investigator-initiated research projects related to these areas make up a significant proportion of the Skin Diseases Program of the NIADDK.

The Role of Keratins and Retinoids in Psoriasis and Acne

Prior Findings

Keratins are a group of high-molecular-weight proteins formed in the epidermis. Their organization into a densely packed structure forms the bulk of the stratum corneum, the dead outer layer of the human skin that acts as the main protection against both physical trauma and loss or gain of fluids through the skin. Much work has been done to elucidate the specific biochemical structure of various members of the keratin families and also the genetic basis for their inheritance.

From work on human epidermal keratins, the amino acid sequence for over 90 percent of the amino acids in one of the major forms of human epidermal keratin has been described. This is the first such filament protein to be described in humans with this degree of completeness.

In addition, scientists have been investigating the question of control of the assembly of keratin into the structures found in the stratum corneum. There are strong implications in this work for the evaluation of a number of dermatologic diseases characterized by specific and reproducible alterations in stratum corneum structure and function.

Neither psoriasis nor acne is characterized by the excessive keratinization seen in hyperkeratosis or hyperkeratinizing diseases such as ichthyosis, but the pathology in both involves abnormalities in keratin behavior. Also, in both cases, the possible therapeutic role of retinoids, derivatives of vitamin A, has received research attention.

Recent Advances

It is now known that vitamin A and estrogens regulate the keratinization process and that the dramatic therapeutic effect of oral 13-*cis* retinoic acid, isotretinoin, in acne is due to its inhibition of sebaceous gland function in the hyperkeratinizing phase of acne. There is a reduction in the number of cells that differentiate into sebum cells, or sebocytes, rather than a change in the amount of sebum produced per cell. By keeping the level of this waxy deposit below the critical level necessary for undesirable bacterial colonization, the inflammatory phase of acne is prevented. The therapeutic effect of estrogens in acne appears to be a replacement of deficient estrogen levels in the skin, which also shows an excess of androgens.

In the abnormal keratinization of psoriasis, the fibrous proteins of the stratum corneum are themselves abnormal; however, if treatment of the disease results in reversion of the skin to its normal clinical appearance, the abnormalities are reversed. Of considerable interest is the recent evidence that generalized pustular psoriasis (a potentially lethal variant) responds to oral 13-*cis* retinoic acid with resolution of pustules and disappearance of fever. Although this point has not yet been proven, the therapeutic effect may be due to the action of retinoids on epithelial keratinization.

Research Directions

Much work needs to be done in the investigation of the structure and assembly of the human keratins, both in normal and disease states. Once the structure and function of these macromolecules have been determined in the normal state, it should be possible to evaluate better the abnormalities in numerous diseases and to design treatment modalities specifically directed at remedying the resultant functional defects. It may also be possible to alter normal human stratum corneum more specifically in desirable ways, such as to facilitate the delivery of drugs through the skin.

Evidence That Vitiligo Is an Autoimmune Disease

Prior Findings

Although it is far from clear why an individual should build up antibodies against components of his own tissues, the reality of the resulting autoimmune disease is beyond question. Studies into some of these diseases are discussed in other sections of this report. The skin disease known as vitiligo, which is characterized by localized and irregular losses of skin pigment, is 10 to 15 times more common in patients with other autoimmune diseases but has not been considered an autoimmune disease itself heretofore. While organ-specific antibodies have been detected in patients with the disease, the evidence that its destruction of pigment cells (melanocytes) has an immune basis had not been clear in prior work.

Recent Advances

Using a technique of tissue culture of human melanocytes developed in their laboratory, with more sensitive assays of immune responses, NIADDK grantees have demonstrated the presence of antibodies to cell surface antigens in patients with vitiligo. These antibodies are not found in people without the disease or in people with nonpigmentary disease. In patients with pigment cell cancer, melanoma, such antibodies are uncommon but do occur and may explain the more frequent occurrence of vitiligo in melanoma patients. The vitiligo antigen was shown to be made up of three proteins with molecular weights of 77, 85, and 250-plus kilodaltons that are almost exclusively expressed on pigmented cells. Antibodies to melanocytes were found in 84 percent (73 of 87) of patients with vitiligo, including all of a group of 22 with common vitiligo not associated with other immune diseases. Preliminary evidence has shown that melanocyte antibodies from patients with vitiligo can kill normal melanocytes and that animals with vitiligo also have such antibodies to surface antigens on their pigment cells.

Research Directions

Genetic and immunologic mechanisms controlling expression of these abnormal antigenic proteins on melanocytes need to be explored, along with the mechanisms by which antibodies to them are able to kill normal melanocytes. At the same time, it is possible that further immunologic studies can suggest new approaches to treatment of vitiligo. Some 500,000 Americans are affected by this disease and can suffer severe social handicaps and psychological difficulties because of it.

Lupus of the Newborn: Immune and Genetic Determinants From the Mother

Prior Findings

Neontal lupus erythematosus is similar to the disease known as subacute cutaneous lupus: both have annular, or ring-shaped, reddened scaly skin lesions, a low incidence of kidney or central nervous system lesions, and antibodies to an antigen in the cell nucleus (the anti-Ro or SSA antigen, a soluble tissue RNA). A heart arrhythmia, congenital heart block, is a serious feature of the neonatal form of lupus. The disease is related to the passage of maternal autoantibodies across the placenta to the fetus.

Recent Advances

In work supported by the NIADDK, six families with this disease were studied for the detection of factors that could explain its development. The investigators found a significant association with the presence of the histocompatibility antigen HLA-DR3 in five of the six mothers but not in the infants. Other antigens known to be linked with HLA-DR3 were also associated (HLA-B8, HLA-M2, and HLA-MTZ). No associations were found between HLA antigens and expression of disease in infants. All six mothers and six of seven infants had antibodies to SSA/Ro antigen, although the infants lost them by the age of 8 months. Most of the mothers were free of symptoms, but their autoantibodies, perhaps with other HLA-associated gene products, were able to cause the neonatal disease, by mechanisms as yet unclear. These studies imply the histocompatibility antigens regulate autoantibody production but not clinical expression of subacute cutaneous lupus.

Research Directions

A means of preventing neonatal lupus transmission and the development of the disease is needed. Such prophylaxis could then be coupled with screening of expectant mothers for the presence of SSA/Ro antibodies. Application of this type of screening might be helpful in the diagnosis of fetal arrhythmias.

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, education, and community and health-services research. Center funds are used to support pilot

and feasibility studies in any of the three components of the center. These developmental projects often form the basis of regular research grant applications and supplement the traditional investigator-initiated NIH research grants of researchers at the center.

Many exploratory research projects now under way could not have been started without the interaction of individuals brought together under the aegis and support of the arthritis centers grants. This research encompasses a wide range of disciplines and interests from basic biomedical research to health-services research.

Through computer- and telephone-based systems centered in certain MAC's, physicians who are not rheumatologists can obtain clinical consultations on arthritis problems in areas where the necessary expertise is not locally available. In addition to developing new mechanisms for providing medical student training in the MAC's, the centers develop new programs to improve rheumatic diseases care given by primary-care practitioners. Selected centers also sponsor special programs and model demonstrations of care in locations outside the center and methods to increase public awareness of arthritis problems and provide high-quality care. The coordinated approach to arthritis research exemplified by the MAC program assures that the application of research advances 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.

Cooperative Systematic Studies in the Rheumatic Diseases

Research on treatment of rheumatic diseases is one of the major objectives of the Arthritis Program of the NIADDK. Studies on evaluation of drugs and drug toxicity are of particular importance in that patients suffering from the major rheumatic diseases are likely to require pharmacotherapy for many years. Well-designed systematic cooperative studies have yielded important information about the efficacy of antirheumatic drugs, and the requirements for such studies are expected to continue.

The investigations undertaken by this program are those highly unlikely to be performed by individual investigators, individual medical centers, or pharmaceutical companies. The investigations include definitive studies of promising new drugs, controversial treatments, and accepted but unproven treatments. Long-term studies by cooperating clinics, headed by a center with strong biostatistical expertise and data management, are meeting these needs.

Previous multicentered clinical trials have produced highly significant information on efficacy and risks of various agents (e.g., cortisone, gold salts, cyclophosphamide, D-penicillamine) in treatment of rheumatoid arthritis and have had major impacts on patient care.

Multicentered controlled trials that have been completed recently or are ongoing include:

- Oral gold compound versus injectable gold salts in rheumatoid arthritis.
- Methotrexate in psoriatic arthritis.
- Pulsed methylprednisolone in lupus nephritis.
- Dimethyl sulfoxide (DMSO) in systemic sclerosis (scleroderma).
- Azathioprine versus D-penicillamine in rheumatoid arthritis.
- Low-dose methotrexate in rheumatoid arthritis.
- Classification and treatment of polymyalgia rheumatica.
- Early undifferentiated connective tissue disease.

Special Education and Information Programs

The following activities are being developed to address specific features of the National Arthritis Acts of 1974 and 1976 and several recommendations of the Arthritis Plan submitted to the Congress in April 1976 by the National Commission on Arthritis and Related Musculoskeletal Diseases.

Education Programs

Creation of the Education Program Office has brought the challenge of communication of arthritis information into sharp focus and has resulted in a greater public recognition of the need for coordination of various efforts. Beyond mere coordination, however, lies the need to ensure development of practical, useful materials to aid arthritis health professionals. The primary goal of the Education Program Office is the maximum use of the tools of communication to inform and educate arthritis health professionals about arthritis. Significant progress is being made toward stimulating and assisting development of public, patient, and professional education as essential elements in achieving optimal treatment and management of arthritis. The office also serves as an important instrument for bringing together Government, the private sector, the health professions, and others in a cooperative educational effort to combat arthritis.

Arthritis Information Clearinghouse

A major component of the Education Program Office is the Arthritis Information Clearinghouse (AIC). Established by the NIADDK following authorization by the Na-

tional Arthritis Act and recommendation by the National Commission on Arthritis and Related Musculoskeletal Diseases, the clearinghouse strives to improve the lines of communication among health professionals serving arthritis patients. Major functions of the clearinghouse are to collect, screen, store, and disseminate information about educational materials and programs on the rheumatic diseases. In addition to this service to providers, the clearinghouse seeks to acquire a better understanding of information needs, especially the unmet ones, of arthritis patients and to communicate these needs to the field.

In serving as a "broker" to foster the flow of arthritis information, thus helping users to locate and select educational materials, the clearinghouse refers clients to the appropriate developer or source rather than acts as a distributor of the material itself. The clearinghouse is discussed further under "Program Accomplishments."

Epidemiology/Data Systems Program

The Epidemiology/Data Systems Program provides an administrative core for efforts to encourage epidemiologic research in the fields of arthritis and musculoskeletal diseases. Epidemiologic studies of arthritis and musculoskeletal diseases contribute knowledge related to four concerns: assessing the community disease and disability burden, studying the natural history of diseases, investigating disease etiologies, and identifying risk factors. Currently, epidemiology grants include regular research grants, training grants, an individual fellowship, and New and Clinical Investigator Awards and contracts, at a cost of approximately $1 million. In addition, there are epidemiology projects within other grants, such as those for the multipurpose arthritis centers. Accomplishments of the epidemiology research program are described below.

Arthritis Data Systems Program

The Arthritis Data Systems Program fosters systematic acquisition, storage, retrieval, and analysis of information concerning the rheumatic diseases. Program effort is focused on assuring validity, confidentiality, and comparability of data collected in separate institutions and integrating data resources with data needs. Rheumatic diseases data collection efforts and instrument development are prominent in three major settings: (1) American Rheumatism Association Medical Information System (ARAMIS), (2) Health and Nutrition Examination Survey (HANES I) Epidemiologic Followup, and (3) multipurpose arthritis centers. These activities facilitate data programs in the following ways:

- ***American Rheumatism Association Medical Information System***

  ARAMIS is a multi-institutional rheumatic diseases data bank system, funded by the NIADDK and administered from Stanford University, that currently contains data from 19,217 patients with 107,487 patient visits, representing 90,000 patient years of experience. The overall size of the data banks has increased by approximately 15 percent over the past year, and two new data banks are online. Data are gathered prospectively, and efforts to maintain long-term patient followup are vigorous. ARAMIS' goals include: improved diagnostic classification of rheumatic diseases, including establishment of acceptable criteria; identification of risk factors associated with good or poor patient outcomes, based on prognostic studies among defined patient subsets; and improvement of evaluation instruments for these purposes.

- ***Health and Nutrition Examination Survey Epidemiologic Followup***

  In cooperation with the National Institute on Aging, the National Center for Health Statistics, and several other Institutes, the Arthritis Data Systems Program participated in designing the instrument for collection of data in this resurvey of 14,407 individuals, originally sampled in 1971-75.

- ***Multipurpose Arthritis Centers***

  MAC's continue to be active in the development, refinement, and application of health-status measures, such as an Arthritis Impact Measurement Scale (AIMS), which detects small improvements in health. The MAC program is described more fully in chapter VI.

Program Accomplishments

Consensus Development Conference on Osteoporosis

An NIH Consensus Development Conference on Osteoporosis was held in April 1984. There was great public interest in the topic as evidenced by the large number of attendees (over 750) and by the broad coverage from news media. The findings of the experts are given below.

Primary osteoporosis is an age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other recognizable causes of bone loss. It is a common condition affecting as many as 20 million individuals in the United States. About 1.3 million fractures attributable to osteoporosis occur annually in people age 45 and older. Among those who live to be age 90, 32 percent of women and 17 percent of men will suffer a hip fracture, most due to osteoporosis. The cost of osteoporosis in the United States is estimated at $3.8 billion annually.

Osteoporosis is a major public health problem. Although all bones are affected, fractures of the spine, wrist, and hip are most common. The risk of developing osteoporosis increases with age and is higher in women than in men and in whites than in blacks. Its cause appears to be in the mechanisms underlying an accentuation of the normal loss of bone, which follows the menopause in women and occurs in all individuals with advancing age. There are no laboratory tests for defining individuals at risk or those with mild osteoporosis. The diagnosis of primary osteoporosis is established by documentation of reduced bone density or mass in a patient with a typical fracture syndrome after exclusion of known causes of excessive bone loss. Prevention of fracture in susceptible patients is the primary goal of intervention. Strategies include assuring estrogen replacement in postmenopausal women, adequate nutrition, including an elemental calcium intake of 1,000 mg to 1,500 mg a day, and a program of modest weight-bearing exercise. There is great need for additional research on understanding the biology of human bone, defining individuals at special risk, and developing safe, effective, low-cost strategies for fracture prevention.

Evaluation of the Musculoskeletal Diseases Program

A major project to evaluate the Musculoskeletal Diseases Program was completed during 1983. Each task group of experts provided a detailed report on the past activities and future recommendations for a segment of the program. The scientific areas addressed by four task groups were: basic bone properties and metabolism, bone diseases and healing, articular joints, and other skeletal support structures and functions. A fifth task group considered the organization and management of the program. A steering committee report summarized the total project and provided an overview. The final report on the evaluation of the Musculoskeletal Diseases Program has been printed and is being distributed to researchers in the field. Implementation concepts are now under development.

Clinical Trial of Fluoride for Osteoporosis

A clinical trial is under way to evaluate the safety and efficacy of fluoride in the treatment of osteoporosis. Most of the expected 400 patients have been enrolled. Much baseline data on risk factors and related disorders have been gathered in the recruitment phase. The anticipated outcome of reduced fracture incidence will require several years of data gathering.

Workshop on Bone and Cartilage Transplantation

A workshop on bone allograft transplantation was held this year to assess current results with bone and cartilage transplantation and to review methodologies. Special emphasis was placed on immunosuppression of tissue rejection and on microvascular surgical approaches. Replacement of damaged or diseased bones and joints with viable transplants may represent a long-lasting solution. The potential for application to younger patients is very significant.

Several research projects on transplantation have been supported in recent years, but the progress has been slow. New directions may be in the areas of histocompatibility, reduced immunogenic rejection, and microvascular enhancement. The ideas generated in the workshop are expected to supply the direction and stimulation for new research activity.

The workshop was summarized in an article to be published in Clinical Orthopaedics and Related Research.

Program Announcement—Program Interest in Bone-Cell Regulatory Factors

Major advances in understanding have been made in bone-cell regulatory factors, and support for this work, along with initial studies in clinical application of these new developments, should go forward. The continuous remodeling of bone is a complex, multifactorial process. Several controlling proteins recently have been identified and isolated. These new leads should be pursued.

The Institute has supported several of the leading investigators in this area. A workshop on this topic was held at the NIH in the spring of 1983. Factors that regulate bone metabolism and remodeling were discussed indepth. Other factors that induce the formation of bone in gap areas were described. Current and future clinical applications were identified. A summary of the workshop (on local factors influencing bone formation) was published this year in the *Journal of Calcified Tissues.*

By stimulation of research interest in this area, this program announcement should contribute to the expanded base of knowledge required for future development of useful applications.

Survey of Research Needs in Dermatology: An Update

This effort brought together a group of leaders in the field of dermatologic research to evaluate accomplishments and new areas of research that have developed since the publication, in 1979, of the report *Analysis of Research Needs and Priorities in Dermatology.*

The report has provided the framework for much of the Skin Diseases Program planning since that time. Most of the material in that report was generated in 1977 and 1978 and thus is approximately 5 to 6 years old. There have been many advances in research in that time period. A number of the items indicated in the original report as

areas that needed investigation have already been investigated; some of the areas that were underserved at that time remain underserved, while others are now being supported. Because of the advances in the past 5 to 6 years, there are many new areas that were not even thought about in the original report that now should be addressed.

Recognizing the need for an update to this analysis, Congress mandated that the NIADDK support such an effort during fiscal year 1983. Therefore, a workshop was organized and preliminary data gathering completed. The workshop was held in September at the end of fiscal year 1983; however, the preparation of the report to be presented to Congress and the final edition of the report of the workshop to be published in the literature have taken place in fiscal year 1984.

Arthritis Information Clearinghouse

Daily scanning of journals and data bases to locate publications, audiovisuals, and meetings of interest has continued. Relevant materials have been acquired, catalogued, abstracted, indexed, and keyboarded for entry into the data base.

The clearinghouse has grown significantly in its 5 years of operation, both by introducing new educational materials and by expanding the more traditional lines of communication. Included in the data base, which is now in place with an established mechanism for acquiring and processing these educational materials, are printed and audiovisual materials, journal articles, reports, and textbooks. The identification and description of new educational programs and their incorporation into the data base are continuing priority functions of the clearinghouse.

Data Base of Educational Materials

During this past fiscal year, the clearinghouse consolidated its "holdings" in the National Combined Health Information Database (CHID). The CHID is the outgrowth of a meeting 2 years ago by members of seven federally supported health information and health education clearinghouses to discuss the possibility of combining their individual bibliographic files into an online data base to avoid duplicative efforts, share information and expertise, and increase ease of access for users. The data base, now a reality as a private file on Bibliographic Retrieval Service (BRS), presently includes the files of the Arthritis Information Clearinghouse, the National Diabetes Information Clearinghouse, and the Center for Health Promotion and Education. Three other clearinghouses are considering joining and are presently making arrangements to reformat their records.

The general information in the new data base does not duplicate the National Library of Medicine's MEDLAR system but rather focuses on somewhat different areas: health resources and patient education materials (particularly so-called fugitive literature), patient and professional educational programs and curricula, and evaluation material in the specific category of information that each clearinghouse represents. Many of these materials are not available through libraries, online data bases, or other sources considered traditional. Fugitive literature is so named because it is not published in the traditional medical journals but rather comes from hospitals, voluntary health organizations, pharmaceutical firms, and specialized health-information publishers. The health professionals who look for these materials usually direct patient education or are involved in developing patient education programs. They need such materials for patient education documents such as teaching manuals, program design instructions, and evaluation materials, and for information about new interventions or procedures.

The new data base, consisting of the files of the three current participants, became available this past fiscal year and contains more than 10,000 records. As of the end of fiscal year 1984, the arthritis file on BRS contained 3,593 records, and regular updates on new materials to the file continue to be made.

Biblio-Profiles

Biblio-Profiles, a new kind of publication for health professionals, are now available from the Arthritis Information Clearinghouse. A Biblio-Profile is a brief yet comprehensive state-of-the-art report, the profile, followed by a selected bibliography, the biblio. The intent of the Biblio-Profile is to provide an overview of a topic, indicate its current importance to the field, and point to areas where little is known or where gaps in knowledge exist. The clearinghouse and its advisory group select the topics for this new series, and subject experts prepare them.

Other Products and Services

Five annotated bibliographies and eight reference sheets covering such subjects as ankylosing spondylitis, diagnostic radiology in the rheumatic diseases, infectious arthritis, juvenile arthritis, lupus (professional education materials), biofeedback, diet and arthritis, drug information for patients, gout (patient education materials), Lyme disease, multipurpose arthritis centers, scleroderma (patient education materials), and splints were completed by the clearinghouse during the year. Each of the bibliographies and reference sheets has been reviewed by authorities in the field. Two issues of the clearinghouse newsletter were prepared and distributed.

Names of 1,447 individuals or organizations were added to the clearinghouse mailing list, bringing the total to 6,782. The mailing list has been coded to make the identification of specific professionals—physicians, librarians, health educators, and pharmacists—possible.

Advisory Group

An 11-member advisory group composed of rheumatologists, educators, library scientists, and other health professionals has continued to help the clearinghouse in effective planning and accomplishment of goals. The group, through twice yearly meetings and periodic telephone and letter communications, provides recommendations to the clearinghouse project officer and staff.

Epidemiology Research Program

The number of investigator-initiated research grant applications focused on epidemiology has continued to grow during the past year, although the rate of fundable applications remains low. A positive trend has been noted in the increasing volume of successful amended applications.

Arthritis Data Work Group

The Arthritis Data Work Group has been formed in response to an ongoing need for reliable data on the various forms of arthritis. Over the years, the NIADDK, the NAAB, and the Arthritis Foundation (AF) have been the frequent recipients of requests for data on arthritis. For some of the requests, usable data do not exist, while for others different overlapping sources of data are available but must be used with caution. To address this problem, the NAAB, the AF, and the NIADDK have set up a joint committee whose mandate is to review critically data available from national surveys and from other data sets of well-defined populations and to publish the best available estimates on parameters such as prevalence, incidence, and economic costs. The group will keep in mind the problem of definition—both the clinical definition of the various forms of arthritis and the tendency of the clinician, the epidemiologist, and the lay community to define and report arthritis differently.

Examples of research accomplishments made possible by NIADDK support of epidemiologic activities have been given in the section on research advances. Two additional accomplishments are cited here:

Rheumatoid Arthritis and Oral Contraceptives

Findings from three studies suggest a negative association between the use of oral contraceptives and the development of rheumatoid arthritis. In reports from England and Holland, the incidence rate of rheumatoid arthritis among oral contraceptive users was half the nonuser rate. In a study of incidence and prevalence in Rochester, Minnesota, Mayo Clinic investigators noted that during the period 1950 through 1974, incidence rates for males remained relatively stable whereas rates for females declined dramatically during the last 10 years of the study. No explanation was found for the observed decline, but the authors believe that a factor introduced in the 1960's and acting selectively on females affected the incidence rates. Proposals were solicited for a case-control study of the risk of rheumatoid arthritis in relation to oral contraceptive use and for study of the effects of contraceptive steroids in lupus by the National Institute of Child Health and Human Development, with the NIADDK in an advisory role.

Raynaud's Phenomenon

Little is presently known concerning the prevalence of Raynaud's phenomenon, or vasospasm. The role of Raynaud's phenomenon as a risk factor for scleroderma and other connective tissue diseases is poorly understood. Approximately 95 percent of patients with scleroderma suffer from Raynaud's phenomenon. Currently, there are no reliable data to predict what proportion of patients with Raynaud's phenomenon will eventually develop scleroderma. Investigators at the University of South Carolina are attempting to identify criteria that will be useful in differentiating between Raynaud's phenomenon with benign or with serious prognosis. Such information would be useful in the identification of a high-risk Raynaud's phenomenon group and would alleviate the anxieties of subjects with benign Raynaud's phenomenon, if such proves to be the case.

Epidemiologic Activity in the Multipurpose Arthritis Centers

Nine centers have statistical and epidemiologic core units designed to enhance efficiency and effectiveness of the center's activities. The Stanford Biostatistical, Computer, and Education Methodology Core Unit, for example, provides consultation and review of all projects. It offers to center personnel expertise in biostatistics, computational consultation, intervention methodology, outcome measurement, and independent assessment.

The Research Evaluation and Support Core Unit (RESCU) at Boston University focuses on development and application of the AIMS instrument. RESCU also works to coordinate and organize analyses of research data with the MAC. Data on amyloidosis, an area of special research emphasis in this center, are being computerized within this core.

At Brigham and Women's Hospital MAC (Boston), the Core Unit for Clinical Epidemiology and Evaluation in the Rheumatic Diseases assists in formalization of research questions, aids in design of studies, provides computerized methods for data storage and retrieval, and assists in statistical analyses.

The centers also help development of individuals skilled in pursuing epidemiologic studies of rheumatic diseases. At the Johns Hopkins center, a postdoctoral fellowship is available for a 3-year program leading to a masters of public health in epidemiology and full training in rheumatology. Epidemiologic training programs also are offered at the Rosalind Russell MAC (San Francisco) and at the Brigham and Women's Hospital MAC. In addition,

epidemiologists familiar with other chronic diseases are being recruited. These programs may help to nurture the interest of young investigators in careers of rheumatic disease epidemiology.

Arthritis Data Systems Program

The ARAMIS data system continues to play an active role in studies of rheumatic diseases classification and prognosis. Within the past year, both the revised systemic lupus erythematosus (SLE) criteria and juvenile rheumatoid arthritis criteria were completed. Evaluation of the rheumatoid arthritis criteria also was completed. Other classification studies in psoriatic arthritis, seronegative rheumatoid arthritis, vasculitis, myositis, and osteoarthritis are in progress.

In one followup study by ARAMIS investigators, the health assessment questionnaire was used to identify the predictors of future disability in moderate or severe rheumatoid arthritis patients. Three factors, radiographic grade, presence of symmetrical arthritis, and age of the individual, were found to be the most useful predictors of future disability of nearly 40 factors analyzed. Studies of long-term impact of disease on patients with rheumatoid arthritis are under way with regard to mortality, disability, and cost. Preliminary findings indicate markedly increased mortality in rheumatoid arthritis patients and relate the increase in deaths to initial disease severity. Recent studies include the effect of methotrexate in rheumatoid arthritis and the effect of antihypertensive drugs in treatment of scleroderma. A questionnaire to measure side effects has been developed and is currently being validated. Another questionnaire, to measure both direct and indirect economic impact, has been completed and added to the ARAMIS outcome assessment protocols.

The followup of HANES I (see page 40) is completed, and data collection for the extensive arthritis section has been free from serious difficulties. The followup instrument was able to serve four principal study objectives: retrospective morbidity and mortality associated with suspected risk factors, prospective mortality associated with suspected risk factors, changes in patient characteristics between HANES and current status, and natural history of chronic disease and functional impairments. Plans are under way by the participating institutions to coordinate and cooperate in data analysis. In addition, plans have been made to follow the cohort over a longer time period.

The multipurpose arthritis centers have made progress in the evaluation of the ability of health-status measures to detect small improvements in health. In recent studies carried out by Boston University arthritis center investigators, standard measures were compared to the AIMS instrument in a drug trial. Both measures gave essentially identical results. Thus, the aims instrument was reported to be quite sensitive to clinically meaningful, drug-induced improvements and may be useful in clinical trials in rheumatology.

Conferences

Conferences in research and clinical developments and advances in biomedicine facilitate the immediate exchange of information among those working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions. It is the fastest and most effective type of cross-fertilization process in biomedical research.

The Arthritis Program provided support for four research conferences relevant to research on the rheumatic diseases.

The program supported the second Gordon Conference on Basement Membranes, which brought together 150 investigators from a wide spectrum of biomedical disciplines. There were eight sessions, each of which was devoted to one of the major areas of current basement membrane research with the emphasis on provocative new and unpublished findings. Also featured was a special lecture on the subject of the neuromuscular basement membrane in differentiation. The topics covered in the conference included ultrastructure and immunochemistry; biochemistry; biochemistry of the collagen, proteoglycan, and glycoprotein components; biosynthesis, including gene expression; interaction of basement membrane components with cell receptors; and the role of basement membrane in morphogenesis and development. Two sessions focused primarily on the effect of disease on basement membranes.

The Federation of American Societies for Experimental Biology conducted a Summer Research Conference on Lymphocyte and Antibody Networks and the Impact of Infectious Agents. Basic immunobiologists, scientists studying experimental models of infectious disease, and clinical immunologists were brought together to discuss normal functioning of the immune system and the impact of infectious agents upon it. Topics for discussion included basic immunological regulatory systems, models of lymphocyte abnormalities, and the effects of viruses, bacteria, and parasites on immune function.

A conference was held in October 1984 under the auspices of the New York Academy of Sciences to discuss recent advances in collagen research, particularly as related to humans. It was designed to present new developments in the rapidly changing area of biology of collagen and to acquaint physicians and biologists with this new information and to promote close interactions between them.

The Arthritis Program convened a group of experts as an ad hoc arthritis research advisory group representing major areas of interest in rheumatology, which met on

February 28, 1984. Their task was to discuss recent research advances, opportunities, initiatives, and issues concerning research training. The possibility for insights into the cause and control of rheumatoid arthritis was again stressed, based on current available knowledge and the remarkable advances in applicable technology. It now seems possible to develop new and advanced concepts with acceleration of research in this field. Rheumatic diseases research should focus on new technologies and resources.

Scientific discussions included the field of infection and arthritis, approaches to the study of mycoplasma, collagen-induced arthritis, mediators and cellular response of inflammation, collagen and the need to understand better the extracellular matrix and basement membrane, the sensitivity of DNA probes, the need for a DNA library, and the appropriate involvement of molecular genetics.

On April 6, 1984, the Multipurpose Arthritis Centers Program convened a group of experts in Bethesda, Maryland, to review all aspects of arthritis center activities. Major areas discussed included progress in the research, education, and community and health-services research components; roles of developmental and feasibility studies and core units; effectiveness of administrative structure; how to facilitate and increase research in orthopedics and pediatric rheumatology; and the potential of specialized centers of research (SCOR's). SCOR's were recommended for implementation, both by this MAC advisory group and the NAAB. The NAAB had specifically recommended that $2 million be added to the centers program in fiscal year 1984 for SCOR's in the rheumatic diseases.

The Multipurpose Arthritis Centers Program held its annual center directors meeting on July 18-19, 1984, in Bethesda, Maryland. The meeting provided an opportunity for staff members of various centers to present progress reports on current projects and laid the groundwork for future collaborative activities among the centers. Numerous examples were provided to show how developmental and feasibility studies yielded results that provided the basis of subsequent research grants. Examples include an investigation of proteoglycans in osteoarthritis, which led to a research grant and a change of career direction by the principal investigator, and a research grant and an Arthritis Foundation fellowship for an associate also working on the study; a study of the interaction of mycoplasma and lymphoid cells that resulted in five publications, a regular research grant, and a Research Career Development Award; and work on bursae that led to 11 journal publications and 6 abstracts and was later given additional funding by the Veterans Administration. Clinical research in orthopedics also was highlighted at the meeting. Examples include prospective studies of avascular necrosis of the femoral head, evaluation of total knee-joint replacement, development of an instrument for measuring pressure within the knee, and the use of new imaging techniques to detect pathologic changes in articular cartilage and bone in patients with osteoarthritis.

The Muscle Biology Program provided partial support for three research conferences during 1984.

The Gordon Research Conference on Muscle-Contractile Proteins was held on July 2-6, 1984, in Plymouth, New Hampshire. A subject of increasing importance in terms of understanding muscular differentiation is the expression of genes determining the different forms of the contractile protein, myosin. Current techniques allow identification of the amino acid sequence of functionally important regions, and then this can be related to the different specializations of muscle. Another topic was the structure of actin, the second major contractile protein. Discussions were held on the structure of myosin, including the character of the site interacting with actin, the apparent site of force generation. Regulation of contraction, i.e., the interaction of actin and myosin, was the next topic. This question is now being probed using monoclonal antibodies to various subunits. Many attempts are being made to correlate biochemical studies with physiological studies peformed on whole muscle or muscle bundles.

In collaboration with the National Heart, Lung, and Blood Institute, the Muscle Biology Program provided support for a conference on Skeletal, Heart, and Smooth Muscle Energetics, held June 4-8, 1984, in Burlington, Vermont. The goals of the conference were to identify and examine important problems in muscle energetics, to discuss interdisciplinary strategies, and to relate new findings to other aspects of muscle contraction. Topics covered were energetics of cross-bridge cycling in skeletal muscle, mechanics and energetics of heart and smooth muscle, energetic implications of phosphorylation of contractile proteins, and energetics of simplified contractile systems. New directions in the field include techniques to monitor the movement of calcium ions during tension development, the role of the various protein phosphorylations, the role of myosin isoenzymes, and opportunities offered by nuclear magnetic resonance to study the phosphorous species within muscles.

In conjunction with two other Institutes and the Fogarty Center, the program provided partial support to enable U.S. scientists, particularly junior investigators, to attend the 8th International Biophysics Congress, held in Bristol, United Kingdom, July 22 to August 4, 1984. The Congress was sponsored by the International Union of Pure and Applied Biophysics. Subjects of interest to the Division of Arthritis, Musculoskeletal, and Skin Diseases included research on connective tissues and bone, contractile systems, mechanisms of transport across membranes, energetics, and further development of probes, such as nuclear magnetic resonance, x-ray and neutron diffraction techniques, and electron resonance.

The Musculoskeletal Diseases Program supported the third Gordon Conference on Bioengineering and Ortho-

paedic Sciences in the summer of 1984, in New Hampshire. Sessions included research on intervertebral disks; synovial cartilage; functional assessment of joints, tendons, and ligaments; and mechanical factors in bone remodeling. The open and informal format promoted exchange of ideas and stimulated future research.

Two meetings of the Ad Hoc Interagency Dermatology Working Group were held in December 1983 and June 1984. The working group includes members of all NIH Institutes and several other Federal agencies. In the past year, the group has made good progress in compiling a list of areas of research interest for each of the Institutes and agencies, along with the names and telephone numbers of the contact individuals for each Institute or agency. The centralized NIH computer file has been used to identify skin-disease-related research throughout the NIH. Skin-disease-related research at non-NIH facilities has been identified by the individual contact people for those other agencies. A compilation of all such research by subject matter area, following the outline of the Analysis of Research Needs and Priorities in Dermatology, has been undertaken. This categorized list of active research will be available to all of the contact individuals at each of the Institutes and agencies. Use of these data will be made in an attempt to coordinate identification and support of underserved areas of research in skin disease. The working group was instrumental in facilitating the development of the program announcement on epidermolysis bullosa and biology of the basement membrane, which has the support of this Institute along with the National Institute of Child Health and Human Development and the National Institute of Dental Research.

The conference Tuberous Sclerosis Workshop: Cause, Diagnosis, and Management, held April 8, 1984, at MIT (Cambridge, Massachusetts), was cosponsored by the Skin Diseases Program and the National Institute of Neurological and Communicative Disorders and Stroke. This workshop brought together basic scientists working in areas related to tuberous sclerosis and clinicians interested in the disease for an informal series of presentations designed to foster interdisciplinary contacts and research.

The Skin Diseases Program contributed significant support to the 33rd Annual Symposium on the Biology of Skin, at Gleneden Beach, Oregon, October 21-25, 1983, on the subject of cutaneous oncogenic viruses. At this meeting, strong emphasis was placed on the papilloma and herpes families of viruses, both of which have members capable of transforming cells in vitro. The proceedings of this symposium were published in the July 1984 issue of the *Journal of Investigative Dermatology*.

The Skin Diseases Program also contributed to the support of the New York Academy of Sciences' International Conference on Intermediate Filaments. One day of this 3-day meeting was devoted to keratin, the intermediate filament characteristic of skin. The proceedings of this meeting will be published in book form.

Other conferences supported by the Division in fiscal year 1984 include the following:

- Conference on Extracellular Matrix, Keystone, Colorado, April 22-29, 1984.
- Gordon Conference on Proteoglycans, Plymouth, New Hampshire, July 23-27, 1984.

Program Plans

Program Announcements

Program announcements are broadly disseminated notices to the biomedical research community concerning particular areas of research that an NIH Institute would like to stimulate and in which it stands ready to receive research grant applications.

Program Announcement—Rheumatoid Arthritis: Research on Causes and Mechanisms

Findings from research over the past few years indicate that rheumatoid arthritis is caused not solely by a single micro-organism such as a virus or bacterium or a deranged host factor but rather by different agents generating immune responses that later lead to chronic inflammation in those with genetically determined abnormal immune regulation and biochemical abnormalities.

Many new basic research methodologies have been developed and are now available for finite experiments to test this and other hypotheses. These new technologies include monoclonal antibodies, recombinant DNA, and molecular biology. In addition, new experimental animal models have been developed such as that induced by immunization with type II collagen. Using these and other techniques, the following research areas can be investigated:

- Primary initiating events (triggering agents): viruses, bacteria, collagen.
- Cellular basis of immune response: T- and B-cell maturation, subpopulations, and interactions.
- The roles of idiotypes, anti-idiotypes, and their immune complexes.
- Activities of lymphokines and monokines.
- Mediators of inflammation: prostaglandins, leukotrienes.
- Enzymes participating in joint destruction: collagenase, elastase.

- Molecular genetics, including mapping of the mixed histocompatibility complex.
- Correlative interdisciplinary research (of the above) to elaborate the kinetics of the pathophysiology of rheumatoid arthritis.

This broadly disseminated program announcement will serve to stimulate concerted research efforts capitalizing on these new advances.

Program Announcement—Research Grants for Ankylosing Spondylitis and Related Spondyloarthropathies

Diseases of interest include ankylosing spondylitis, Reiter's syndrome, arthritis of inflammatory bowel disease, psoriatic arthritis, and reactive arthritis.

The striking association between the genetic marker HLA-B27 and ankylosing spondylitis (95 percent) and related spondyloarthropathies such as Reiter's syndrome (75 percent) was established 10 years ago. Yet, the mechanism by which HLA-B27 exerts its role in pathogenesis remains obscure. Any hypothesis must account for the facts that not all B27 patients (approximately 20 percent) develop the disease and that a small percentage of Caucasians and a larger percentage of blacks with the disease do not possess HLA-B27.

Two major concepts have been advanced to explain this association. The first is that HLA-B27 by itself is unimportant; rather, it predisposes to the development of the disease, perhaps by modifying immune responsiveness. The second is that B27 itself is directly involved, in some way, as a facilitator or receptor for a triggering agent such as a bacterium or other environmental agent. Various infectious causes have long been suspected but never established. Further work needs to be carried out to establish a possible role in ankylosing spondylitis for gram-negative enteric infections such as shigella, salmonella, yersinia, and chlamydia. Also unresolved is whether the major genetic factor is HLA-B27 itself or a closely linked gene. An immunogenetics conference is planned to address this issue thoroughly and provide further specific direction to research activity in this area.

Several organisms have been demonstrated or proposed to be etiologic agents in Reiter's syndrome. The etiologic role of chlamydia in sexually acquired Reiter's syndrome needs to be settled. Putative pathogenic bacteria need to be subtyped; the association of particular subtypes with Reiter's syndrome needs to be tested, and the carriage of plasmids by putative pathogenic bacteria needs to be examined for disease associations.

A major recommendation of the Prevention Conference on Arthritis held in 1983 was an epidemiologic study to identify triggering agents, specifically a prospective cohort study in a high-risk group. This group would be families of HLA-B27-positive spondylitic patients with a large sibship of adolescent males, residing in areas of high exposure to putative infectious agents.

Several research grants will be awarded under this initiative, with the intent to determine whether and if so, how, HLA-B27 or other related immunogenetic determinants predispose to spondylitic disease and to ascertain any role from gram-negative enteric or other organisms in triggering these diseases.

Program Announcement on Intensive Search for Infectious Agents in Early Arthritis

"Infectious arthritis," characterized by acute or subacute arthritis in one or more joints, is caused by direct invasion of the synovium by various micro-organisms, mostly bacteria and a few viruses. Such arthritis can be caused by various pyogenic bacteria such as staphylococci, streptococci, and pneumococci; gonococci seem to have a special predilection for joint invasion. Micro-organisms can participate in the etiology of arthritis in other ways, for example, by serving as inciting or triggering agents in a susceptible individual. One illustration of this is the role of streptococci in the pathogenesis of rheumatic fever. Another more recent example is the spirochete of Lyme disease causing the late development of arthritis.

In certain major rheumatic diseases of unknown etiology such as rheumatoid arthritis, systemic lupus erythematosus, and the spondyloarthropathies, there is current interest in several micro-organisms as primary initiating factors in a possibly genetically determined immunocompromised host. New biomedical research methodologies have been developed enhancing the potential for identifying such micro-organisms or their products in tissues. At present, from research in both animals and humans, there is special interest with respect to rheumatoid arthritis in mycoplasmas, Epstein-Barr virus, and parvovirus. In the spondyloarthritic group of rheumatic disease, candidate agents are salmonella, shigella, klebsiella, yersinia, and chlamydia.

Advice and guidance concerning the design and protocol for this study have been obtained from a special panel organized by the NAAB from the Institute's Ad Hoc Arthritis Research Advisory Committee and from a special workgroup convened to discuss the details, feasibility, and strategies for initiating and performing this study. These groups were both encouraging and supportive of this research initiative. By means of cooperative agreements among research facilities, this program initiative will attempt to stimulate new activity utilizing modern advances in biotechnology to determine the role that infectious agents may play in the etiology of rheumatoid arthritis and other forms of inflammatory joint disease of unknown causes.

Program Announcement of Research Interest in Vascular Spasm and Scleroderma

Scleroderma, or progressive systemic sclerosis, is a chronic disorder characterized by diffuse fibrosis of the skin and internal organs. Dominant hypotheses concerning the etiology of systemic sclerosis center around connective tissue, immunologic, and vascular abnormalities. Immunologic studies have been concerned with lymphoid pathology, specific autoantibodies, and cell-mediated immunity. The connective tissue hypothesis suggests that scleroderma fibroblasts may play the primary pathogenetic role, synthesizing excessive amounts of collagen even after multiple passages in tissue culture. Current interest is greatest in the vascular hypothesis because Raynaud's phenomenon is the first manifestation of scleroderma, often by years, and recent demonstrations by modern tracer techniques indicate that vasospasm is responsible for the kidney, heart, and lung involvement of scleroderma. Serum factors directed to destruction of vascular endothelial cells have been discovered.

Recently, several new agents with diverse specific pharmacologic actions have been reported highly effective or promising in correcting the vascular pathology of scleroderma. Treatment with captopril, the inhibitor of angiotensin-I-converting enzyme, has proven lifesaving in scleroderma patients with malignant hypertension and early renal failure; digital ulcers have improved, perhaps from a bradykinin-like action of captopril. New calcium-channel-blocking agents, such as nifedipine, have been effective in combating Raynaud's phenomenon and scleroderma. In addition, there have been recent preliminary favorable reports of an antiserotonin agent, ketanserin, in treating Raynaud's phenomenon and scleroderma. With the help of basic research on the circulation and ascertaining the finite mechanism of action of these agents, there is promise of gaining understanding of the etiology of Raynaud's phenomenon. Thereafter, the relationships between the vascular pathology and connective tissue overgrowth may be better addressed.

Attention is being devoted to pathologic changes taking place in the smallest peripheral blood vessels, or microcirculation. A program announcement will be issued to stimulate research on disturbances of the microcirculation and pharmacological interventions in Raynaud's phenomenon and systemic sclerosis.

Workshop in Immunogenetics and Rheumatic Diseases

Numerous advances have been made by rheumatologists in the areas of immunogenetics, immunopathology, and immunological expression of rheumatic disease in general. Understanding of the precise pathogenetic roles of immunological events in these disorders is still incomplete. A workshop is needed in these areas to bring together people working on various aspects of these phenomena and to relate what is known in basic immunology, both cellular and humoral, to the pathophysiology of specific rheumatic diseases. The exchange of ideas will stimulate, promote, and give direction to research in these important areas.

Workshop on Etiology of Osteoarthritis

Osteoarthritis is one of the leading causes of disability and pain. Many biochemical and mechanical changes occur as this disease progresses, but the underlying initiating event, cause of progression, and lack of healing are not well understood. Several animal models now exist to study the etiology of osteoarthritis. Advances have been made in mechanical and biochemical analyses of small samples from diseased tissue. Technology improvements have set the stage for major advances over the next 5 to 10 years. A workshop with leading investigators from several scientific fields is planned for the summer of 1985, emphasizing basic scientific advances, future directions, and interdisciplinary studies.

Workshop on Bone Mineralization

Mineralization is a key phenomenon in the development and continued remodeling of bone. Recent advances have challenged previous theories. New types and distributions of extracellular components have been found, and new proteins have been discovered that seem to regulate mineralization. Diffraction and nuclear magnetic resonance studies point to a less-organized crystalline (not amorphous) initial form of hydroxyapatite. Many projects have been supported in this area, with interesting outcomes, new technologies, and new theories. In some areas, controversial results and interpretations have led to the need for clarifying research.

A workshop is scheduled for the fall of 1984 that may generate new research ideas and be a broad stimulus to new efforts. Leading international scientists will discuss the complex process of bone cells laying down a matrix that is subsequently mineralized. A state-of-the-art book will be prepared from the workshop manuscripts.

Research Conference on Bone Destruction in Paget's Disease

Several bone disorders may be traced to defects in osteoclast activity. A workshop will be held to discuss current knowledge on the biology of the osteoclast and its role in bone diseases such as Paget's disease and to promote expanded research. In Paget's disease, excessive bone breakdown and subsequent bone formation leads to

dense, irregularly structured bone that may be misshapen and fragile.

Osteoclasts are cells that resorb bone in a continuous remodeling process. The origin of these cells, attraction to the site of activity, and mode of action have been the subject of much recent research. New culture technology has allowed development of high-purity osteoclast cell lines to further enhance progress. No workshop has yet focused on this important topic.

Program Announcement on Osteoporosis: Risk Factors and Predictors of Fracture and Bone Loss

One of the recommendations of the April 1984 Consensus Development Conference on Osteoporosis (see "Program Accomplishments") was to support observational and epidemiological studies on the causes of this disease.

Osteoporosis affects as many as 15 to 20 million individuals, primarily postmenopausal women, causing spinal crush fractures and hip fractures. The condition affects over half of women above age 45 years and 90 percent of women above age 75. About 1.3 million fractures attributable to osteoporosis occur annually.

While many factors have been related to the presence of osteoporosis, a better understanding of etiology and early detection would be extremely valuable in treatment.

A study of risk factors is being encouraged for submission for fiscal year 1985 funding. A large prospective study is proposed to identify predictors of hip and wrist (Colles') fractures and to identify predictors of rapid bone loss. The study cohort will be a subset of a recently initiated project on systemic hypertension in the elderly. Connecting the osteoporosis evaluation to a well-controlled existing study will be an economic method to include a very large cohort.

Program Announcement on Epidermolysis Bullosa and the Biology of the Basement Membrane Zone

The basement membrane is the layer of cells on which the outer, protective epidermis of the skin rests. The recent development of several techniques, including monoclonal antibodies and gene cloning, has allowed a much more basic and specific type of research that can be directed at structural and functional components of the basement membrane zone, both in the normal state and in the hereditary group of diseases epidermolysis bullosa. Epidermolysis bullosa is a group of several diseases in which there is abnormal separation of the epidermis from the dermis. Different forms of the disease show defects at different levels within the basement membrane zone. Thus, this disease becomes a model system for the study of the function of the basement membrane zone and the structures therein. This initiative will have wide application not only to epidermolysis bullosa itself but potentially to other diseases where the major defect resides in the basement membrane zone and to a number of normal healing processes such as wound healing, the development of artificial skin, and the treatment of burn patients.

Studies supported under this program will examine structural defects in proteins of the basement membrane zone and their relationship to different forms of epidermolysis bullosa, enzymatic defects and their relationship to different forms of epidermolysis bullosa, identification of abnormal genes or gene products in different forms of epidermolysis bullosa, and application of the above data to more general questions concerning the structure and function of the basement membrane zone in health and disease states.

It is hoped that with this multi-Institute program announcement, appropriate interdisciplinary and additional basic research related to epidermolysis bullosa will be fostered.

Epidermolysis Bullosa Registry

Epidermolysis bullosa is a severe genetic multisystem disease; little is known about the specific cause of most of its forms, although much research is ongoing. A valuable adjunct to an acceleration in basic research in epidermolysis bullosa will be the availability of well-characterized patients with various forms of the disease who are willing to provide the tissue specimens necessary for the continued research.

The epidermolysis bullosa registry initiative intends to develop by contract a roster of well-characterized patients with different forms of epidermolysis bullosa willing to contribute specimens and be followed as part of a research protocol, to develop a registry of patients with this disease to obtain appropriate epidemiologic data concerning the various forms of the disease, and to determine the natural history and value of various therapeutic interventions in the different forms of epidermolysis bullosa, by longitudinally following a selected group of patients from the above two groups.

There has been a recent increase in interest in epidermolysis bullosa because of several new developments in research and technology. The Skin Diseases Program now supports several research grants related directly to it. It is hoped that with this contract, we will be better able to support appropriate interdisciplinary and basic research related to epidermolysis bullosa.

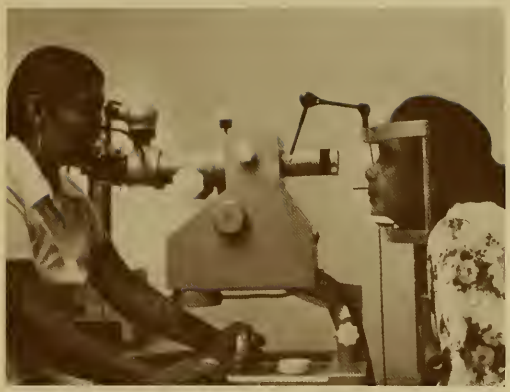
III. Research Focus—Diabetes, Endocrinology, and Metabolic Diseases

Overview

The three major program areas of the Division of Diabetes, Endocrinology, and Metabolic Diseases support the study of diseases that have devastating results in human terms. An example is diabetes mellitus, the fifth leading cause of death due to disease in the United States. Diabetes is characterized by a deficiency in insulin production or an impairment of insulin action. If the specialized cells of the pancreas that secrete insulin are damaged, the loss of the hormone can lead to various other endocrine and metabolic disturbances that affect the regulation of the body's metabolism and may lead to widespread chronic degenerative lesions that affect every tissue of the body. If the mechanisms regulating the secretion or the action of insulin are defective, similar consequences can ensue.

Endocrine and metabolic diseases may be described as specific disorders that result in generalized malfunction of the body's system for "information processing." The information being processed may be derived from genetic coding, neural transmission, hormonal messengers, immunologic responses, or cell-to-cell communication. For example, if genetic information is miscoded, the result can be an inborn error of metabolism such as cystic fibrosis. If the hormonal and hormone-like messengers of the body are malfunctioning, the result can be an endocrine disease affecting the whole body such as dwarfism.

Alterations in the mechanisms by which genetic and immunologic information is expressed in metabolism underlie much of the disease pathology with which the Division is concerned. The key to the successful treatment or cure of these diseases is the ability to correct the misinformation that is expressed or results in signs and symptoms of disease. At the present time, treatment measures often must focus on the repeated replacement of an absent or abnormal hormone (a failed messenger) such as insulin, but NIADDK-supported research into basic mechanisms of these diseases could lead to measures that prevent or redirect the initial failure, permitting normal functioning of the body's systems to continue.



Retinopathy can lead to blindness for patients with diabetes. New research suggests that measuring a growth factor in the blood may identify patients at high risk for vision loss.

Facing page

The portable insulin pump administers insulin in a continuous fashion and adjusts dosage for meals and exercise.

Diabetes

Diabetes mellitus is a complex disorder of carbohydrate, protein, and fat metabolism that affects an estimated 11 million Americans.* The diabetic condition can result in long-term complications that may involve virtually every tissue of the body, particularly the blood vessels, nervous system, kidneys, and eyes. Approximately 300,000 people with diabetes die every year; about half of these deaths are directly attributable to diabetes and its complications.* Since 1976, the economic costs of diabetes have doubled in terms of medical care and losses due to disability and premature death. The financial impact of diabetes now exceeds $10 billion annually.*

In general terms, diabetes can be divided into two clinical types, with different prognoses, different treatments, and different causative mechanisms. The two types are called insulin-dependent (formerly "juvenile") diabetes (IDDM)

* Source: National Commission on Diabetes

and noninsulin-dependent (formerly "maturity-onset") diabetes (NIDDM). IDDM usually begins in early life—before age 40—and it is characterized by a requirement for daily insulin injections. Unless insulin is provided for this condition, patients will develop ketoacidosis, a buildup of acids and ketone bodies in their tissues and fluids, with a fatal outcome. Insulin-dependent diabetic patients frequently experience greatly accelerated degeneration of blood vessels in many organs, which can lead to kidney failure, gangrene in the extremities, heart attacks, neuropathy, and blindness. Even with insulin treatments, the life expectancy of such patients is measurably shortened.

About 85 percent to 90 percent of all individuals with diabetes have the noninsulin-dependent form of the disease, which usually begins after age 40 and is characterized by a slower progression of glucose intolerance and complications of the disease. Many people who have NIDDM can maintain relatively normal blood sugar levels by adhering to prescribed diets, controlling body weight, and if necessary, using oral agents to lower blood sugar levels. However, people with NIDDM also have a decreased life expectancy because of a variety of chronic vascular and neurological complications.

During the past year, the Diabetes Research Program supported research grants and contracts in a variety of scientific disciplines that are contributing to the fundamental knowledge base needed to define the disease and its complications. Work continues on the development of improved medical capabilities for preventing, diagnosing, treating, and curing diabetes. These studies are focusing primarily on defining the natural history, etiology, epidemiology, and pathogenesis of diabetes and the resulting complications. Areas of particular research interest include studies involving islet cell transplantation (the beta cells of the pancreatic islets, which produce and secrete insulin); insulin delivery systems; secretion, transport, action, interaction, and inactivation of islet hormones; the physiology and pathophysiology of pancreatic islet cells; abnormalities of carbohydrate, lipid, and protein metabolism associated with diabetes and its complications; the possible relationships among various genetic, viral, immunologic, toxicologic, and nutritional parameters in the etiology and pathogenesis of diabetes; and the psychosocial aspects of diabetes.

Endocrinology

The Endocrinology Program supports research into the endocrine system, one of the body's major messenger networks. The program's major emphasis is on basic research into hormone structure and mechanisms of hormone synthesis, regulation, and action. A smaller but significant portion of the program effort focuses on clinical research. Studies of thyroid, parathyroid, adrenal, pituitary, hypothalamic, thymic, and pineal hormones are supported, as well as studies on the growth factors, neuropeptides, and prostaglandins.

Basic life processes such as growth, metabolism, reproduction, and aging rely not only on the amount of circulating hormone available but also on factors within the target cells that influence the nature and intensity of the response. Moreover, a critical characteristic of the endocrine system is that few, if any, hormone-sensitive processes are regulated by a single hormone. Instead, several hormones appear to work in concert to effect or maintain body functions. Because these interactions are poorly understood, research is aimed at defining the nature of these interrelationships.

Thyroid and parathyroid diseases are among the most common in medicine. Together with adrenal and pituitary abnormalities and growth disorders, thyroid and parathyroid diseases have an enormous impact on individual well-being and on 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, the 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.

Metabolic Diseases

The primary objective of the Metabolic Diseases Research Program is to support investigator-initiated studies of fundamental metabolic processes and basic and clinical studies of various inborn metabolic diseases (cystic fibrosis, lysosomal storage diseases, glycogen storage diseases, and others). Major foci of basic research investigations include membrane structure, biological transport, and enzymatic mechanisms as they regulate normal and abnormal metabolic processes. Additional areas of emphasis include studies related to the diagnosis, etiology, pathogenesis, and treatment of a large number of inborn metabolic diseases.

Because 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 a devastating effect on its patients is cystic fibrosis, a disease to which the NIADDK traditionally has devoted considerable research support.

Although individual genetic disorders are not common, they have a profound public health impact as a whole. Genetic disorders account for approximately one-third of all infant deaths in the United States and approximately 30 percent to 40 percent of all admissions to children's hospitals. 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.

The NIADDK's mission in the area of metabolic diseases is to acquire an understanding of the etiology and pathogenesis of acquired or inborn errors of metabolism. To carry out its mission, the Institute supports a wide range of basic and clinical studies with the ultimate goals of improving the diagnosis of metabolic disorders, developing rational and effective methods of treatment and, where possible, achieving their outright prevention. Basic research is vital to the understanding of these diseases and includes the study of normal metabolic processes and the fate of metabolic fuels such as carbohydrates, lipids, and amino acids.

Highlights of Research Advances

The following section briefly highlights a number of areas in which the Division of Diabetes, Endocrinology, and Metabolic Diseases has reported recent progress in its research programs.

- In the development of IDDM, there may be a lengthy prediabetic phase showing decreasing beta-cell responsiveness. During this period, autoantibodies to a specific component of the pancreatic islets may appear, signaling a possible later loss of the insulin-producing beta cells and insulin deficiency.
- Genes for histocompatibility antigens, especially the HLA-DR4 gene region, may show altered DNA structure, and these may convey special susceptibility to IDDM.
- Antibodies against insulin may develop even before insulin treatment in IDDM. A new assay for these antibodies may prove useful for early and specific detection of damage to the insulin-secreting beta cells.
- Studies of the role of diet and obesity in the development of NIDDM are in progress in two South Pacific populations at high risk. Differences in diet and response to urbanization, especially as reflected in adiposity or outright obesity, appear to account for differences in the prevalence of NIDDM and provide data on NIDDM itself.
- Identification of the process through which newly synthesized insulin is either stored or secreted is under intense study. Delineation of the conditions that influence the secretion of insulin in normal islet cells would provide an exciting opportunity to attempt to regulate this response.
- A major advance was made in understanding the pathways of carbohydrate metabolism that are affected by insulin and are important in diabetes—specifically, the effects of insulin and glucagon on a key regulatory enzyme, phosphofructokinase.
- Transplantation of pancreatic tissue for treatment of IDDM has been facilitated by pretreatment of donor blood with ultraviolet light. This rapid and simple process apparently depletes the blood of rejection-stimulating antigens.
- A trial of the drug sorbinil for treating pain due to nerve involvement among long-term diabetes patients showed marked relief of symptoms in most patients, with improved muscle strength and nerve function.
- Diabetic patients with rapidly progressing retinal vascular disease show a gross elevation of an insulin-like growth factor called somatomedin C. The presence of this growth factor may help identify patients at risk.
- Elevated growth hormone levels appear to contribute to the poor control of diabetes seen in adolescence, physiologic stress, or inadequate insulin therapy. Reducing GH levels may help avoid complications.
- It has been found that a deficiency of GH, which occurs in children with short stature, may in some cases be due to a deficiency of the GH-releasing factor in the hypothalamus rather than to a deficiency of GH itself in the pituitary gland. GRF has been isolated and is easier to synthesize than GH and should be useful in future therapy.
- Excessive pituitary secretion of GH and prolactin and the gigantism and sex disturbances that they cause—as the consequence of some pituitary tumors—can be controlled with pergolide. The drug shrinks the size of the tumors and reduces the excessive hormonal secretion.
- Novel experimental techniques, such as injection of foreign genes into a fertilized mouse egg, have produced giant mice by injecting mouse eggs with either rat or human genes for the production of GH—with wide-ranging scientific and commercial implications.
- It has been shown that inherited defects in a single enzyme, hypoxanthinequanine phosphoribosyl transferase (HPRT), underlie two severe metabolic disorders, the Lesch-Nyhan syndrome and hereditary gout; the type of molecular alteration determines whether HPRT will be totally inactive or only partially deficient, respectively.
- An inherited deficiency of the enzyme biotinidase prevents the recycling of the body's vitamin biotin, required for the functioning of certain enzymes; the resulting clinical disorder in children (seizures, lack of muscle coordination) can be controlled by the administration of pharmacologic doses of biotin.

- Growth retardation and serious metabolic abnormalities may be caused by a long-term inherited intolerance to fructose in older children with a genetic defect in the enzyme aldolase B. Strict avoidance of fructose in the diet, once the condition is diagnosed, can control this metabolic disorder.

Diabetes Research

Insulin-Dependent Diabetes Mellitus: Causes and Development

Prior Findings

In IDDM (also called type 1 diabetes), there is structural or functional damage to the insulin-producing cells (beta cells) of the pancreatic islets, resulting in the loss of insulin secretion and complete dependence on administered insulin. Both immunologic and genetic mechanisms appear to be involved.

The serum of many diabetic children at the time of diagnosis contains an antibody specific to pancreatic islet cells. It appears that a defect in the immune system causes antibody production against the body's own pancreatic insulin-producing cells, an autoimmune response. Further evidence of the role of autoimmune mechanisms is seen in experimental transfer of the disease from animals with severe diabetes to nondiabetic animals, using spleen cells.

It appears that genetic coding associated with the disease process occurs on chromosome 6 (HLA sites DR3 or DR4, among the histocompatibility genes) and seems to convey susceptibility to the disease. Testing for these genes permits identifying people at risk of developing diabetes; about 90 percent of IDDM patients have these genes.

According to one current hypothesis, there are at least two distinct forms of IDDM, one associated with HLA-B8 and DR3 and another with HLA-B15 and DR4. The HLA-B8/DR3 disease is the autoimmune form associated with an increased presence of pancreatic islet-cell antibodies, cell-mediated immunity directed against the islets, and a lowered antibody response against externally supplied insulin. This form of diabetes may have its onset throughout life and may be responsible for those cases of IDDM where onset occurs after the age of 20.

The second form of diabetes is associated with the HLA-B15/DR4 antigens. This disease is not associated with autoimmune disease or islet-cell antibodies but is accompanied by an increased antibody response to insulin, possibly after viral-induced damage to insulin-secreting cells and by an earlier, more rapid onset of the disease.

These proposed types of diabetes also explain the course of diabetes in those people unfortunate enough to have both B8/DR3 and B15/DR4 alleles. This group appears to have the earliest age of onset of IDDM, the greatest islet-cell damage, and the highest rate of concordance among identical twins. With concordance, if one twin is found to have this disease, the other one also will develop it. The model that the investigators propose to explain this phenomenon is that the DR3 and DR4 antigens act through different pathogenetic mechanisms and that in an individual with both alleles, the diabetogenic effect is synergistic, leading to increased susceptibility.

Recent Advances

Results in the prospective study of twins *discordant* for diabetes have added to data showing that a prolonged prediabetic phase may occur and that in this phase there is progressive beta-cell dysfunction associated with immunologic abnormalities. What appears to be an acute onset of diabetes may actually be the result of a long period of increasing damage to the beta cells. These same investigators now have observed islet cell antibodies and decreased insulin responsiveness prior to overt type 1 diabetes in HLA-related relatives who are not twins, suggesting that this may be a general phenomenon.

The study of twins also affirmed that the HLA-DR3 and HLA-DR4 genes, expressed as histocompatibility antigens, serve as a marker pointing to IDDM. However, the study found no clear differences between those individuals with DR3 compared to those with DR4, either in the presence of islet-cell antibodies or in susceptibility to disease. Further, three twins with both DR3 and DR4 antigens did not develop the early and severe disease that current theory would predict. This finding can be interpreted as encouraging, suggesting that a fear of imminent and crippling IDDM may not be warranted by any particular genetic pattern, even when a twin already has the disease.

Analysis of the DNA structure of the HLA-DR4 gene region of diabetic and nondiabetic individuals has shown differences that suggest a correlation of altered structure with IDDM—even though the immunologic function is the same in both cases. This work indicates that the type of DR4 gene in IDDM patients may have conveyed a special susceptibility to diabetes.

In a new development, antibodies to insulin have been demonstrated in IDDM patients prior to treatment with insulin. Although the relation of these antibodies to other immunologic features of IDDM (islet-cell antibodies and HLA types DR3 and DR4) is unclear, their presence in a large percentage of diabetic patients and their specificity may indicate that they are immune markers of beta-cell damage. The assay technique, which shows the binding of insulin by serum antibodies, may hold promise for large-scale application because it is easy to perform and because past measurements of islet-cell antibodies, either in the cell or on its surface, were not very specific for diabetes and were harder to carry out.

Most recently, investigators have found autoantibodies to a specific protein component of the pancreatic islets in experimental animals (the BB rat) prone to spontaneous

IDDM similar to that in humans. The protein is of the same molecular size, 64 kilodaltons, as an islet-cell protein already identified in human IDDM patients, and the serum of these patients shows islet-cell autoantibodies against these proteins in the same way as in the diabetic rats. In both, the antibodies are present well before the onset of diabetes, and detection of these antibodies may therefore be used to predict an early immune reaction against pancreatic beta cells. The islet-cell protein may be a major target for the immunologic process leading to the loss of beta cells and the resulting insulin deficiency and inability to control glucose metabolism.

Research Directions

The role of the immunologic components in possible pathogenetic mechanisms should be further elucidated. Identifying the various antigens associated with diabetes may lead to the discovery of the gene or genes that actually allow the initial insult to take place. The role of viral infections and other external agents as etiologic or provocative factors should be established, and their relationship to specific HLA types and beta-cell destruction should be evaluated.

Establishing distinctive types of IDDM associated with various HLA alleles could help in understanding whether the HLA genes code directly for the susceptibility to IDDM or whether they are only coincidently inherited with an as yet undefined gene that actually codes for diabetes. Further work is needed to identify and establish the role of other non-HLA genes that may contribute to IDDM or protect against it.

The risks and potential benefits of immunosuppressive therapy in preventing the clinical onset of IDDM should be evaluated but only under carefully controlled conditions and with adequate safeguards.

Prospective studies of the natural history of IDDM prior to the development of clinical symptoms and of the factors (including genetic features) that contribute to the clinical onset of the disease and its complications should be expanded.

Diet and Obesity in Noninsulin-Dependent Diabetes Mellitus

Prior Findings

NIDDM, or type 2 diabetes, is characterized by hyperglycemia, elevated blood sugar level. NIDDM is usually associated with obesity and is usually controlled by diet restrictions, exercise, and when necessary, administration of either oral hypoglycemic (blood-sugar-lowering) drugs or insulin. One of the strongest risk factors for NIDDM is obesity; a lean body and exercise appear to protect against the development of this form of diabetes. The development of NIDDM is complicated further by its relationship to a gradual decline in glucose tolerance, a phenomenon associated with general aging.

Evidence for a strong genetic input in the development of NIDDM exists, although no definitive markers have been identified. As in IDDM, there is evidence for the involvement of environmental factors.

A continuing study is being performed in several South Pacific island groups to determine the genetic and environmental aspects of type 2 diabetes and its complications in circumscribed populations that are at high risk for developing NIDDM. Although there has been some indication of HLA association with NIDDM, evidence of the genetic basis for the disease is sporadic. Therefore, the major thrust in studying these populations has been to define the disease in susceptible individuals. Factors to be studied include diet, obesity, stress, aging, socioeconomic status, and environmental toxins.

Recent Advances

Two recent studies examined the role of diet in two different populations in the South Pacific. Dietary studies were conducted in Kiribati and in Nauru in conjunction with a diabetes and cardiovascular disease prevalence survey. Both of these populations have recently undergone urbanization.

In Kiribati, 24-hour dietary recall data were obtained from 1,062 randomly selected adults 20 years and older. These samples included both rural and urban groups. The percentage contributions of protein, fat, and carbohydrate to the total energy intake did not differ between rural and urban Kiribati, but the urban group consumed an increased amount of imported foods that contributed to their total energy intake.

Urban dwellers consumed more rice, sugar, drippings, canned meats and fish, condensed milk, and bread and less coconut, coconut sap, taro, and pandanus than their rural counterparts. Energy intake of rural males was significantly higher than that of urban males. There was no statistical difference between the energy intakes of urban and rural females.

Age-standardized diabetes prevalence was 9.1 percent and 8.7 percent for urban males and females, respectively, and 3.0 percent and 3.3 percent for rural males and females. It was apparent that urbanization in Kiribati is accompanied by a marked change in food habits, a decreased level of physical activity, obesity, and an increased prevalence of NIDDM.

In a similar study in Nauru, it was determined that although the contributions of protein, fat, and carbohydrates were similar for the Nauruans and the Caucasian population on the island, the average dietary fiber intake of the Nauruans is much lower than that of the Caucasians. Thiamine intakes were found to be below recommended dietary allowances, and the ascorbic acid intake was found to be marginal in susceptible groups.

Diabetes prevalence rates for adult male and female Nauruans are among the highest reported, 24.7 percent and 23.5 percent, respectively. Marked obesity also is evident in these people.

It appears from these and other studies of these groups that in the Nauruans gross obesity and a high degree of urbanization contribute to the disease, whereas in the Kiribati both adiposity and urbanization, independent of obesity, are associated with the increased risk for developing diabetes. This type of information is contributing substantially to our knowledge of not only the genetic heterogeneity associated with the disease but also the diverse environmental factors that are involved.

Research Directions

Studies of such isolated populations at risk for developing diabetes can provide a great deal of insight into the cause of this disease in Western populations. It is possible in these isolated populations to assess the relative contribution of heredity, diet, and exercise to the development of diabetes and its complications.

It is hoped that studies such as these will continue and stimulate more interest in determining the factors involved in the development of type 2 diabetes. There is a need for more detailed studies of all the risk factors involved, particularly in populations where changes bearing on these factors can be defined and used to establish prevention and control programs.

This new form of indirect calorimetry is helpful in determining the action of insulin in the body.

The Process of Insulin Secretion

Prior Findings

Insulin is released from beta cells of the islet of Langerhans in response to a variety of normal physiologic stimuli and chemical substances, including glucose, hormones, and growth factors. High extracellular glucose concentrations are known to cause the expedited release of insulin in response to this potent stimulant. However, the complex processes between the exposure of the islets to glucose and the release of insulin have yet to be thoroughly elucidated. The fine details of synthesis, compartmental storage in secretory granules and vesicles, and the regulation of the secretion event are in the process of being deciphered. Understanding of the timing and regulation of this response could lead to a capability to modulate, mute, or amplify the secretion of insulin in aberrant states.

Recent Advances

In a recent study, investigators incubated islet cells in vitro with radioactive leucine for a brief period to label newly synthesized proteins. After removal of the radioactive protein precursor, islets were exposed to a buffer containing either high or low concentrations of glucose in a specifically timed sequence that corresponded to that interval in which secretory vesicles are formed and proinsulin is converted to the fully mature insulin protein (in the Golgi apparatus of the cell). The investigators then challenged the prelabeled islets with combinations of glucose and other physiologic or therapeutic compounds to determine what would cause a preferential release of the newly synthesized radiolabeled insulin. Usually, insulin is stored in these vesicles until the islet cell releases the insulin as part of normal secretory events or in response to an external secretory challenge.

The results in these experiments show that islets previously exposed to *low* concentrations of glucose will release both old and new insulin in response to a glucose or therapeutic challenge. However, islets initially exposed to *high* concentrations of glucose will preferentially release newly synthesized insulin in response to either a glucose challenge or glucose in combination with other chemical or therapeutic substances.

The investigators concluded that exposure to high concentrations of glucose during the critical time of transfer of insulin to secretory vesicles "marks" those vesicles for immediate release of hormone at a subsequent glucose challenge. This marking process allows the cells to secrete insulin in a nonrandom way and is, perhaps, regulated by a novel glucose-activated secretory route. In contrast to the normal islet cells, secretory vesicles of islet cell tumors did not respond to marking by glucose, nor did they show differences in the secretion of old and new insulin when stimulated by various secretagogues, thus suggesting that these tumor cells had aberrant storage and secretion characteristics.

Research Directions

Understanding how the cell marks and recognizes vesicles would be of significance in furthering our knowledge of the modulation of the secretory apparatus in response to various stimuli. The ability to influence and control insulin secretion to maintain euglycemia is potentially useful in identifying secretory dysfunctions in the diabetic state, especially for individuals with type 2 diabetes who are being treated with oral sulfonylureas to potentiate their insulin secretion.

Because nonrandom secretion occurs in other secretory systems, marking may prove to be a common mechanism of the secretory process. Further experiments are needed to explore how the beta cell responds to physiologic and nonphysiologic regulators of insulin secretion. Understanding these factors may lead to more effective treatment modalities for the regulation of insulin secretion.

In general, research needs in this area include studies to clarify the integration and quantitative contribution of various metabolic, hormonal, and neurologic factors involved in regulating insulin synthesis, storage, and secretion; increased availability of animal models with genetic or experimental aberrations in insulin secretion; and development of new methods to assess islet cell function and control, in both diabetic and nondiabetic human subjects.

Insulin: Action and Mechanisms

Prior Findings

The mechanism of action of insulin has received intensive attention. Insulin is concerned primarily with controlling the transport, storage, and metabolism of the three major macronutrients and metabolic fuels—carbohydrates, proteins, and fats. This activity takes place principally in liver, muscle, and adipose tissue. Metabolic alterations at the level of these target tissues are influenced not only by insulin, but also by various other hormones that counter the action of insulin such as peptide hormones (glucagon, growth hormone, β -endorphin, and peptide growth factors), steroid hormones (cortisol, estrogen, and progesterone), thyroid hormones, and catecholamines.

Three pancreatic hormones that regulate blood glucose illustrate the delicate balances involved. The counterregulatory effect of glucagon, opposing insulin, is suppressed by somatostatin. This action of somatostatin can be used in the treatment of IDDM: the effectiveness of insulin in limiting hyperglycemia after meals can be enhanced significantly by the simultaneous administration of a derivative of somatostatin, WY-41,747, that is longer acting and more selective than somatostatin itself.

One of the major problems in diabetes is the inability to maintain carbohydrate/glucose homeostasis. The liver is the main focus for the control of blood glucose levels. Glucose is stored in the liver as glycogen. Glycogen is broken down into glucose and released into the circulation in response to hormonal signals or to low levels of glucose in the plasma. Insulin stimulates glycogen synthesis when plasma levels of glucose are high, and the hormone glucagon stimulates glucose production from glycogen when plasma levels are low. When ingestion of carbohydrates does not produce a level of glucose sufficient for the individual's energy purposes, the body can mobilize fat precursors in the adipose tissue or can synthesize glucose from noncarbohydrate sources in the liver and kidneys by a process called glyconeogenesis.

Glycolysis is the process whereby glucose is converted to its metabolites. Glyconeogenesis and glycolysis are usually reciprocally regulated so that one pathway is quiescent while the other is highly active. The enzyme phosphofructokinase (PFK) is the pacemaker of glycolysis. It acts as a catalyst to commit the system to proceed toward the breakdown of glucose. Research results indicate that fructose 2,6-biphosphate (Fru-2,6 P_2) is an important regulator of hepatic glyconeogenesis by its effect on activating PFK and thereby stimulating glycolysis and turning off glyconeogenesis.

Recent Advances

A recent study demonstrated an effect of insulin on the glycolysis/glyconeogenesis pathways. Glucagon inhibits PFK and allows the system to produce glucose. Insulin suppresses this inhibition and thus allows the system to break down the glucose. The action of these hormones on PFK probably results from their influence on the level of Fru-2,6 P_2, which is a potent activator of the enzyme PFK. Insulin opposes the action of glucagon and exogenous cyclic AMP to lower Fru-2,6 P_2 levels. Insulin also counteracts the effect of maximal concentrations of epinephrine on Fru-2,6 P_2 levels. This action of insulin is thought to be one of opposing the action of glucagon and epinephrine by affecting the phosphorylation/dephosphorylation state of a bifunctional enzyme that controls the level of Fru-2,6 P_2. Data showed that the Fru-2,6 P_2 level in fed diabetic rats (or starved rats) was greatly reduced, and the activity of another enzyme, 6-phosphofructo 2-kinase, also was reduced. It is felt that these factors contribute to the diminished rate of glycolysis and enhanced rate of glyconeogenesis that is observed in the diabetic rat liver.

This work has been a major breakthrough in understanding how glycolysis and glyconeogenesis are reciprocally controlled through alterations in key regulatory enzymes.

Research Directions

Studies of the distribution of insulin following endogenous secretion or peripheral injection are desirable and may help define differences in metabolism between the insulin-treated diabetic and the nondiabetic populations. Increased efforts to define the earliest steps in insulin ac-

tion, especially the characterization of the active sites and enzymatic nature of the insulin receptor complex, should be made and should allow the development of strategies to mimic or modify insulin action at the cellular level. These efforts may lead to simple, orally active insulin-like agents.

Further studies of insulin action on tissues involved in diabetic complications, particularly on the vascular endothelium, are needed. A more detailed understanding of the process of insulin degradation and receptor turnover is necessary and may allow the development of selective inhibitors that could enhance hormone action. The exact structure and amino acid sequence of insulin receptors must receive attention and may provide important clues concerning the mechanisms by which insulin regulates cell function. Studies are needed to define further the post-receptor defect that is believed to be responsible for the insulin resistance in NIDDM patients.

Transplantation of Pancreatic Tissue to Treat Diabetes

Prior Findings

It should be possible to treat the lack of insulin production seen especially in IDDM by replacing the defective pancreas or islet cells of the pancreas with normal tissue. A major practical problem is posed by the rejection of the transplanted tissue by the host's immune system.

New techniques have been developed that can prolong the survival of transplanted rat pancreatic islet cells across major strain and species tissue compatibility barriers by procedures that do not require the continued administration of immunosuppressive agents. In general terms, these procedures involve diminishing the lymphoid cells that activate cytotoxic, or cell-killing, T lymphocytes, which are white blood cells active in tissue immunity, and cause the subsequent rejection of the transplanted tissue by the host.

In humans, daily immunosuppressive therapy is required to maintain grafts. A more useful approach to human transplantation would be to evoke a state of immunologic unresponsiveness in the host, so that grafts are maintained without the need for continued immunosuppressive therapy.

Recent Advances

A recent study demonstrated a rapid and simple method for generating antigen-depleted donor blood for pre-immunization by treatment with ultraviolet (UV) light. For many years, it has been known that treating blood cells with UV light eliminated the capacity of these cells to stimulate other lymphocytes to divide in the classic mixed lymphocyte reaction, a standard immunological tool used to test tissue compatibility of donors and recipients. The investigators hypothesized that for the purposes of pre-immunization, the antigen-bearing cells need not be eliminated from the blood but only inactivated, leaving the rest of the immune system intact.

The blood was diluted in a sterile saline solution and exposed for 20 minutes to UV lights positioned 10 cm from the surface. Recipient diabetic rats were injected with UV-treated blood from donor rats prior to receiving islet cells from rat donors. Diabetic animals thus treated showed 100-percent conversion to normoglycemia for a period of over 160 days after grafting, indicating that the transplanted islet cells survived that long and produced therapeutic quantities of insulin in the new environment. Other animals, either not immunized or immunized with blood from a third, unrelated species before transplantation, showed mean survival time of the grafts of only 8 days after transplantation. In addition, animals immunized with nonirradiated blood from rat donors also rejected the islet cells by the seventh or eighth day after transplantation.

These results demonstrate that transfusion of UV-irradiated whole blood from donors can lead to prolonged survival of islet-cell grafts in recipients. This treatment appears to induce donor-specific unresponsiveness, and this result can be obtained without the use of immunosuppressive drugs. The induction of the rejection process apparently requires cells that are metabolically active; UV irradiation inactivates the causative cells so the host becomes unresponsive.

Research Directions

This relatively simple method of inactivating immunologically reactive cells offers a promising new approach for the induction of donor-specific unresponsiveness in recipients of islet-cell grafts. Use of this approach may prove to be useful in the transplantation of human organs, where donor-specific blood transfusions are already in use, especially for kidney transplantation. More research is needed to determine if this procedure is applicable to higher species, especially humans. If prolonged survival of grafts is achieved by this procedure, it may be possible to eliminate, or at least reduce, the use of immunosuppressive agents to maintain transplanted tissue.

All possibilities relating to the successful transplantation of the pancreas islet cell should be explored. The ability of such transplants to normalize carbohydrate metabolism and prevent clinical complications in humans needs to be established precisely. The laboratory procedures that have prevented the rejection of islets in rats and mice should be applied to islet transplantation in larger animals and should be extended to human islets. Immunologic studies concerning the mechanism of the rejection reaction and the means to suppress it should be expanded. New techniques for islet encapsulation to prevent immunorejection are required. The importance of the anatomic site of islet-cell transplants needs to be determined.

Complications of Diabetes: The Pain of Neuropathy

Prior Findings

Disabling pain is one of the serious consequences of diabetic neuropathy. The pathogenesis of the neuropathy associated with diabetes is not clearly understood, although localized vascular and generalized metabolic derangements have been implicated. Among the biochemical and metabolic disturbances, the sorbitol pathway has received the most attention.

In experimental diabetes, there is a slowing of nerve conduction, possibly due to abnormal accumulation of certain carbohydrates, sorbitol and fructose, in peripheral nerves. A new drug, sorbinil, is a potent inhibitor of the enzyme involved in these changes. During 9 weeks of daily treatment, patients with stable diabetic control and no signs of nerve pathology showed greater nerve conduction velocity in all three nerves tested (both sensory and motor nerves) than during a 9-week period without the drug. Within 3 weeks after the discontinuation of the drug, conduction velocity for all three nerves decreased significantly. These effects did not relate to the control of blood sugar, which remained unchanged during the study.

Recent Advances

A recent study was performed with 11 subjects (6 males, 5 females; 7 type 1 and 4 type 2 diabetics) who had a mean duration of diabetes of 16 years. All individuals required insulin, and all were incapacitated by severe pains attributable to diabetic neuropathy. Eight of the 11 alternately received the drug sorbinil and acted as their own controls; the other 3 only received the drug after other treatment proved unsuccessful. Eight of the 11 had moderate to marked relief of symptoms from the drug, 2 had equivocal responses, and 1 showed no change. Although the results varied, there was evidence of improved muscle strength and sensation, autonomic nerve function, and autonomic nerve conduction velocities.

This investigation suggests the potential of this class of agents as a treatment for symptoms of diabetic neuropathy. Although improvement was not universal, clinical improvement seemed to be related to an increase in nerve conduction velocity. These observations must be interpreted with caution since some research workers have drawn attention to the lack of a correlation between nerve conduction measurements and symptomatic improvements. On the other hand, other studies have documented good correlations between nerve conduction velocities and nerve function.

These and other studies support the role of sorbinil as a primary agent in treating the effects of diabetic neuropathy. This study showed a definite effect of sorbinil in relieving the severe neuropathic pain in diabetic patients. It also showed a small but constant improvement in cardiac autonomic indices as well as somatic neuropathy.

Research Directions

Future studies may define a use for sorbinil as a prophylactic agent in preventing peripheral and autonomic neuropathy. The worldwide prevalence of diabetes and associated neuropathy calls for more extensive study of such agents. The seemingly low toxicity of sorbinil and the evidence of its ability to improve, subjectively and objectively, peripheral somatic and autonomic nervous functions make it promising as an agent that may alleviate some of the morbidity associated with diabetic neuropathy.

Studies are needed to define the role of accumulated sorbitol in the tissues and how it contributes to the structural and functional disturbance in diabetic nerves.

The usefulness of sorbinil and other similar agents in the prevention or treatment of neural degenerative changes should be tested in larger clinical trials. The relationship of abnormalities in nerve conduction velocity to the clinical symptoms of nerve damage should be established. Further studies of the roles of insulin and glucose in both central and peripheral nervous system metabolism are needed. Nerve biopsy materials from patients with diabetes and animal models demonstrating diabetic neuropathy are required to permit more detailed studies of the pathogenesis and treatment of this complication. Studies of other abnormal findings in diabetic neuropathology clearly are needed, not only to determine their significance and pathogenesis but also to identify ways in which these abnormalities may be modified or prevented.

Insulin-Like Growth Factors in Diabetic Retinopathy

Prior Findings

More than 30 years ago, it was noted that a patient with diabetic retinopathy recovered from the vascular pathology in his eye after loss of pituitary function (Simmonds' disease). Since then a relationship between pituitary growth hormone and the condition of the capillaries and other small blood vessels has been described in the medical literature; however, it is now known that functions attributed to growth hormone may actually be due to a secondary action of other peptides, collectively known as growth factors.

Somatomedin C (insulin-like growth factor I, or IGF I) and IGF II both bear structural homology with proinsulin and are of interest for their possible involvement in the vascular changes of diabetic retinopathy.

Recent Advances

Serum concentrations of IGF I and IGF II were measured in 80 adults with diabetes and in 62 control subjects. It was found that IGF I levels are higher in IDDM than in NIDDM patients, who also have lower levels of IGF II. A gross elevation of IGF I occurs in diabetic adults with rapidly progressing proliferative disease of the retina. This last finding may serve to identify patients at high risk for rapid deterioration of vision, so that more intensive or alternative forms of therapy may be applied to such individuals.

Research Directions

The value of IGF I levels as a marker for progressive retinopathy in diabetes needs to be verified, as does the possible role of IGF I in such accelerated retinal vascular deterioration. Other candidate mechanisms of action for IGF I and its relation to growth hormone's pathogenic effect need to be examined. The possible role of the kidney in contributing to elevated IGF I levels should be investigated.

Effects of Raised Growth Hormone Levels on the Control and Complications of Diabetes

Prior Findings

Pituitary growth hormone levels are elevated whenever diabetic blood sugar levels are uncontrolled. Successful insulin therapy lowers GH levels to the normal range. GH is known to antagonize the actions of insulin; the hyperglycemia produced by GH can be opposed by the secretion of more insulin in nondiabetic but not in diabetic patients. Surprisingly, little attention has been given to the possibility that GH may be an active mediator of the metabolic disturbances of diabetes, as opposed to a passive result of poor diabetic control.

Recent Advances

In 12 teenaged patients with poorly controlled diabetes, 24-hour GH levels were found to be twice as high as in age-matched nondiabetic controls. In a second group of 14 adults whose diabetes was well controlled by insulin pumps, the effects of raising GH levels to those seen in the uncontrolled state were examined. Exogenous GH was infused, in 100 g pulses, for 21 to 45 hours without adjusting meals or the insulin pump settings. It was found that blood sugar levels doubled by 8 to 10 hours and stayed high until GH infusion was stopped. This was due mainly to the stimulation of glucose production in the liver, without a change in insulin or glucagon levels. Not only hyperglycemia, but the other signs of poor diabetes control such as increased levels of free fatty acids, ketones, and branched-chain amino acids were induced.

These results indicate that the treatment of diabetes is complicated by elevated GH levels, which lead to poor control of the diabetes. There may even be a cycle effect, with inadequate insulin therapy worsening control by causing elevated GH levels. And raised GH levels could help explain the difficulty of controlling IDDM in adolescence and in conditions of physiologic stress or illness. Insulin pumps regulating insulin and GH levels effectively may enable a cycle of worsening control to be interrupted.

Research Directions

Elevated GH levels have been implicated as contributing to small blood vessel disease in diabetes, and more research is needed to establish or disprove this possibility. The relationship of poor control to the development of complications is under intense examination and is the major question underlying the Institute's Diabetes Control and Complications Trial (described below).

The mechanism of GH stimulation of hepatic glucose production and of other metabolic disturbances should be examined.

Endocrinology

Clinical Experience With Growth Hormone and Its Releasing Factor

Prior Findings

There has been continued progress related to the production of human growth hormone (hGH) by genetically modified bacteria. Currently, natural hGH is available only in very limited quantities. Bacterially produced hGH, however, is now being manufactured commercially. Published reports show that the hGH from this source causes growth in test animals that is indistinguishable from that caused by natural hGH. On the basis of the animal studies, clinical trials have been initiated in children in several centers. There was a threefold increase in the growth rate of 22 hGH-deficient children between the ages of 4 and 16, a rate of progress comparable to that of children receiving the human-source hormone.

Many physicians suspect that at least some growth failure is due not to an inability of the pituitary gland to produce growth hormone but to a failure of the hypothalamus to produce growth-hormone-releasing factor, which in turn stimulates the pituitary gland to produce and release GH.

In the fall of 1982, GRF was isolated from a pancreatic tumor, and the structure of this previously unelucidated material was determined. The complete GRF molecule from the tumor has 44 amino acids, although preparations con-

taining only 40 amino acids appear to have essentially equivalent biological activity. GRF-40 has been synthesized and tested in normal adults, in adults who as children were diagnosed and treated for growth-hormone deficiency, and in children currently under treatment with growth hormone.

Recent Advances

Twelve adult patients who were diagnosed and treated in childhood for growth hormone deficiency were injected with synthetic GRF-40 on 2 consecutive days. GH secretion was stimulated in some of the patients but to a lesser extent than in normal controls. These results may mean that GH deficiency in some patients results from hypothalamic GRF deficiency rather than from an inability of the pituitary gland to produce GH.

An additional finding was that after GRF, somatomedin C levels increased in most patients, even in those with minimal effects on GH levels. Somatomedin C is produced in response to circulating GH and is generally considered to be the substance that actually causes growth in most tissues. It is unknown why somatomedin C is increased more than GH in response to GRF. GRF is not known to cause somatomedin C production directly, although this possibility must be considered.

In another study of GRF-40, four children receiving therapy to correct GH deficiency were tested with GRF during a hiatus in therapy. In these still-growing children, GH titers in the blood were increased much more dramatically than in the adults described above.

The findings from this work show that GRF may be a more specific therapeutic agent than GH in some children with growth failure in whom the basic defect is impaired secretion of GRF. Since the molecule is shorter than hGH, 44 amino acids versus 194 amino acids, it is synthesized more easily and may be made available more readily for future clinical use.

Research Directions

When bacterial hGH becomes available for routine use, a fully adequate supply will be available to treat short-stature children, but it also should be available for use in other clinical studies involving accelerated healing of bone fractures, burns, and ulcers. Although hGH 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 treating short stature.

Administration of GRF, along with other releasing factors, can be used as a clinical assay of the pituitary's ability to secrete the corresponding hormone. (Absence of response to any of the releasing factors indicates a primary pituitary impairment or lesion.) Use of GRF may allow identifying a subset of patients with growth hormone deficiency secondary to a hypothalamic lesion. The recognition of these patients may have important prognostic and therapeutic implications. It is possible that the use of GRF, or some analogues, may well replace the need to treat some children with GH. Studies are being done to determine the optimum mode, dose, and frequency of GRF-40 administration. The finding that somatomedin C levels were elevated more than GH levels after stimulation with GRF raises interesting questions about the action of GRF, GH, and somatomedin C in the body. Production of the relatively small GRF molecule in large quantities now will be possible. Clinical investigation is expected to begin in the near future. The action of GRF should be explored in animals and humans, both in normals and in patients with pituitary disorders. Analogues should be sought that have different activities and lengths of action. Analogues or antagonists may have value in treating some cases of acromegaly.

Clinical Treatment of Secretory Pituitary Tumors

Prior Findings

Pituitary tumors may be functioning (producing hormones) or nonfunctioning. Both types cause local effects, including destruction of the normally functioning pituitary and blindness from damage to the optic nerve. The two most common functioning pituitary tumors produce excess prolactin, causing abnormal lactation and reproductive failure, or growth hormone, causing abnormal growth of certain tissues, or acromegaly. Both prolactin and growth hormone secretion are inhibited by the neurotransmitter substance dopamine. Bromocriptine, a drug with dopamine-like effects, has been demonstrated to suppress excess hormone production and to shrink the size of tumors that produce these hormones.

Recent Advances

Patients with hypersecretory pituitary tumors were treated with a long-acting derivative of the drug ergot, pergolide. This drug reduced both GH levels and prolactin levels and decreased the size of the tumors. The drug was able to restore menses and fertility in women, and in men it raised male hormone (testosterone) levels to normal. Side effects were minimal or absent in most patients. Pergolide provides a possible alternative to surgery and x-ray treatment for the most common tumors of the pituitary gland associated with excessive secretion of certain hormones, and it may provide an advantage over the current drug therapy due to its longer duration of action and low incidence of side effects.

Research Directions

Just as pergolide may represent a considerable improvement over the ergot derivative previously used for pituitary tumors, bromocriptine, other derivatives may be

found to be even more potent, long-lasting, and effective in a greater number of patients. The drug already may be superior to surgery or radiation for selected responsive patients, and the search for pharmacologic alternatives to these therapies will continue.

Dramatic Growth Increases in Experiments With the Growth Hormone Gene

Prior Findings

Growth hormone is thought by many investigators to stimulate growth by causing the liver to produce the polypeptide hormone IGF I, or somatomedin C, which in turn stimulates receptors in peripheral connective tissue, muscle, and bone. If so, the presence of large amounts of GH in the liver and other sites of IGF I synthesis would have the effect of stimulating the synthesis of large amounts of IGF I and would cause increased growth in different body tissues. A wide distribution of GH appears to be essential for uniform growth in all tissues. One way to achieve this result would be to introduce the genetic instruction for GH into the developing organism. Such research has major implications for understanding human genetic diseases and growth disorders.

Recent Advances

Genes from one mammalian species can now be introduced into selected other species, permitting studies on mechanism of gene action. One method of doing this is to inject a gene from one animal into the pronucleus of a fertilized egg, anticipating that the foreign gene will become incorporated into the genetic makeup of the embryo and will express itself in a detectable fashion as the animal develops. The wide distribution of large amounts of GH in an individual animal is now possible experimentally by the process of introducing rat GH genes into fertilized mouse eggs; recently, this was attempted using human GH genes.

Results of the experiment with rats show that the GH gene was activated in the mice and produced GH, since all mice in which a rat GH gene was shown to have survived grew up to be twice as large as their litter mate controls. Some mice were able to pass on the enhanced growth tendency to their offspring, indicating that at least in these cases the new gene was incorporated into the genome of the mice.

In a separate experiment using human (rather than rat-derived) GH, the same experimental procedure produced comparable results in the recipient mice, including the heritability of the enhanced growth rate in the offspring of the recipient. This finding is especially interesting because hGH is related less closely to mouse GH; in fact, rat and hGH differ in 67 out of 191 amino acids. Another interesting finding is that the effect on growth was not apparent until 3 weeks after birth and ceased after 3 months of age. It is possible that other members of the GH family (e.g., chorionic somatomammotropin) stimulate fetal and newborn growth.

Research Directions

Successful microinjection of foreign genes helps answer many important developmental, genetic, and endocrine questions. Analyses of gene inheritance and expression should continue, and analysis of the effects of excess GH production on body processes is of vital importance. Additional studies on other peptide products and with other animal species should be carried out.

The results of this experiment raise the possibility that similar methods might be applied to commercially valuable animals to increase meat production or shorten growing times; the economic impact of such novel biological technologies is self-evident and considerable. The technique also might be valuable in the study or cure of certain genetic diseases, where replacement of a gene may alleviate severe symptoms. Finally, since these mice developed high GH levels in the blood as a result of this manipulation, insertion of genes for the production of various other peptides might raise their levels high enough so that animal factories could be developed in which the recipient would manufacture large amounts of hormones that could be harvested from the blood.

Origin and Structure of Opiate-Like Hormones

Prior Findings

The brain secretes several hormones that act to reduce pain. These hormones are referred to as endogenous opiates (the endorphins and enkephalins). Leu-and Met-enkephalin are peptide hormones that contain five amino acids each and are identical except for the terminal amino acid, which is either leucine or methionine. They are naturally occurring hormones that have a morphine-like effect on pain in the body.

Met-enkephalin is produced in the pituitary gland as part of a larger molecule known as pro-opiomelanocortin (POMC), which is also the precursor molecule for several other hormones. The structure of POMC contains sequences of ACTH, the hormone that stimulates the adrenal gland, melanocyte-stimulating hormone (MSH) named after the cells responsible for pigmentation, and the endorphins. β-endorphin contains two smaller endorphin molecules, which in turn contain the very small Met-enkephalin molecule.

The adrenal medulla also produces enkephalins. To facilitate a greater understanding of biological processes and possible commercial synthesis of useful hormones, it is desirable to know whether the adrenal gland utilizes the same process as the brain in sythesizing enkephalins.

Recent Advances

The structure of the adrenal precursor molecule for the enkephalins now has been determined using recombinant DNA methods and has been shown to be 267 amino acids long. The interesting feature of this protein sequence is that it consists of six molecules of Met-enkephalin and one molecule of Leu-enkephalin. The enkephalins are scattered throughout the length of this large molecule, and at present, there is no known activity for the remaining peptide segments.

In addition, each enkephalin molecule in the precursor molecule is flanked on both sides by pairs of basic amino acids. These amino acids appear to be the site of cleavage of the large molecule by trypsin-like enzymes; in this fashion, the enkephalins are marked a priori for enzymatic cleavage from the parent molecule.

Since the complete sequences of enkephalin precursors from both the pituitary and the adrenal medulla have been established and are shown to be different, it now is known that the enkephalins from each source are produced by different genes. In addition, it is of interest to note that several molecules of the same hormone are produced by each precursor, indicating an economy of effort in production.

Research Directions

Research of this type has been and will be applied to the production of hormones in bacteria for commercial use. In addition, this type of research is useful in determining how hormones and other products are produced in the body. Since the total adrenal precursor molecule contains 267 amino acids, but only 63 amino acids have known functions (35 contained in the seven enkephalin molecules and 28 regulating the excision process), studies should continue to determine what role the remaining portions of the parent molecule may play in the regulation of these hormones.

The chemical synthesis of important peptides also should be pursued and improved. Molecular modifications that stabilize peptides and make them more potent, as has been possible in the case of melanocyte-stimulating hormone, offer a promising direction for further work.

Metabolic Diseases

The Molecular Basis of Two Enzyme Deficiency Diseases

Prior Findings

In general, inherited metabolic diseases are caused by gene mutations that result in a defective enzyme protein unable to perform its function as a catalyst for a chemical reaction in the body. Thus, unwanted and unneeded chemical products produced during vital metabolic processes can accumulate in various organs. The physiologic consequences of such deposits can be devastating to the body and can result in prolonged suffering and premature death.

The Lesch-Nyhan syndrome is due to a deficiency in the enzyme hypoxanthineguanine phosphoribosyl transferase; HPRT activity is virtually absent. The disease is characterized by an overproduction of uric acid, retardation of growth and mental development, severe central nervous system disorders, involuntary movements, and a compulsive form of self-mutilation. In hereditary gout, HPRT activity is *partially* deficient, so that afflicted people accumulate uric acid, but they do not suffer from neurologic abnormalities.

It has been established that HPRT is coded by a single structural gene located on the X chromosome. Recently, scientists isolated DNA sequences that are complementary to the mRNA that codes human HPRT. This resulted in the identification of 90 percent of the nucleotide sequence of human HPRT mRNA and subsequently led to the understanding of the HPRT gene structure. The native fully active human enzyme has been isolated and purified and its amino acid sequence established. The amino acid sequence predicted from the nucleotide sequence of the coding region was identical to that defined by traditional protein-sequence analysis.

Recent Advances

Researchers supported by the NIADDK were able to establish the exact molecular changes that render HPRT partially active or inactive in Lesch-Nyhan syndrome and hereditary gout. Thus, the research group purified, to apparent homogeneity, HPRT from erythrocytes and cultured lymphoblasts of five unrelated patients from five different locations, all of whom had HPRT deficiency. $HPRT_{Toronto}$, $HPRT_{London}$, $HPRT_{Ann\ Arbor}$, and $HPRT_{Munich}$ were from patients with gout; $HPRT_{Kingston}$ was from a patient with the Lesch-Nyhan syndrome. Each isolated mutant enzyme had a unique set of structural and functional abnormalities. By determining the amino acid sequences of four of the five HPRT variants, the researchers have established that one amino acid in each variant was substituted for another amino acid. Each substitution occurred at a different location in the enzymes studied. Further studies showed differences in intracellular concentrations and in the activity parameters of the five variant enzymes. It is possible that all of these differences are due to the individual amino acid substitutions discovered.

Detailed analysis of the isolated HPRT variants indicates that HPRT deficiency frequently is caused by single base mutations in the gene that lead to the deleterious amino acid substitutions in the expressed enzyme. In the Lesch-Nyhan syndrome, most patients retain little if any enzyme protein. In gout, a majority of the apparent defects in gene

expression are probably caused by gene mutations that either result in a labile enzyme variant or affect the normal processing of HPRT mRNA. Elucidation of the heterogenous nature of these diseases and understanding their molecular biology and genetics will be instrumental in developing new treatment modalities.

Research Directions

Greater knowledge of the specific molecular defects in the Lesch-Nyhan syndrome may lead to fuller understanding of its pathogenetic mechanisms and eventually may suggest rational and effective therapeutic approaches in this and other inherited enzyme-deficiency disorders. Continued studies of gene mutations and gene-RNA interactions are essential for such progress.

An Inherited Enzyme Deficiency Causing Vitamin Depletion

Prior Findings

Vitamins are essential cofactors needed for the normal functioning of a variety of enzymes. It is known that at least three enzymes, carboxylases, require the vitamin biotin for their normal functioning and that biotin is chemically attached to a specific amino acid of each enzyme. Until recently, biotin-dependent carboxylase deficiency, an inherited disease, was assumed to be due to a disorder in biotin metabolism or transport. Both the neonatal and early childhood forms of this disease are known to exist, and even though they are distinct syndromes, both forms are generally associated with an increase in body acidity and ammonia levels, failure of muscle coordination, and developmental delay.

The neonatal form of biotin-dependent carboxylase deficiency has been shown to result from the lack of formation of the carboxylase itself. Babies with this defect exhibit vomiting and lethargy and lack muscle tone. The late onset form of the disorder is characterized by seizures, loss of hair, and a skin rash.

Recent Advances

Recently, researchers showed that in the late onset form, the primary biochemical defect is a deficiency in biotinidase activity, rather than a defect in the intestinal absorption of biotin or in the synthesis of carboxylase. Biotinidase is an enzyme essential for regeneration of free biotin from a complex with an amino acid moiety of the carboxylase enzymes. It is now clear that significantly reduced concentrations or a complete absence of biotinidase will cause partial or complete depletion of biotin in afflicted children. These children, being unable to recycle biotin in the normal fashion, are entirely dependent on biotin supplementation. Indeed, administration of pharmacologic doses of biotin can lead to a complete remission of symptoms by restoring normal enzyme activity. The researchers also developed an assay for the in vivo measurement of biotinidase. By using this assay in studying afflicted subjects, the research group found that the neurologic or cutaneous symptoms are the first to appear, and the increase in the level of body acids is a secondary manifestation of the disease.

With the identification of the biochemical basis of biotinidase deficiency, this disease was added to the growing group of inherited metabolic disorders that are understood and treatable. Because of this understanding, early diagnosis—and therefore the early initiation of treatment—is feasible. These findings also suggest that a diagnosis of biotinidase deficiency should be considered in any infant or child with the characteristic neurologic or cutaneous findings regardless of the levels of body acids. If a diagnosis of biotinidase deficiency cannot be conclusively confirmed, such individuals should be given a therapeutic trial of pharmacologic doses of biotin.

Research Directions

These research results raise the important issue of the reutilization of vitamins in general and of biotin in particular. More studies of this nature are needed to improve our understanding of human nutritional requirements and how they are affected by inherited metabolic defects.

Growth Retardation Due to Chronic Fructose (Fruit Sugar) Intolerance in Older Children

Prior Findings

In fructose intolerance, fructose intoxication is the result of a genetic defect in an enzyme, aldolase B, responsible for cleaving phosphate from fructose phosphate. The result is that this phosphate accumulates in the liver, kidney, and small bowel. In the acute form of the disease, there is abdominal pain and vomiting within minutes of exposure to fructose or to sucrose (table sugar, which is digested in the gut into fructose and glucose). In its chronic form, there is failure to thrive, recurrent vomiting, liver enlargement, and dysfunction of the liver and kidney. By 2 years of age, affected children have an aversion to foods containing these sugars.

Recent Advances

Avoiding fructose and its dietary sources prevents the symptoms of fructose intoxication in older children. Nonetheless, it has been found recently that amounts of fructose too small to cause readily apparent acute symptoms may still cause serious growth retardation and chronic metabolic abnormalities such as depletion of phosphate

and degradation of key nucleotides like ATP and ADP to uric acid, with a loss of the magnesium complexed to them. The recognition of this syndrome in two boys ages 4 and 5 years has led to an appreciation of the need for much stricter control of the diet to eliminate all sources of fructose in children that have shown this defect. In the case of these two children, stringent restriction of dietary fructose was instituted, and growth velocity increased from the 25th to the 97th percentile in one boy and from well below the 3rd to the 75th percentile in the other. In all children with unexplained growth retardation, the diagnosis of hereditary fructose intolerance should be considered.

Research Directions

As with other enzyme defects, it is essential to understand how the faulty genetic instruction arises and to discover ways of preventing or correcting it. In the meantime, reliable methods are needed to diagnose hereditary fructose intolerance prenatally and postnatally.

Special Programs

Diabetes Centers

Both diabetes research and training centers and diabetes-endocrinology research centers are required to have a strong base of high-quality ongoing biomedical research. The center grants provide for core facilities, or shared resources, pilot and feasibility studies, and program enrichment. Funding for the centers is intended to strengthen existing programs, increase productivity, and foster new ideas and innovative research approaches. Although each center is expected to develop its own independent program in accordance with local needs, interests, and resources, each is also expected to be responsive to national needs and must be willing to work cooperatively with the NIADDK and, in the case of DRTC's, with other federally supported diabetes programs.

Biomedical research is the sole focus in each of the five DERC's; the seven DRTC's 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, where the seven DRTC's are identified. The five DERC's now in operation are located at the University of Pennsylvania, Philadelphia; University of Washington, Seattle; University of Iowa, Iowa City; Baylor College of Medicine, Houston; and University of Massachusetts, Worcester. A mechanism for support has been developed that gives DERC's the opportunity to become DRTC's. A DERC may apply for a modest exploratory grant to develop resources necessary for initiation of DRTC training and information transfer activities.

National Diabetes Information Clearinghouse

The National Diabetes Information Clearinghouse (NDIC) is the central point for collecting and disseminating educational and scientific materials and information on programs and resources related to diabetes. Over 4,000 pieces of diabetes educational materials available for purchase or at no cost have been identified and abstracted.

Answering requests for information is a continuing NDIC activity. The NDIC receives 1,500 letters and telephone calls a month asking for information about every aspect of diabetes.

Because health-care providers often need information about a variety of health conditions, the director of the NDIC took the lead in developing the Combined Health Information Database. The Centers for Disease Control, the DHHS Office of the Assistant Secretary for Health, and other information dissemination programs at the NIH joined with the NDIC to develop this data base. Materials included in the data base are described in chapter VI. The CHID file has now been tested and placed with a vendor and should be available to the public in 1985.

Over the past 4 years, the staff of the NDIC, in consultation with the NDIC advisory board members and the major diabetes organizations, has been writing and pilot testing the *Diabetes Dictionary,* an illustrated booklet that explains in easily understood language more than 300 words and phrases related to diabetes. Through the generosity of Eli Lilly and Company, 20,000 copies of the *Diabetes Dictionary* were printed in August 1983 and distributed throughout the world by the NDIC. Lilly printed another 50,000 copies of the dictionary for distribution in 1984. In addition, the dictionary has been translated into Spanish by a member of the Chilean Diabetes Association, and plans are being made to translate the dictionary into Italian as well by members of the Milan chapter of the Juvenile Diabetes Foundation International.

To keep the diabetes community aware of meetings of interest and to assist meeting planners to avoid scheduling conflicts, the NDIC established a meeting registry during the past year. This registry includes information about regional, national, and international meetings, congresses, and symposia. Its usefulness will be evaluated in the coming year.

In addition to providing information, the clearinghouse identifies areas needing additional educational materials and assists in developing such materials. The clearinghouse is committed to increasing community awareness and understanding of diabetes as a health problem and to encouraging effective patient, family, and community educational programs.

National Diabetes Data Group

The National Diabetes Data Group fosters, coordinates, and integrates national resources for the collection, analy-

sis, and dissemination of data on diabetes to provide a sound basis for the development of scientific priorities and the planning of public health programs. Concerns of the data group include defining diabetes-related data needs, coordinating the collection of data from multiple sources, standardizing collection procedures and terminology, making data available to users, and measuring the medical and socioeconomic impact of diabetes. The data group continues to serve as the Federal source where the lay and scientific communities can turn for reliable statistics on diabetes.

The National Diabetes Data Group, which was authorized by Congress in 1980, consists of a nationwide group of expert advisors, including epidemiologists, individuals with expertise in the biomedical, nutritional, and socioeconomic aspects of diabetes, and representatives of Federal agencies (the NIH, the Centers for Disease Control, the National Center for Health Statistics, and the NDAB) and the private sector (ADA and the Juvenile Diabetes Foundation).

The data group also promotes opportunities for new research on the epidemiologic and public health aspects of diabetes by advising grant applicants on the suitability and feasibility of proposed epidemiologic research and by serving as a consultant to the NIH Division of Research Grants and to the staff of the Division of Diabetes, Endocrinology, and Metabolic Diseases. The data group provides national data to researchers to contrast with their community-based epidemiologic data and was instrumental in forming a Council on Epidemiology within the ADA to stimulate epidemiologic research through that body.

The Hormone Distribution Program and the National Hormone and Pituitary Program

In 1963, with support from the College of American Pathologists, the NIADDK instituted the National Pituitary Agency, now known as the National Hormone and Pituitary Program (NHPP). Since then, the program has provided supplies of hGH isolated from pituitary glands obtained at post mortems for research related to the treatment of hypopituitary dwarfism and other growth disorders. Each year, this program helps about 2,000 children with hypopituitary dwarfism to achieve more normal growth; last year, 234 clinical projects received hGH for research and treatment purposes.

Research advances have demonstrated that other anterior pituitary hormones could be extracted from the same glands. The scope of the program was therefore expanded to provide for the distribution of follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, prolactin, adrenocorticotropic hormone, and lipotropin.

Support by the NIH has allowed expansion of the program to include the distribution of hormones and antisera for immunochemical research projects; about 10,000 projects were supplied with approximately 25,000 vials of standardized hormones and antisera. For human studies, 10 different hormones and their antisera were provided. Similar materials specific for rat, ovine, bovine, and porcine experiments were supplied. The availability of these rare substances has proved invaluable in many extensive programs of basic and clinical investigation.

The NHPP also illustrates the impact of advances in endocrinology research on clinical medicine. Already, hGH has been synthesized by recombinant DNA methods in bacteria. A pure and effective synthetic hGH preparation can be expected to supplement and eventually displace hGH extracted from pituitary glands.

The Hormone Distribution Program continues to collaborate with the National Institute of Child Health and Human Development and with the U.S. Department of Agriculture on the distribution of hormones and antisera for research in the United States and in foreign countries. Since shipment of these products to individual investigators in some countries involved problems with U.S. and foreign customs agencies, plans have been implemented to ship larger batches of material to countries such as India. The investigators in these countries work through local sources to obtain needed material.

Program Accomplishments

The Division Director has established a Program Advisory Committee both to review recommended planning initiatives and to develop, refine, and set priorities for long-term program objectives. Membership on this committee includes senior representatives from the Division of Intramural Research as well as various other authorities in diabetes, endocrinology, and metabolic diseases from the extramural research community.

The program staff completed an analysis of the priority score performance of applications for research grants submitted to the Division over the past 2 fiscal years. This study disclosed several nonrandom characteristics of applications to the various programs in comparison with each other and with the Institute in general. The findings of this study were presented to the Division's subcouncil of the NIADDK Advisory Council at its May 1984 meeting and to the research subcommittee of the NDAB. These data contributed to the Institute's recent decision to experiment with percentile ranking in the awarding of research grants.

Clinical Trials Program

The Diabetes Control and Complications Trial (DCCT) is a controlled clinical trial designed to determine if maintenance of near-normal levels of blood glucose in patients with IDDM can prevent, delay, or ameliorate its microvascular and neurologic complications. In the past 5 years, new ways to treat IDDM have been developed, and the application of these new techniques now enables this ques-

tion to be rigorously tested. It is not known whether these new techniques, which allow near-normalization of blood glucose, are any better than standard management in preventing or ameliorating the serious complications of IDDM. These complications include stroke, blindness, heart disease, kidney failure, gangrene, and nerve damage. Defining the best treatment method has been the single most important and controversial clinical question in diabetes; the answer will affect how diabetes is managed in the future.

The study was designed to have four phases: planning, feasibility study, full-scale clinical trial, and data analysis and reporting. Phase I, planning, was initiated in February 1982 and completed in February 1983. Twenty-one clinical centers were funded in fiscal year 1982 with research cooperative agreement grants; the data coordinating center was funded by contract.

In January 1983, the DCCT Policy Advisory Group (PAG) and the DCCT Data, Safety, and Quality Review Group (DSQ) independently reviewed and approved the revised draft protocol and recommended that the study proceed into phase II. The PAG and the DSQ are independent advisory groups whose members represent expertise in all scientific and technical areas related to the clinical trial and are not in any way involved in the conduct of the study. The PAG provides advice on the overall policy and direction of the trial; the DSQ oversees all aspects of study operation to ensure data quality and the safety and well-being of volunteer participants.

In March 1984, the DCCT completed recruiting and randomizing 278 volunteers for its feasibility phase (phase II). Recruitment goals were met essentially on time, and all volunteers accepted their treatment group assignments.

Financial support for designated components of the DCCT has been obtained from two other NIH Institutes, the National Institute of Neurological and Communicative Disorders and Stroke and NHLBI, for evaluation of neurological and cardiovascular complications of diabetes. In the latter case, the NHLBI provided surplus electrocardiograph (ECG) machines for use in the DCCT clinics and provided funds to support central reading of ECG's, lipid analyses by the central biochemistry laboratory, and data management costs related to this aspect of the protocol.

In addition, the NIH Division of Research Resources has actively promoted the DCCT among the directors of the general clinical research centers (GCRC). Seventeen of the 21 participating DCCT centers have GCRC's, and the Division of Research Resources has encouraged the directors to facilitate the use of these centers by the DCCT investigators. The National Eye Institute has contributed study materials as well as technical assistance in developing study documents. The National Institute of Allergy and Infectious Diseases provided technical guidance in development of infection-related aspects of the protocol. In addition, various commercial organizations have donated supplies, equipment, and services. It is conservatively estimated that the market value of these donations or discounts exceeds $1 million. In July 1984, a briefing session was held with representatives from the commercial sector to provide an update on the progress of the study and to discuss their continued participation should the trial proceed to phase III. All participants at this meeting indicated enthusiasm for continuing to support the DCCT.

National Diabetes Data Group

The National Diabetes Data Group has embarked on three major projects:

- A comprehensive data book on diabetes is being developed to respond to the data needs of researchers, public health officials, clinicians, and other persons and agencies concerned with diabetes. In this project, the data group continues to work in close collaboration with the National Center for Health Statistics in assessing the national data on diabetes collected by that agency. The Divisions of Analysis, Mortality Statistics, and Health Care Statistics are participating in development of the data book by supplying NCHS data on multiple causes of death among diabetics, sociodemographic characteristics of diabetics, and medical care aspects, including ambulatory, hospital, and nursing home care. The Centers for Disease Control is collaborating by assessing hospitalizations for diabetes and acute metabolic complications. Many epidemiologists in universities and medical schools in the United States are also contributing to this data compilation and assessment.

- With the Division of Health Examination Statistics, the data group has analyzed oral glucose tolerance tests on a statistical sample of the U.S. population to develop norms and standards for plasma glucose levels and to determine the prevalence of undiagnosed diabetes and impaired glucose tolerance. The Division is also conducting a study of Hispanic-Americans, for which the data group developed the medical history and household questionnaire and the clinical and laboratory tests to be used. The data group is also collaborating with the Epidemiology and Field Studies Branch of NIADDK in assessing NCHS survey data to examine the issues of screening for diabetes, etiologic relationships in undiagnosed diabetes, and impaired glucose tolerance, obesity, nutritional factors, and family history of diabetes.

- The data group has taken the lead in establishing a consensus on classifications and diagnostic criteria for diabetes. An expert committee has been convened to review and assess data collected since the 1979 data group report. This report will serve as the American recommendations to the WHO Expert Committee on

diabetes, and it is anticipated that the American consensus may influence an international consensus so that future research data may become more comparable, facilitating our ability to compare diabetes incidence and complications in populations with differing genetic and environmental characteristics.

Workshop on Methods for Measurement of Glycosylated Hemoglobin

Glycosylated hemoglobin (HbA1C) has rapidly become a common research tool for assessing blood glucose control in diabetics over an extended period of time. The medical literature is replete with studies that use this measurement to differentiate diabetic from nondiabetic persons, to screen for diabetes within populations, and to assess blood glucose control under varying experimental research conditions. However, it is recognized internationally that the several laboratory methods to measure glycosylated hemoglobin are so different that results are not comparable from one research center to another, severely limiting the ability to apply conclusions from one study to another. This situation will soon become further compounded because commercial manufacturers are now developing HbA1C measurement kits.

In May 1983, a workshop was held to discuss methods for HbA1C measurement and to establish a dialogue between industry and researchers. In December 1983, another workshop addressed the development of an international consensus on methodology, based on the discussions presented at the May workshop. This second workshop resulted in recommendations for promulgating guidelines for use in clinical practice.

A Centralized Supply Resource for Human Tissues

A contract was negotiated and funded to support the National Diabetes Research Interchange (NDRI). This organization acts as a clearinghouse for procuring human tissues and organs on a nationwide basis and subsequently dispensing these valuable research materials to the diabetes-related biomedical and scientific communities.

Studying normal and diseased human tissue in the laboratory is crucial to understanding many disease mechanisms; obtaining the tissue, however, is a serious problem for many investigators in virtually every area of interest to the NIADDK. In many cases, the acquisition of appropriate tissue for study is a problem because the scientific question being investigated calls for material that may become available infrequently at any one location. Such a situation could be helped by a centralized agency that has the ability to procure tissue on a regional or national basis rather than from a single location.

Another problem for investigators is assuring that the tissue they receive has been harvested and preserved in such a way that its study will yield results generalizable to tissue in vivo. Often neither a local source of tissue, such as a pathologist, nor the investigator is an expert in methods of preservation, and thus the viability of the tissue being studied may not be well known. A centralized tissue resource would have as a part of its mission to be fully knowledgeable of the state of the art of tissue preservation and reconstitution and to act as an advisor to investigators in this regard.

It is fully acknowledged that a centralized resource of this kind cannot answer every investigator's needs for human material. For example, some studies of the functional behavior of tissues must be conducted on material that has been removed from the donor no more than 1 or 2 hours earlier. Even so, in such a situation, the tissue resource staff could possibly suggest acquisition or preservation procedures to extend the viability of tissues.

The NDRI was begun in 1981 under the sponsorship of the Juvenile Diabetes Foundation and funded by a grant from the Pew Foundation. In its first year of operation, it established procurement arrangements with a number of hospitals and other organizations to obtain post mortem tissue, outdated transplant tissue, and surgical waste. It operates exclusively as a brokerage agent and does not store any tissue in its own facility.

The NDRI has found that the demand for tissue is high and that a substantial amount of tissue is available when sources are appropriately approached and developed. In the first 18 months of operation, over 1,500 tissue samples were procured and delivered to investigators. More recently, the NDRI has conducted discussions with investigators from other disease areas (for example, CF), and pilot efforts are under way to deliver tissues in these areas as well as in diabetes.

Coordination of NIH Efforts to Develop, Characterize, Maintain, and Disseminate Animal Models for Diabetes Research

The need for the development, maintenance, and distribution of animal models in the study of diabetes and its complications has been documented in the reports of many advisory groups during the past few years. The most recent of these include the report of a task force assembled by the NIH Diabetes Coordinating Committee in 1981 to explore how existing or new animal models can be used to help answer questions about the etiology, pathogenesis, and underlying mechanisms of diabetes and its complications and the endorsement of plans to support the BB Wistar rat model by the Division of Diabetes, Endocrinology, and Metabolic Diseases Director's Advisory Committee in February 1983.

Many varieties of animal models are currently available, and each is suitable for studying specific aspects of diabetes; however, support for these models has been an ongoing problem. As the size of a colony and the demand for a given model increases, the investigator-initiated research grant becomes less and less appropriate as a mechanism to support expanded programs of breeding, maintenance, and distribution.

The general strategy developed by the Division to deal with this problem has been to initially support the identification, characterization, and development of a model through the research grant mechanism but then to use the contract mechanism to support the further development, maintenance, and distribution of models when demand for them exceeds that which could be conveniently handled under an investigator-initiated research grant. Of course, if at any time in the development of a model it becomes commercially attractive to the private sector, core funding of the model by the Institute would be reduced or phased out entirely on the assurance that the model will continue to be available to investigators through normal commercial channels.

The spontaneously diabetic BB rat is an example of this strategy. The BB rat has been particularly useful to the diabetes research community because it has characteristics similar to those found in human IDDM. It was originally identified in a commercial breeding house but was soon found not be be commercially viable. The Institute supported early work on it under the research grant mechanism; however, the model is now being used by dozens of investigators in this country, and the support of breeding and distribution has been converted to the contract mechanism.

Accomplishments in Cystic Fibrosis Programs

Cystic fibrosis has been given recognition and emphasis as a separate program in both the extramural and the intramural activities of the Institute. Since 1983, the Institute has supported a CF core center at Case Western Reserve University. The CF group at Case Western Reserve has received continuous support from NIH for over 20 years, mainly through the program project mechanisms, and is widely recognized as an outstanding center for clinical and basic research on this disease. The medical school and the department of pediatrics at Case Western Reserve have the second largest CF center in the country in terms of patients. Therefore, they are ideally suited to provide a much-needed multidisciplinary and interdisciplinary approach to this disease. The support in general administration, communication, program enrichment, patient care, biological samples, pulmonary function studies, computer technology, microbiology, endoscopy, morphology, mucin processing, and central instrumentation are expected to increase productivity of the individual research projects and enhance the probability of realizing the goals of identifying the molecular defect and discovering new and more effective methods of therapy.

Intramural NIADDK research on CF has been reorganized as an interdisciplinary team, designed to take advantage of the specialized backgrounds of experienced investigators from closely related basic science areas as well as to attract new interest in CF on the part of clinicians who want to acquire research skills. Some of the areas of study represented include infectious diseases, molecular biology, genetic mechanisms, glycoproteins, and receptor studies. Developed as a special interest of the director of intramural research, the new team is expected to contribute a combination of ideas, the ability to study them in fresh ways, and the ability to pursue trial implementation of promising leads. At the same time, because the team members are being drawn primarily from people *not* previously engaged in CF research, the team will not be competing for staff members from established CF research centers, and the approach will enlarge the number of researchers with experience in this challenging area.

Cell Lines for Genetic Research in Cystic Fibrosis and Diabetes

The basic biochemical defect in CF remains unknown, and there is no reliable test to detect carriers of the disease. Thus, a pressing need exists to identify the CF gene so that a test to identify carriers can be developed, and the basic defect underlying the disease can be identified and characterized. Currently, several laboratories are devoting considerable effort to identifying the CF gene, and other groups have expressed interest in such investigations. What is needed to allow these studies to go forward efficiently is a bank of well-characterized genetic material (DNA) from families in which CF exists.

Because relatively large amounts of DNA are required for analysis, transformed lymphocytes are needed (white blood cells, stimulated to cell division). Connective tissue cells, fibroblasts, from the same individuals will also be retained in the bank. Extensive literature already describes many of the physiological characteristics of CF fibroblasts, and these familial lines will provide important bases for comparison with previous studies.

For a number of years, the Mutant Human Cell Repository, supported by the National Institute of General Medical Sciences (NIGMS), has maintained a collection of CF fibroblasts, and these lines have been among the most often requested from the repository. However, the collection was not designed as a resource for present-day molecular biologists. This initiative is designed to make the repository useful to such investigators.

The cell repository is experienced in setting up such special collections, and it has expressed a willingness to work with Institute staff and Cystic Fibrosis Foundation representatives to locate families and secure materials. Twenty-

five families will be located that have at least three living children with CF. Blood and skin samples will be taken from all affected and unaffected siblings, both parents, and any available grandparents.

Groups funded by NIGMS and by the Medical Research Council of Great Britain are making significant efforts toward identifying the CF gene, and it is expected that a number of other groups and commercial firms would enter the field if genetic material were readily accessible at a modest cost. DNA from the several families that have been identified is in such great demand that transformation of the cell lines is becoming a necessity; the individual investigators who have found and obtained cells from these families do not have the resources to properly maintain and distribute material to all interested and qualified parties.

An interagency agreement was established between the NIADDK and the NIGMS to support work designed to collect and store cells from patients with diabetes and CF. The newly established cell collections will facilitate research on this genetic disease by providing cell cultures that are of high viability and quality to the research community at large. Publication of this notice of availability appeared in the January 6, 1984, issue of the *NIH Guide for Grants and Contracts.*

Genetic Sequence Data Bank

Another interagency agreement was established between the NIADDK and NIGMS for partial support of GenBank™ (Genetic Sequence Data Bank). This computerized repository stores published nucleic acid sequence information on all residues greater than 50 nucleotides in length and is catalogued and annotated for site of biological interest. This data bank is becoming a major resource for genetic researchers all over the world.

Request for Research Grant Applications: Genetic and Metabolic Defects in Cystic Fibrosis

Much of the basic research in CF sponsored by the NIADDK has been directed toward searching for the so-called CF factor, which has been assumed by many to be a gene product found in the circulation and to be a primary cause of many of the clinical manifestations of the disease. To date, such a substance has not been isolated and characterized, and current studies in this area supported by the NIADDK do not appear likely to achieve this goal in the near future.

Other studies looking for morphological or biochemical anomalies in CF patients have not led to insights into the nature of the defect, often because of the problem of discriminating between primary and secondary characteristics of the disease.

On the other hand, basic investigational techniques potentially relevant to CF have undergone rapid development. These techniques include improved methods of organ culture, culturing differentiated tissues, and investigating intracellular processes involved in the secretion of electrolytes, macromolecules, and water. Molecular biologists have developed methods for searching for specific genetic defects even in the absence of identified defective or missing gene products.

Prior to this announcement, the NIADDK was receiving relatively few applications from investigators in the forefront of these areas and fewer still from outstanding individuals who also show awareness that their interests could be related to CF. To increase the likelihood that significant progress will be made soon in understanding this prevalent and devastating disease, more investigators in potentially related areas must be encouraged to address questions of direct relevance to the CF defect.

Of 63 applications received in March 1984 and reviewed by an ad hoc Special Review Study Section in July 1984, 56 were designated as NIADDK primary. These applications will be reviewed by the NIADDK Advisory Council in September 1984 for funding early in fiscal year 1985.

Conference on Growth Hormone

A conference grant was provided to the University of Maryland (principal investigator Dr. Salvatore Raiti) for a November 1983 conference on human growth hormone in Baltimore, Maryland, planned and hosted by the NHPP. The conference was sponsored by the NIADDK and several pharmaceutical companies. In 3 full days of discussions by experts working in the field, the conference covered such topics as neuroendocrine control and GRF, clinical studies with hGH from the pituitary, clinical studies using hGH made by recombinant DNA biosynthesis, the chemistry of hGH and its receptors, studies of gene expression and its defects, and studies of the somatomedins, peptides with growth substance actions. The proceedings of the symposium will be published soon.

Request for Applications on Immunologic Mechanisms in the Development of Diabetes

An announcement was issued requesting research grant applications in the area of the immunopathogenesis of diabetes. Recent evidence for an altered immune response in the development of IDDM prompted this solicitation in an effort to stimulate additional research on the immunopathogenesis of diabetes.

This NIADDK request for applications, sponsored with the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases, was prompted by a perceived need to elucidate the immunopathogenetic mechanisms important in the

development of IDDM and to obtain new basic information from population studies that relate these various factors to the incidence and prevalence of the disease and the development of its complications.

A recent workshop sponsored by the NIADDK, the National Institute of Allergy and Infectious Diseases, and the National Institute of Dental Research reviewed the available data in the areas of population and family studies, identical or fraternal twin studies, the relationship between IDDM and virus infection and other autoimmune diseases, lymphocyte invasion of the pancreas, detection of islet-cell antibodies and islet-cell surface antibodies, association of histocompatibility types with IDDM susceptibility, and successful intervention in the immune suppression in diabetic animal models. Assessment of the available data provided the basis for workshop participants to make recommendations on the need for future research on the epidemiology, etiology, and pathogenesis of diabetes as they relate to the immune system.

This request for applications has stimulated interest in these areas, particularly by encouraging investigators with a background in immunology to study the mechanisms of immunopathogenesis associated with IDDM. Applications received are under review, and some awards have been made.

Conferences

Conferences on research and clinical developments and advances in biomedicine facilitate the immediate exchange of information and cross-fertilization among researchers working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions.

Some of the conferences supported by the Division this fiscal year were described above. Other conferences include the following:

- The Eighth International Conference on Calcium Regulating Hormones, in Kobe, Japan, October 16-21, 1983.
- Gordon Conference on Peptides, Santa Barbara, California, February 5-10, 1984.
- Symposium on Dual Regulation of Adenylate Cyclase, Steamboat Springs, Colorado, March 4-8, 1984.
- Symposium on Intracellular Protein Catabolism, Airlie, Virginia, May 29-June 2, 1984.
- Gordon Conference on Cyclic Nucleotides, June 11-15, 1984.
- Conference on the Adrenal Cortex, Buffalo, New York, June 27-28, 1984.
- International Symposium on Flavins and Flavoproteins, Brighton, England, July 8-13, 1984.
- Third International Congress on Cell Biology, Tokyo, Japan, August 26-31, 1984.

The NIADDK joined several other NIH Institutes, various foundations, voluntary health agencies, and corporations in supporting the Second National Conference on Diabetes, organized by the NDAB and held at Reston, Virginia, in September 1983. The purpose of this conference was to assess the significant advances in diabetes research that have occurred since the last national conference (October 1979) and to identify directions for the future. The report of the conference was published in March 1984.

Program Plans

Diabetes Control and Complications Trial: Phase III Under Study

The feasibility of moving the DCCT to a full-scale clinical trial (phase III) will be determined on the basis of an analysis and review of the data after a minimum of 1 year of followup. During fiscal year 1984, data will be collected on which the assessment of the feasibility of proceeding to phase III will be based. These data will be analyzed and presented to the DSQ and the PAG in mid-1985. A recommendation as to continuation or termination of the DCCT will be presented to the NIADDK Advisory Council in September 1985.

Key feasibility questions that need to be answered include whether a statistically significant and clinically meaningful differential in blood glucose control in the experimental and control groups can be achieved and maintained, whether the biochemical and clinical outcomes of the study can be measured and documented with acceptable precision, and whether the treatment regimens are safe and acceptable. With positive answers to these questions, DCCT should be able to proceed to the long-term study of the impact of the two therapeutic strategies on the complications of IDDM using an expanded patient population. This decision will be based on advice provided to the NIADDK Director by the PAG and the DSQ. Each of these oversight groups will assess independently the results of the feasibility study to determine whether the goals have been met and the desirability of proceeding with phase III.

The primary complication to be assessed in the full trial is diabetic retinopathy. Two categories of patients will be recruited: those with no evidence of retinopathy and others with early signs of this complication. This study will make it possible to determine simultaneously whether tight blood glucose 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 the data generated from 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.

Reassessment of the National Hormone and Pituitary Program

Since 1962, the NHPP has collected human cadaver pituitaries and has shipped them to grantees or contractors for the extraction of hormones. The purified products have been returned to the NHPP for distribution to qualified investigators for clinical research purposes. More recently, animal hormones and antisera to various hormones were added to the NHPP inventory.

Recent advances in the development of bacterially produced hGH using recombinant DNA techniques and the discovery of GRH, as well as newer information on other pituitary hormones, require a reevaluation of the program for extraction, purification, and distribution of hGH and the collection of human pituitaries. As long as no other sources of these hormones were available, the NHPP performed a necessary and invaluable service. Now the NHPP inventories of animal hormones, products, and antisera must be reviewed. Such a review might recommend the addition of products to the inventory and the deletion of materials that are no longer needed by investigators or are available in adequate supply from commercial firms.

Diabetes Workshop for Medical Students

The need has never been more acute for physicians who elect to pursue careers in diabetes research. The remarkable progress made in the diabetes research program in the past several years has created new and expanding opportunities for clinically trained investigators. These opportunities, unfortunately, are appearing at a time when the proportion of physician-investigators in the universe of physicians is declining. The Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel noted in its report to the National Academy of Sciences (1981) that the number of M.D.'s in NIH research training programs has not changed appreciably since 1976 and is currently well below what is considered an appropriate level. The committee urged throughout the report that a great effort be made to address this problem. In addition, the NDAB has consistently noted the severe shortage of physicians engaged in diabetes research.

Although physicians enter research training most commonly at the end of the last year of their residency program, many points along the continuum of medical education offer the opportunity to influence the physician's decision to embark on a research career.

In January 1982, the Juvenile Diabetes Foundation sponsored a workshop for medical students to introduce them to current research in diabetes. The response from attendees was extremely positive, and the foundation has since held the meeting annually, in 1983 at the DRTC training center at Washington University in St. Louis and in 1984 at the University of Massachusetts DERC in Worcester. Funding to support these workshops has been obtained from many sources, including an annual contribution from the NIADDK.

Program Announcements

Program announcements are broadly disseminated notices to the biomedical research community concerning particular areas of research an NIH Institute would like to stimulate and in which it stands ready to receive research grant applications.

Program Announcement of Support for Diabetes Research

A program announcement was prepared for publication in the September 1984 issue of the *NIH Guide for Grants and Contracts*. The purpose of this trans-NIH diabetes program announcement is to give additional visibility to those areas of diabetes-related research that are recommended for future studies in the NDAB's recently published *Report of the Second National Diabetes Research Conference*, held in Reston, Virginia, in September 1983. Recommendations from the conference covered the following areas: the etiology and pathogenesis of IDDM, etiology and pathogenesis of NIDDM, insulin secretion, insulin biosynthesis and gene studies, hormone action, transplantation, insulin delivery systems, pregnancy, eye complications, kidney complications, neurological complications, and cardiovascular complications.

Program Announcement of Support for Endocrinology Research

The areas of research supported by the NIADDK's Endocrinology Research Program have been influenced in part by *Evaluation of Research Needs in Endocrinology*, a systematic and comprehensive report requested by the U.S. Senate and published in 1981. An extensive updated status and evaluation report enumerating the considerable research advances of the past 3 years was provided by NIADDK to the Senate in this past fiscal year.

From time to time, inquiries are received about the kind of work supported by the endocrinology program. A program announcement alerts the scientific community to the scope and areas of research supported by the program and stimulates some new and exciting approaches to problems that remain to be solved. It also assures scientists that work in both basic and clinical endocrinology is being supported.

During the coming fiscal year, an announcement of the Endocrinology Research Program's interest in supporting basic and clinical research in the broad areas of endocrinology will be issued, including research into the cause and treatment of various endocrinopathies, basic research on mechanisms of hormone action, production of various hormones either in the body or by artificial means (recombinant DNA techniques, chemical synthesis), and methods of hormone assay and isolation. Support also includes studies on hypothalamic factors, prostaglandins, and other hormone-like materials.

Request for Applications: Need for Research on Autoimmunity in Endocrine Diseases

Publication of a request for research grant applications is expected to encourage studies of immunology and immunogenetics as applied to various endocrinopathies, a development that should encourage closer cooperation among scientists of different disciplines. Thyroid disease is a major disorder that is believed to have autoimmune components, but such studies may also encompass hypoparathyroidism and hypoadrenalism.

At a recent meeting of NIADDK advisors, it was suggested that certain types of studies should be done relating to autoimmunity. The following list of thyroid studies was suggested; similar studies might be applied to other autoimmune endocrine diseases and include: (1) prospective studies of children at risk for autoimmune thyroid disease to assess the possible ordered appearance of autoimmune phenomena and the relationship to HLA antigens; (2) the relationship of manifestations of Graves' disease, its control, long-term remissions, and relapses to HLA antigens, and of autoimmunity to exophthalmos and pretibial myxedema; (3) the investigation of specific and nonspecific suppressor cell function in patients with autoimmune thyroid disease; (4) the development of methods for in vitro immunization to assess abnormalities in lymphocytes that may lead to excessive immune responses among patients with autoimmune thyroid disease; (5) the characterization and purification of antigens involved in autoimmune thyroid disease; (6) the development of methods for producing anti-idiotype antibodies that might be used in therapy; and (7) the development of clinically useful methods for detecting thyroid-stimulating antibodies.

Other similar studies might be applied to other autoimmune endocrine diseases. This announcement to the research community will be cosponsored with two other NIH Institutes.

Program Announcement in the Area of Enzymes in Metabolic Diseases

One major goal of the Metabolic Diseases Research Program is to facilitate an understanding of the role of enzymes in metabolic diseases within the purview of the NIADDK. The elucidation of the role of gene mutations, posttranslational modifications, and structural manipulations by means of drugs on enzyme function is of paramount importance in the quest to understand, prevent, and cure metabolic diseases due to enzyme defects. This announcement proposes to use expert consultants to identify research areas that could benefit from broad-based publicity provided by specific program announcements. Examples of areas to be considered include the genetics of normal and defective enzymes; posttranslational modifications of enzymes; enzyme recognition, transport, inhibition, and induction; models for the study of enzyme defects and their correction; research on enzymes; and prevention of inborn errors of metabolism.

Scientific Instrumentation Grants

At its meeting in May 1984, the NIADDK Advisory Council endorsed a request that the staff consider providing an additional funding mechanism for the purchase of scientific instrumentation. The council members noted that the extramural scientific community believes that existing mechanisms of support have not met the need for state-of-the-art scientific instrumentation, thus hindering progress in biomedical research.

In this regard, the National Science Foundation (NSF) is conducting a national survey of academic research instruments and instrumentation needs. The NSF has recently released the results in three selected fields—computers, physical sciences, and engineering. The findings included the following: about one-fourth of the inventoried equipment was believed to be obsolete; only 16 percent was characterized as state of the art; one-half of departmental chairpersons reported existing equipment to be "insufficient"; and more than 90 percent of departmental chairpersons reported that the lack of equipment inhibited the conduct of critical research. The survey is continuing to gather data in the biological and medical sciences. However, it is fair to assume that such studies will document similar, if perhaps not as severe, shortcomings in NIH-supported research laboratories. The NIH Director has expressed this concern as well (J. Med. Educ. 59, 155-161 (1984)). The existing NIH support programs for scientific instrumentation are limited to large expensive systems. No specific mechanism to

support more moderately priced devices exists, except for the supplemental grant to existing grants. The supplemental grant mechanism has not been widely used because it limits the request to a single investigator and requires approximately 1 year for processing (submission to award).

This initiative proposes a program to provide funds for the purchase of scientific instruments for holders of individual research grants from the Division of Diabetes, Endocrinology, and Metabolic Diseases.

Initiation of a Short-Term Fellowship for Established Researchers as a Mechanism to Facilitate Rapid Exchange of New Technologies

An initiative to provide short-term fellowships for established researchers has been designed to offer a mechanism that provides 3 to 9 months of support for grantees interested in learning a new methodology. This learning could be done by visiting a laboratory where the respective methodology is in full use or by hosting an expert for the required time, if the means to apply the methodology in the host laboratory are in place. The turnaround time for review of applications is short, about 3 months.

There are a number of important new methods for studying proteins and mutant enzymes—for example, cloning technology and other aspects of gene manipulations, monoclonal antibodies, the patch clamp technique for single channel conductance recording, and immunofluorescent microscopy. Setting up these and other methods in a research laboratory sometimes requires a long time and could significantly delay research progress. The proposed senior fellowship mechanism could reduce or eliminate such delays.

NIADDK and World Health Organization (WHO) Collaborating Center on Diabetes Research, Information, and Education

NIADDK has applied to serve as a WHO Collaborating Center to provide clearinghouse services for WHO member nations that seek specific expertise in diabetes. The center will identify U.S. scientists who complement expertise on diabetes in other nations, identify and promote opportunities in the United States for research training of foreign scientists, and jointly sponsor international conferences and workshops on diabetes.

Numerous opportunities exist outside the United States to advance our understanding of diabetes. To take advantage of these opportunities, better communication and exchange of expertise between the United States and foreign nations is needed.

The WHO has established collaborating centers in seven locations internationally. The WHO Collaborating Center on Diabetes Research, Information, and Education will be the first in the United States. In April 1984, the Division of Diabetes, Endocrinology, and Metabolic Diseases was invited by WHO to submit an application to become a member. The application for the collaborating center was submitted in August 1984 for review by WHO in September 1984.

Classification and Diagnostic Criteria for Diabetes

Under this initiative, two meetings of an international expert committee will take place to examine the validity of the National Diabetes Data Group criteria for diabetes, to refine the criteria and classification scheme based on new knowledge, and to reconcile differences with WHO criteria.

The data group sponsored an expert committee in 1978-79 to develop a consensus on classification and criteria for diabetes. Its recommendations have become widely accepted in the United States. New studies have been conducted since the 1979 diabetes criteria of the data group were published that need to be considered by an expert committee to determine if the 1979 recommendations should be altered to provide criteria for diabetes that are more prognostic to its complications. Consequently, in July 1984, a second expert committee was convened. The new data group category of impaired glucose tolerance needs to be examined for its clinical significance. To ensure comparability of diabetes research conducted internationally, differences in NDDG and WHO criteria need to be reconciled.

Data Collection Pertaining to the Use of Immunosuppression in Insulin-Dependent Diabetes Mellitus

Immunosuppression is now being used in the treatment of a number of diseases thought to be of immune origin or to have a major component involving the immune system. Recent evidence suggests that some types of IDDM may result from autoimmune components. Because of the devastating effects of this disease, some investigators believe that efforts to suppress, abort, or possibly reverse the initial pathogenic sequence of the disease are justified and have initiated studies using immunosuppression in IDDM patients.

At its winter 1983 meeting, members of the Metabolism Study Section, which reviews grant applications for scientific merit, voiced their concern about research projects that proposed to use immunosuppressive drugs in IDDM patients. Based on their concern, they recommended that the Institute convene a consensus meeting to consider the various immunologic aspects of type 1 diabetes mellitus and the role of immunosuppressive approaches to IDDM.

This meeting was held on May 13, 1983. A summary of the meeting was published in the *New England Journal of Medicine* (November 1983). The participants were divided in their assessment of the benefit of using immunosuppressive drugs in diabetic patients at this time. Those in favor of the therapy believed that the risk of using this potentially toxic treatment to prevent the disease was justified because of the possibility of alleviating the devastating effects of diabetes. Those opposed felt that the major damage to the B cells has probably occurred by the time of diagnosis. In addition, it was thought that the use of these agents during the prodromal period was too risky until the long-term consequences have been determined.

Those in favor of the trials recommended that any such trials should be strictly controlled and only performed at centers when the patient population is large enough to allow for randomization and where the most modern techniques are available to assess B-cell function and to monitor a large number of immunologic indicators. All participants did agree, however, that immunotherapy in IDDM should be regarded as an experimental procedure at this time. Their recommendation was that a registry be developed as a repository for the collection, storage, and rapid dissemination of the results of the use of immunosuppression in IDDM.

This initiative proposes to convene a group of consultants to develop a format for use in collecting the data to be stored in the registry and to negotiate a contract to solicit, store, and disseminate the available data. We will notify professionals working in the field once this registry is available.

Facilitation of Research in Endocrine Transplantation

Recent years have seen many significant accomplishments directed toward the transplantation of fetal and adult islet cells of the pancreas. Methods have been developed that will prevent the rejection of isolated adult islets transplanted between different strains of animals as well as between different species (rat to mouse). New methods for separating islet cells from pancreatic acinar tissue and their further purification have been developed. Studies of transplant sites have led to the selection of the omentum as a potential site, since its blood supply drains into the portal venous system, and it is easily accessible for both insertion and removal of the islet transplants. In addition, studies in rats have shown that isografts of islets will prevent, reverse, or arrest the complications of diabetes involving the eyes, kidneys, and autonomic nervous system of diabetic recipients.

A workshop report from the Second National Conference on Diabetes expressed the belief that these advances had brought islet transplantation near the threshold of being applied to human diabetic patients. However, the report also expressed some possible concern about the timely and effective application of these advances in relation to assurance that the human islet transplantation will be done in a safe, reliable, and reproducible manner; that the translation of these approaches to human diabetes would be accomplished as rapidly as feasible; and that the ultimate goal of determining whether human islet transplants will prevent or arrest diabetic complications may be attained.

One approach to facilitating more organized and effective multidisciplinary efforts in this area would be to establish specialized centers of research for endocrine transplantation. These centers would provide funds for highly focused research projects and core resources that are specialized to the research projects. It is expected that this approach will also develop an excellent environment for postdoctoral research training specifically directed toward transplantation and immunology.

Before embarking on a large-scale investment in centers or program projects, it would be beneficial to convene a workshop to stimulate a discussion of the scientific, technical, and medical issues involved in pancreatic transplantation, coordinate further efforts in this field, and consider the advisability of establishing centers as proposed above. It is felt that the technology and knowledge developed would be applicable at least in part to the transplantation of other endocrine cells, possibly, for example, parathyroid and adrenal cells.

Genetic Methods for the Diagnosis and Treatment of Familial Disorders

The objective of this initiative is to organize a 2-day workshop to stimulate the development of genetic techniques such as DNA restriction fragment length polymorphism (RFLP) for use as genetic markers of inherited metabolic diseases and for gene transfer into somatic cells to correct metabolic defects.

A major goal of the Metabolic Diseases Research Program is the development of procedures to diagnose and treat metabolic disorders in humans. The techniques of gene manipulation offer a potential breakthrough toward this goal. Fundamental studies of the techniques for delivering genes into cells, the nature of the tissue-specific expression of various genes, and the possible consequences of including retroviral vectors into somatic cells must be thoroughly studied. The use of RFLP's to map the location of genes for human disorders that at the present time have no genetic marker could lead to methods for the early detection of affected individuals. Application of RFLP's would be especially effective for dominantly inherited and X-linked disorders, which include many fatal diseases such as Huntington's disease.

An assessment of the state of the art in these and other aspects of genetic technology and the encouragement of biochemists and molecular biologists skilled in these procedures to work on metabolic problems will be addressed through the planned workshop.

Grouped Analysis of Data on NIDDM Populations

NIDDM represents by far the most prevalent type of diabetes. Population-based studies have been conducted in American Indians, Mexican-Americans, natives of some South Pacific islands, and a few communities of North American Caucasians. Evidence suggests that genetic heterogeneity and environmental differences among these various ethnic groups are strongly related to the differences in incidence and prevalence of diabetes. However, to determine the importance of various environmental risk factors (diet, obesity, physical activity, and lifestyle), analyses of the grouped data from these populations is necessary. These analyses would assess the importance of one risk factor while controlling for the impact of the others, a step that is difficult or impossible to perform in each of the individual populations.

NIADDK has funded prospective studies on the above populations for a number of years; hence, the data are already available. The planning of this study of the etiology and natural history of NIDDM and its complications in various populations will require an advisory group composed of the epidemiologists who have conducted research on these populations.

Noninvasive Study of Metabolism: A Workshop

Positron emission tomography (PET) and NMR imaging are promising candidates as noninvasive techniques for the study of in vivo metabolic processes. This initiative will organize a 2-day workshop to facilitate communication between clinicians and biochemists on the role, uses, and relevance of PET and NMR imaging in vivo.

Both PET and NMR imaging are significant future tools for the elucidation of in vivo normal and abnormal metabolic processes. However, the high cost of the instruments is seriously limiting the ability of basic researchers to gain access to and utilize both methods. A workshop that brings together basic scientists and clinicians who are experts in the utilization of the techniques has the potential of improving communication and initiating collaboration in this area of research.

Proposed Workshop on New Techniques for Crystallization of Intact Membrane Proteins

The submission of a conference support grant application is under consideration by interested scientists to organize a 5-day workshop or course to help membrane scientists learn the experimental details of this new technique that is currently available in Europe.

Recent successes in crystallizing intact, or integral, membrane proteins from solutions of protein-detergent complexes of purified proteins are a potential breakthrough in the relationship between the extracellular and cytoplasmic domains of proteins. The potential is attributable to the synthesis of detergents with special properties and high purity and to the introduction of small molecules to reduce micelle size. With easy access to the simple techniques developed recently, great progress could be achieved in understanding the properties and mechanism of action of membrane receptors and transport proteins in health and disease.

Proposed Workshop on Pathophysiology of Inherited Metabolic Disorders

The purpose of this initiative is to organize and conduct a workshop to discuss ways to use existing or new animal or cell systems in studies of inborn metabolic disorders. The workshop could lead to the development of a program announcement or request for grant applications.

Advances in the understanding of the basic enzymatic defect in inborn errors of metabolism have not been matched by an understanding of the steps linking enzyme deficiency and impaired cell function. It is difficult to gain insight into what happens between the gene and disease by using patients or patient-derived materials. When animals with a human equivalent of an inherited metabolic disease are identified or produced through genetic engineering techniques applied to specific germ-cell lines, they can become the subject of pathophysiologic studies and can also provide cell systems amenable to culture or maintenance in vitro. An assessment of the state of the art in this area, as well as a discussion of ways to deal with related needs, seems appropriate to accelerate the rate of understanding the pathophysiology of these rare diseases.

The submission of a conference support grant application is under consideration by interested scientists.

Workshop on Stimulus-Secretion Coupling in Pancreatic Islet Cells

Growing out of the *Report of the National Diabetes Advisory Board* (1983) and the recommendations from the Second National Conference on Diabetes, this initiative is to convene a workshop to stimulate the coordination of studies in the areas of cell biology, morphology, and physiology as they relate to stimulus-secretion coupling in the pancreatic islet cells.

The mechanisms by which the pancreatic islet cells store and secrete hormones are fundamental to our understanding of the defects involved in diabetes. Understanding the biochemistry, physiology, and pathology of the islets and how they store and secrete hormones is fundamental to the

development of new treatment modalities, including transplantation, pumps, and oral agents.

It is becoming evident that the interrelationships of the local effects of the various hormones and the neurotransmitters, the stimulus-secretion mechanism, at the biochemical level and the biophysical phenomena involved are very complex.

We propose to convene a workshop of scientists who are experts in these various areas so the problems involved can be discussed in terms of an interrelated mechanism and recommendations can be made as to what areas of research need to be pursued and how a coordinated approach can be developed. It is hoped that the interdisciplinary nature of the workshop will result in recommendations for new ways to coordinate research in this area to benefit from more integrated studies that address the problem as a whole.

Promotion of Interdisciplinary Research in Diabetes and Endocrinology

More and more advances in diabetes research originate from projects that are multidisciplinary in nature. These projects could benefit from additional services, in that they often require complex methodologies for which additional training is necessary or need special techniques not easily acquired by individual investigators. Some of the recommendations made at the recent NDAB-sponsored Second National Conference on Diabetes (in the workgroups on insulin biogenesis and gene studies, insulin secretion, and hormone action) illustrate this point.

An effective approach to fostering interdisciplinary efforts is the Research Core Center Program. These center grants do not contain funds for research projects per se, but provide for establishing cores, or shared resources. These core resources are designed to provide materials and services to funded investigators who need to use identical methodologies or materials. The investigators may not charge for such services from their regular research grants. The provision of services, while very beneficial, is probably only equally as important as three other aspects of core resources—namely, the availability of expert consultation, the opportunity for training in new techniques, and the multidisciplinary environment that is developed. Most core resources also result in a greater cost savings due to bulk purchasing, less deterioration of radioactive preparations because of rapid turnover, and greater efficiency of operation. Other real advantages are greater standardization of results and more efficient quality control.

To promote greater interdisciplinary efforts in the study of diabetes and its complications, an additional core center grant award is proposed for the coming year.

Workshop on Prospective Study of the Etiology of IDDM

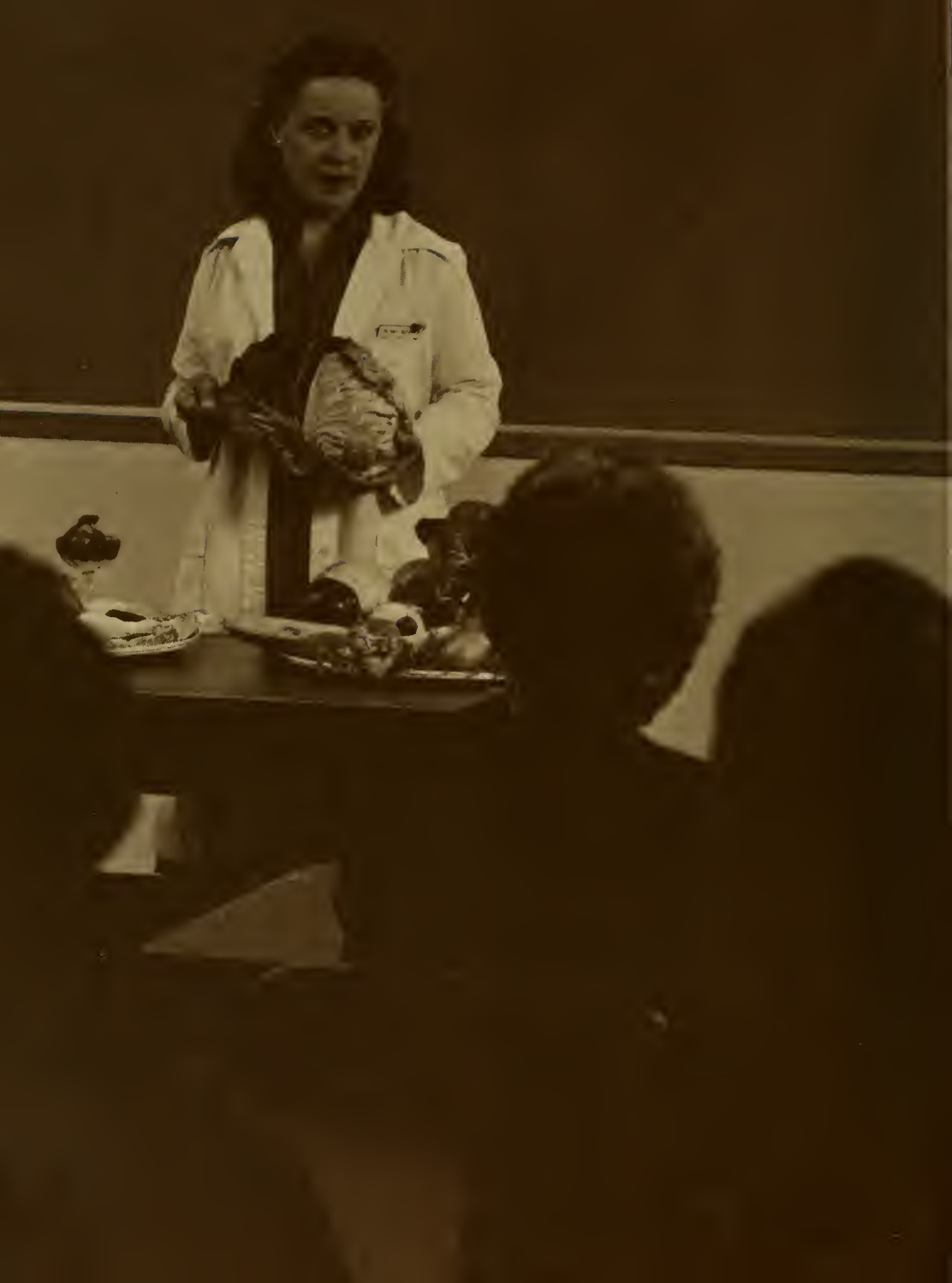
Current efforts to understand the etiology of IDDM are scattered, and often no one investigator has access to a sufficient number of IDDM patients in which to test etiologic hypotheses. Further, findings in any single study will have to be tested in a larger, free-living population to ascertain their general applicability. A prospective study examining environmental, genetic, and clinical features simultaneously will greatly enhance the possibility of obtaining a conclusive understanding of the causes of IDDM. However, before such a study is undertaken, a workshop to define all the parameters of this study is essential, including study design, variables to be measured, measurement techniques, number of subjects to be enrolled, and potential study locations.

Repository for New Cell Lines Containing Modified Genes for Metabolically Important Enzymes

Introduction of modified genes into cells to create lines useful for studying the regulation of a specific pathway could be the next major breakthrough in metabolic research. For example, the successful introduction of a suitably engineered vector, containing a gene for pyruvate kinase with a modified regulatory domain, would allow the study and better understanding of the glycolytic pathway in these cells. Several candidate genes could be identified for different enzymes and enzymatic pathways. Once the feasibility of transforming cells is positively established, a resource could assure broad distribution of the transformed cells to all interested laboratories.

This initiative proposes to explore whether the development of transformed cells relevant in the study of metabolic processes is practical and, if it is, to establish a centralized resource for development, storage, and distribution of such novel cell lines.

During phase I, a meeting of six to eight consultants will be convened to cover a spectrum of issues related to the timeliness, usefulness, potential benefits, and costs of developing such a resource. The consultants will produce a report for staff review and evaluation.



IV. Research Focus—Digestive Diseases and Nutrition

Patients with duodenal ulcers confirmed by endoscopy participated in a recent clinical trial. The study compared the effectiveness of two different drugs in healing ulcers and preventing their recurrence.

Facing page

Clinical Nutrition Research Unit awards stimulate progress in nutrition research, patient care, and nutrition information for the public.

Overview

The Division of Digestive Diseases and Nutrition is responsible for the extramural support of grant awards and contracts pertaining to diseases and disorders of the gastrointestinal (GI) tract, the liver, and other associated organs and to nutrition. NIADDK's mission, addressed through this Division's efforts, is twofold—to reduce the suffering associated with these diseases and to reduce their economic impact.

Digestive diseases constitute a health problem of great magnitude. More than 34 million Americans are afflicted with diseases of the digestive system, some 20 million of whom have chronic disorders. These disorders exact a high toll in terms of disability, suffering, and economic costs.* Of all the causes of disability due to illness in our country, digestive diseases rank second. Over 2 million Americans are impaired to some degree by these diseases; 1.2 million people are limited in the work they can perform; and 400,000 are disabled.* Digestive diseases account for 200,000 absences from work each day and are the leading cause of loss of time from work for male employees.* Almost 140,000 veterans receive payments for service-connected disability due to GI conditions, at a cost to the Nation of approximately $100 million each year.* But the greater cost is the number of lives lost; digestive diseases cause approximately 200,000 deaths each year (including those associated with malignancies).*

Investigations sponsored by the Division's Esophageal, Gastric, and Colonic Diseases Program and by its Intestinal and Pancreatic Diseases Program are directed at the structure, function, and diseases of the esophagus, stomach, small and large intestines, anorectum, pancreas, and salivary glands. Of particular concern are heartburn and esophagitis, hiatus hernia, gastritis, peptic ulcer disease, diverticulitis, ulcerative colitis and Crohn's disease, intestinal malabsorption syndrome, sprue, diarrhea, functional disorders such as spastic colon, acute and chronic pancreatitis, the Zollinger-Ellison syndrome, and general studies of the GI hormones.

A new emphasis is being placed on anorectal disorders through the Special Emphasis Program.

Through its Liver and Biliary Diseases Program, the Institute supports studies of the structure, function, and diseases of the liver, biliary tract, and gallbladder. Included in these studies are inflammatory, toxic, metabolic, and genetic diseases of the liver such as hepatitis, cirrhosis, Wilson's disease, primary biliary cirrhosis, fatty liver, hepatic encephalopathy, the Dubin-Johnson syndrome, and Gilbert's disease. Other investigations focus on liver regeneration, liver assist (artificial liver) devices, and liver transplantation as well as on 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.

* Source: National Commission on Digestive Diseases. Economic costs are estimated to be at over $50 billion annually, including $17 billion in medical costs. More Americans are hospitalized for digestive disorders than for any other family of illnesses. Digestive diseases are responsible for 15 percent of all admissions to general hospitals, 12 percent of all admissions to Veterans Administration hospitals, and 25 percent of all surgical operations (excluding tonsillectomies).

The NIADDK Nutrition Program continues to foster and support research and training in the broad areas of fundamental and clinical nutrition. Nutritional factors and diet are believed to play a significant role in heart disease, stroke, cancer, diabetes, atherosclerosis, and cirrhosis of the liver, 6 of the Nation's 10 leading causes of death from disease. Nutrition research traditionally has been an important area of interest for NIH in general and for NIADDK especially. The common occurrence of nutrition-related diseases or conditions such as obesity, anorexia nervosa, bulimia, diabetes, osteoporosis, alcoholism, anemia, and atherosclerosis in segments of the U.S. population attests to the need for a better understanding of the role of nutrients in these clinical problems. The greatest promise for solutions to such problems lies in fundamental research on the mechanism of action of specific nutritional factors and nutrient interactions and on the role of diet or nutrients as metabolic regulators and physiological modifiers of behavior. The Nutrition Program continues to stress the following priority research areas: fundamental studies on the metabolic role of specific dietary components, including essential amino acids, protein, vitamins, minerals, essential fatty acids, fats, carbohydrates, and metabolizable energy; investigation of the underlying causes of obesity, with the goal of developing appropriate methods for prevention and control; studies on nutritional requirements in health and disease, with emphasis on individual and environmental differences; studies on nutritional support of the patients as it affects nutritional status of the whole individual in such conditions as obesity, surgical trauma, burns, or chronic renal failure; basic studies on the role of dietary fiber on transit-time, digestion, rate of absorption, intestinal microflora, and interactions with nutrients, drugs, bile salts, and other substances; and research on nutrition and infection and immune competence.

Recent technological advances, including mass spectrometry, using stable isotopes, high-pressure liquid chromatography, radioimmunoassay, and rapid analysis of amino acids and trace metals, offer promise for rapid progress in such basic nutrient-focused studies in human health.

Highlights of Research Advances

The following section highlights areas in which the Division of Digestive Diseases and Nutrition has reported recent progress in its research programs:

- Bleeding esophageal blood vessels (varices) in patients with cirrhosis of the liver can be a life-threatening emergency. A careful experimental comparison of alternative methods for control of bleeding varices in the esophagi of dogs demonstrated that injection of sclerosing solutions, using an endoscope, results in the best combination of safety with obliteration of varices.

- Evidence was obtained that the synthesis of certain prostaglandins, fatty-acid derivatives with hormone-like action, is a normal mechanism in the upper intestine (duodenum) for protection against stomach acid and duodenal ulcer and is deficient in some ulcer patients.

- Duodenal ulcer patients responded equally well to the drug cimetidine and to intensive antacid treatment, both in healing and in rate of recurrence of the ulcer. In another study, the related drug ranitidine was more potent than cimetidine and had fewer side effects in patients with Zollinger-Ellison syndrome characterized by gastric hypersecretion.

- The mechanism of life-threatening diarrheas, specifically, of the cholera-like diarrhea seen with a type of pancreatic tumor, appears to involve the action of a secretory stimulant, vasoactive intestinal peptide (VIP), causing losses of sodium, potassium, and water. This has suggested new therapeutic agents to prevent such stimulation.

- Bacteria must first adhere to intestinal lining cell membranes to cause diarrhea; mechanisms used in this specific adhesion process and possible ways to interfere with it have been identified.

- In inflammatory bowel disease (ulcerative colitis and Crohn's disease) there is a decrease in the ability of the body to attack bacterial cells or viruses that may stimulate detrimental immune reactions against cells lining the colon. The decrease is in "natural killer lymphocyte" activity, a finding that may lead to new approaches to treatment.

- A possible genetic marker indicating susceptibility to primary biliary cirrhosis, a potentially fatal liver disease, has been found. In individuals with this disease, there is a consistent impairment of immune-suppressor-cell activity.

- Further experience with dissolution of cholesterol gallstones using the drug chenodiol has shown that about one-fifth of patients can achieve complete dissolution (over a 4-year period, at a dosage of 750 mg/day), with no worsening of side effects with the passage of time.

- Individuals deficient in the enzyme lactase who cannot ingest dairy products, which contain the milk sugar lactose, without diarrhea and flatulence can benefit from eating yogurt. Bacterial lactase in yogurt facilitates human digestion of its lactose.

- The use of laxatives to effect weight control in obsessive overeating is ineffective and potentially dangerous.

- The hormonal form of vitamin D acts to increase calcium absorption in the small intestine, the jejunum and ileum, with no change in the secretion. It also increases magnesium absorption in the jejunum. This pattern shows it could not be responsible for the disorder absorptive hypercalciuria.
- Use of oral zinc supplements show promise in the treatment of specific symptoms of sickle cell disease in the young such as restoring normal growth and in the treatment of selected patients with Wilson's disease such as eliminating excess copper accumulation.
- In obesity, the type of regional fat distribution in the body has distinct health implications.

New noninvasive diagnostic tools provide safer, more effective ways of identifying disorders of the digestive system.

Digestive Diseases

Endoscopic Methods for Control of Esophageal Hemorrhage: A Comparison

Prior Findings

Hemorrhage from esophageal blood vessels—a life-threatening emergency—arises in cases of hepatic cirrhosis. Cirrhosis of the liver is a major cause of morbidity, mortality, and health-care expense, but an effective form of therapy has not been developed as yet. In cirrhosis, when venous pressure rises in the liver, collateral channels, varices, tend to develop in the submucosa of the esophagus and stomach, where they pose the problem of rupture. The frequency of varices in cirrhotic patients varies from 14 percent to as high as 77 percent, depending on the type, duration, and severity of the cirrhosis.

The successful use of injecting a sclerosing solution into bleeding varicose blood vessels in the esophagus, with control of hemorrhage, was reported last year. A single injection sufficed to control the acute bleeding in 70 percent of patients; repeated injections permitted control of 95 percent of these emergencies. Preliminary studies in other centers confirmed these findings. Moreover, repeated injections were found to *prevent* bleeding episodes for 1 year or longer in the majority of patients. An exciting finding was the complete disappearance of both gross esophageal and gastric varices even though only the esophageal varicosities were injected. In the United States, the procedure is to use a flexible fiberoptic endoscope without anesthesia. Although the direct injection of the individual varices with a sclerosing agent to thrombose the vessels was first described in 1939, it was not used extensively until 1955, when the procedure was used in the United Kingdom.

Injection sclerotherapy is only one of many methods that have been tried for the control of esophageal hemorrhage. As performed by different clinicians, both safety and efficacy of these methods have varied widely. An NIH consensus development conference on therapeutic endoscopic methods, held in 1980, cautioned that uncontrolled use of these methods should be discouraged until careful studies could be made, and the results of these studies could be evaluated and shared. The life-threatening nature of esophageal hemorrhage means that systematic and controlled comparisons of methods must be done experimentally in animals prior to human trials.

Recent Advances

An experimental evaluation of the various methods of endoscopic hemostasis was conducted under NIADDK support, using a reproducible canine model of esophageal varices. In addition to sclerotherapy, two methods of laser coagulation, two methods of electrocoagulation, a procedure for thermal coagulation combined with pressure, and a method of closure of the vessels using magnets with the clotting substance thrombin were included in the evaluation. It was found that sclerotherapy and one of the laser methods (the neodymium-yttrium-aluminum-garnet, or YAG, laser) provided reliable hemostasis in acutely bleeding canine varices. The thermal method worked well 50 percent of the time, but all of the other methods stopped bleeding in less than half the trials. Only the two most successful methods did not permit rebleeding in the face of renewed pressure. It was observed that while the YAG laser was easier to use than the injection method, it also caused more esophageal ulcers or erosions and did not actually obliterate the varices (the injections obliterated about one-third of the varices with only one injection).

Research Directions

More extensive studies are warranted to evaluate the short- and long-term differences among several possible sclerosing agents—especially their effectiveness in obliterating varices, rates of obliteration, and frequency of ulceration. Similarly, evaluation of different powers of the YAG laser is desirable. Studies using the canine model will try to determine ways to reduce tissue injury while increasing obliteration of vessels. When safe and effective procedures have been worked out, a comparative clinical trial of sclerotherapy and the YAG laser is an essential next step.

These methods offer a means of preventing bleeding that does not involve major surgery. Although presently being used only after a bleeding episode occurs, *prophylactic* use for patients may be justified in the future, if the techniques are confirmed to be relatively safe and if patients at high risk for a first variceal bleeding episode can be identified.

The Clearance of Stomach Acid From the Esophagus

Prior Findings

The reflux of stomach acid into the esophagus is common and can lead to inflammation of the esophagus, reflux esophagitis, with later scarring and stricture requiring surgical correction. While clearance of refluxed acid is important in the prevention of esophagitis, the mechanism by which this is done is not well understood.

Recent Advances

Examination of acid clearance under standard conditions in normal individuals not suffering from symptoms of reflux esophagitis has shown that normal peristalsis, rhythmic movement along the length of the gut due to wave-like contraction, empties virtually all acid volume in one or two waves. Any residual acid is neutralized by swallowed saliva within minutes. An upright position contributes little to esophageal acid clearance if peristaltic wave activity is normal.

Research Directions

Study of problems of acid clearance in patients with impaired peristalsis due to neuromuscular dysfunction and in patients with deficient saliva production may help to prevent reflux esophagitis in these patients and in others. Research on selective use of drugs to enhance peristalsis and saliva production may contribute to treatment and prevention of this condition.

The Role of Prostaglandins in Peptic Ulcer

Prior Findings

The hormone-like fatty-acid derivatives known as prostaglandins (specifically, structures similar to prostaglandins of classes A, B, E, F, and I) can be effective in preventing acute gastric erosions, ulcers, induced by such stressor substances as alcohol, strong alkali or acid, bile salts, aspirin, and bacterial sepsis, in experimental animals. Prostaglandin E_2 (PGE_2) treatment for 10 days cured a patient of gastritis with hemorrhaging. After 6 days, his gastric lining had been restored to normal appearance as shown by endoscopic examination.

Prostaglandins have been reported to accelerate healing of duodenal, or peptic, ulcers in humans and to prevent such ulcers in animals. Inhibition of their normal synthesis in the gastric or duodenal lining can cause ulcers, and stimulation of their synthesis can protect against them.

Under NIADDK support, it was decided to explore the role of the prostaglandins in the pathogenesis of peptic ulcer and to measure their synthesis in relationship to the delivery of gastric acid to the duodenum.

Recent Advances

Using a system of two radioisotope markers at different levels on intubation, investigators measured the effect of a test meal (an amino acid soup) on gastric secretion, acid output, meal emptying, and duodenal acid load. Prostaglandin (PG) synthesis was measured in biopsy specimens from the duodenum. Ulcer patients were able to synthesize prostaglandins, but their PG synthesis after a meal decreased. This finding was in contrast to the normal controls, in whom a meal increased PG synthesis. The researchers concluded that PG synthesis is an important protective mechanism in normal duodenal mucosa and that a failure of or defect in this mechanism may lead to the development of duodenal ulcer. An imbalance between the acid load from the stomach arriving in the duodenum and the availability of protective PG synthesis appears to be instrumental in developing the disease.

Research Directions

Confirmation of these important findings with a variety of technical approaches and larger (and randomly selected) groups of patients and controls is essential. Examination of the alternative possibility that inflammation of the duodenum may be the cause of decreased PG synthesis rather than its result should be made.

The identification of the specific PG molecules having the greatest protective effect would facilitate development of prospective therapeutic applications. A metabolite of prostacyclin, 6-keto-PGF_{1a}, is a candidate, based on this study.

Gastric Acid Secretion Control and Ulcer Treatment

Prior Findings

Studies on histamine and its role in gastric acid secretion have led to the development of two important antiulcer agents: cimetidine, presently in widespread use, and ranitidine, which is now approved by the Food and Drug Administration for the treatment of duodenal ulcer.

Cimetidine, a histamine (H_2)-receptor antagonist, is an effective drug for healing peptic ulcers and for preventing their recurrence; however, it can produce certain antiandrogenic side effects such as gynecomastia (enlargement of the breast) and sexual impotence in male patients receiving large doses of the drug for prolonged periods of time.

In a carefully controlled evaluation of cimetidine for the healing of uncomplicated gastric ulcer, an NIADDK-supported study compared the drug's use with low-dose antacid and with a placebo. The response to cimetidine was significantly better than to the placebo; it definitely hastened the healing process. For relief of *symptoms*, however, neither cimetidine nor antacid was more effective than the placebo. The presence or absence of symptoms was not a reliable indicator of the presence or absence of a gastric ulcer.

In another study, an intramural NIH research team evaluated cimetidine's tendency to cause clinically important antiandrogenic side effects and studied the usefulness of the newer antihistaminic agent, ranitidine, as an alternative therapy in patients with the Zollinger-Ellison syndrome.

Recent Advances

The question of whether successful treatment of duodenal ulcers with cimetidine or antacid will prevent recurrences of the ulcers was examined in a study reported this year. Patients with endoscopically documented duodenal ulcers received cimetidine (1,200 mg daily) or intensive antacid therapy, in a carefully controlled trial. Ulcer healing was almost identical in the two groups, about 63 percent at 4 weeks and 83 percent at 6 weeks. The 114 patients with healed ulcer were maintained on cimetidine or antacid and were examined for recurrence at 3, 6, and 12 months; again, there was no difference between the two treatments (about 55-percent recurrence at 6 months). Factors associated with delayed healing and with relapse included smoking, long duration of the disease, high pain frequency, and high acid secretion. Males did less well than females.

The NIADDK intramural research comparison of cimetidine and ranitidine yielded some new results. Thirteen patients with excess gastric secretion were studied; 12 of these had the Zollinger-Ellison syndrome, a disease characterized by a marked increase in gastric acid secretion and peptic ulcers caused by gastrin-secreting pancreatic islet-cell tumors. In these patients, ranitidine appeared more potent than cimetidine; its use for 6 to 25 months showed that it can inhibit acid secretion adequately, is safe to use, and does not cause the antiandrogenic side effects frequently seen with high doses of cimetidine. Similarities between the two drugs included rate of onset of effect, relative dosage for a given patient, and tendency to develop resistance to the drug with prolonged use in a given patient. Results to date suggest a somewhat greater risk of side effects for cimetidine, and additional experience should clarify this issue.

Research Directions

The problem of relative resistance in some patients and the fact that long-term use of these drugs leads to increasing dosage requirements with time means that still more powerful antisecretory agents will be needed to ensure that gastric secretion can be controlled in the future.

In view of the promise of ranitidine as a safe and effective antihistamine for healing peptic ulcers and preventing their recurrence, its further evaluation is indicated, to verify and extend findings to date and to determine optimal clinical conditions of its use—particularly the minimal effective doses. Synthesis of compounds structurally related to ranitidine may identify even more effective or longer acting drugs equally free of side effects. Study of the mechanism by which the antiandrogenic effect of cimetidine is produced may lead to ways of modifying this undesirable action.

Further research on delayed healing and recurrence of ulcers may suggest ways of improving long-term results of treatment.

Secretory Diarrhea: The Role of Vasoactive Intestinal Peptide

Prior Findings

In the normal functioning of the intestine, there is a balance between the absorption of fluid and electrolytes and their secretion back into the lumen of the intestine. Regulation is primarily local, although many hormones influence this balance. Local endocrine-type cells in the intestinal epithelial lining produce and release serotonin and neurotensin, which both favor secretion, and somatostatin, which is antisecretory. It was reported last year that somatostatin inhibited gastric acid secretion, pancreatic enzyme and bicarbonate secretion, intestinal motility, and splanchnic (regional intestinal) blood flow. It also inhibits the release of hormones or neurotransmitters such as VIP, gastric inhibitory polypeptide, gastrin, and secretin that may contribute to diarrhea. It can stimulate electrolyte absorption in the isolated rabbit ileum and water and electrolyte absorption in patients with severe secretory diarrhea due to malignant carcinoid syndrome. In fact, somatostatin might be a clinically useful therapeutic agent in the treatment of diarrheal syndromes.

The innervation of the intestinal mucosa plays an integral role in the balance that prevents secretory diarrhea. In addition to adrenergic (antisecretory) and cholinergic (secretory) nerve fibers, the rich and complex innervation includes peptidinergic fibers that release peptides such as substance P, kallikrein, and VIP, all of which stimulate secretion. These fibers can also cause synthesis of PG, by activating substances called kinins, which also stimulate secretion.

In secretory diarrhea, the finely tuned regulation of intestinal activity breaks down, and secretion is continuously stimulated without a balancing absorption process. The most common cause of such a breakdown is a bacterial enterotoxin such as cholera, which attaches to intestinal epithelial cells and activates the enzyme adenylate cyclase. As a result, an intracellular mediator, cyclic AMP, accumulates and is the immediate cause of the diarrhea, by inhibiting salt absorption and stimulating chloride secretion. Less common causes are hormone-secreting neoplasms such as carcinoid, mast-cell tumors, neural-crest tumors, and bronchogenic carcinoma. One such neoplasm is a tumor of the pancreatic islets, other than the beta cells, that is not a gastrin-secreting tumor. The diarrhea it causes is given the name of pancreatic cholera because of its resemblance to the diarrhea of cholera infection. In fact, the diarrhea from this neoplasm can be more life-threatening than the neoplasm itself.

Recent Advances

Investigators supported by NIADDK attempted to reproduce the diarrhea of the pancreatic cholera syndrome with prolonged (10-hour) intravenous administration of VIP in five healthy, nonfasting volunteers. By 2 hours, the VIP concentration in the blood had risen to levels found in pancreatic cholera, and at times ranging from 2 to 6.3 hours, profuse watery diarrhea developed in all subjects. Losses of sodium and bicarbonate were especially prominent, lowering the blood pH (leaving it more acid), as happens in pancreatic cholera. The investigators concluded that VIP is an important mediator of the watery diarrhea.

Vasoactive intestinal peptide is one of two secretory stimuli known to act directly on the enzyme adenylate cyclase, leading to accumulation of cyclic AMP in intestinal cells. Other secretory stimuli may have cholera-like effects, alone or in combination, by less well-understood mechanisms.

Research Directions

Because uncontrolled profuse diarrhea is a danger to life, preventive and therapeutic measures based on avoiding excess secretory stimulation can have a lifesaving impact. Somatostatin is one therapeutic candidate, in the case of VIP effects, while PG inhibitors such as indomethacin may also be of help under some circumstances. This is an area in which basic research on secretory mechanisms can have immediate clinical application.

Intestinal Mucosa Receptors for Bacteria in Infectious Diarrheas

Prior Findings

Diarrhea from infectious causes still contributes considerably to neonatal and infant morbidity and mortality in much of the world; moreover, acute diarrheal disease is a major cause for sickness and loss of productivity even in Western societies. Chronic diarrheal diseases, often manifested as states of intestinal malabsorption, though less common, are important because of their long-term morbidity in the young.

It has recently become clear that a number of infectious diseases of the GI tract are mediated by attachment of micro-organisms to the intestinal mucosal surface of the host. Examples of such mucosal adherence include specific enteric infections of pigs, calves, rabbits, and humans by enterotoxigenic and enteropathogenic *Escherichia coli* as well as infection of animals and humans by *Vibrio cholerae.* Such attachment or adherence of micro-organisms promotes successful colonization of the GI tract by the invading organism. The attached organisms retain the ability to multiply at the surface while resisting being washed away by secretions produced all along the digestive tract and by the normal peristaltic movements of the intestines. Evidence suggests that in each case mucosal adherence is mediated by a specific binding site-receptor site interaction between surface structures elaborated by bacteria and naturally occurring elements of the host mucosal surface, respectively. Rapid progress has been made in localizing the colonization factor antigens, adhesins, of bacteria to a class of hair-like appendages termed "pili" or "fimbriae." In a number of cases, these structures have been isolated, purified, and characterized immunologically and biochemically. The pili from different organisms are often antigenically distinct. Research on pili may provide the basis for developing vaccines against a number of human and animal intestinal and other diseases. The idea is to elicit production of antibodies against the pili and thus prevent the attachment of bacteria bearing these projections to intestinal cell surfaces. Vaccines consisting of pili are now being tested in human volunteers for immunization against gonorrhea and against *E. coli*-induced diarrhea. In addition, vaccines to protect newborn calves and pigs against diarrheal diseases are already being marketed in Canada and Europe.

Very little progress has been made in defining the specific receptors on the GI surface of the host that mediate adherence. Evidence has been presented that these are genetically determined and age related and that they vary at different levels of the GI tract, thus providing a molecular basis for understanding the levels of colonization, age-related onset of diseases, and resistant and susceptible host

populations. Host receptors might be present in the intestinal mucous gel, a layer of complex glycolipids and glycoproteins covering the epithelial cells of the intestinal lining, or on intrinsic cell membrane glycoproteins or glycolipids.

Recent Advances

It is now well established that a glycolipid, GM_1 ganglioside, is a specific receptor for cholera toxin. The toxin exerts its effect after first binding to the oligosaccharide moiety of this ganglioside on the surface of the intestinal lining cell. The strict specificity of the receptor structure for the binding of cholera toxin is indicated by the fact that when N-acetyl neuraminic acid is removed from or added to GM_1 ganglioside, a substantial reduction in the binding affinity occurs. Recently, evidence has been presented indicating that rat intestinal microvillus membrane glycoproteins may also bind to cholera toxin. However, the relative pathophysiological significance of glycolipid and glycoprotein receptors for cholera toxin has yet to be decided.

It has been known for many years that certain strains of *E. coli* can agglutinate red blood cells and that agglutination can be inhibited by D-mannose. Subsequent investigation revealed that certain strains of *E. coli* have on their surfaces lectin-like molecules, fimbriae, that bind to mannose receptors on epithelial cells. Another strain of *E. coli*, possessing fimbriae that consist of the antigen K-88, produces a severe and often fatal diarrhea in neonatal pigs. This strain of *E. coli* appears to bind via the fimbriae to porcine intestinal cell surface glycoconjugates, particularly those with terminal N-acetyl galactosamine or N-acetyl glucosamine residues in the carbohydrate side chains.

With regard to parasitic diseases, adhesion of trophozoites of *Entamoeba histolytica* to monolayer cultures of human intestinal cell lines has been shown to be mediated by a carbohydrate-binding protein, lectin, present on the trophozoites. The in vitro interaction of amoebae with intestinal cells in this system could be inhibited by either purified amoeba lectin or by analogous plant lectins. A giardiasis lectin responsible for hemagglutination has also been described.

Adhesion for some pathogens may be more complicated than a simple attachment of bacterial pili to receptors on mucosal cells, requiring, in addition, penetration of the mucous gel barrier before they can reach the cells. In the case of the cholera organism, only motile *Vibrio cholerae* bacteria are capable of penetrating the mucous gel. It appears that to be able to penetrate the gel and colonize the intestine, they must also be attracted by and follow the gradient of an as yet unidentified chemical. Bacterial adhesion to epithelial cell surfaces, therefore, represents only the final step of several leading to successful (from the organism's standpoint) association with the mucosa. Consequently, there may be a number of points at which it is possible to interfere with the early stages of infection.

Research Directions

The research on pili and bacterial adhesion has provided some promising new leads for prevention of a wide range of important bacterial diseases. Protection against infectious diarrheas may be possible either by immunization with the bacterial pili or by developing appropriate mucosal surface receptor site analogues to either prevent colonization or dislodge the causative micro-organisms from the intestinal mucosal surface of the host.

A great deal of work needs to be done in defining the mucosal receptors for bacteria, viruses, and protozoa. Questions that need to be answered include: Do these receptors share other important digestive or absorptive functions? At what age do they develop, and what is their distribution in the host? Are bacteria-host cell interactions modified by alteration of the receptors? What is the relationship of binding to the host cell and surface recognition to uptake, invasion of the intestinal epithelium, or destruction of the infecting agents by host defense mechanisms? To what extent do receptor-adhesin reactions determine the composition of the normal intestinal flora? What is the role of mucus in the balance between colonization and clearance, and does the mucus share receptors with the epithelial cells? Will receptor analogue therapy promote clearance of organisms?

Inflammatory Bowel Disease Patients May Lack Natural Killer Lymphocyte Activity

Prior Findings

The major inflammatory bowel diseases (IBD's), ulcerative colitis and Crohn's disease, appear to be associated with abnormalities of the body's immune system. Evidence suggests that, regardless of the primary causative agent or factor in IBD, certain immune processes in the body play a part in the persistence or chronicity of the disease. Among the immunologic disturbances found in patients with Crohn's disease or ulcerative colitis are high levels of antibodies to cells lining the intestine and the apparent cytotoxicity of circulating lymphocytes for these epithelial cells.

Institute-supported studies have shown that the cytotoxicity of circulating lymphocytes to the cells lining the colon is seen only in patients with IBD and is specific to the colon. There is evidence that antigens from bacteria normally in the intestine can stimulate the cytotoxicity, if these antigens cross-react with (are similar to) the antigens of the cells lining the patient's colon.

The search for an explanation of immune system defects such as these in IBD patients plus the increased incidence of colon cancer in IBD led to research on a type of lymphocyte known to have a role in the body's defense against both

tumor growth and viral infections, the NK (natural killer) cell. The NK cell represents a third population of lymphocytes, in addition to B cells, which are important for their antibody production role, and T cells, which are important in tissue immunity. Because NK cells do not require prior exposure to an antigen for their cytotoxic effect, they may be important at the early stages of host defense.

Recent Advances

Confirming an earlier report of decreased NK-cell activity in the peripheral blood of patients with Crohn's disease, investigators also examined the NK-cell activity in ulcerative colitis. Lymphocytes from 31 of 34 patients with either disease showed decreased NK-cell activity, with an average cytotoxicity level 25 percent of normal. Ten other age-matched patients with other inflammatory conditions of the intestine all showed normal levels of NK-cell activity. Interestingly, this deficiency in IBD does not appear to be due to decreased *numbers* of NK cells in the circulation, a finding ascertained by a cell sorting and counting based on the ability of NK cells to bind with nonaggregated antibodies made fluorescent. B cells lack this quality, and it was possible to estimate the NK-cell population using a fluorescence-activated cell sorter.

The impairment of NK-cell function was found to be independent of type of disease (ulcerative colitis or Crohn's disease), disease activity (mild or severe), or previous use of anti-inflammatory corticosteroid drugs in treatment.

Research Directions

Understanding of the mechanism and implications of decreased NK-cell activity in IBD becomes a matter of central importance for the development of new approaches to therapeutic intervention. For example, the defect could be one of precursor cells present in normal numbers not maturing into active NK cells; if so, methods to stimulate cellular maturation might be possible. The mechanism of immunoregulation of NK-cell functions, including the role of the protein substance interferon and of suppressor T cells, is a key research area of concern.

Primary Biliary Cirrhosis: Genetic Abnormalities of Immunoregulation

Prior Findings

Primary biliary cirrhosis is a chronic and often fatal disease of unknown cause with (usually) slowly progressive destruction of the bile ducts inside the liver in the absence of a bacterial or viral infection. The patterns of inflammation and antibody formation suggest that immunologic mechanisms are involved, and indeed, circulating complexes of antibodies with unidentified antigens have been found in 60 percent of patients with the disease. Such complexes correlate significantly with levels of antibodies against a patient's own mitochondria, subcellular organelles that are the sites of cell respiration and energy production and balance, and with the severity of the inflammatory process surrounding the bile ducts.

Genetic factors have also been implicated. The disease has a familial pattern; first-degree relatives have an increased incidence of autoantibodies, and the disease is associated with the presence of certain genes for tissue compatibility antigens, HLA-D alleles.

Recent Advances

It was known experimentally that previously stimulated immunoglobulin G (IgG, or antibody) synthesis can be suppressed by addition of the substance concanavalin A (conA, a lymphocyte-stimulating lectin derived from the Jack bean). ConA acts by stimulating suppressor-type T cells, which then inhibit IgG synthesis.

To investigate possible immunogenetic factors in the development of primary biliary cirrhosis—specifically, whether there is an abnormality of suppressor T-cell function involved—the ability of T cells to suppress IgG synthesis was assessed in several populations. It was found that 13 of 16 patients with the disease and 6 of 23 healthy female relatives had significant impairment of IgG suppression. No abnormal suppression was found in unrelated household contacts of patients, in patients with other types of cirrhosis, or in healthy control subjects. This finding suggests that abnormal suppressor-cell function could be a genetic marker for susceptibility to primary biliary cirrhosis. There was no correlation of this assay test with degree of activity of the disease, which suggests that a T-cell-function disorder is not a direct cause, or at least not a sufficient cause, of the disease.

Research Directions

A longitudinal study is needed to see if healthy relatives of patients with primary biliary cirrhosis who show the same T-cell abnormality as the patients will later develop the disease. The known familial pattern would predict fewer than six cases in 23 relatives, which suggests that some other genetic, hormonal, or environmental factor must also be present to cause the disease. Research is needed to identify what may be a second class of genes that acts to determine the nature of the immunoinflammatory response and the organ involved. Also, because several other autoimmune diseases, such as systemic lupus erythematosus, show similar abnormalities of T-cell function, work is needed on the relationships of these diseases to each other.

Further Experience With Dissolution of Cholesterol Gallstones

Prior Findings

In last year's report, a clinical trial was discussed that tested the effectiveness of three dosages of ursodeoxycholic acid in dissolving cholesterol gallstones, as well as its effects on the liver and elsewhere. Results from this trial were that at a dose between 250 and 1,000 mg a day, the compound is both safe and effective. Overall, 42 of the 53 patients achieved partial dissolution of gallstones, and 27 of these were classified as complete dissolution. The drug was given orally to patients with functioning gallbladders for 6 to 38 months. Most biliary symptoms seemed to disappear within 3 months, and no patient developed diarrhea. There was no evidence of liver damage or other undesirable side effects. Two-thirds of the complete dissolutions took place in the first year and all but one by 2 years. High-dose therapy shortened treatment time for those with small stones, but in general, all dose levels were equally effective. Increased gallstone size and numbers were found to hinder the dissolution process.

This method of treatment, while safe and effective, is not a permanent cure; gallstones can recur. According to one report, as many as 50 percent of patients may have a recurrence within 7.5 years. In addition, there is some evidence that resistance to dissolution therapy may be associated with gallstone calcification and that ursodeoxycholic acid may itself lead to gallstone calcification and resistance to further therapy. For these reasons, it is desirable to have alternative or supplementary therapies available.

The National Cooperative Gallstone Study, supported for the past several years by NIADDK, evaluated dissolution therapy with the related compound, chenodeoxycholic acid (chenodiol). Both compounds are bile acids. Results of that study showed that the drug administered orally at the level of 750 mg/day 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 only 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. Because the group of patients having partial dissolution after 2 years of therapy was larger than the group with confirmed, complete dissolution, it was considered important to determine the frequency with which complete dissolution would occur if these patients received further therapy.

Recent Advances

Of the 138 eligible patients from the study, 61 continued to receive 750 mg/day of chenodiol and 25 continued with 375 mg/day for 1 year. Of these groups, 28 patients at the higher dose and 11 at the lower dose showed further (i.e., more than 50 percent) dissolution at that time. These patients continued with the treatment for 1 final year (or a total of 4 years of the therapy). No evidence was found that the side effects of the drug observed in the first 2 years were more frequent or severe when treatment was continued beyond 2 years. Complete dissolution occurred in 23 percent of those at higher dose and in 16 percent at the lower dose, in the second 2 years. For the full 4 years, the 750 mg dose had dissolved stones completely in one-fifth of the patients. This meant resistance to the drug was still a problem.

Research Directions

Work is needed on factors determining resistance to drug-induced dissolution of gallstones and on possible approaches to the problem of associated calcification of stones. In the case of chenodiol, it is not known whether doses larger than 750 mg a day would prevent resistance.

Work is also needed on factors determining the subsequent formation of gallstones after dissolution of the initial ones and on ways to prevent recurrence by maintenance therapies.

The search for other substances and for alternatives to surgery should continue, in view of the fact that removal of the gallbladder as a treatment for gallstones is associated with the usual risks of abdominal surgery.

Nutrition

Significance of Fat Distribution by Body Region in Obesity

Prior Findings

Obesity is associated with metabolic disturbances such as high levels of insulin and blood lipids, susceptibility to type 2 diabetes, and increased blood pressure. This is true for both sexes, but evidence has accumulated suggesting differences in risk patterns related to the type of body-fat distribution and type of fat cell in the excess adipose tissue.

There exist two basic types of fat distribution in obesity: the abdominal type, typical of males, and the lower-body type, involving primarily the hips, thighs, and buttocks (gynoid), typical of females. Superimposed is the fact that women have more body fat than men at all ages, for the same relative degree of excess weight. The two basic adipose tissue cell patterns in obesity are enlarged fat cells in response to an increased body burden of fat (hypertrophic obesity) and increased number of fat cells (hyperplastic obesity).

Recent Advances

Research investigators supported by the Institute have clarified the relationships of regional fat distribution and cell pattern in obesity and their health implications. The regional distributions of fat typical of each sex were verified. At a similar degree of relative overweight, men are more at risk for metabolic and blood pressure abnormalities—although women with abdominal obesity followed the male pattern of increased risk of these complications. The ratio of waist to hip circumference was the best predictor of the obesity complications examined.

Consistent with these findings, the hypertrophic cell pattern was found more in the abdominal area and was associated with greater risk of complications. The hyperplastic pattern was found more in the lower body, where the adipose tissue cells typically increase in both number and size with increasing obesity, with relatively less dependence on cell enlargement. Nevertheless, in *moderate* expansion of body fat, cell enlargement is the general response, followed later by increase in cell number.

Research Directions

The role of sex hormones in influencing regional deposition of fat and in the metabolic aberrations associated with obesity should be examined, as should the roles of other variables that could explain these findings. It is possible, for example, that direct exposure of the liver (via the portal circulation) to excessive lipid substances from intra-abdominal fat cells could be associated with metabolic abnormalities, although this is unproven and deserves further study. There are regional differences in hormonal sensitivity and metabolic rate of fat cells, which may prove to be correlated with the observed effects.

Purging With Laxatives Does Not Help Weight Control

Prior Findings

Persons who use laxatives for weight control believe that purging causes large losses of calories in their diarrheal stools. This practice is common in bulimia nervosa, in which frequent bouts of binge-eating are coupled with induced vomiting or purging. This can cause depletion of fluid and electrolytes as well as other problems. About 5 percent of college students, usually women, admit to purging.

Recent Advances

The efficacy of purging in reducing caloric absorption was subjected to study. A method was devised to measure calorie absorption during a single day, using a nonabsorbable radioactive marker in a test meal given after the gut was rinsed free of calories. Caloric content of both intake and effluent was measured by bomb calorimetry, the measurement of calories liberated as heat. The marker measured completeness of collection.

It was found that while laxatives containing phenolphthalein and dioctyl sodium sulfosuccinate caused voluminous diarrhea, they decreased intestinal caloric absorption only slightly. These agents appear to act primarily on the colon, causing water excretion and rapid evacuation, and have relatively little effect on the small intestine, the primary site of caloric absorption. The small intestine is highly efficient in absorbing calories, and even a rapid intragastric infusion of saline was unable to induce appreciable caloric loss. In addition, the preliminary wash methods used in the study nullified any contribution that colonic bacteria might have made to breakdown and reabsorption of any leftover carbohydrates in the colon; therefore, the method used may have actually overestimated the effects of purging.

Research Directions

An important followup to this study is the dissemination of its results. Bulimic patients are usually aware they have an eating disorder and are receptive to education and counseling. They need to learn the futility and the life-threatening risks of this pattern of behavior, select other, more desirable and effective methods of control of food intake, or overcome the attraction associated with overvaluation of thinness in our society.

Use of Yogurt in Lactase Deficiency

Prior Findings

Yogurt is popular in many countries and particularly so in the Middle East. In these and other non-European countries, adults tend to have lower levels of the enzyme lactase, which normally allows the body to utilize the lactose, or milk sugar, in dairy products by splitting it into glucose and galactose prior to intestinal absorption of these sugars. These adults seldom drink milk in unmodified form because it can cause abdominal pain, diarrhea, and flatulence. Lactase deficiency can occur as a genetic disease or it may be secondary to intestinal damage with malabsorption, and in these cases severe malnutrition may occur. Because the micro-organisms used in making yogurt, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, have lactase activity of their own involved in the fermentation process, it was of interest to see if the bacterial lactase would allow lactase-deficient individuals to tolerate ingestion of any unfermented lactose left in yogurt without symptoms of diarrhea and flatulence.

Recent Advances

A technique of measuring lactose absorption by the hydrogen gas level in the breath was developed. Undigested and nonabsorbed carbohydrates reaching the colon are acted on by bacteria there to generate hydrogen, some of which is absorbed by the circulation and reaches the breath in amounts proportional to the amount of degraded carbohydrates. This technique showed that the amount of undigested lactose reaching the colon after ingestion of yogurt containing 18 g of lactose was only about one-third the amount that reached the colon after ingestion of milk or a solution containing 18 g of lactose. The enhanced digestion and intestinal absorption of lactose in yogurt was associated with a corresponding decrease in flatulence and diarrhea. Because the lactase activity of the bacteria was shown to survive the passage through the stomach in lactase-deficient individuals, it was assumed that this lactase substituted for the lack of endogenous intestinal lactase and accounted for the improved digestion and absorption of lactose ingested in yogurt. This "auto-digesting" feature of yogurt may explain the popularity of the food in Middle Eastern countries where lactase deficiency in adults is prevalent.

Research Directions

This study offers a model for other carbohydrate intolerance and malabsorption research as well as for the correlation of dietary practices with possible physiological or pathological bases for them.

Specific Effects of the Hormonal Form of Vitamin D in Absorption of Calcium and Magnesium

Prior Findings

The discovery of hydroxylated derivatives of vitamin D has led to new concepts of calcium balance. The liver converts the vitamin to the plasma transport form, 25-hydroxycholecalciferol, and the kidney converts the plasma form to the hormone-like form, 1,25-dihydroxycholecalciferol ($1,25\text{-}(OH)_2D_3$) which acts to express the function of the vitamin. Target tissues responsive to this active form include the intestinal mucosa, bone, kidney, parathyroid gland, pancreas, pituitary gland, and others. These basic discoveries have led to renewed interest in the role of vitamin D in calcium and phosphorus transport and retention in bone and its relationship to bone disease states, including osteodystrophy of renal disease, osteoporosis, hypoparathyroidism, pseudohypoparathyroidism, and vitamin D-resistant rickets. As little as 0.5 *ug* of $1,25\text{-}(OH)_2D_3$ administered daily to postmenopausal women with osteoporosis not only promotes calcium retention, but more important, causes an increase in inner structural bone volume and decreases the bone fracture rate.

The measurement of vitamin D metabolites also is being used in the diagnosis of disease. Thus, low plasma levels of 25-hydroxycholecalciferol may indicate intestinal vitamin D malabsorption, biliary secretion failure, or poor vitamin D nutrition.

The hormonal form of the vitamin is the major hormone controlling calcium absorption, and small doses of it were found by NIADDK grantees to correct abnormalities of calcium absorption such as occurs in chronic renal failure. In basic studies designed to further elucidate the mechanism of action of the metabolically active form of vitamin D, it has been found that a specific calcium-binding protein is synthesized by the intestinal mucosa 30 minutes after addition of the active vitamin D hormone. At least 1 hour is required before active intestinal absorption of calcium takes place.

To make intelligent medical usage of this hormone in the treatment of various disease conditions, it is essential to understand its actions in normal as well as abnormal states. For example, in the condition known as absorptive hypercalciuria, there is excessive absorption of calcium in the jejunum, which is the middle of the small intestine, but not in the ileum, which is the lower segment. Absorption of magnesium is normal. Knowing how $1,25\text{-}(OH)_2D_3$ acts in the intestine would indicate whether it is involved in the pathogenesis of this condition.

Recent Advances

For 1 week, $1,25\text{-}(OH)_2D_3$ was given to 10 healthy volunteers, at a dose of 2 *ug* a day; this provided at least twice the amount synthesized each day by the kidneys. Before and after the week, the intestine was perfused with a solution containing a volume marker and the substance for which absorption was to be measured. An isotope of calcium was used to measure unidirectional fluxes of calcium. It was found that $1,25\text{-}(OH)_2D_3$ significantly increased calcium absorption rates in both the jejunum and ileum, by like amounts, even though the subjects were also receiving an estimated 1,000 mg of calcium a day in their diets (a generous daily allowance). It also increased magnesium absorption in the jejunum but to a much smaller extent in the ileum. This pattern is quite different from that seen in absorptive hypercalciuria and suggests that this condition is independent of $1,25\text{-}(OH)_2D_3$ effects. The changes this substance produced in net movement of calcium were due to an increase in the intestine-to-bloodstream flux, without a change in the reverse direction. Finally, the effects on the intestine of $1,25\text{-}(OH)_2D_3$ were not general ones, because it did not increase intestinal absorption of xylose, a pentose used in a standardized test of intestinal absorption, or of sodium and water.

Research Directions

Separation and a more exact definition of the regulatory and counter-regulatory forces governing absorption of calcium, magnesium, and other minerals is necessary to further understanding of their role in health and disease and should continue.

Zinc in the Treatment of Sickle Cell Disease and Wilson's Disease

Prior Findings

Evidence is strong that adults with sickle cell anemia have a deficiency of zinc and that this is related to some nonhematologic problems associated with the disease such as growth retardation, hypogonadism in men, high blood-ammonia levels, abnormal dark adaptation, and cell-mediated immunity disturbance.

Studies in experimental animals established that a competition exists between zinc absorption and copper absorption in the intestine and that high levels of zinc in the diet induce copper deficiency. When trials of oral zinc for the treatment of sickle cell anemia were undertaken, it was recognized that the treatment regularly induced a copper deficiency. This observation, plus the low toxicity of zinc, led to the trial of oral zinc therapy for Wilson's disease, an inherited disorder of excessive copper absorption and accumulation, especially in the liver, pancreas, and heart muscle, that is fatal if untreated.

Recent Advances

With NIADDK support, investigators developed a reliable and sensitive assay for zinc deficiency—the level of zinc in neutrophils, a type of white blood cell. In teenage and young adult sickle cell disease patients with growth retardation, neutrophil zinc levels correlated significantly with height and weight and with serum testosterone levels in men. Oral zinc supplementation in the men (15 mg, as the acetate, twice a day for a year) produced significantly greater height and weight gain than placebo treatment, bringing treated patients up to expected levels of annual growth.

In a separate study, these same investigators were able to induce net loss or a stable level of copper in all of five patients with Wilson's disease who were receiving no therapy other than zinc every 4 hours. After a variable lag period of a few weeks, the fecal excretion of copper increased significantly. A likely mechanism for this effect appears to be that oral zinc induces formation of a protein in intestinal cells that binds zinc, metallothiorin. Its affinity for copper is even greater than that of zinc, and further absorption and reabsorption of copper is blocked; when these intestinal cells are sloughed, which is a constant process in the intestine, the copper is lost in the stool. These workers recommend maintenance zinc therapy for patients who are intolerant of the standard treatment of Wilson's disease with the drug penicillamine, which may induce toxic side effects, especially if most of the copper from earlier accumulation has been eliminated. Zinc has not yet been tested for possible use in this initial elimination process.

Research Directions

In sickle cell anemia, the incidence and severity of zinc deficiency needs to be ascertained, along with the mechanism of zinc loss (e.g., whether red blood cell sickling interferes with renal tubular reabsorption of zinc or whether there is malabsorption of zinc from the intestine). Dosage levels and individual differences need further study. Trials of zinc in female patients have yet to be carried out. Screening studies for zinc deficiency in sickle cell anemia are needed.

In Wilson's disease, the effectiveness of zinc for removal of accumulated copper needs to be studied further. Dosages and dose intervals, the degree to which concomitant food ingestion blocks availability of zinc, and the implications of higher levels of copper intake than those studied (which were at the normal American dietary levels of about 1 mg/day) for optimal levels of zinc dosage all need evaluation.

Special Programs

Clinical Nutrition Research Units

Research in human nutrition is truly interdisciplinary and complex, being dependent on the close interactions of several basic research disciplines for breakthroughs in fundamental knowledge and on the appropriate medical specialties for rapid integration into clinical studies. In a joint effort with the National Cancer Institute, the NIADDK has fostered the development and operation of clinical nutrition research units (CNRU's) 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 providing an enhanced 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 the NIADDK. These are located at the University of Chicago (Dr. Irwin Rosenberg), University of Wisconsin (Dr. Alfred Harper), Vanderbilt University (Dr. Harry Greene), Medical College of Georgia (Dr. Elaine Feldman), and Columbia University (Dr. Myron Winick).

The CNRU awards have been conspicuous in stimulating progress in multidisciplinary research in clinical nutrition,

enhancing patient care, strengthening training environments, and generating nutrition information for the public. CNRU accomplishments during the past year are given under "Program Accomplishments"; a discussion of plans and forthcoming activities is given under "Program Plans."

National Digestive Diseases Education and Information Clearinghouse (NDDEIC)

As a major information service of the Institute, the NDDEIC 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 subgroup. Another NDDEIC publication, "Letter From the Clearinghouse," discusses current research and the activities of various government and private-sector organizations. The clearinghouse has collaborated with organizations of laymen in distributing the fact sheets, a flyer describing the clearinghouse, a glossary of digestive diseases terms, and a directory of organizations concerned with digestive diseases to their chapters nationwide.

NDDEIC accomplishments of the clearinghouse in fiscal year 1984 are summarized under "Program Accomplishments."

Program Accomplishments

The Division of Digestive Diseases and Nutrition continues to receive large numbers of meritorious applications for research and research training support and has supported research in a broad area.

A modest but important initiative has been implemented in response to last year's RFA for exploratory center grants. These grants prepare awardee institutions to apply for core center grants. Twenty-four applications were received for exploratory grants for digestive diseases core centers. Twenty-three were approved, and eight were funded.

The anticipated digestive diseases core centers program is described under "Program Plans" in this chapter. Two RFA's were issued this year inviting submission of applications under the program. Ten applications have now been received and are under review.

The Division has been guided in its research program for digestive diseases by the long-range plan proposed by the National Commission on Digestive Diseases, by the research report of the National Digestive Diseases Advisory Board, and by ad hoc advisory committees. In nutrition, it has also been guided by advisory committees.

The NDDAB is responsible for updating and implementing the long-range digestive diseases plan. It has identified needs and opportunities for research in the digestive diseases field and the need for a center grants program, an epidemiology and data systems program, and the National Digestive Diseases Information and Education Clearinghouse.

The six subcommittees of the Board continue to update and develop the recommendations and intent of the National Commission on Digestive Diseases as expressed in the commission report of 1977. The Centers Subcommittee addressed needs, issues, and policy related to implementation of a centers grant program in digestive diseases by the NIH. It assisted the NIADDK with the concepts and development of an RFA for exploratory grants.

The Research Subcommittee convened the chairmen of the research committees of professional digestive disease organizations. They identified 14 key areas and then selected 14 experts in GI research to provide leadership in updating the commission's research plan for these areas. A report on digestive diseases research advances and research opportunities was released in the fall of 1983.

The Education Subcommittee developed a national digestive diseases education program. This program includes support from volunteer health agencies, Federal agencies, and the private sector. It achieved support for and completed a survey concerning public knowledge of attitudes toward digestive diseases conducted by Louis Harris and Associates. The program received support from a pharmaceutical firm for the development, production, and distribution of a brochure on digestive diseases.

The Epidemiology Subcommittee completed the consolidation of the *International Classification of Diseases*, ICD 8 and ICD 9, codes for the classification of digestive diseases. The members completed a study of the ICD 9 listings and developed a comprehensive list of digestive disease categories. This represents the first such listing for the field. Using these disease categories, the subcommittee is reviewing Health Care Financing Administration data (1980 MEDPAR file) on a 20-percent sample of discharges of Medicare beneficiaries.

The Patient Care Subcommittee planned and prepared a conference on the application of decision analysis to the problems of digestive diseases. This conference reviewed major elements in decision analysis and applied them to the development of a program for surveillance of individuals with a familial history of cancer of the colon.

Accomplishments of the NDDEIC

Distribution of digestive diseases materials continues primarily through professional and lay organizations. The clearinghouse collaborated with lay digestive diseases organizations for distribution of material to their chapters and members. These clearinghouse education materials included:

- Cirrhosis of the Liver.
- Diarrhea: Infectious and Other Causes.
- Heartburn.
- Gallstone Disease.
- Bleeding in the Digestive Tract.
- Milk Intolerance.
- Constipation.
- Directory of Digestive Diseases Organizations.
- Glossary of Digestive Diseases Terms.
- Notes.
- Letter From the Clearinghouse.

Two new fact sheets were published. These are:

- Facts and Fallacies About Digestive Diseases.
- Dyspepsia.

Other fact sheets under development include:

- Common Digestive Disorders.
- Your Digestive System: How It Works and What It Does.
- What You Should Know About Inflammatory Bowel Disease.
- X-rays and Ultrasound: Diagnostic Techniques for Digestive Diseases.
- Alcohol and Digestion.
- Smoking and Digestion.
- Malabsorption and Maldigestion.
- Irritable Bowel Syndrome.
- What You Should Know About Stomach Ulcers.
- Yellow Baby.

Other notes and publications under development include What Is Hyperacidity?, Research Update: New Drugs for Control of Gastric Acid Hypersecretion, and Peptic Ulcers and Surgery. In cooperation with the National Institute on Aging, two "Age Page" publications are under development: Aging and the Digestive System and Comfort and Your Digestive System.

The *Directory of Digestive Diseases Organizations* was updated, and a bibliography of patient education materials in digestive diseases was produced. Two listings of digestive diseases materials were produced, a listing of Digestive Diseases Patient Education Materials (including a listing of audiovisual materials) and a listing of Digestive Diseases Health Professional Materials.

The plan for designing the Combined Health Information Database with an accompanying thesaurus was developed by seven HHS clearinghouse and information centers, including the NDDEIC. The purpose of the data base is to combine references and full text of short patient education materials from all seven information programs. Users of the data base will have access to information from all seven DHHS clearinghouses. A pilot testing of the data base was carried out with the cooperation of the National Library of Medicine, the National Health Information Clearinghouse, and the Veterans Administration Library. A thesaurus is under development for the digestive diseases clearinghouse. The CHID file has now been placed with a vendor and should be available to the public in 1985.

The clearinghouse participated in the National Digestive Diseases Education Program with the NDDAB's Subcommittee on Education and with the Coalition of Digestive Disease Organizations, an organization of many of the lay and professional digestive diseases societies. The clearinghouse also had exhibits at eight professional meetings and one health fair.

Accomplishments of the CNRU's

Through the CNRU mechanism, the NIH has made great strides toward upgrading the role of clinical nutrition in the participating institutions. The CNRU program has helped to initiate and improve multidisciplinary research projects in clinical nutrition, recruit new investigators to the field, and strengthen training environments.

A report on the evaluation of the CNRU's has been prepared in collaboration with the National Cancer Institute. Emphasis on shared core laboratory facilities has proven especially valuable in increasing the number of multidisciplinary studies. An average of 23 new clinical research protocols, ranging from 7 to 40, are now active at each CNRU. Studies include the role of nutrition in diabetes, cystic fibrosis, digestive diseases, renal disease, cardiovascular disease, and cancer and care of seriously ill patients as well as growth, aging, and metabolism. Improvements also have resulted in the coordination and delivery of nutrition-related patient care and in communication of nutrition research advances to professionals and to the public. Education of medical staffs in clinical nutrition also has been strengthened as a result of the CNRU's.

The New Investigator Awards, supported temporarily with CNRU funds, are expected to yield a meaningful number of well-trained clinical research scientists in the near future.

The fourth annual meeting of the CNRU directors was held January 9 and 10, 1984, in New York. The meeting provided a forum to exchange information and pursue opportunities for institutional collaboration in the areas of nutrition-related laboratory methodology, educational activities, and clinical research.

Workshops

Workshops provide an opportunity for recognized experts in a specific field to conduct an intensive examination of progress in that field and of needs for further research. Recommendations for program emphases and directions are the major end products of this process. Conferences organized or conducted by the NIADDK staff are an expression of program commitments and of collaborative efforts with other groups. During the year, the Division was involved in the following activities:

- Conducted a workshop on Mechanisms of Hepatocellular Injury, as a satellite meeting to the American Association for the Study of Liver Diseases. The meeting was held in Chicago, Illinois, November 4, 1983.
- Organized and presented an orientation session on NIH Digestive Diseases Programs and Mechanisms for Support of Research and Training in St. Louis, Missouri, April 5, 1984.
- Conducted a workshop titled Is the Marmoset an Experimental Model for the Study of Gastrointestinal Disease? The meeting was held at Oak Ridge, Tennessee, April 18-20, 1984.
- Conducted a tutorial program on the use of chronobiologic methods in digestive diseases research, at Digestive Diseases Week in New Orleans, May 22, 1984.
- Conducted a poster session on NIH programs and grant support mechanisms at Digestive Diseases Week, New Orleans, May 22, 1984.
- Conducted a workshop on Structured Lipids and Their Use in Clinical Nutrition, September 1984.

U.S.-Japan Malnutrition Panels

The NIADDK has continued to administer the U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Science Program. The research fostered under the U.S.-Japan Malnutrition Program is targeted primarily at those problems and solutions that most benefit the undernourished of Asia. The most common states of undernutrition are protein-energy malnutrition and iron and vitamin A deficiencies. Superimposed are various disease states, particularly diarrheal infections in the young, which cause impaired utilization and loss of nutrients, and loss of fluids and electrolytes, which constitute the primary cause of death of children under 5 years of age. Iron deficiency, which is widespread, is believed to interfere with immune response, cause lowered resistance to infection, reduce the functional physical capabilities, and possibly impair mental and learning processes. Vitamin A deficiency in turn causes many cases of damaged vision and total blindness in young children each year.

The annual joint meeting of the U.S.-Japanese Malnutrition Panels was held February 27, 1984, in Bethesda, Maryland. Following the meeting, a well-attended 2-day workshop was held on Vitamin A and Cancer Prevention, which was sponsored by the U.S.-Japan Malnutrition Panels in association with the NIADDK and the National Cancer Institute. The meeting focused on epidemiologic and clinical studies related to vitamin A and its possible role in cancer risk. The amount of interest shown and the discussion on the subjects presented supported the impression that the workshop served a useful purpose of bringing together and stimulating exchange among people from the more basic sciences and epidemiological and clinical researchers. The presentations will be published as a journal supplement and will be made available upon request.

The next joint meeting will be held in Japan in early December 1984; the workshop will address calcium metabolism and aging.

Further Encouragement of Specific Areas of Research

The next group of items represents actions on the part of the programs of the Division of Digestive Diseases and Nutrition to encourage research in specific areas. These actions were in the form of program announcements—broadly disseminated notices to the biomedical research community concerning particular areas of research that an NIADDK program would like to stimulate and in which it stands ready to receive research grant applications. For a discussion of the programs intended under these announcements, please see "Program Plans."

Program Announcement: Stimulation of Research in Liver Transplantation

Investigators currently involved with liver transplantation, having access to liver transplantation patients or material, and groups working on problems in general transplant immunology and pharmacology who could apply their expertise to problems of the liver are encouraged to submit applications under this announcement. Potential benefits of this approach are discussed in "Program Plans." A separate RFA was issued in 1984 to encourage methodology development. Four other NIH Institutes participated in this announcement.

Program Announcement: Stimulation of Research on Anorectal Disorders

Other than research on neoplasms and to a lesser extent on infectious diseases, there is little NIH research support in anorectal disorders. A program announcement has been issued, cosponsored by the National Institute on Aging, to stimulate applications for research support in this area.

Program Announcement on Obesity

The multi-Institute program announcement entitled Studies on Overnutrition and Obesity was published in the very widely disseminated *NIH Guide for Grants and Contracts*, March 30, 1984. This was done collaboratively with nine other Institutes through the NIH Nutrition Coordinating Committee. The director of the Nutrition Program helped to lead this effort.

Other Program Announcement Actions

- A request for research applications concerning the preservation of the donor liver and assessment of function was issued on March 2, 1984, with a receipt date of July 16, 1984, and earliest funding on April 1, 1985.
- A request for proposals for a liver transplant data base, to be awarded as a contract, was issued on February 7, 1984, with a receipt date of April 30, 1984, and earliest award in November 1984.
- A program announcement, through the Digestive Diseases Interagency Coordinating Committee, on research opportunities in digestive diseases was made in the *NIH Guide for Grants and Contracts*, August 1984.
- Initiative planning was begun on biobehavioral research on functional disorders of the digestive tract, in collaboration with the National Institute of Mental Health. The initiative will be an RFA funded by a special appropriation.
- The announcement for core grants for clinical nutrition research units, published in 1979, has been updated and revised and was issued in August 1984, as a combined effort of the National Cancer Institute, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, and the National Institute on Aging.

Publication on Recommended Daily Dietary Allowances

A 2-year completion contract with the Food and Nutrition Board, National Academy of Sciences, is being renewed. This contract, initiated December 15, 1979, is entitled Preparation of the Tenth Edition of Recommended Dietary Allowances and Related Studies. The revised recommended dietary allowances (RDA's) are to be completed in 1985. Guidelines for the use of the RDA's are to be prepared for publication at the same time. These activities are proceeding on schedule. The committee on dietary allowances and its subcommittee on uses of the RDA's have held several working meetings using the committee-study and miniworkshop approach. A revised draft report has been prepared on guidelines for uses of the RDA's.

Conferences

Conferences on research and clinical developments and advances in biomedicine facilitate the immediate exchange of information among those working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions. It is the fastest and most effective type of cross-fertilization process in biomedical research.

Among conferences organized or sponsored by the Division in fiscal year 1984 were:

- Liver Transplant Data Systems, NIH, Bethesda, Maryland, November 1983.
- Conference on Physical Chemistry of Bile in Health and Disease, held at the Kroc Ranch, Santa Ynez, California, on December 5-9, 1983. Cosponsored by NIADDK and the Kroc Foundation.
- U.S.-Japan Science Program on Vitamin A and Cancer Prevention, NIH, Bethesda, Maryland, February 17-19, 1984.
- 1984 International Symposium on Viral Hepatitis, San Francisco, California, March 8-10, 1984.
- The Marmoset: An Experimental Animal for the Study of Gastrointestinal Diseases, Oak Ridge, Tennessee, April 1, 1984.
- FASEB (Federation of American Societies for Experimental Biology) Research Conference on Vitamin A and Retinoids, Saxtons River, Vermont, June 17-25, 1984.
- Workshop on Intestinal Immunity and Inflammation, Fort Lauderdale, Florida, October 8-10, 1984.

Program Plans

Stimulation of Multidisciplinary Basic and Clinical Research in Digestive Diseases Through Initiation of a Digestive Diseases Centers Program

Many of the research areas in the various digestive diseases require a coordinated, multidisciplinary approach that can best be fostered within a research center environment. Digestive diseases research centers are being planned to be based at institutions with demonstrated research excellence. A nucleus of funded investigators will coordinate and expand their efforts via a core center grant. Each center should conduct both basic and clinical research and should bring current basic science knowledge and techniques to bear upon clinically relevant digestive diseases. There will be solicitations for all areas considered to fall within digestive diseases, but some areas especially in need of a center are diarrheal diseases, pancreatitis, functional bowel disease, and chronic liver diseases. 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 the cooperative participation of practitioners and their patients from other specialties appropriate to the digestive disease under study.

The centers approach also offers a model environment for the training of specialists in the study of digestive diseases. There are currently two centers for liver disease and one for ulcer disease.

Two other objectives of this program are to foster development of research resources and to provide central coordination of multiunit clinical studies. Justifications for two examples of core centers, one for chronic liver diseases and one for functional bowel disease, are given below.

Chronic Liver Diseases

Although during the past decade there have been outstanding advances in understanding the liver and its diseases and disorders, tremendous opportunities for research lie ahead due to the development of sophisticated new approaches in molecular biology, immunology, cell culture techniques, and diagnostic and surgical procedures. For example, sensitive techniques for detecting picogram quantities of viral material in the blood offer superior methods for preventing blood-borne hepatitis B infection. Finding viral DNA sequences integrated into host liver-cell DNA has provided a clue as to how chronic liver disease may progress to liver cancer. New and improved techniques and new immunosuppressants that selectively repress certain T cells from responding to foreign antigens have enabled liver transplantation to become a viable option for selected patients with end-stage liver disease. Noninvasive radiological techniques of increasing specificity such as ultrasonography and computerized tomography (CT) scanning and skinny-needle aspirations guided by the above techniques are allowing noninvasive diagnosis of focal liver diseases such as cystic masses, abcesses, and tumors. Development of a mixed collagen matrix has enabled researchers to establish colonies of liver cells that are viable for 4 to 6 months and permit the study of specialized receptors on liver cells, transport processes, and bile secretion.

Diseases such as primary biliary cirrhosis and chronic active hepatitis are among the most difficult to diagnose and manage. Recent advances, however, have made possible earlier and more accurate diagnosis and have highlighted numerous opportunities in the study of the etiology and natural history of these diseases. The implications both in the United States and worldwide are enormous. To maximize research progress in the above diseases, expertise in the areas mentioned above and other areas is needed. Several affiliated hospitals or several medical centers may need to work together to obtain sufficient patients for intensive study. These patients can then be the focus for multiple studies, each study approaching the disease from a different research interest. For example, the osteoporosis of primary biliary cirrhosis, the heterogeneity of the natural history of primary biliary cirrhosis, and the sequence of viral integration into the genomic material of liver cells in chronic hepatitis B are areas of interest that will involve orthopedists, nutritionists, epidemiologists, and molecular biologists and virologists. Trials of new modalities of treatment may be more readily and inexpensively supported with the involvement of biostatisticians, pharmacologists, and clinical hepatologists. With a focused multidisciplinary attack on these chronic liver diseases, progress in these complex areas can be enhanced.

Functional Bowel Disease*

There is much scientific and clinical interest and concern about functional bowel disease (also known as irritable bowel syndrome). Functional diseases are among the most common diseases seen in gastroenterology and account for a high percentage of office visits in internal medicine.† The need for additional studies is demonstrated further by the fact that the American Gastroenterology Association established a Council on Nerve-Gut Interactions. This council, under the direction of Dr. Thomas Almy, has sought to bring together clinicians and basic scientists to discuss ways of categorizing and treating functional diseases. It has been pointed out that some progress has been made in controlling these diseases by biofeedback techniques.

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* Functional diseases of the digestive tract are the symptom complexes, referred to the upper or lower GI tract, affecting patients in whom other diagnoses have been excluded.

† Source: Report of the National Commission on Digestive Diseases.

Over the last several years, the functional diseases have been singled out by the Division of Digestive Diseases and Nutrition as an area of scientific and clinical importance. In October 1979, a workshop on functional disorders of the GI tract was cosponsored by NIADDK and the National Institute of Mental Health. It was clear from that workshop that further intensive study of behavior and the physiology and biochemistry of the brain-gut axis is critical for the understanding of this symptom complex.

Although in the past there has not been an animal model for the investigation of functional diseases, there is increasing anecdotal evidence that such a model may be available in tamarins or marmosets. It appears that these animals and some other primates are very susceptible to novel behavioral stimuli that produce almost immediate GI reactions.

It is clear that conventional approaches to research where an investigator pursues a single focused line of investigation will not be as productive as an integrative approach to the complex problem of functional disorders. Expertise from physiology, biochemistry, pharmacology, psychology, and internal medicine will be necessary to make significant inroads into this problem. For this reason, the center mechanism appears to be the most cost-effective approach to study of the functional bowel disorders.

Need for Multidisciplinary Research on Enterotoxin and Microbial Adherence in Infectious Diarrheas

It has recently become clear that a number of infectious diseases of the GI tract are mediated by attachment of micro-organisms to the intestinal mucosal surface of the host. Evidence suggests that in each case mucosal adherence is mediated by a specific binding site-receptor site interaction between surface structures elaborated by bacteria and naturally occurring elements of the host mucosal surface. Rapid progress has been made in localizing the adhesions of bacteria to pili or fimbriae. In contrast, very little progress has been made in defining the specific receptors on the intestinal surface of the host that mediate adherence. The best molecular candidates for the host receptors for pili are the carbohydrate portions of mucosal glycolipids or glycoproteins, molecules present in the apical epithelial cell membranes but also abundant in the intestinal mucous gel. Support of multidisciplinary research on the structure, specificity, and role in enterotoxin and microbial binding of the carbohydrate and other potential recognition systems of the host receptor sites is proposed. These studies would very likely serve as a basis for developing a rationale for therapeutic intervention in diarrheas from infectious causes. Thus, protection against these diseases may be possible by developing appropriate mucosal surface-receptor site analogues to either prevent colonization or dislodge the causative micro-organisms from the intestinal mucosal surface of the host.

Need for Multidisciplinary Research on Pathogenesis of Human Pancreatitis

Pancreatitis is a general term that designates a group of diseases in which the basic lesions are injury of acinar cells and inflammation of the pancreas. Although we know a number of clinical settings that are associated with pancreatitis and a number of conditions thought to cause it, we know almost nothing about its pathogenesis. Of prime importance to pancreatic disease research is development of new knowledge about the basic mechanisms of inflammation. Biopsy of the pancreas has long been regarded as a dangerous procedure. The ability to obtain percutaneous or transduodenal biopsy samples of the pancreas would allow techniques from various disciplines to be applied to the analysis and characterization of the changes in the pancreas that accompany the onset and propagation of the various disease states. A large number of animal models of pancreatitis have been reported; however, the utility of information derived from studies of the animal models has been limited by our ignorance of the extent to which the disease process in animals resembles human pancreatitis. Better understanding of the pathogenesis of human pancreatitis should facilitate development of meaningful animals models. Other systems with potential for being used to establish models of human pancreatic diseases include pancreatic tissue maintained in tissue or organ culture. Support of multidisciplinary research focusing on the development of techniques to obtain pancreatic tissue from patients with pancreatitis, the elucidation of the pathogenesis of the various types of human pancreatitis, and the development of meaningful experimental models of the various diseases constituting human pancreatitis are proposed.

Data Base for Research on Liver Transplant Patients

No single liver transplant center is able to accumulate sufficient data on certain important questions that need to be answered about liver transplantation, such as the selection of patients for surgery and the effects of liver transplantation on patients with specific liver diseases. The collation of relevant data, after common definitions, criteria, and procedures for gathering data are agreed upon by the participating treatment centers, can provide the necessary quantity of data to answer some crucial questions.

Some of the questions that such a data base may answer are: What are the role and the optimal regimen of immunosuppressive agents, and what are their effects in the short term and in the long term, particularly on renal and hepatic function and development of infections and neoplasms? What are the factors in the liver donor that are useful in predicting the immediate postoperative function of the liver in the recipient, i.e., cause of death, clotting factors, cardiovascular stability, or hypoxemia? What is the

time threshold for the preservation of the donor liver? Is the surgeon's assessment of the donor liver, based on such factors as color, consistency, fatty changes, and gross morphology, a valid predictor of liver function? At what point in the history of a specific liver disease should the decision be made to perform a liver transplant? What are the effects of a venovenous bypass of the splanchnic and vena caval circulations during implantation of the new liver as an alternative to the occlusion of these circulations?

Many other questions concerning the donor, the preservation, the operation, the short-term postoperative period, and the long-term postoperative period will be addressed by data collected from the participating liver transplant groups.

No arrangement exists that will allow the pooling of data to answer such questions as those described above. At the Consensus Conference on Liver Transplantation held in June 1983, an attempt was made to collate the medical and surgical data that were available in published reports and from solicited unpublished data. It became quite obvious that it was extremely hazardous to pool such data because of the lack of common definitions, criteria, and manner of reporting. Consequently, the consensus panel recommended that "a registry or clearinghouse be established for collection and evaluation of all available data on liver transplantation. Such a center would develop unified criteria for selection of patients for transplantation and for reporting and evaluating all data related to the outcome of the operation and the patients' postoperative and long-term condition."

In addition to informal consultations with many individuals directing data systems in other disease areas, two formal meetings with expert consultants were also held to obtain advice on the general concepts involved and on more specific questions that could reasonably be asked of such a data system. The first meeting was an Advisory Meeting on Data Systems held at the NIH on September 28, 1983. The second meeting was a Peer Level Concept Review of a Data System for Liver Transplantation held at the NIH on December 7-8, 1983.

These meetings provided the necessary background for the data base development program, to be funded by contract. The data base will attempt to answer research questions by the use of collated data from all patients before, during, and after they have been evaluated for and received a liver transplantation.

Encouragement of Research on Preservation of the Donor Liver and Assessment of Function

An effort is being made to encourage investigators with interest and expertise in the area of organ preservation and assessment to submit research grant applications in the area of liver research on methods of assessing and prolonging organ viability and the effect of graded donor-liver viability on the recipient success rate.

The number of institutions now performing liver transplantation and the number of liver transplants being performed is increasing. The need for donor livers may prove to be a limiting factor in transplantation, especially the need for livers for children. Improved methods of preserving donor livers and of assessing the adequacy of their function before transplantation could make a major difference in the number of livers available for necessary transplants. Many liver donors are individuals involved in automobile accidents who sustained closed head injuries and who have been maintained on respirators. Frequently they have had a period of low blood oxygen (hypoxemia) or low blood pressure (hypotension) at the time of their injury or during some point in their resuscitation. The effect of a short period of hypoxemia and hypotension on donor liver tissue is unknown. More than 4 hours of hypoxemia causes massive and irreversible liver damage. As a consequence, such organs cannot be used.

Currently, the liver from the donor is flushed with physiological solutions and put on ice for preservation and transportation. This preservation is effective for 8 to 10 hours without apparent harm to the liver and facilitates using organs from one part of the country for suitable recipients in another part of the country.

Stimulation of Research on Liver Transplantation

Much basic information about the control of liver function is still unknown. The availability of increasing numbers of patients at university health centers where multidisciplinary investigators can study these patients will provide a major resource. Because the donor liver will carry its own genetically determined processing information and the host organs will carry another set of determinants, the stage is set to explore what governs various synthesis, secretion, and detoxification processes.

In the last 4 years, the clinical results have improved significantly for the short-term survival of liver transplants. The introduction of cyclosporine as an immunosuppressant in transplantation has been one positive factor. In addition, many technical improvements in the surgical procedure itself have been instituted such as various modifications in reconstructing the biliary tract, including use of the gallbladder as a conduit, making bile leakage uncommon, and bypassing parts of the circulation without anticoagulant. From 1963 to 1983, Dr. Thomas Starzl was performing the vast majority of liver transplants in the United States. He has been supported by the NIADDK for these 20 years. Now, new transplant centers are starting up at a surprising rate. Among those that have been active for about 1 year are the University of Minnesota (Drs. Ascher and Najarian) and the University of Tennessee (Drs. Britt and Williams).

In addition, newer centers are Yale (Dr. Flye), the University of California, San Diego (Dr. Orloff), the University of California, Davis (Drs. Ward and Blaisdell), and Massachusetts General Hospital (Dr. Malt). Those actively considering starting liver transplant centers are the Mayo Clinic; University of Wisconsin; Virginia Commonwealth University; Deaconess Hospital, Boston; University of Nebraska; Good Samaritan Hospital, Phoenix; and Marquette University, Milwaukee.

After the consensus conference held in June 1983 on the subject of liver transplantation, a group of experts met and recommended several research areas that should be pursued. The program announcement on research on liver transplantation was partly the result of those recommendations and should stimulate investigators to utilize the increasing number of patients with liver transplants to study important problems in metabolic liver diseases as well as basic problems such as pathogenesis of disease, technical aspects of liver transplantation, research use of resected diseased liver, immunology of liver rejection, monoclonal antibody and liver transplant survival, immunology of liver rejection in cancer patients, effect of immunosuppression in the cancer patient, immune response to hepatic tumors, pharmacology of immunosuppressant drugs, and development, regeneration, and nutrition.

Encouragement of Research on the Nerve-Gut Axis and Functional Bowel Disease

Observations by a number of investigators in this century support the hypothesis that the GI tract is directly influenced by neurohumoral and neural factors, even though a significant amount of autoregulation is possible in the gut. Studies on behavior conditioning and investigations using stereotaxic procedures have identified neural circuitry in mammalian forebrain structures that appear to respond to external events. These investigations have suggested anatomical sites that may serve as a focus for GI disturbances that accompany emotional reactions.

There is reason to hypothesize that short-term GI disturbances, which produce troublesome symptoms, may be related to psychosocial events. The data for long-term or chronic disorders such as IBD or duodenal ulcer being the result of psychosocial pressures are more equivocal. Anecdotal and descriptive evidence, however, suggest a link between these diseases and psychosocial factors.

This program announcement will try to stimulate investigators to work in this subject area, to generate new knowledge about the complex interaction among patients' psychosocial problems, the nervous system, and the digestive tract.

Stimulation of Research on Anorectal Disorders

Anorectal diseases and disorders represent a major national problem in terms of morbidity. Those represented in this initiative include hemorrhoids, fissures, fistulas, proctitis, rectal prolapse, constipation (in part), and fecal incontinence. In contrast to the national significance of anorectal health problems, this field has always been markedly underrepresented in medical school training of physicians and in NIH research and research training support.

For treatment of hemorrhoids alone, there are over 2.5 million patient-physician visits each year, resulting in about 240,000 hemorrhoidectomies requiring hospitalization.* Current data on hemorrhoids, as on other anorectal disorders, are not available. The prevalence in 1972 of hemorrhoids in the United States was about 10 million, and the annual incidence was about 1 million.* These figures have probably continued upward with the proportional increase in the adult (and aged adult) population.

Epidemiologic data on anorectal diseases and disorders are limited. Diagnostic criteria are often inadequate. For example, problems attributed to hemorrhoids are frequently not due to hemorrhoids. A tendency for the public to attribute all anal problems to hemorrhoids leads to a likelihood of postponing needed evaluation. Overall, there is a marked ignorance of anorectal disorders on the part of the public.

Encouragement of Research on Obesity

The emphasis of this program announcement was on the support of research on the biomedical and behavioral aspects of exogenous obesity. The goal of this research, which includes both basic and clinical research, is to establish a clear understanding of the etiology, prevention, and treatment of this multifaceted condition. Obesity is either a risk factor for or is associated with a number of diseases, including diabetes, hypertension, coronary heart disease, complications of pregnancy, osteoarthritis, and some cancers and infections. Obesity may also be an adverse prognostic factor in certain diseases such as early-stage breast cancer and cancer of the endometrium.

Research on Oral and Parenteral Nutritional Requirements

This initiative will try to encourage research growing out of the long-term application of total parenteral nutrition (TPN—the feeding of a patient with an impaired GI system through infusion of sterile solutions of the needed nutrients by vein) with the goals of observing the effects of nutrients on the body's endocrine-metabolic system,

* American College of Surgeons.

observing the state of nutrition when nutrients bypass the GI tract and enter the systemic circulation without first passing through the liver from the portal circulation, and obtaining, where possible, more complete information about human dietary requirements and safe levels of nutrients. In addition, it will encourage the adoption of a standardized data collection system for monitoring outcome and metabolic consequences of TPN.

Special needs for nutrients arise from such problems as inherited metabolic disorders, chronic diseases, and infections. Little is known about the effects of stress, drug use, toxicants, nutrient imbalance, activity level, food consumption patterns, disease states, and other environmental and host factors on nutrient requirements and interaction in humans.

At present, approximately 1,000 individuals of various ages are being maintained on long-term TPN, and the number is doubling each year. The nutritional needs of most of these individuals must be met entirely by the TPN mixtures used. It is critically important for these patients that the levels and proportions of biochemical substances needed for normal cell functions is known, so they can be provided. Individuals who are entirely dependent on TPN mixtures for long-term sustenance offer a unique opportunity to determine quantitative and qualitative aspects of requirements of humans for nutrients.

The research to be supported under this program should obtain more complete information about human dietary requirements and safe levels for nutrients and factors that influence these requirements. An immediate research goal is to determine the range of safe levels for those nutrients that are most likely to be provided in inadequate or toxic amounts or that may be affected by drugs or nutrient imbalances. Nutrients of particular concern are the trace minerals, certain vitamins, and essential amino acids. Advantage will be taken of the unique opportunities offered by long-term TPN in determining nutritional requirements. Opportunities for comparative integrative physiological studies relating to the function of GI hormones, lipoprotein metabolism, glucose homeostasis, and effects of recycling of nutrients (e.g., trace minerals) exist. Other current concerns for TPN include the interaction of nutrients (especially the type of lipid administered: saturated versus unsaturated, short- versus long-chain) on the immune system and levels of potentially toxic substances such as aluminum and nickel that may be present in TPN solutions at unknown levels.

Expansion of the CNRU Program

Research is needed to develop improved methods of nutritional status assessment and more complete information about the nutritional needs of patients.

The CNRU's are upgrading the role of clinical nutrition in the institutions involved. This program strengthens the perception by clinicians of the vital role of clinical nutrition in medicine, stimulates appreciably the development of multidisciplinary research and research training in clinical nutrition, and materially improves the nutritional support of hospital patients. The Nutrition Program plans to expand the number of CNRU's.

V. Research Focus—Kidney, Urologic, and Hematologic Diseases

NIADDK-supported hematologic research has led to improved techniques for diagnosing hereditary anemias such as Cooley's anemia and sickle cell disease.

Facing page

New techniques are improving the ability of artificial kidneys to remove poisonous wastes from the blood.

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. Continual assessment of the programs of the Division is based on liaison with the extramural scientists, including ad hoc advisory committees. This process allows the Division to direct support to important new areas of research that are most responsive to the needs of the research community and, ultimately, to patients with kidney, urinary tract, and hematologic diseases.

The kidneys are vital organs critical to the maintenance of the body's internal environment, particularly the composition, volume, and pressure of the body fluids. The Renal Physiology/Pathophysiology Program continues to support research on the structure and function of the kidney, including metabolic studies and transport and fluid-electrolyte dynamics; diseases and mechanisms leading to chronic renal disease such as immunologically mediated glomerular and systemic diseases, including glomerulonephritis and interstitial and lupus nephritis; polycystic kidney disease; and effects of drugs, nephrotoxins, and environmental toxins on the kidney. In past years, such research has increased our knowledge of renal metabolism and the causes of renal disease and has resulted in the development of several lifesaving 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 advanced sufficiently. The condition affects more than 10 of every 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 to 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. For example, hemodialysis, the 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.

The Chronic Renal Disease Program supports research in both fundamental and clinical investigation of disease mechanisms responsible for ESRD, its complications, and all aspects of its treatment. There are three main subdivisions of the program: pathophysiology of chronic renal failure, renal transplantation, and maintenance therapies of ESRD.

Inseparable from the function of the kidneys is the function of the lower urinary tract, the primary concern of the Urology/Urolithiasis Program. Urinary tract infection,

* National Kidney Foundation.

neuromuscular disorders of bladder function, obstruction, and urolithiasis, or kidney stone disease, account for about 20 percent of deaths from kidney disease. Together, these interrelated conditions account for a major portion of all disability caused by disorders of the urinary tract and affect an estimated 8 million people in the United States each year.

The program also supports research and training on benign prostatic hyperplasia, vesicoureteral and intrarenal reflux, and sundry conditions such as Peyronie's disease, impotence, congenital anomalies of the lower urinary tract, and others. To provide insight into the causes and development of these multiple diseases, the NIADDK supports 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 have been developed that permit effective treatment of serious infections and prevent recurrence of certain types of kidney stones, and advances in urologic surgery have led to the ability to repair congenital anomalies and surgically reconstruct diseased organs.

The NIADDK supports hematologic research as a part of its mission to eliminate the threat of the chronic diseases that cause suffering, disability, and early death. Many of these chronic diseases exhibit manifestations that include anemia, caused by impaired or abnormal red blood cell production or by inherited defects in red blood cell components. Anemias of chronic disease rank high among the clinical disorders that threaten life or diminish the quality of life. The anemia of chronic renal disease occurs in most of the chronic renal disease patients treated annually in the United States. Anemia is commonplace in patients with endocrine disorders, the collagen diseases, rheumatoid arthritis, ulcerative colitis and other digestive diseases, liver disorders, and a variety of inflammatory syndromes. These anemias, all of which are acquired secondary to chronic diseases, fall within the NIADDK responsibility because of the NIADDK mission related to hematology, renal disease, endocrine disorders, arthritis, and digestive and liver diseases.

Basic and clinical research of particular interest includes anemias of genetic origin, nutritional anemias, metabolic disorders, disorders of blood cell production, and autoimmune hematologic disease. Research studies in these categories, 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 red blood cells to act as oxygen carriers, to clinical application and evaluation of new treatment methods of certain hematologic disorders 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.

Congenital or hereditary anemias generally result from some specific fixed disorder in body chemistry and metabolism or molecular design. Research support for hereditary anemias has led to a nearly complete analysis of normal and certain abnormal human hemoglobin gene sequences and to safer and more accurate techniques for prenatal diagnosis of sickle cell disease and Cooley's anemia. Basic work on the hemoglobin molecule has been instrumental in establishing concepts in molecular disease, and today hemoglobin and hemoglobin diseases represent models for research progress in other genetic diseases.

Highlights of Research Advances

The following section briefly highlights a number of areas in which the Division of Kidney, Urologic, and Hematologic Diseases has reported recent progress in its research program:

- Encouraging long-term results have been obtained with kidney transplants in diabetic patients who had intractable kidney disease. Complications due to diabetic changes in the transplanted kidney were few, and long-term rehabilitation now appears possible.
- The molecular nature of defects in specific kidney diseases is beginning to be understood in terms of abnormalities in molecular size and charge. Congenital nephrosis may result from failure of development of negatively charged sites in the kidney filtration membranes.
- The pathologic changes in the mesangial region surrounding the renal filtration apparatus, glomeruli, have been identified in an experimental animal model of diabetic kidney disease. These changes help explain a diverse group of human glomerular diseases.
- Recurrence of kidney stone formation from calcium deposition has been prevented effectively, virtually eliminating the need for surgical intervention in such cases, with use of potassium citrate, taken orally in a coated, slow-release form.
- Changes in cell biochemistry associated with prostate gland enlargement of advanced age, benign prostatic hypertrophy, have been identified. Cell nuclei in the nonglandular component, stroma, have increased amounts of the cell receptor for the androgenic hormone dihydrotestosterone, which stimulates excessive prostatic tissue growth. Normally, this hormone is converted to an inactive form by enzyme action. An experimental drug inhibiting formation of the hormone shows promise.
- Prenatal diagnosis of hereditary anemias like sickle cell disease and Cooley's anemia and other genetic disorders is now possible more safely and rapidly, using methods of direct analysis of the DNA fragments ob-

tained from amniotic cells or placental tissue rather than by sampling fetal blood.

- Experimental treatment successes in hereditary anemias, by stimulating the formation of nondefective *fetal*-type hemoglobin, have been possible with several drugs from a class of compounds that inhibit cell division in a specific manner. One of these, hydroxyurea, is less toxic than most and will undergo clinical trial.
- Inheritance of the iron storage disease hemochromatosis has been shown to be linked to histocompatibility antigens possibly coded by genes on chromosome 6 and to require a genetic determinant from both parents. Earlier recognition of individuals at risk and effective early intervention should now be possible by combining genetic techniques with measurement of stored iron.
- A simple and reliable test for mild iron deficiency has been developed, based on the more rapid and greater intestinal uptake of low doses of oral iron seen in mild iron deficiency. The test avoids the need for radioisotopes and can be applied widely.

Kidney Diseases

Long-Term Success of Kidney Transplants in Diabetes

Prior Findings

Severe and intractable kidney disease in diabetic patients is known as end-stage diabetic nephropathy. Correction of this eventually fatal complication has been possible with kidney transplants, although the diabetic recipients of these transplants very often show microscopic signs of the old disease in the new kidney when biopsied 4 years later. Such findings have raised the question of whether the new kidney inevitably develops the diabetic nephropathy that afflicted the old one and whether long-term survival of the graft and the patient is thus compromised.

Recent Advances

A study of 26 IDDM patients in end-stage renal failure who received kidney transplants 10 to 14 years earlier, funded by the Institute, showed that while all of the kidney transplants showed microscopic evidence of diabetic nephropathy, only two showed deterioration of function from this cause. Three kidneys that failed after 10 years all had features of chronic graft rejection (immunologic incompatibility). As expected, patients who received a graft from an immunologically identical donor, a sibling with the same HLA tissue type, did better (43 percent survival) at 10 years after transplant than those with nonidentical but related living donors (38 percent survival), and those in turn did better than recipients of kidneys from unrelated cadaver donors. Many of the complications occurring in the 26 patients were not necessarily related to diabetes and are seen to the same extent in nondiabetic recipients of renal transplants. Blindness as a complication was due to diabetes, but most such patients were already blind before transplantation. It appears that progression of diabetic complications to the point of disability is not inevitable, and it is possible, although not proved, that control of diabetes is better in some patients after transplantation than before.

Research Directions

Continuing improvement in both patient and renal graft long-term survival rates can be anticipated due not only to improved surgical and preservation techniques and to better understanding of immunological events leading to graft rejection but also to improvements in treatment of the clinical complications of diabetes. A trial is in progress to test the effect of standard versus strict control of blood glucose levels on posttransplant course and outcome. Transplant patients also should benefit from the experience gained in the Diabetes Control and Complications Trial now under way, described elsewhere in this report. Total long-term rehabilitation of diabetic transplant patients is now possible, and research will continue to explore new ways of advancement with the goal of further improvement of these results.

Clinical Studies of Cyclosporine in Kidney Transplantation

Prior Findings

As a result of a better understanding of tissue compatibility systems, use of pretransplant blood transfusions to precondition potential renal transplant recipients, improved preservation techniques, and better selection of patients, a decline in morbidity and mortality associated with renal transplantation has been observed in recent years. Overall graft survival has not improved in the past decade, but, armed with new information about the immunology of rejection, tissue matching, and new modes of therapy, we may be at a turning point in the history of transplantation.

Cyclosporine (CsA) is a potent immunosuppressant agent used in the prevention of graft rejection and is derived from the fermentation broth of the fungus *Trichoderma polysporum*. Since the initial clinical trial of CsA in 1978, every clinical series has demonstrated that CsA treatment induces graft survival outcomes at least as good as those of any other immunosuppressant regimen.

Discrepancies exist among published results obtained from collective data analysis derived from clinical studies conducted in European, Canadian, and American trans-

plant centers. Some of these data indicate dramatic improvement in both patient and graft survival rates when CsA-treated patients are compared with patients on standard immunosuppressive regimens. These data should be read and interpreted with extreme care, because in the majority of cases, a comparison is established between actual CsA-treated patients and available data that are not necessarily comparable.

Recent Advances

The interim analysis of an ongoing prospective randomized controlled clinical trial of CsA plus low doses of a steroid drug, prednisone, versus the standard immunosuppressive regimen of prednisone and azathioprine (AZA) plus antilymphocyte globulin (ALG) in the immediate posttransplant period demonstrates no significant difference in patient or graft survival rates when the two groups are compared. Overall patient and graft functional survival rates up to 36 months posttransplant in all CsA and standard immunosuppression renal graft recipients show that renal graft survival rates are only slightly better in CsA-prednisone-treated recipients than in AZA-prednisone-ALG-treated renal graft recipients. The renal graft survival rate in diabetic recipients of cadaver grafts, the highest risk group, is improved from 66 percent with standard immunosuppression to 84 percent with CsA at 1 year followup and from 66 percent with standard immunosuppression to 76 percent with CsA at 2 years' followup. Patient survival rate is slightly better in the conventional treatment group. Differences between groups or in subgroups are not statistically significant.

The advantages to the use of CsA include fewer viral and bacterial infections, shorter hospitalization times, and fewer rejection episodes. Some of the disadvantages associated with the use of CsA, as opposed to the conventional regimen, include a longer duration of the loss of renal tubule integrity (acute tubular necrosis), if it occurs; higher creatinine levels at all times posttransplant, which can indicate abnormal renal function; and more difficult management of hypertension and hyperkalemia, an increased serum potassium level.

Based on preliminary data, it is apparent that the highest risk group, the diabetic recipient of a cadaver graft, is the one that more readily benefits from CsA prescriptions.

Research Directions

When certain features are incorporated into the standard immunosuppression regimen such as patients being heavily transfused and receiving ALG, graft survival rates can be maximized. There still needs to be a clinical consensus as to whether CsA significantly improves the outcome of kidney transplantation.

Clinical studies have shown CsA to be effective in the prevention of graft rejection and to decrease the incidence of serious infections. The main concern is toxicity to the kidney at doses that are therapeutic for immunosuppression. How this immunosuppressive effect manifests itself is not well known. The drug's metabolism and immunosuppressive action need further investigation. Both the modes of drug action at a cellular level and drug behavior (pharmacokinetic) characteristics, including means to optimize efficacy while minimizing toxicity, need further analysis.

A Molecular Basis for Congenital Nephrosis

Prior Findings

In kidney diseases such as severe nephritis and nephrosis, there is usually damage to the glomeruli, which are the tufts of capillaries that collectively serve as the main filtration apparatus of the kidney. The partial loss of this barrier function is associated with leakage of plasma proteins into the urine; significant proteinuria is one of the major diagnostic features of kidney disease. It is now known that the capillary membrane barrier is effective through molecular size, acting as a sieve, and molecular charge, an electrostatic effect. Negatively charged (anionic) plasma proteins are barred in part by the presence of negatively charged sites within the glomerular basement membrane (GBM).

Proteinuria is the main clinical feature of the nephrotic syndrome, along with edema and low blood protein. Congenital nephrosis is a rare and hereditary form of nephrotic syndrome, often with massive proteinuria that may be rapidly fatal. Studies were undertaken with NIADDK support to examine the basis for the proteinuria in this disease.

Recent Advances

A method was designed for the quantitative demonstration of anionic sites in the human GBM. A cationic, or positively charged, polymer, polyethyleneimine, was used to label these sites in tissue samples, which were then prepared for electron microscopy. In eight fetal and adult samples, these anionic sites were found to be distributed at regular intervals along the basement membranes, but in five patients with congenital nephrosis, relatively few such sites were present. The sites were shown to be rich in the complex polymer heparan sulfate by prior incubation of sections of normal kidney in a purified enzyme specific for heparan, heparinase; the enzyme digested the sites, causing a marked reduction in number. The investigators concluded that congenital nephrosis results from failure of development of anionic sites, which are rich in heparan sulfate, in the GBM.

Research Directions

To define and extend these results, it is desirable to apply the same technique to examine other diseases with known

characteristics, such as lipid nephrosis, which has a charge-selective defect in the glomerulus, membranous nephropathy, which has a size-selective defect, and renal diseases without serious proteinuria. A mapping of the locations of the anionic charge-selection sites, especially those within the basement membrane, is needed in view of differences in their reported locations. More information is necessary on the reason for the loss of anionic sites in several types of glomerular diseases. Other possible functions of the anionic sites, such as cell/tissue attachments and immune complex formation, need to be examined, as does the behavior of these sites in organs other than kidney in renal disease.

Immunologic Mechanisms in Kidney Diseases

Prior Findings

Evidence accumulated in the last few decades implicates immunologic factors in a variety of renal diseases. In the majority of immunologically mediated glomerular diseases, immune complexes (complexes of antigen plus antibody) can be found in glomeruli. This is true of both primary renal diseases such as membranoproliferative glomerulonephritis (GN) and systemic diseases such as lupus nephritis. The responsible immunologic mechanisms thus far defined involve either deposition of immune complexes from the circulation or their formation in situ. Less common are diseases in which antibodies are directed against native GBM, as in Goodpasture's syndrome.

Although these immunopathologic mechanisms are important in the major forms of GN, it appears that additional immunological mechanisms also are involved. Thus, some forms of GN lack antigen and antibody deposits but have clinical and laboratory features suggesting immunological causes. For example, lymphoid cell infiltrates in renal tissue also suggest that direct cell-mediated immune injury may be a component of many forms of nephritis, with or without associated antibody deposition. This evidence has led to notable advances in understanding the pathophysiology of chronic renal failure as well as elucidation of the expression of immune-mediated renal injury.

Recent Advances

Research supported by the NIADDK is consistent with the hypothesis that cationic antigen induces glomerular immune complex deposition by directly binding to the GBM through electrostatic interaction and thus predisposes to in situ immune complex formation. In contrast, negatively charged antigen seems to require the formation of circulating immune complexes which then deposit in the glomerular capillary wall. To test their hypotheses, Institute grantees studied the differential effects of the substance protamine sulfate and the immunosuppressive drug methylprednisolone. The rationale for using protamine sulfate is that it is a weakly immunogenic, highly cationic, and freely filtered molecule. Therefore, it would be expected to bind to the anionic sites in the glomerulus and protect from the subsequent binding of a positive-charged immunogen. Their in vitro experiments showed that when protamine was incubated with isolated GBM, it subsequently inhibited the binding of cationic serum albumin (BSA). When cationized BSA was administered to rabbits, the antigen was observed to bind to the outer portion of the GBM, where antibody to this antigen subsequently deposited to form immune aggregates in situ. In some of the animals that developed subepithelial immune deposits, the continued administration of protamine led to the disappearance of the deposits and to the restoration of the normal structure of the glomerular capillary wall. The experimental evidence indicates that protamine's therapeutic effect appears to be mediated by its electrical charge rather than through any of its other pharmacologic properties.

Research Directions

These observations are of potential importance in unraveling the pathogenetic events associated with the development of immune-mediated glomerular injury and kidney disease and may lead to relevant new therapeutic approaches. Further exploration is needed to delineate the relationship of genetic factors, the complement system, physical and chemical aspects of the basement membrane, and the dynamic equilibrium of immune complexes to development of renal injury in renal diseases.

A Model of Mesangial Renal Pathology, as in Diabetes

Prior Findings

Within the tufts of capillaries serving to filter the blood to produce urine and between the capillaries is a special region called the mesangium. Since its initial description and characterization by electron microscopy, it has become the subject of considerable investigation and analysis. The mesangium is a common locus for the deposition of immune complex material, which often occurs exclusively in this site. Studies in animals using a variety of tracers indicate the plasma normally percolates through the mesangium. There is supportive evidence that morphologic expansion of the mesangium in human disease, though clinically silent in early stages, ultimately is associated with physiologic alterations of glomerular functions and anatomic encroachment upon the glomerular capillary loops, leading to distortion of the glomerular structures. This ultimately may lead to progressive alterations of renal function. A diverse group of important glomerular disorders in man is characterized by their pathologic changes in the mesangium. These disorders include IgA nephropathy, type I membranoproliferative glomerulonephritis,

lupus nephritis, diabetic nephropathy, and amyloidosis. The clinical manifestations of progressive glomerular pathology may not be evident until histological abnormalities such as mesangial expansion are advanced, and the mesangium may be exposed to chronic injury in the disease state.

Recent Advances

NIADDK support has permitted the development of an animal model that shows marked mesangial expansion when administered polyvinyl alcohols (PVA). Administration of PVA results in the appearance of monocytic cells or white blood cells that become macrophages in the tissues and protect against foreign material in the mesangium, alterations in the mesangial uptake and processing of macromolecules, and GBM thickening. Light-microscopy observations suggest that mesangial expansion in PVA-treated rats along with observed proteinuria is analogous to that seen in humans with diabetic nephropathy who have significant proteinuria (in excess of 400 mg/24 hours). These findings, therefore, raise significant implications regarding the pathogenetic factors associated with glomerular dysfunction in diseases where the mesangium is altered, such as diabetes mellitus. Measurements of the area of the mesangium, capillary lumen, and peripheral capillary filtering surface in PVA rats should prove to be helpful in elucidating pathogenetic events that have relevance to human diseases associated with mesangial expansion.

Research Directions

Diseases causing mesangial expansion account for significant morbidity, mortality, and social cost. The mechanisms by which these and other disorders characterized by marked expansion of the mesangium lead to proteinuria, hypertension, and renal failure are largely unknown. Therefore, in light of these recent findings, it becomes critical to gain a better understanding of the structural-functional relationships of the mesangium. Examination of these relationships in animals with graded severities of mesangial expansion may provide insights into pathogenetic mechanisms that may have relevance to human disease.

The information accumulated in the recent past by studies of the structure and function of the glomerular mesangium in laboratory animals demonstrates a number of potential mechanisms to explain some aspects of human glomerular disease. It seems likely that additional understanding of these concepts may lead to improved therapeutic approaches as well as control and prevention of several important forms of renal disease in man; therefore, research on the mesangium should be intensified.

Nitrogen-Free Amino Acid Substitutes for Renal Insufficiency

Prior Findings

The basic principle for the management of renal insufficiency is the restriction of protein intake; in patients with chronic renal failure, the institution of a protein-poor diet results in improvement of the general condition, disappearance of uremic symptoms, and a decrease in serum concentration of urea and other end products of protein metabolism. It seems clear that accumulation of nitrogenous metabolites plays a major role in the pathogenesis of the uremic syndrome. Several recent studies suggest that nutritional or metabolic factors also may affect the rate of progression of renal diseases. The evidence, although not conclusive, indicates that low-protein diets, particularly when associated with careful control of phosphorus and calcium intake, may retard the rate of progression of renal failure in animals and humans.

Nitrogen-free branched-chain keto analogues (BCKA) of essential amino acids have been used experimentally for treatment of chronic renal failure, liver insufficiency, and certain genetic diseases because these compounds are converted to essential amino acids *without* increasing the nitrogen load. To assess their value as therapeutic agents, it was necessary to evaluate the manner and efficiency of their biological utilization.

Recent Advances

Simultaneous human and animal studies using radioisotope labels and tissue distribution methods showed that nitrogen-free BCKA can replace branched-chain amino acids (BCAA) in the diet of animals and humans, although not with complete efficiency. The methodology applied allowed both the extent and the rate of incorporation of labeled BCAA and BCKA into newly synthesized protein to be quantitated simultaneously in both human and experimental animal subjects. These studies show that skeletal muscles are able to produce BCAA in the postabsorptive period and that administered BCKA moves from peripheral tissues centrally to be used equally by the liver, gut, and kidneys. It is believed that enterally administered BCKA becomes incorporated into liver proteins sent to other tissues less efficiently (relative to BCAA) than into the liver's own intracellular proteins or peripherally synthesized proteins. The probability of a BCKA molecule becoming incorporated into newly formed protein depends on a series of complex steps such as transport, oxidation, and transamination processes and protein synthesis and degradation in the organ where protein synthesis takes place as well as within the organ where it is measured.

Research Directions

Further studies along these lines, coupled perhaps with mass-spectrometric techniques, should further understanding of the metabolic, catabolic, and overall in vivo behavior of nitrogen-free BCKA in promoting stimulation of protein synthesis, inhibition of protein degradation, and overall nitrogen balance. The goal of pursuing this research work is to define further the potential role and relevance of nitrogen-free analogues of essential amino acids in the treatment of progressive renal disease, chronic uremia, and serious liver diseases as well as other diseases.

Urologic Diseases

Prevention of Calcium-Based Kidney Stones With Citrate

Prior Findings

Urolithiasis is a major cause of morbidity of the urinary tract. Reliable rates of occurrence in defined populations are not readily available. In the United States and most other developed countries, stones are most common in the upper urinary tract, in the kidneys or near them; in less-developed countries, bladder stones predominate—especially in children. A large percentage of upper urinary tract or kidney stones contain calcium oxalate as a major constituent. Epidemiologic data strongly suggest that environmental factors such as diet, climate, geologic mineral concentrations, and fluid consumption play a strong etiologic role.

There are several causes of kidney stone formation. One of the kidney stone-forming disorders is associated with increased absorption of calcium from food. About one-quarter of the U.S. population with kidney stones form calcium stones. Certain of these patients can be treated successfully with a low-calcium diet, along with the avoidance of excessive salt and excessive vitamin C intake, but there is a need for simple and reliable preventive medication—especially in those at high risk of stone formation *recurrence.*

It was reported last year that the drug sodium cellulose phosphate (SCP) has demonstrated effectiveness in inhibiting stone formation in patients whose kidney stones are due to excessive absorption of dietary calcium. Within the GI tract, SCP binds calcium from food, thereby lowering the amount of calcium absorbed into the circulation from the intestines. The Food and Drug Administration recently approved SCP for commercial marketing. This action climaxes a significant advance based on research supported for several years by the NIADDK. It represents a major achievement in the prevention of a serious recurring disorder and in the development of a so-called orphan drug (one for which there is little incentive for development because of a relatively small market).

Recent Advances

About half of all those requiring treatment for kidney stones, approximately 150,000 patients, have lower than normal levels of citrate, citric acid salts, in their urine. A study was made of 78 such patients to determine if taking potassium citrate by mouth in coated, slow-release form would help prevent recurrence of stone formation. The group showed a dramatic response, from an average of 5.18 stones a year before the treatment to 0.73 stones a year during treatment. Most of the group, 74 percent, stopped forming stones, and 96 percent showed a reduced rate of formation. Existing small stones decreased in size after treatment, and the need for surgery was virtually eliminated.

Citrate acts as a natural inhibitor of kidney stone formation from calcium. Potassium citrate is a common substance found in orange juice, although drinking orange juice is not as effective as using the compound in the concentrated form of a medication. The drug is already in use for other conditions and is expected to be approved soon by the Food and Drug Administration for use against the formation and recurrence of calcium stones.

In related research, it has been observed that the combination of citrate with small radius ions of ferrous iron, Fe(II), inhibits stone crystallization more effectively than either the citrate or Fe(II) alone. This may lead to improved methods for retarding the formation of stones.

Research Directions

Other inhibitors of stone formation are being investigated to correct other types of kidney stone disorders, especially the recurring types. More studies are needed in this area and are under way in all of the NIADDK's three center-like comprehensive program projects in urolithiasis.

The Formation of Kidney Stones

Prior Findings

Passage of a kidney stone is one of the most painful medical disorders and one of the most common disorders of the urinary tract. If a stone does not pass, it results in an acute medical emergency that requires surgical intervention. Research in this area has focused on the mechanisms of formation and dissolution of stones and on means for medical intervention in this process.

An example of the use of basic knowledge about stone formation to interrupt the process and prevent development of new stones was given last year. In patients with chronic urinary tract infections, the bacterial organisms present often produce an enzyme, urease, that splits the

urea molecule and causes a buildup of ammonia salts in the urine in the form of magnesium ammonium phosphate, or struvite. With increased alkalinity, the urine becomes supersaturated with struvite, and crystals form that become kidney stones. Institute-supported studies have shown that acetohydroxamic acid (AHA) blocks the action of bacterial urease, preventing the sequence of events leading to formation of struvite stones. Using these studies as a basis, the Food and Drug Administration recently has approved the marketing and use of AHA for reducing the urinary alkalinity in bacterial infections of the urinary tract and for blocking the bacterial urease to prevent the development of struvite stones. AHA is another example of an orphan drug.

Advances in noninvasive destruction of kidney stones using shockwaves and surgical techniques limiting the need for more extensive kidney invasion using the nephroscope, along with the medical treatments for stones, suggest that therapeutic interventions may be progressing more rapidly than basic understanding of the dynamics of stone formation. The chemistry of stone formation in the kidney and the role of naturally occurring inhibitors to stone formation in the urine continue to be investigated.

Recent Advances

A quantitative technique based on a urine sample has been developed that will predict the likelihood that a person will form kidney stones. This method assesses the crystallization of calcium salts from the urine in terms of the increment of the salt components, oxalate and calcium ions, permissible before spontaneous precipitation (nucleation) begins. Calculated ratios that estimate the level of urinary saturation and the amount of inhibitor or promoter activity present statistically correlate highly with these permissible increments. The permissible increments were significantly lower in patients with renal stones and were raised by treatment with SCP and other substances. Their use offers a simplified method for evaluating severity of stone disease and in assessing response to treatment.

Research Directions

Current and future research in this area should contribute to more efficacious therapeutic approaches to the prevention of stone development and recurrence, based on better understanding of the physicochemical dynamics of crystallization.

To aid in the elucidation of the precise etiology and pathogenesis of calcium oxalate stones, the degree of correlation between stone occurrence and standard of living should be established, and the factors responsible for the higher frequency of the disorder in those of lower socioeconomic status, as indicated in the present study, should be identified.

Benign Prostatic Hyperplasia

Prior Findings

Benign prostatic hyperplasia (BPH) is characterized by excessive growth and expansion of the prostate gland and is associated with retention of urine and disruption of normal voiding. The morbidity and estimated medical costs, which exceed $1 billion annually, associated with BPH make this disease a significant national health problem. BPH is present in the younger as well as older male. The disease has been detected as early as age 20. It occurs frequently, with evidence of symptomatic disease in about 45 percent of men at age 45 and nearly 80 percent in men over 60. It is prevalent among males in Western, Asian, and African countries. When these findings are considered with those showing that 5 percent to 10 percent of all prostatic specimens obtained from surgery for BPH show microscopic evidence of cancer (adenocarcinoma), it is clear that prostate research deserves special attention at the national level.

Recent Advances

Research attention has focused on the mechanism of action of the active androgenic hormone, dihydrotestosterone, responsible for growth of the prostate gland.

Methods have been developed for separating stromal, nonglandular framework tissue, and epithelial tissue of the prostate. Studies suggest that human BPH results from growth potential present in stromal components. Prostatic stromal tissue capable of inducing growth of the prostate has a greater amount of dihydrotestosterone receptors than does prostatic epithelial tissue.

BPH tissue shows a significant reduction in converting dihydrotestosterone responsible for abnormal prostatic growth to a biologically inactive form, when compared to normal prostatic tissue.

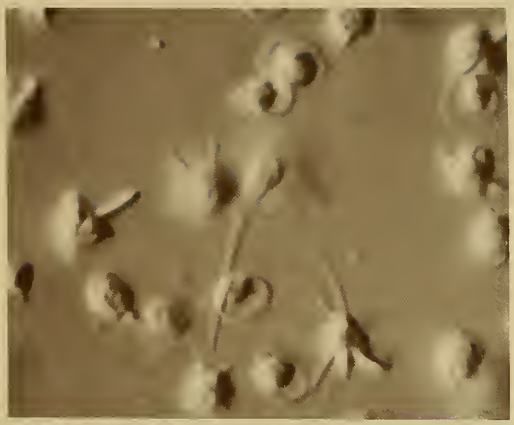
The nuclei of tissue taken from patients with BPH have higher concentrations of dihydrotestosterone receptors than nuclei taken from the normal prostates, whereas total prostate gland contents of androgen are the same for BPH and normal glands. A major proportion of the steroid-binding capacity of nuclei from prostate tissue is contained in the nuclear matrix, which also serves to anchor certain DNA sequences and RNA processing.

Recent advances help to increase understanding of the biochemical and hormonal events associated with abnormal growth of prostatic tissues and to provide the rationale for experimental drugs currently under development for the nonsurgical treatment of BPH. One such approach uses an inhibitor, 17β-N, N-diethylcarbamoyl-4-aza-4-methyl-5α-androstan-3-one, of the enzyme that converts testosterone to the active androgen. The enzyme inhibitor has been shown to decrease prostatic volume in the beagle, which, like humans, naturally develops BPH. The close association

in the nuclear matrix of bound steroid hormone and certain nucleic acids may offer more understanding in the future of hormone-gene interactions.

Research Directions

The primary goal of research in this area is to continue to stress multidisciplinary approaches to assessing normal and abnormal growth of the prostate gland to better understand the onset and progression of BPH. These findings can be used in turn to provide alternative rationales for the development of biochemical and pharmacological treatments of BPH. It is clear that further studies of the morphological and physiological consequences of abnormal prostatic growth are required because there is a relative lack of research and knowledge concerning the association of BPH and urine retention or disrupted micturition.



NIADDK hematologic research is closely coordinated with other NIH blood disease programs. This research has increased basic knowledge about blood and has led to improved management of hematologic diseases.

Hematologic Diseases

Safe and Rapid Prenatal Diagnosis of Hereditary Anemias and Other Genetic Disorders

Prior Findings

Prenatal diagnosis of sickle cell anemia and thalassemia (Cooley's anemia) was introduced in 1974 and has been performed in medical centers in the United States, Europe, and Australia since that time. Early methods relied upon obtaining samples of fetal blood by either placental aspiration or fetoscopy. These procedures, while effective, carry a risk to the fetus. Recent development of techniques to analyze nucleic acids has paved the way for prenatal diagnosis by analysis of DNA from cells derived from amniotic fluid obtained by amniocentesis without the need of an intermediate step for the culturing of the cells in special media. This procedure greatly lowers technical difficulty and risk and can be performed at a much earlier stage of fetal development.

Recent Advances

Prenatal diagnosis of sickle cell anemia, thalassemia, and other genetic disorders can be accomplished by direct DNA analysis of amniotic cells and of first-trimester transvaginal amniotic biopsies.

Restriction enzymes cleave DNA at specific sites. After cleaving, the DNA fragments are separated by electrophoresis, with immobilization on filters, and are identified by hybridization with radioactive probes. With this procedure, normal DNA yields distinct and reproducible patterns with each restriction enzyme. Some human gene mutations that cause genetic disorders can be detected directly, by identifying an aberrant pattern after restriction enzyme use, or indirectly, by identifying a characteristic pattern that is linked to the mutated gene.

Direct analysis may be applied to sickle cell anemia, where the mutation abolishes a known restriction enzyme site. When normal DNA is digested with the enzyme, two fragments of 1.15 and 0.2 kilobases in length are produced. The sickle mutation abolishes the cleavage site, and a fragment 1.35 kilobases long results.

The indirect method has been used for β-thalassemia because most mutations causing this disease do not involve alterations in restriction enzyme sites in the gene. However, the investigator responsible for most of the work on direct techniques has now prepared synthetic gene fragments to detect directly the mutation in the DNA that results in β-thalassemia. A synthetic probe for a thalassemia mutation binds only to the defective β^{s}-thalassemia DNA, while the synthetic probe for normal DNA binds only to the normal DNA, under appropriate conditions. Both probes bind to a DNA fragment from heterozygous (one DNA strand normal, the other defective) β-thalassemia. Thus, it is possible to distinguish among the clinically normal heterozygous, or carrier, individuals and those homozygous for specific types of β-thalassemia.

The application of direct DNA analysis can be made in all pregnancies at risk for disorders involving hemoglobin and, ultimately, for any genetic disorder. Converting the method of diagnosis from fetal-blood sampling to amniotic-cell or amniotic-tissue sampling greatly reduces the risk to the fetus. Such techniques are widely applicable to areas of the world where these disorders are common and would allow rapid, inexpensive, and safe screening of fetuses in the United States.

Research Directions

Further work should devote attention to specific applications of this technology to other genetic diseases such as growth hormone defects, Huntington's disease, and Duchenne muscular dystrophy.

Mechanism of Fetal Hemoglobin (HbF) Stimulation by Drugs in Hereditary Anemias

Prior Findings

It was reported last year that the drug 5-azacytidine (azaC, an analogue of the DNA component cytosine) stimulated HbF synthesis in experimental animals and in both sickle cell disease and thalassemia patients. The drug reduced the degree of anemia. Because the production of impaired, abnormal hemoglobin molecules in sickle cell disease and thalassemia is manifested in the adult form of hemoglobin but not in the fetal red blood cells, interest in enhancing the synthesis of HbF as an effective form of replacement therapy has been high.

The drug 5-azacytidine was chosen to stimulate the synthesis of HbF because it cannot be methylated and because the degree of methylation of DNA has been shown to be important in the control of some types of gene activity, especially in gene expression. Even though azaC is a drug that inhibits the replication of rapidly dividing cells (i.e., it is an S-phase-specific inhibitor of mitosis), it seemed reasonable that its effect on hemoglobin synthesis was due to lessened methylation. Both of these alternatives are still possible explanations for its action.

Recent Advances

The possibility that azaC acts primarily by stopping the growth of dividing cells instead of by decreasing methylation raises a significant issue; because azaC is an S-phase-specific inhibitor of mitosis, other members of this class of drugs might be useful in treating hereditary anemias. An Institute-supported investigator tried one of these drugs, cytosine arabinoside, in baboons and found that the response was exactly the same as that produced by azaC. Another investigator tried hydroxyurea, from the same class of drugs, in baboons and obtained the same response. Reinforcing the possibility that the basis of the effect produced by all three of these drugs is one of arresting cell growth are the extreme rapidity of the effect (within 24 to 48 hours after a single dose of azaC) and the finding that both azaC and cytosine arabinoside arrest the development of the more mature rapidly dividing precursors of red blood cells in the bone marrow, which would force the unaffected early progenitor cells to differentiate rapidly and therefore produce HbF. It also is possible that the S-phase effect is the basis for the early action of azaC and that decreased methylation is associated with more persistent effects of the drug on HbF.

Research Directions

These results need to be confirmed and extended, and the mechanism of action of drugs such as azaC on hemoglobin synthesis must be further defined. Less toxic drugs with the same action, such as hydroxyurea, are desirable inasmuch as azaC is capable of *causing* cancer as well as *treating* it. A clinical trial of hydroxyurea is planned.

The development of one or more drugs that can stimulate safely the synthesis of HbF in amounts sufficient to reverse the anemia of sickle cell disease and other hereditary anemias should be pursued. Such a drug could revolutionize the treatment of patients and potentially alleviate one of the gravest aspects of these diseases.

Inheritability of Hemochromatosis

Prior Findings

Hemochromatosis is an iron-storage disease affecting a variety of systems of the body. In hemochromatosis, the selective ability of the intestinal lining to absorb only as much food iron as the body requires and to reject any excess is absent or impaired. The resulting tissue iron overload is associated with skin pigmentation, liver cirrhosis, diabetes, and other abnormalities. Prior to recent studies, it was agreed generally that the disorder was inherited, but the mode of inheritance was disputed. The inability to resolve this question was complicated by the influence of other factors, including age, sex, alcohol consumption, iron intake, and iron loss. A study of families with hemochromatosis was necessary to resolve these questions.

Hereditary hemochromatosis is a progressive and potentially fatal disorder if not recognized and treated at an early age. It is not rare; in Utah and localities studied in France, 10 percent to 13 percent of the Caucasian population is heterozygous for the gene. About 5 in 1,000 individuals are homozygous, or have the gene from both parents. Heterozygous individuals do not have clinical symptoms of the disease, but homozygous individuals who consume enough dietary iron can and will develop this serious and potentially fatal disease.

Recent Advances

A major contribution towards resolving the mode of inheritance was the 1975 discovery of an association between specific HLA antigens of the cellular immune system and hereditary hemochromatosis. The association with specific HLA antigens (mainly A3) was so strong that it was likely that the hereditary hemochromatosis gene and the HLA genes were present in the same chromosome, chromosome 6.

Studies of 25 patient pedigrees, in which at least one individual with clinically apparent hemochromatosis has been detected, have now been completed. A recessive mode of inheritance was supported by pedigree studies in which unaffected parents produce multiple offspring with hemochromatosis, by clinically evident hemochromatosis in 25 percent of siblings of individuals with hemochromatosis but in very few parents or offspring, and by an increased incidence of marriages between relatives among parents of affected individuals. The specific HLA genes linked to a hemochromatosis gene vary from pedigree to pedigree but are consistent within a given pedigree.

Linkage to HLA genes on chromosome 6 has been established, and the mode of inheritance has been determined to be recessive. Full expression of the disease is found in many homozygous individuals. Recognition of the mode of inheritance should lead to a more frequent identification of homozygotes with consequent dietary and other possible medical intervention, leading to prevention of serious illness before onset of organ damage and end-stage disease.

Research Directions

Improved genetic understanding can be coupled with the recent development of a technique of direct noninvasive magnetic measurements of hepatic iron stores to determine precisely the degree of illness of patients and should lead to the application of appropriate therapy.

The specific metabolic defect and mechanisms by which the hemochromatosis gene on chromosome 6 leads to progressive iron accumulation and eventual organ damage need to be studied. Because heterozygotes often display certain aspects of the disease, studies are needed to determine the need for therapy for these individuals.

Criteria for preventive treatment of homozygotic patients need to be refined.

Advances in Bone Marrow Transplantation for Hematologic Cancer

Prior Findings

In the mid-1970's, bone marrow transplantation was considered as a tool for managing hematologic disease only in patients with far-advanced drug-resistant cases. Advances in chemotherapy of acute leukemia in children and, more recently adults, have enabled complete remissions in 95 percent of children with acute lymphoblastic leukemia (ALL) and in about 70 percent of adults. Some of the patients with remissions relapsed on chemotherapy or after chemotherapy was halted. These patients could not be saved until now. Impressive progress, however, has been achieved recently in bone marrow transplantation once a second remission has been obtained. Nearly all of these patients now can be cured.

Recent Advances

Bone marrow transplantation remains a technologically complex procedure, currently requiring the availability of an immunologically compatible sibling. The high incidence of chemically induced remissions now allows stabilization of disease in most patients with ALL. Techniques have been developed to achieve destruction of the patient's leukemic cell population and immune system by chemotherapy and by total body irradiation. Plasmapheresis (plasma withdrawal and replacement) may be used to circumvent blood group incompatibility if present, or antibodies may be removed by insolubilized antigen or by selective removal by a red blood cell separator. Following preparation of the patient, donor marrow is infused intravenously. These highly demanding procedures now can be accomplished with resulting engraftment into the recipient marrow. Survival of most of the low-risk patients (those under 45 years of age with well-matched siblings) has been reported, and relapses after 2 years of followup have been rare.

Early bone marrow transplantation in acute leukemia cures the highest proportion of patients of any currently available treatment modality.

Research Directions

There is a need to extend the permissible donor pool to nonidentical nonsibling donors. Marrow graft rejection and posttransplant graft-versus-host disease need to be overcome. Effective means to control opportunistic viral infections in the immunosuppressed graft recipient must be developed.

Bone marrow transplantation represents a promising direction for the development of a complete therapy. Properly selected patients include primarily those under 45 who have well-matched siblings. However, even among these relatively favored individuals, nearly half succumb to the disease or to complications associated with the procedure. Therefore, simpler, more effective means for the management of acute leukemia must be developed.

A Simple Test for Mild Iron Deficiency

Prior Findings

It has been known for several years that in anemia due to iron deficiency the absorption of dietary iron from the intestine is increased greatly. Even in mild iron deficiency, such as occurs in healthy individuals after donating blood, the absorption percentage of ingested iron jumps from less than 10 percent to between 30 percent and 70 percent. In anemia, when this absorbed iron enters the blood plasma, almost all of the iron is used by developing red blood cells, erythroblasts, to make hemoglobin. Excess iron is removed by iron storage cells, which make the protein ferritin for this purpose.

In previous studies of iron absorption, iron tolerance tests, the test dose of iron was 50 to 250 mg, 10 to 50 times the amount of iron in an ordinary meal. Such doses overwhelmed the absorptive mechanism and did not distinguish requirements in iron deficiency from normal replenishment needs. A more sensitive and reliable test for deficiency was suggested by earlier experience with low doses of iron used as a carrier for radioactive iron in absorption tests. At the same time, it was desirable to simplify such tests and to avoid the need for human exposure to radioisotopes and the use of isotope counting equipment.

Recent Advances

Measurements of plasma levels of iron after a test dose of 5, 10, or 20 mg of iron was given were made over a period of several hours to compare iron uptake and usage in normal controls with that in individuals mildly deficient in iron (male blood donors). Men with normal iron stores showed little change in plasma iron, while mildly deficient men showed large increases. Some individuals had mild anemia, and their blood iron levels showed a faster return to prebleeding levels than did those of the mildly deficient men, who were not actually anemic. The slope of the curve of plasma iron levels over several hours provided a sensitive indication of the presence of mild iron deficiency and mild anemia.

Research Directions

The availability of a simple and reliable test for mild iron deficiency, without the need for radioisotopes, has many potential applications, including use in surveys of the health status of populations and in testing the efficacy of dietary iron supplements. Further work is needed to see how plasma iron levels from low-dose testing vary among diseases and conditions known to affect iron absorption or use, such as hemolytic and iron storage diseases or gastric surgery or intestinal inflammation.

Program Accomplishments

The Division of Kidney, Urologic, and Hematologic Diseases conducts a variety of activities to support and stimulate research within its subject areas. In addition to funding specific studies, the staff assists in identifying new research opportunities, assessing research progress, and publicizing findings and new methods of treatment. The Division holds meetings with experts to share new knowledge and advise the Institute on advances, opportunities, and high-priority research needs. The Division publishes program announcements and requests for applications or proposals in the areas where high-priority research needs have been identified. The Division also publishes a variety of scientific and educational materials and disseminates information concerning new research directions for investigators in the field.

Two major trans-NIH reports pertaining to chronic renal disease were prepared in the past year. The NIH Coordinating Committee for Chronic Renal Disease submitted to the Director of the NIH its report regarding the current level of research support and outlining the new opportunities that can be brought to bear in the prevention and treatment of conditions causing chronic renal diseases. A report of the Public Health Service Coordinating Committee on End-Stage Renal Disease also has been submitted that included recommendations for approaches to facilitate data collection from patients with ESRD, activities for prevention of certain chronic renal diseases, and identification of fruitful areas of research into the causes of ESRD as well as treatment of ESRD by transplantation and dialysis.

The Division organized and sponsored two widely attended conferences at the NIH in 1984. A Consensus Development Conference on Analgesic-Associated Kidney Disease was held in February 1984, and a conference on the Use of Monoclonal Antibodies in Renal Research was held in May 1984.

Consensus Development Conference on Analgesic-Associated Kidney Disease

Experts estimate that each year more than 250 people in the United States develop end-stage kidney disease from overuse of analgesics, about one new case per million population. The incidence is much higher in some parts of the Nation, such as one region of North Carolina. The products involved are those containing mixtures of aspirin, acetaminophen, salicylamide, or salts of salicylates.

Large doses of these antipyretic (antifever) analgesics taken in combination over a long period cause a specific form of kidney disease, analgesic nephropathy, and can lead to chronic kidney failure. An example of heavy use would be 10 or more tablets a day for 3 years or longer.

The condition, described as a chronic tubulointerstitial nephropathy, is slowly progressive and usually asymptomatic until the patient's kidneys fail. For every patient whose kidneys fail, many other habitual users of painkillers develop milder forms of the disease.

In an effort to resolve some of the questions about this type of kidney disease, the NIH convened a Consensus Development Conference on Analgesic-Associated Kidney Disease on February 27-29, 1984. After a day and a half of scientific presentations by experts of the available data about the problem, a consensus panel composed of representatives from the fields of nephrology, pathology, internal medicine, family medicine, pharmacology, biostatistics, and epidemiology and from the public considered the scientific evidence and concluded that the sustained use of *mixtures* of antipyretic analgesics in large doses is not advisable and that serious consideration should be given to limiting over-the-counter products to those containing a *single* antipyretic-analgesic agent.

The panel called for more epidemiological research, evaluation of the effectiveness of measures designed to reduce analgesic abuse, research on factors that may predispose patients to the disease, and study of the nature of the toxic metabolites.

More research also was recommended on the mechanisms of cell injury in the kidney, the role of ischemic (impaired blood flow) versus toxic factors, and the interactions of drugs in causing renal tissue damage. In addition, the panel said more information is needed on the relationship between analgesic nephropathy and cancer.

Monoclonal Antibody Conference

A conference on the Use of Monoclonal Antibodies in Renal Research was held at NIH in May 1984. A rich interchange of information was shared among participants from the nephrology, industry, technology, and basic and clinical immunology communities in regard to the use of monoclonal antibodies in kidney research. The topics covered included antibody production and characterization, kidney antigens and their monoclonal antibodies, the use of these antibodies in defining cells of the immune response, their use in monitoring kidney transplantation, and their role in immunotherapy.

Monoclonal antibodies are highly specific proteins produced in immunological response to selected specific antigens on cells that have been coupled to modified tumor cells; the joined cells are known as hybridomas. Hybridoma-monoclonal antibody technology appears to have considerable promise, although this is a technology in a state of rapid evolution, and its application to problems of the kidney appears to be just emerging. Consequently, this technology leads to a proliferation of data difficult to interpret and almost impossible at present to compare between laboratories. Nevertheless, it is anticipated that the continued refinement of this new technology may enhance greatly the assault on immunologic kidney diseases, which appear to have multifaceted etiologies.

The application of hybridoma-monoclonal antibody technology also may provide further assistance in the definition of the role of cell-mediated mechanisms in human renal diseases. For example, the use with histochemical (immunoperoxidase) techniques may facilitate the identification of subsets of T cells and of other mononuclear cells in tissue sections. New markers and new ways of assessing functional activity of cells in infiltrates also may evolve.

Further Encouragement of Immunological Research

The Renal Physiology/Pathophysiology Program has recognized the underdevelopment of immunological research pertaining to the pathogenesis and treatment of chronic renal diseases. This concern is based on the recognition that the majority of diseases causing end-stage renal failure appear to involve immunological mechanisms.

A program announcement entitled the Immune Basis of Renal Disease has identified research areas intended to provide greater insights into the immunopathogenetic mechanisms that may cause renal injury and in which further research is being encouraged. Some of the research areas include:

- Studies to define better the role of lymphoid cells, which may directly produce renal injury or may cause disordered humoral immune responses.
- Development of new markers and new ways of assessing functional activity of cells within infiltrates developed during the immune response.
- Studies of purported nonimmunologic mechanisms that may influence immunologically initiated renal diseases.
- Basic laboratory or clinical studies that have relevance to the immunologic basis of renal disease.
- Investigation of host factors that predispose to the development of antibody-mediated injury.
- Studies to define the role of cell-mediated immunity in glomerulonephritis.
- Development of animal models in which cell-mediated injury is demonstrable.

Evidence accumulated in this century clearly demonstrates that immunologic mechanisms are responsible for a variety of renal diseases, including various forms of glomerulonephritis, nephrotic syndromes, and vascular diseases involving the kidney. Glomerulonephritis, a relatively infrequent medical problem, causes an enormous loss of human potential. This disease most frequently affects children and young adults and, in this country, has an annual mortality of 12,000, a morbidity of 4 million days, a work loss of 765,000 days, and an estimated loss of earning power of greater than $15 million. Furthermore, the diseases listed above are considered to be responsible for the lack of renal function in more than half of the patients presented to centers for management of end-stage kidney disease by dialysis or renal transplantation, at an estimated annual cost of $600 million. Research in the above areas is being encouraged to clarify the structural and functional role of individual glomerular components at a molecular level and attempt to link the process with new understanding of the mediation of immune injury.

Organization of a Cooperative Clinical Study of Effects of Dietary Modification on the Course of Progressive Renal Disease

Because current basic knowledge is still remarkably limited as to the natural history and underlying mechanisms of renal diseases progressing to chronic renal failure and because the current methods of treatment for ESRD are not perfect, the Division has begun efforts to develop a clinical trial to evaluate the impact of dietary protein restriction on the progression of chronic renal disease. Initiatives in this area have been prompted by scientific reports, including uncontrolled clinical observations, that suggest that protein restriction can attenuate the maladaptive compensatory mechanisms that normally emerge following nephron injury. The proposed study also would provide information as to whether the need for maintenance dialysis therapy can be delayed by dietary intervention. An RFA for a cooperative agreement program for a multicenter Collaborative Clinical Study of Dietary Modification on the Course of Progressive Renal Diseases was issued in August 1983. This RFA evolved from a program interest entitled the Natural History and Mechanisms of Chronic Renal Disease. Two statutory requirements (P.L. 95-292 and P.L. 96-499) mandate research pertaining to the effect of dietary modification in chronic renal disease.

This clinical study is envisioned to consist of four sequential phases as follows:

- **Phase I,** the development of a protocol and an operations manual (9 to 12 months), will be concerned with the cooperative development of a single study protocol and manual of operations for phase II by the steering and planning committee, which is composed of the principal investigators of the participating clinical centers and the data coordinating center and members of the Kidney-Urology Branch of NIADDK.

  The dimensions and directions of this study will be determined by the steering and planning committee and, thus, are viewed as critical to the success of this initiative. In addition, an external monitoring committee comprising experts selected by the representatives of the clinical centers and data coordinating center will be appointed to review all activities of the trial and will assess progress of the study and advise the steering and planning committee on whether and how the next phase should be undertaken.

  In general, the protocol is anticipated to include adults with chronic progressive renal diseases having glomerular filtration rates of less than or equal to 50 percent of normal at study entry. Patients with chronic glomerulonephritis should make up the major study group, but additional groups will be considered for separate randomization, including patients with chronic interstitial nephritis, hypertensive nephrosclerosis, polycystic kidney disease, and hereditary nephritis. Patients with active nephrotic syndrome or malnutrition, as well as patients with diabetic nephropathy, do not appear to be suitable for inclusion in the study.

- **Phase II** will be a limited pilot study, 18 to 24 months, with an initial control and observation period followed by randomization of a limited number of patients to an experimental or control diet. This phase should indicate the availability of qualifying patients; assess the appropriateness of randomization; and test procedures and forms, including informed consent and other previously detailed plans to identify and document problems. If the results of phase II demonstrate feasibility and the likelihood that a successful full-scale study can be conducted that will allow for meaningful conclusions, phase III will be initiated. Entrance criteria, number of patients, randomization process, dietary prescription, monitoring guidelines, and selection of measures of outcome will be reviewed critically before the initiation of the phase III study.

- **Phase III** will consist of a full-scale cooperative study, lasting 3 to 5 years, with recruitment of adult patients with chronic progressive renal diseases who meet the entrance criteria. Following a precisely monitored initial control and observation period during which the patients will remain on their own usual diets, status of renal function and its rate of change over time will be established, and each patient will be characterized according to clinical, laboratory, dietary, nutritional, and metabolic findings.

  These patients then will be assigned randomly to either a control or a protein/phosphate-restricted dietary regimen and will follow the detailed study protocol. It is anticipated that patients selected for the study will be trained intensively so that they will have a clear understanding of the objectives and dynamics of the study and the need for compliance and adherence to the specific dietary prescription.

  Reevaluation of renal function status and of clinical, biochemical, and dietary parameters, including compliance with the dietary prescription, will be assessed periodically, and the standard procedures to monitor possible medical complications will be followed.

  Patients will be followed longitudinally until the designated experimental period has ended or study outcome has been reached. In some cases, this will include limited followup into dialysis to ascertain the overall safety of the dietary intervention.

  Interim data analysis will be performed and reports prepared as indicated. There will be periodic reviews by the external monitoring committee pertaining to

quality of data, safety of dietary prescriptions, evaluation of treatment effects, and performance of participating clinical centers and the data coordinating center.

- **Phase IV** is anticipated to last 1 year and will be used by the data coordinating center to complete the data analysis from the clinical trial. After final analyses, preparation of reports of the study for publication will be undertaken cooperatively by the principal investigators, the data coordinating center, and the staff of the NIADDK.

At this point in the development of this clinical trial, applications have been reviewed, and it is anticipated that six participating clinical centers and a data coordinating center will begin preparation in the fall of 1984 of a uniform protocol to be utilized by all centers. A pilot clinical study is expected to begin in mid-1985.

Feasibility of the Restriction Fragment Length Analysis Approach to Polycystic Kidney Disease (PKD)

Restriction fragment length analysis depends on cutting the gene-bearing DNA molecule at characteristic places along its length by use of restriction enzymes with specific actions on DNA. Analysis of the cleavage fragments can detect abnormalities correlated with clinical features.

Recent success in the application of restriction fragment length analysis to a number of genetic diseases, sickle cell, the thalassemias, and Huntington's disease, provides optimism that this approach can be directed at the PKD problem. The purpose of a September 1984 meeting organized by the Renal Physiology/Pathophysiology Program was to bring together experts in nephrology, genetics, and molecular biology who would provide the program with advice regarding future directions that need to be taken in addressing this disease.

Although attempts have been made to find a genetic marker for the PKD gene, and an association between the HLA-B5 gene and PKD has been reported, a subsequent study did not confirm the finding. Results of the latter study showed an absence of linkage between the disease and the major histocompatibility system and an absence of an association between PKD and any given HLA-A or HLA-B antigen or Bf allotype.

New Program Emphasis on Benign Prostatic Hyperplasia

The high incidence and the prevalence of BPH in older men, with its potential for producing obstructive uropathy, account for BPH being the leading cause of kidney and urinary tract disorders. Modern techniques for accurate measurement of prostate size and advances in radioimmunoassay of hormones utilizing specific titers of antibodies make this a most opportune time for accelerated research in this area. Progress in the past 2 to 3 years has made it possible to study the physiological and biochemical nature of the underlying causes of this disease, and it is hoped that such studies eventually will facilitate *medical* management of BPH. Effective medical management would obviate the need for surgery and its associated hazards in the elderly.

Program efforts have concentrated on stimulating more research on BPH. A program announcement was issued (1983) reemphasizing the NIADDK's continuing interest in studies of the onset and progression of BPH, the potential medical therapeutic modalities for its treatment, and the uropathy associated with it. The announcement emphasized that research was needed particularly to:

- Develop alternatives to surgery for treating BPH.
- Assess the interrelationships of anterior pituitary and sex hormone plasma levels with precise quantification of prostate size in the onset and progression of BPH.
- Explore more intensively the physiology of receptor systems in both normal and diseased prostate tissues.
- Characterize more fully the contribution of the testes to the onset and progression of BPH by using gonadotropin-releasing hormone agonists and antagonists; this approach would obviate the necessity of castration, which potentially may affect liver uptake and clearance of serum hormones.

Evaluation of the Hematology Program and of Hematology Research Needs

A major evaluation of research in hematology in relationship to the NIADDK program was completed last year. The project was initiated 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 the NIADDK in relation to the identified needs. The purpose of the evaluation was to provide a rational basis for planning to meet the needs for fundamental and clinical research on hematologic diseases, analyze and evaluate any overlapping with other NIH programs and the means for resolving them, identify areas of research not receiving sufficient emphasis, identify new or static areas of research that would benefit from stimulation, and explore the need for a detailed study to assess manpower needs for research. The study was supported by a contract under which a steering committee of consultants oversaw the activities of about nine work groups addressing areas of hematology research within the NIADDK's mission. Close coordination with the blood programs of other NIH Institutes was maintained.

The result of the evaluation was the production of a 600-page report in book form entitled *Research Needs in Hematology*. It will be invaluable as a guide in formulating a plan for allocation of resources according to realistic research priorities. This report will be useful in determining the directions of research support by the NIADDK, assisting evaluation of grant proposals within the Institute, assisting scientists at research institutions in developing their own priorities in the choice of research direction, providing the various legislative bodies and executive agencies responsible for evaluating priorities in this field with an assessment of needs and opportunities in hematology by experts working in the field, and providing the public with information concerning the prevention and cure of hematologic disease. The scope of research covered in this report ranges from that leading to an understanding of the basic mechanisms of normal function and the pathogenesis of diseases of the blood through development of treatment modalities to the clinical application and evaluation of treatment.

Workshop on Metals in Medicine

Investigation of the role of metals in biologically important molecules has increased at a rapidly changing rate in the last 10 years, and interest can be measured by the increased numbers of collaborative approaches between researchers in inorganic chemistry and biochemistry, the broader experimental approaches used by investigators trained in each individual discipline, and, finally, the training of new investigators in inorganic biochemistry.

The time is appropriate to provide an opportunity for basic scientists to become more aware of the medical implications of their research and for physicians to become more aware of the relevance of research in inorganic biochemistry to their concerns, as was done in the February 10-11, 1984, workshop at Santa Barbara, California. At least 30 different metals are known to be important in biological systems. For conversation to occur at the interface of basic science and medicine involving such metals, the research in each area needs to be reasonably developed. Unfortunately at this time, such is not the case for all metals important in biology. Accordingly, subjects for the workshop were selected for the efficacy of providing information that engages the interest of both groups and that emphasizes the pathology of abnormal metal metabolism and the therapeutic use of metal complexes related to inorganic biochemistry. Relevant pathological conditions are exemplified by osteoporosis (calcium), hemochromatosis, thalassemia (iron), Menkes' and Wilson's diseases (copper), acrodermatitis enteropathica (zinc), and Alzheimer's disease (aluminum).

Conferences

Conferences on research and clinical developments and advances in biomedicine facilitate the immediate exchange of information and cross-fertilization among those working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions.

In the past year, in addition to the conferences already mentioned in this section, the Division of Kidney, Urologic, and Hematologic Diseases has supported or shared responsibility for supporting the following scientific conferences:

- Fifth International Symposium on Urolithiasis and Related Clinical Research, Garmisch-Partenkirschen, West Germany, April 1-5, 1984.
- Fifth Cooley's Anemia Symposium, New York, New York, June 1, 1984.
- Workshop on Research Needs in Cooley's Anemia, New York, New York, May 31-June 1, 1984.
- Ninth International Congress of Nephrology, Los Angeles, California, June 11-16, 1984.
- Third International Symposium on Peritoneal Dialysis, Washington, D.C., June 17-20, 1984.
- Gordon Research Conference on the Mammalian Genital Tract, Plymouth, New Hampshire, July 9-13, 1984.
- Tenth International Congress of Transplantation Society, Minneapolis, Minnesota, August 26-31, 1984.
- Second International Workshop on Human Leucocyte Differentiation Antigens, Boston, Massachusetts, September 17-20, 1984.
- Fourth Conference on Hemoglobin Switching, Airlie, Virginia, September 30-October 3, 1984.

The NIADDK contributed support for the International Conference on Arginine Vasopressin, held August 19-25, 1984, in Aspen, Colorado. The major objective of the conference was to bring scientists together from many disciplines, including neuroanatomy, neuropharmacology, neurophysiology, cardiovascular physiology, nephrology, protein biochemistry, and endocrinology, to discuss all aspects of the actions of vasopressin as well as recent developments in vasopressin research. During the conference, discussions centered on the role of arginine vasopressin in water balance and systemic cardiovascular regulation, neural control of vasopressin release, and the role of vasopressin in pathological states. Competitive antagonists of the hormones, in terms of their biochemistry, pharmacology, and function, also were discussed.

Jointly sponsored by the NIADDK and the Fogarty International Center, the conference on Ion Gradient-Driven Membrane Transport convened under the auspices of the New York Academy of Sciences in New York on October 2-4, 1984. The conference focused on the biochemical, biophysical, and physiological aspects of cotransport and antiport transport mechanisms driven by ion gradients, a field that has seen explosive growth during the past 5 years.

Program Plans

The process of planning for research support has been discussed in chapter I. Examples of the progress of program planning to the implementation stage were seen in the previous section, with issuance of program announcements or requests for applications in such areas as dietary intervention in chronic renal failure, the immunologic basis of renal disease, and others. Some of these are awaiting receipt of grant applications and decisions on research support. Panels of experts continually advise the Institute and suggest refinements of prior programs or support staff recommendations on new initiatives to be accomplished through development of new program announcements or requests for applications or proposals.

The Urology Program has solicited extensive input from leaders in multiple disciplines to identify new research opportunities and to develop new initiatives for research in the area of urinary tract structure, function, and diseases. Planning has been completed for a Division-sponsored multidisciplinary conference on BPH in 1985.

Planning for research support in the area of hematologic diseases has been facilitated immensely by the recent publication of the report of the evaluation of the Institute's Hematology Program entitled *Research Needs in Hematology*. Planning is now in progress in a systematic manner across a broad base of research in hematologic diseases, particularly emphasizing red blood cell disorders, hematopoiesis, and immunohematology as well as research in hemoglobinopathies, nutritional anemias, and iron metabolism, among others.

Acute Renal Failure: Mechanisms of Development and Design of Treatment

A request for applications will be issued to stimulate research intended to improve the overall outcome of acute renal failure (ARF) through furthering the understanding of the pathogenetic mechanisms of ARF, defining means of protection against basic events occurring at cellular and subcellular levels that may lead to the establishment of "fixed" ARF, and exploring therapeutic interventions that can maximally accelerate functional and morphologic recovery following the initial insult.

ARF is one of the most common and dramatic syndromes encountered in clinical nephrology and continues to be a major cause of morbidity and mortality. Mortality rates for surgically related ARF are approximately 60 to 70 percent, whereas ARF in a medical setting is associated with mortality rates of 20 to 50 percent.

ARF is a clinical syndrome of diverse etiology characterized by an abrupt reduction in glomerular filtration rate from the blood sufficient to result in an impairment of the ability of the kidneys to maintain the composition of body fluids. Specific disorders that can lead to ARF include:

- Perfusional (ischemic) disorders such as major trauma, massive hemorrhage, transfusion reactions, septic shock, vascular surgery, and myocardial failure.
- Nephrotoxins such as antibiotics, radiographic contrast media, chemotherapeutic drugs, heavy metals, organic solvents, and pesticides.
- Diseases of glomeruli and small blood vessels such as acute poststreptococcal glomerulonephritis, SLE, postpartum renal failure, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, systemic vasculitis, acute glomerulonephritis, and acute interstitial nephritis.
- Diseases of major blood vessels, including renal artery thrombosis/embolism and bilateral renal vein thrombosis.
- Miscellaneous disorders of pigment release, including traumatic or nontraumatic rhabdomyolysis, intravascular hemolysis, acute uric acid nephropathy, urinary tract obstruction caused by calculi, clots, and tumors and prostatic hyperplasia.

The precise pathophysiology of ARF remains uncertain, but it is evident that both tubular and vascular mechanisms are key factors to the initiation and maintenance phases of ARF. It generally is accepted that ARF is often multifactorial.

There is strong evidence that insufficient blood supply to the kidney, renal ischemia, of sufficient degree and duration represents the initiating event in a variety of settings associated with ARF and that tubular obstruction occurs following the temporary ischemic insult or direct toxicity to the kidney. There appears to be a critical interval of ischemia beyond which renal cells are damaged irreversibly, and recovery depends mostly on regeneration of new cells.

The identification of ischemia as one of the precipitating factors in ARF has led to the search for endogenous vasoactive mediators of vasoconstriction. Those most extensively explored are renin and angiotensin, thromboxanes, PG, antidiuretic hormones, adrenergic hormones, and the complement systems. Current evidence does not indicate that any of these systems independently plays a major role in either the initiation or maintenance phases of ARF. Nevertheless, evidence is not conclusive, and further evaluation is necessary. Other pathophysiologic mechanisms identified in ongoing experimental work include cellular shifts of free calcium ions, which cause the mitochondrial dysfunction observed in ischemic ARF, free oxygen radicals, particularly superoxide, and free radical formation during renal ischemia.

In general terms, until recently the management strategy for ARF consisted of providing supportive care to allow the kidneys to heal. Concomitantly, the role of dialysis was to correct acid-base electrolytes and volume imbalances and to remove retained toxins and nitrogenous wastes so that the extracellular environment for renal

cellular repair became more favorable. Preliminary experimental studies suggest that renal tissue regeneration can be accelerated by providing nutrients currently not supplied through conventional treatment regimens. Evidence indicates that infusion of intravenous essential L-amino acids and glucose improves survival and accelerates recovery of renal function and that infusion of additional quantities of BCAA such as isoleucine, leucine, and valine may be particularly effective in stimulating protein synthesis and reducing overall tissue degradation.

Preliminary results in experimental models of ARF suggest that repair of cellular high-energy stores through administration of high-energy adenosine phosphate (ATP) and magnesium chloride after renal ischemia results in enhanced restoration of cellular ATP levels and leads to functional and morphologic recovery from ARF and that calcium-channel-blocking agents, such as verapamil, appear to have a salutory effect in reducing ischemic-induced injury by possibly preventing massive intracellular calcium overload.

The rational design of therapeutic interventions that can accelerate maximally functional and morphologic recovery ultimately will result from a better understanding of the pathophysiologic mechanisms that lead to the establishment of ARF as well as of those factors that prevent or mediate repair of the injured renal tissue.

Conference on Cell/Tissue Culture Techniques in Renal Research

Utilization of tissue cell culture to study renal and epithelial transport processes and metabolism is an active field with great potential. For example, cultured kidney epithelia provide the possibility for isolating certain kidney transport characteristics and metabolic and biochemical mechanisms. Moreover, the transport properties of kidney. epithelial cells and other features of these cell lines remain to be identified. Studies designed to determine the processes by which epithelial cells derived from the kidney dedifferentiate or alter their differentiation must be encouraged. Also, new cell lines with additional relevant properties should be fostered.

The use of cell culture techniques for a variety of pathophysiological studies is also a potentially important use of this methodology. For example, cultured cells can be monitored for the effects of drugs, toxins, and hormones on cell growth, metabolism, and cell-specific transport events. Similarly, correlations with disease processes in vivo could be made by culturing cells from diseased kidneys. For example, cultured glomerular mesangial cells from diabetic rats may have altered morphology. Species with inbred disease may provide renal cells of unique pathophysiologic interest for studies in vitro.

The availability of cultured endothelial cells now provides a resource for unraveling the effects of agents such as hormones or pertubations such as anoxia on vascular cells in comparison to renal parenchymal cells. Free radical formations or alterations in the cyclo-oxygenase and lipoxygenase pathways in vascular endothelial cells are leading candidates as mediators of a variety of pathological states. Cocultures of endothelial cells with glomerular mesangial cells, for example, may serve as useful models for the evaluation of the sequential effects of noxious stimuli. Endothelial "products" could be monitored separately and in coculture for their effects on mesangial function, synthetic rates, and maturation.

There has been a recent burst of discovery in cell biology relating to understanding and methodology of cell-culturing and cloning techniques. Relatively few laboratories studying renal tissues have adapted these new techniques in their research. The purpose of the proposed workshop is to review the state of the science to enhance the opportunities available for investigators in renal research.

At a July 1984 planning meeting, which brought together investigators who are in the mainstream of developing and using cell and tissue techniques, preparations were made for a future broad-ranging conference in this area, which will afford the opportunity to discuss the state of the art, examine strengths and weaknesses of the existing methodology, and identify its future application.

Benign Prostatic Hyperplasia: NIADDK Symposium

A new conference on BPH is being planned for fiscal year 1985. The last one was held in 1975. Since the last meeting, a number of findings have resulted in conceptual advances in the understanding of BPH and have contributed new rationales to treatment approaches to BPH. There are still inconsistencies within research on BPH that need resolution to complete our understanding of the onset and progression of this disease.

The purpose of the symposium will be to bring together a multidisciplinary group of investigators to ascertain the state of the art of research in this area, the status of our understanding of the divergent approaches to the dynamics of the onset and progression of BPH, the presence or absence of new clinical approaches to treatment of BPH, and the most fruitful-appearing future approaches in basic and clinical science efforts.

A program announcement was issued in 1983 reiterating the interest of the NIADDK in basic and clinical research on BPH. The response to this announcement resulted in some increase in activity in this area. A new journal, *The Prostate,* is being published, specializing in articles and research pertaining to prostatic disease. More articles concerning prostatic research are being published, suggesting a new vigor in this research area. These factors, combined with the high morbidity associated with BPH and the fact that it has been 10 years since the last NIH-sponsored conference on BPH, indicate that the fiscal year 1985 meeting will be timely.

The members of the planning and coordinating group selected to advise the NIADDK on the symposium are dis-

tinguished researchers and leaders in the areas of understanding and treating BPH. The conference is intended to focus on state-of-the-art techniques, findings, and unresolved issues in research on BPH; to project new directions for research areas requiring further attention and to stimulate multidisciplinary research efforts; to attract attention and new investigators to the field of BPH; and to encourage industrial development of novel pharmacological approaches to its treatment.

Controlled Clinical Trial of Hematin: Therapy for Acute Porphyric Attack

The inducible hepatic porphyrias, acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria, are hereditary autosomal dominant disorders that result from a deficiency of a specific enzyme in the heme synthetic pathway and an increased excretion of synthetic precursors. Acute attacks exhibited in patients with these disorders include abdominal pain, muscle weakness, neurologic problems sometimes progressing to coma, respiratory insufficiency, and death.

Hematin was used as therapy first by the late C. J. Watson and his collaborators, who found that timely hematin administration reduced the severity of the attack or even prevented its occurrence in cases where regular attacks could be predicted. Other clinical investigators have begun to use hematin for such cases, but no rational criteria have been developed for timing, amount of dose, formulation, and other key parameters. Data are needed on potential side effects, including possible interference with hemostasis, and association with renal insufficiency. A controlled trial would answer questions about hematin use in patients.

Hematin has been designated as an orphan drug by the FDA and the Pharmaceutical Manufacturers Association. In July 1983, the Abbott Drug Company received a license from the FDA to manufacture and sell hematin. The intent of the FDA in issuing a license was both to provide a drug for use by physicians experienced in treating porphyrias and to ensure a supply for investigative use. Therefore, the supply is adequate for a clinical study. Since fewer than 200 porphyria patients are known at widely separated institutions, a well-designed study involving several collaborating institutions should be initiated. A workshop on hematin held in 1983, sponsored by the National Center for Drugs and Biologics (FDA) in collaboration with the NHLBI and the NIADDK, resulted in agreement that a controlled study could be designed and should be initiated.

No satisfactory treatment for acute porphyric attacks is known, other than hematin administration. The attacks are devastating to the affected individuals, and considerable public and congressional interest in efforts in this area has been demonstrated.

An RFA is expected to stimulate the necessary collaborative efforts among experienced investigators. The clinical trial should obtain objective and controlled data about the efficacy and safety of hematin therapy for acute porphyric attack, determine the optimal timing and dosage for hematin administration, and assess reported side effects.

Program Announcement: The Separation of Blood Cell Precursors—New Methods Needed

Normal blood cell formation, hemopoiesis, is a series of differentiation events beginning with the undifferentiated, or pluripotent, bone-marrow cell and culminating in the release of functional blood cells. Dramatic improvements in the use of in vitro assays for morphologically unrecognizable blood-cell progenitors have facilitated the quantitation of the progenitors and the definition of their physical properties.

Elucidation of the mechanisms by which pluripotent cells are committed to one or another blood cell development pathway is a current research issue. Pluripotent cells in culture form colonies of cells, exhibiting several stages of differentiation. Colonies containing up to five types of differentiated blood cell elements, erythrocytes, granulocytes, monocytes, eosinophils, and megakaryocytes have been described.

Many assay systems designed to emphasize growth of particular subpopulations have been developed. Soluble growth factors and a variety of cell interactions have been identified, many of which are completely artificial and limited to the tissue-culture system. A few investigators have designed systems from which homogeneous colonies representing pluripotent stem cells or certain other types of stem cells can be isolated and removed with relatively high purity. Such purification has been difficult to achieve. Large-scale purification of target cell populations is necessary to understand cell behavior at the molecular level in a setting where both self-replication and multiple paths of differentiation are possible. Once pure subpopulations are obtained and made generally available, the study of factors and interactions will be simplified.

More rapid clarification of mechanisms of stem cell development, which is critical to development of rational therapy for clinically important problems such as aplastic anemia, bone marrow transplantation, and the leukemias, would be a valuable addition to the clinical armamentarium.

By encouraging applications for research support, the proposed program announcement would contribute to optimizing the study of early events in bone-marrow stem-cell differentiation to increase information needed to understand and prevent or cure stem-cell diseases. The immediate purpose is to facilitate efforts of investigators to develop techniques for obtaining homogeneous populations of cells from hemopoietic culture systems for subsequent study, to apply new technologies to identify cell surface markers and other functional differences of cells, and to develop libraries of antibodies for hemopoietic cells.

VI. Annual Evaluation Reports — Multipurpose Arthritis Centers and Diabetes Research and Training Centers

Preface

The Public Health Service Act, which mandates a program of multipurpose arthritis centers and diabetes research and training centers at NIADDK, directs that the activities of these centers be evaluated each year and be reported to Congress. The center evaluation reports for fiscal year 1984 are presented in this chapter.

Exhibit 6 (chapter I) lists and identifies the 15 multipurpose arthritis centers and the 7 diabetes research and training centers supported by the NIADDK in fiscal year 1984.

Research and training centers counsel patients effectively about home management of their disease.

Facing page

A significant proportion of NIADDK research in multipurpose centers is directed to clinical studies.

Eighth Annual Report on Evaluation of Multipurpose Arthritis Centers

Overview

The NIADDK initiated the Multipurpose Arthritis Centers Program in fiscal year 1977 in response to the National Arthritis Act of 1974 (P.L. 93-640, Section 439), which first authorized a national program of comprehensive arthritis centers. The MAC's now in operation are displayed in exhibit 6 (chapter I). Funding levels for the centers are shown in exhibit 12. The MAC's are designed to demonstrate and stimulate the prompt and effective application of available knowledge for the treatment of patients with arthritis and related musculoskeletal diseases and 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, clinical, and health services research; professional, patient, and public education; and community-related activities. A major goal of the 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 highlights some of the studies conducted during the past year that reflect the diversity of the centers program. These highlights, while indicative of activities of all centers, are by no means to be considered comprehensive for 1984.

Center Research Projects

Inherent in the concept of a multipurpose arthritis center is a strong research component. Center grant support is intended to complement traditional research grant support in a given institution, to establish related special projects, and to stimulate the development of new research projects. Consequently, each potential center is expected to be receiving research grant support for basic or clinical biomedical research related to rheumatic diseases as a prerequisite for a center grant award. Each center, therefore, possesses a substantial research base to study the cause of rheumatic diseases or the means of improving their diagnosis and treatment.

Biomedical research projects supported by center grant funds are almost exclusively developmental and feasibility studies. These studies are designed to encourage investiga-

tors to explore interdisciplinary and highly innovative scientific approaches that may later form the basis of applications for traditional research grant awards from the National Institutes of Health or other agencies.

Investigators at the Case Western Reserve University Arthritis Center in Cleveland, for example, last year began studying a substance known as C-reactive protein (CRP), a molecule synthesized by the liver in response to tissue injury, with a goal of understanding its role and biological significance in acute inflammation. Their first efforts focused on determining the mechanism of CRP induction and how its biosynthesis is regulated. Molecular genetic techniques were used to examine how messenger RNA (mRNA) is formed both in normal rabbit livers and in rabbit livers 24 hours after they have been subjected to an inflammatory stimulus. Initial results have shown that even after such a stimulus, no increase in mRNA formation occurs. This is a surprising result because theory predicted more mRNA to be present as a consequence of inflammation. In related studies, the catabolic rate of CRP was found to be quite rapid and independent of serum CRP concentration. These findings indicate that the liver plays a crucial role in the regulation of CRP synthesis and catabolism during the inflammatory response. Future experiments will involve analyzing CRP mRNA immunochemically and studying the mechanisms of hepatic uptake of extracellular CRP.

EXHIBIT 12. Funding levels of multipurpose arthritis centers in FY 1984 (dollars in thousands)

Boston University School of Medicine, Boston, Mass.	$1,131
Brigham and Women's Hospital, Boston, Mass.	838
Case Western Reserve University, Cleveland, Ohio	598
Indiana University School of Medicine, Indianapolis, Ind.	316
Stanford University School of Medicine, Stanford, Calif.	571
State University of New York, Downstate Medical Center, Brooklyn, N.Y.	323*
University of Alabama School of Medicine, Birmingham, Ala.	813
University of Arizona College of Medicine, Tucson, Ariz.	109
University of California School of Medicine, San Francisco, Calif.	541
University of Connecticut School of Medicine, Farmington, Conn.	939
University of Michigan Medical School, Ann Arbor, Mich.	572
University of Missouri Medical Center, Columbia, Mo.	850
University of North Carolina Medical Center, Chapel Hill, N.C.	373
Washington University School of Medicine, St. Louis, Mo.	360*
Northwestern University, Chicago, Ill.	690
TOTAL	$9,024

** Previous years' levels are indicated where a renewal application is currently being reviewed.*

Another study involving immunology is continuing at the University of Missouri Arthritis Center in Columbia, where investigators are using monoclonal antibodies to study autoantibodies in rheumatic disease. The occurrence of autoantibodies recognizing a number of specific nuclear antigens, the RNP and Sm antigens, is a characteristic feature of autoimmune disorders associated with rheumatic diseases in humans and mice. Mechanisms providing the stimulus and maintenance of these antibody responses, the types of antigens recognized by the antibodies, and the nature of the immune response remain to be elucidated. To examine these questions, the center has been producing hybridomas (artificially produced immune cells that each manufacture a single type of antibody to a specific antigen) that produce antibodies to the nuclear antigens being studied. Most of the hybridoma-produced antibodies have been of the immunoglobulin M (IgM) class and detect small proteins associated with the cell nucleus. During the past year, the antibody reagents have been used to assess the biochemical nature of a variety of normal cellular structures, which are typically inaccessible to conventional antibodies, and to examine in patients whether antibodies are present that may be similar to those found in the mouse model. It is anticipated that the reagents generated during this feasibility study will be important in studying multiple aspects of autoantigens, both as targets of autoimmune responses and as elements of key cellular processes in mammals.

Several studies at the centers are concerned with orthopedics. At Northwestern University's new center in Chicago, for example, a project is under way to define the mechanical properties of cancellous bone (bone made up of a bony lattice in contrast to solid bone) in rheumatoid and osteoarthritis patients undergoing total knee-joint replacement surgery. The investigators hypothesize that mechanical properties of bone and the subsequent bone-cement interface differ in osteoarthritic and rheumatoid patients. If this conjecture is correct, prosthetic design requirements might differ for these two groups of patients.

Another important project related to bone has been initiated by the arthritis center at the University of Michigan in Ann Arbor, where investigators are evaluating the capacity of electron-microscopic imaging techniques to detect pathologic changes in articular cartilage and bone in patients with osteoarthritis. Studies are being made with sonographic (ultrasound) imaging and bone scans (radiology) to detect microfractures in remodeling bone and with nuclear magnetic resonance (behavior of atomic nuclei) to define bone characteristics in experimental models of osteoarthritis. Unlike osteoporosis, where loss of bone can be monitored before overt disease occurs, osteoarthritis,

which involves breakdown of cartilage with almost no changes in bone in early stages, cannot be detected noninvasively. Advanced disease is often present by the time joint changes are apparent by x-ray. If nontoxic and noninvasive scanning methods were available, it might be possible to select patients who could benefit from prophylactic management. This study represents an opportunity to examine one of the most important questions in clinical research related to osteoarthritis: how to assess early cartilage damage by noninvasive techniques.

At the arthritis center at Brigham and Women's Hospital in Boston, investigators are developing a method to evaluate the success of total knee replacement surgery by gait analysis. The orthopedic surgeons involved hypothesize that limb function following total knee replacement relates to factors other than the prosthesis itself, such as muscle function. A group of patients who have had knee replacements will be studied with respect to a number of parameters, including three-dimensional gait analysis and energy consumption as measured by oxygen uptake. These studies represent the utilization of a well-established technology, previously used for children with cerebral palsy, to study a problem of enormous economic and social significance in this country.

Several projects in the arthritis centers deal with rheumatoid arthritis synovial tissue. In a project under way at the arthritis center at the University of Alabama in Birmingham, scientists have noted substantial evidence of local antibody formation at synovial sites in rheumatoid arthritis and propose to characterize B lymphocytes, antibody-producing cells, in synovial tissue in terms of cell-surface markers. Using hybridoma technology, the investigators will determine whether there is a limited number of types of those cells at the inflammatory site. Attempts will also be made to clone cells from the synovial sites and to assay both their antigenic characteristics and the antigenic specificities of the antibodies they produce. It is hoped that the information gained from this analysis will explain how the inflammatory response progresses in rheumatoid arthritis.

In a related study at the University of California in San Francisco, the techniques of molecular biology are being applied to search for a cell or cell line in rheumatoid synovium that exhibits changes in chromosome structure (oncogene expression) that involve the inclusion of nucleic acid information reproducing that found in certain tumors usually associated with cellular transformation, a process of cell stimulation that is also observed in malignant cells. If cells at chronic inflammatory sites are found to have such characteristics, fundamental questions would be raised about the functional significance of oncogene expression. The finding that oncogenes are activated in some nonmalignant conditions, such as rheumatoid arthritis, would be significant for the study of genetic control mechanisms in general and could possibly lead to new approaches in the treatment of rheumatoid arthritis.

The center at the University of Connecticut in Farmington has been attempting to determine whether zinc metabolism is abnormal in patients with rheumatoid arthritis. So far, 42 rheumatoid arthritis patients, 12 patients with other forms of arthritis, and 10 normal volunteers have been tested. Plasma zinc levels were significantly decreased in rheumatoid arthritis patients compared with healthy controls, although zinc bound to red cells, protein, and albumin was normal in these patients. The total level of circulating albumin was lower in rheumatoid arthritis patients than in controls, so the decrease in plasma zinc may be due in part to a decrease in this major zinc carrier protein. On the other hand, patients being treated with gold or penicillamine had lowered plasma zinc levels but normal albumin levels. Future studies will be concerned with increasing the number of patients being examined and determining the clinical relevance of these findings.

Center Education Projects

Another integral aspect of the MAC program involves educational activities designed to facilitate and increase the education of health professionals. For example, the University of Connecticut MAC is continuing to develop and evaluate computer-based education protocols on rheumatoid arthritis, gout, and SLE for physicians and patients. The course includes sections on treatment, medication, exercise, joint protection, the use of adaptive equipment and splints, patient compliance, psychosocial issues, relaxation techniques, and the use of nonprescribed therapies. After the lessons are completely developed, they will be transferred to microcomputers and will be available nationally to anyone with access to a personal computer.

The center at the University of Missouri is conducting a project designed to plan, implement, and evaluate continuing education programs in arthritis for community health nurses in Missouri. To achieve this goal, the arthritis center is working in conjunction with the Missouri Bureau of Community Health Nursing. The center has conducted a needs assessment of over 300 community health nurses and has developed a series of workshops to update the knowledge and skills of nurses who work with arthritis patients in their homes. The Bureau of Community Health Nursing intends to continue these rheumatology workshops after project funding has ended.

At the University of North Carolina Arthritis Center in Chapel Hill, a patient education project is being conducted to systematically identify effective interventions to increase the rheumatoid arthritis patient's compliance with his or her treatment regimen. Each patient is being interviewed to identify the physical, psychological, social, and environmental inhibitors and facilitators of compliant behavior. The information obtained is being used to plan feasible and effective interventions to increase compliance. When complete, this project will contribute to the field of arthritis patient education by providing patient educators

and other health professionals with a procedures manual containing guidelines for a psychosocial diagnosis to identify reasons for noncompliance and for assessing patients' needs for appropriate education or referral sources.

Another patient education program, being conducted at the arthritis center at Northwestern University, will develop, implement, and evaluate an education program to teach aerobic-like exercise to rheumatoid arthritis and osteoarthritis patients. A number of variables will be studied, including physiological variables such as joint inflammation, muscle strength, and functional capacity and psychological variables such as self-regard, level of wellness, and perceived level of pain. Besides attempting to determine if this educational and exercise program can be effective in improving the physiological and psychological well-being of arthritis patients, the investigators hope to learn if the program works better for some types of arthritis patients than for others and if its effectiveness is modified by the patient's level of education or motivation. This study should help to determine the efficacy of aerobic-like exercise for those with arthritis.

At the Brigham and Women's Hospital arthritis center, an educational program has begun to evaluate how low back injuries can be prevented at the worksite. The goals of the study are to reduce the incidence of lifting-related back injuries and to reduce the average duration and total number of days lost from work due to back pain and lifting-related injuries. Subjects will include approximately 4,500 Boston postal workers and supervisors, who will receive either no intervention or education about back injuries along with periodic followups. In addition, physical therapists will monitor actual lifting practices. Study variables to be measured include back pain, psychological well-being, depression, cardiovascular fitness, alcohol consumption, and smoking history. If successful, this study could have important economic implications by reducing the number of work-related back injuries and the level of associated disability.

Center Community Activities and Health Services Research Projects

Community and health services research projects conducted by the MAC's deal with a diverse range of activities, including health economics and the cost of care for persons with rheumatic diseases; measurement of functional outcome variables and disability; epidemiology of rheumatic diseases; the effect of chronic illness on the quality of life for both adults and children; and the assembly, storage, retrieval, and analysis of data dealing with populations of persons with rheumatic diseases.

A study under way at Case Western Reserve University's multipurpose arthritis center is designed to explore the problems that adults with rheumatoid arthritis and children with juvenile rheumatoid arthritis have in obtaining their rights and benefits under current disability and handicap laws. The nature of these diseases makes it difficult at times to establish a definite clinical diagnosis. In addition, characteristic periods of flareups and remissions may make it more difficult for these patients to obtain their rights and entitlements. So far, 100 adult and 200 juvenile rheumatoid arthritis patients have been surveyed to identify the types and frequency of handicap and disability legal problems they have experienced. The information obtained from these interviews will be analyzed by legal experts and correlated with Federal and state laws and regulations. After this analysis is completed, two sets of legal materials, one designed for patients and a second designed for health care and legal professionals, will be written by experts in community education and by lawyers specializing in problems of the chronically ill, handicapped, and disabled.

To manage better the care of patients with rheumatic diseases, especially in locations that may not have the services of a trained rheumatologist, the arthritis center at the University of Missouri is developing a computerized rheumatology consultant system. The clinical situation is that of the physician who feels that he or she may require a rheumatology consultation for a new or current patient. The computer model will determine whether a rheumatologic problem exists, how the patient workup should be structured in terms of physical examinations performed, whether referral is desirable, or which of the therapeutic management plans within the computer would be most appropriate. The system so far contains 26 disease states, including rheumatoid arthritis, SLE, progressive systemic sclerosis, gout, infection-induced arthritides, juvenile rheumatoid arthritis, and osteoarthritis. It has been tested retrospectively against 443 cases with an overall accuracy of 94 percent. The computer will refuse to make a diagnosis for items that are not in its knowledge base, and it also identifies which treatment situations are not safely undertaken by the nonexpert, with or without the computer consultant. After the model is tested completely, it will be adapted to a microcomputer for distribution around the country.

A study has begun at the arthritis center at Northwestern University with the objectives of investigating the prevalence of musculoskeletal disease among three subgroups of the elderly—the institutionalized, the ambulatory or "well," and the homebound or "frail"; assessing the degree of functional impairment associated with musculoskeletal disease among these three subgroups; and developing and testing cost-effective intervention strategies aimed at maintaining independent functioning among these subgroups. This study is necessary because demographic data show that an increased proportion of the elderly, especially those over 75 years old, have musculoskeletal diseases. In addition, an association between decreased manual dexterity and dependence in elderly

women points to a need to assess the relationship between physical therapy and functional status in the future.

As part of a collaborative investigation with the Tecumseh Community Health Study, a longitudinal prospective analysis of a number of diseases in a Michigan community, the arthritis center at the University of Michigan is beginning to analyze the epidemiology and risk factors associated with osteoarthritis. In addition to rereading the initial radiographs of hands and wrists taken approximately 20 years ago, data on weight, socioeconomic status, occupational activity, joint symptoms, and biochemical parameters will be analyzed. This study will prove useful if predictive factors in disease development can be identified.

An epidemiologic study being conducted by Boston University's arthritis center will investigate the association between the use of oral contraceptives by women between the ages of 15 and 44 and the development of rheumatoid arthritis. This study will analyze data on over 100,000 women and provide more detailed information on oral contraceptive use and the development of rheumatoid arthritis than is currently available. It will examine whether the observed protective effect depends on the estrogen or progesterone content of the pill. The effect of duration of oral contraceptive use and dose of estrogen used also will be explored. If the protective effect of oral contraceptives is confirmed, this study will contribute to understanding the pathogenesis of rheumatoid arthritis and will yield information on the relation of sex hormones and autoimmune disease.

Another area of center activities deals with health economics. The center at Stanford University in Palo Alto, in cooperation with the University of California's arthritis center, is developing and testing a method to measure indirect and psychosocial costs of rheumatoid arthritis and osteoarthritis by means of diaries of health services used and daily activity. One hundred individuals from each location, and 50 controls, will be studied. This study will systematically analyze the most important categories of activities affected by disease and make comparisons between rheumatoid and osteoarthritis patient groups and a healthy control group. Measurement of disease impact on patients, aside from direct costs of work loss, is extremely important in assessing chronic debilitating diseases such as arthritis. These investigations could provide significant methodological contributions not only to the study of arthritis but to considerations of chronic diseases in general.

Core Units

During the past year, core units were in operation at several arthritis centers. These common-use facilities or technical resources 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, to name just a few. Core units in other areas are concerned with biostatistics, evaluation methodologies, educational activities, and epidemiology.

The center at Indiana University in Indianapolis has had two core units in operation during the past year. The immunology core unit has functioned as a centralized facility in which specialized tests of human immune function can be performed, including assays for immune complexes, assays of in vitro antibody synthesis, and assessment of T and B lymphocytes in peripheral blood. The core unit concerned with connective tissue biochemistry has been designed to separate and purify proteins and other complex compounds derived from a variety of soft tissues. This core has developed the capability to separate substances by various types of electrophoresis and analyze the results by specially designed computer software.

A core unit at the University of Michigan's center is providing investigators with tissue culture support for a number of diverse projects, including the isolation and characterization of proteins important in activating human connective tissue cells, a study showing that fibroblasts from scleroderma patients have increased rates of hyaluronic acid synthesis, and identification of a new connective tissue activator factor in human urine.

An immunoassay and immunoreagent development core unit at the University of North Carolina is responsible for maintaining a library of human antibodies used by a number of investigators involved in the center, for preparing antibodies to human proteins, and for developing methods for conducting immunologic assays that will be available to center investigators on a routine basis.

A cell culture core operating at the arthritis center at Case Western Reserve University provides investigators with cell and tissue culture laboratory facilities for morphologic and biochemical studies such as those dealing with enzyme purification, proteoglycan and collagen biosynthesis, the in vitro behavior of mammalian chondrocytes and cartilage metabolism in aging, the role of cell-mediated immunity in rheumatoid arthritis and osteoarthritis, and the role of various hormones on the pathophysiology of cartilage and osteoarthritis. At the same center, an education and evaluation core unit provides a mechanism for evaluative review and prospective analyses of ongoing center projects and provides recommendations for new projects and activities. The members of the core group review protocol design, data collection methods, instrument development, and statistical analysis and provide guidance to the project investigators in process, impact, and outcome evaluations.

Similar core units dealing with statistics and evaluation are in operation at the arthritis centers at the University of Connecticut, the University of North Carolina, Boston University, Stanford University, and Northwestern University. These cores provide expertise in research design and planning, data collection, data base management, computer programming, and data analysis and act as a technical resource regarding statistics.

The arthritis center at Brigham and Women's Hospital has several core units, including an immunogenetics core to support the evaluation of genetic factors in rheumatic disease by performing assays to detect the major histocompatibility antigens in patients with various forms of arthritis; a hybridoma core to produce monoclonal antibodies for projects dealing with such areas as complement production, proteoglycan synthesis, and systemic lupus erythematosus; a morphology core that performs a wide range of laboratory procedures such as scanning and electron transmission microscopy, immunocytochemistry, and x-ray analysis; and a biometry core that provides statistical and computational support for many center projects.

Collaborative Use of Resources Within Each Center

The shared facilities and cooperative effort made possible under the center concept permit more efficient use of resources and result in greater productivity than would be achieved by separate research grant awards to each of the participating individuals. Resource sharing is one of the major advantages of the center program and ensures maximal results from available funding. The centers provide an excellent example of the whole exceeding the sum of its parts.

Coordination and Collaboration Among Centers

A special emphasis of NIADDK program management is to foster and effect intercenter communication and activity to make the Multipurpose Arthritis Centers Program more efficient and productive. One way of accomplishing this goal has been to sponsor annual meetings of center directors, center personnel, and Institute staff responsible for administering the program. Meetings of this nature, 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 compiles and updates annually a directory of center personnel as well as a listing of instructional materials produced by the centers and is in regular contact with each center by means of periodic letters and telephone calls. The centers also have been encouraged to use the services of the AIC, which is funded by contract by the NIADDK as a repository for educational and other information materials. This clearinghouse enables health professionals around the country to have access to literature produced by the centers during the course of their investigations.

The arthritis center at Case Western Reserve University, for example, has made available to other arthritis centers its extensive collection of audiovisual materials. In addition, collaborative efforts in biomedical research have been carried out with the Indiana University multipurpose arthritis center and with the Arthritis Clinical Research Center (funded by the Arthritis Foundation) at the University of Miami in studies of osteoarthritis and cartilage metabolism.

The University of Missouri's multipurpose arthritis center is utilizing a variety of instructional materials produced by other centers in its education program, including videotapes for physicians describing how to conduct a physical examination for arthritis patients, produced by the center at Washington University in St. Louis; a patient education handbook produced by the University of Cincinnati's center; and a referral guide for physicians and other health professionals, dealing with occupational therapy in arthritis, developed by the center at the University of Michigan.

Center Evaluation

To assure that the goals addressed by each center in the original grant application are being fully and successfully implemented, several types of evaluative activities are employed. The centers evaluate continually both the quality and effectiveness of their endeavors. The evaluation mechanisms used vary according to the activity being studied, such as pre- and posttesting of students, chart audits of physicians who have received training, and process evaluation based on numbers of attendees at courses and lectures. Some of these measures, which may involve special evaluation core units, already have been described in this report. Many of the centers also have groups of outside consultants visit their institution each year for several days at a time to determine the quality of the ongoing activities.

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

The effectiveness of a center also can be determined by analyzing the results of the developmental and feasibility studies that it has supported. For example, evaluation of the results of the study conducted by the University of Missouri's arthritis center, dealing with antibodies to nuclear antigens (described earlier in this report), has enabled the investigators to obtain additional support to continue these studies by means of a regular NIADDK research grant.

At the University of Alabama Arthritis Center, development and feasibility studies have resulted in 15 publications in peer-reviewed journals, 22 presentations of papers at national scientific meetings, an NIH Research Career Development Award and an extramural fellowship, and 6 peer-reviewed research grants.

Peer review plays a key role in evaluation of the multipurpose arthritis centers in several ways. First, the NIH utilizes expert scientists as peer reviewers to conduct onsite visits and to review and evaluate each center grant application. Second, once in operation, most arthritis centers have an external advisory committee to oversee operations and provide advice on overall operations on an

annual basis. Finally, before individual center projects are submitted for funding consideration, the arthritis center usually convenes a panel of internal reviewers to rate each project to assure that it meets the center's standard of quality.

Conclusions

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 in the areas of biomedical and health services research. The program is continuing to mature with high-quality research developments, prompt application of research findings in patient care, professional and lay education, broad collaboration with health care providers, and productive demonstration activities. Progress made during the past year contributes to fulfilling of the role of these centers as a national resource.

Seventh Annual Report on Evaluation of Diabetes Research and Training Centers

Introduction

The DRTC program, which was authorized by the National Diabetes Mellitus Research and Education Act (P.L. 93-354, Section 435), has been active for several years. This program was initiated in accordance with the recommendations of the National Commission on Diabetes, which was authorized by the same legislation. In its report to Congress (DHEW Publication No. (NIH) 76-1018), the commission recommended that the DRTC's promote the following types of activities:

- Basic and clinical research in the fields of diabetes and its management.
- Training of postdoctoral fellows for research in diabetes and its management.
- Training of health professionals in diabetes and its management.
- Training of practitioners of the health professions in diabetes and its management in the form of continuing education and information programs.
- A model training-education-treatment demonstration facility for people with diabetes to contribute to the above four areas of endeavor.

At present, there are seven DRTC's. These are at the Albert Einstein Medical College/Montefiore Hospital (Bronx), the University of Chicago/Michael Reese Hospital (Chicago), the University of Indiana School of Medicine (Indianapolis), the University of Michigan (Ann Arbor), Vanderbilt University (Nashville), the University of Virginia (Charlottesville), and Washington University (St. Louis). (See exhibit 6, chapter I.) Of the eight centers that were originally established, all have undergone at least one competitive renewal review, and seven have received continued funding. Funding levels for these centers are shown in exhibit 13. The DRTC's are evaluated continually through several varied but complementary processes that include NIH peer review, review of progress reports, staff visits to centers, annual meetings, special evaluation projects by Institute staff, and in-house evaluations by centers.

The DRTC's have two major components—a biomedical component and a training and information transfer component. Within both of these components, center funding may be proposed for three types of activities: shared resources (cores), pilot and feasibility studies, and enrichment. Each of these activities is described briefly below.

A biomedical core at a DRTC is a shared facility that provides a service needed by and available to center research investigators to promote more efficiently conducted biomedical research. In addition to providing a specific service, for example, radioimmunoassays or molecular biology methodologies, the cores serve as focal points for collaboration. Furthermore, they provide consultation and training in highly sophisticated technical areas and make available to multiple investigators large and expensive equipment, enabling its more efficient use. In the DRTC setting, limited developmental work on the latest and best methodologies may be pursued. Overall, DRTC biomedical cores provide services at a substantial cost benefit to investigators and enhance clinical research.

Training and information transfer cores also provide services. Biostatistical consultation, design of evaluation instruments, and developmental design of programs and materials for training of health professionals are illustrative of these services. The model demonstration unit provides short-term training of health professionals and enhanced opportunity for clinical research.

Pilot and feasibility studies provide modest support for a limited time period (3 years or less) to explore the feasibility of a new concept. These studies usually result in sufficient preliminary data to enable an investigator to apply for independent funding through regular research grant mechanisms.

Enrichment constitutes enhancing the multidisciplinary environment through seminars and conferences and through the exchange of information with consultants and lecturers from outside the center.

The proportionate funding for these three activities varies from center to center since institutions are encouraged to build upon their strengths. However, an average of 62 percent of DRTC funding is devoted to biomedical research, including an average of 46 percent for biomedical core resources and 16 percent for pilot feasibility research projects. For the training and information transfer component, which also embraces some clinical research support, an average of 38 percent of the funding is used; less than 1 percent of funding is used for enrichment activities.

A primary and important recommendation of the National Commission on Diabetes was that institutions aspiring to establish a DRTC must have a substantial base of high-quality, independently supported research in diabetes

EXHIBIT 13. Funding levels of diabetes research and training centers in FY 1984 (dollars in thousands)

Albert Einstein College of Medicine, New York, N.Y.	$ 1,305
Indiana University, Indianapolis, Ind.	919
University of Chicago, Chicago, Ill.	1,928
University of Michigan, Ann Arbor, Mich.	1,986
University of Virginia, Charlottesville, Va.	1,154
Vanderbilt University, Nashville, Tenn.	1,265
Washington University, St. Louis, Mo.	1,496
TOTAL	$10,053

and related endocrine and metabolic disorders. The center provides services from shared resources (cores) for the key center participants, pilot and feasibility research studies for recently trained investigators and investigators new to the field of diabetes, activities in training and information transfer, and enrichment of the total research and training efforts. This is intended to create an environment that substantially enhances all aspects of the center—research, research training, and training of health professionals.

Another goal of the DRTC's that emanated from the recommendations of the commission is the development and application of a multidisciplinary approach to diabetes research by bringing investigators from other disciplines relevant to diabetes research into the center environment. Several unique features of the DRTC's contribute significantly to this effort: sharing of resources from cores by new investigators and investigators from other disciplines, availability of pilot and feasibility funds to attract new investigators, consultation about and training in highly technical procedures offered by the cores, and participation in the multiple disciplines and opportunities for enrichment offered by the center.

Types of Evaluation

Evaluation of the DRTC's is accomplished by four independent mechanisms: the NIH peer-review system, organizations external to the NIADDK, NIADDK staff, and individual center-based in-house evaluations. Because the in-house processes at centers are fully evaluated by the peer-review process, they need no further consideration here. The first three approaches will be addressed briefly, since these evaluative processes have been described in detail in previous annual reports.

Evaluation by NIH Peer Review

The peer-review system of the National Institutes of Health provides a rigorous, thorough, and effective evaluation of the centers. This evaluation comprises an initial review group site visit to the proposed center and a subsequent independent review of the report of the initial review group by the National Advisory Council. This two-tiered evaluation serves as the primary basis for determining whether a center will be funded and for how many years (usually for 3 or 5 years). At the end of this period, a renewal application may be submitted. This review includes a consideration of the progress made by the center toward achieving its goals and objectives during the previous period of support. Although conducted only every 3 or 5 years, the close scrutiny accorded this aspect of center evaluation makes it an extremely valuable, and indeed critical, part of the overall evaluative process. All of the eight original centers have undergone competitive renewal review. One of these, although approved in principle, was judged not to have made sufficient progress toward accomplishing program objectives to merit continued funding.

Evaluation by Outside Organizations

The NDAB has a mandate to oversee progress and make recommendations regarding the efforts by all relevant Federal agencies in implementing the "Long-Range Plan to Combat Diabetes" originally proposed by the National Commission on Diabetes (DHEW Publication No. (NIH) 76-1018). Within this comprehensive framework and after careful consideration of center activities, each report of the NDAB has addressed in a positive fashion the progress of the DRTC program toward achieving its goals. The Board's advice and suggestions provide an ongoing external source of valuable guidance to the program. In response to the Board, the DRTC's, along with other diabetes programs, have participated in the preparation, evaluation, and subsequent dissemination of NDAB-sponsored activities such as the publication of *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners*. The DRTC's also have contributed to the current efforts to establish national standards for diabetes patient education programs. In its annual reports, the NDAB has praised the centers and their accomplishments and supported enthusiastically their continuation.

Evaluation by the NIADDK

The NIADDK staff continually monitors the centers through in-depth analyses of applications, summary statements from reviews, progress reports, information submitted on special topics, annual program visits to the centers, and workshops with center participants on special topics. A theme is chosen for each annual report to present information on a special aspect of center accomplishments and activities. This year's report will address the opportunities for training (taken in a broad sense) that may be unique to or enhanced greatly by the presence of the DRTC.

Training Aspects of DRTC's

The importance of maintaining a cadre of new investigators entering the arena of biomedical research cannot be overestimated. The vitality and innovation of biomedical and clinical research are dependent upon a constant infusion of new researchers. The mandate of the centers, the enhanced environment, and the possibilities for multidisciplinary approaches to biomedical and clinical problems all foster the training of new professional personnel. The opportunities for biomedical research and for training health care professionals are important contributions of the centers to the professional development of investigators with interests in diabetes.

In the context of the present discussion, the word "training" will be used broadly, as was proposed in the enacting legislation and the recommendations of the National Commission on Diabetes. Conventionally, research training is limited to National Research Service Awards (NRSA) for individual fellowships and institutional training grants and

to traditional continuing medical education courses for health professionals involved in the care and treatment of patients. This wider definition will include any opportunity for learning or enhancing skills and knowledge as they apply to professional development. In this report, the broad concept of training opportunities in both the research component and the training and information transfer component will be presented. Highlights of biomedical research from each of the centers are discussed in chapter III.

Research Component of DRTC's

Opportunities for training and career development that are not unique to the centers will be discussed briefly. These are the Federal NRSA and career development programs and similar programs from non-Federal funding that are extant in most large medical centers. A more detailed discussion will be accorded to the training opportunities that are unique to the centers, such as the availability of funds for pilot and feasibility studies and the opportunity to acquire new skills from the cores of the DRTC's.

National Research Service Awards

Three types of awards are available under this program: institutional training grants, individual postdoctoral fellowships, and senior fellowships. These grants support costs of research training for students in biomedical research at the pre- and postdoctoral levels. The NRSA provides the opportunity to carry out supervised research to enable biomedical scientists, clinicians, and others to broaden their scientific backgrounds and to expand their potential for research in health-related areas. Senior fellowships also are offered for experienced scientists to make major changes in the direction of their research careers, to broaden their research capabilities, or to augment their command of an allied research field.

All of the universities with DRTC's hold institutional training awards relating either solely to diabetes or to diabetes and a closely allied field (e.g., diabetes and endocrinology). Likewise, there are individuals with fellowships in diabetes and closely related areas in all the centers. The research base of each center includes individual research investigators who hold research project grants. These investigators generally serve as preceptors for research training for postdoctoral investigators in diabetes. A DRTC, with its multidisciplinary approaches and opportunities for continuing professional development and other ancillary forms of knowledge and skills acquisition, provides an enhanced environment to individuals in these programs at centers.

Career Development Awards

The NIH programs that provide additional professional development to individuals beyond the immediate postdoctoral level are fairly well known. These include the RCDA, the CIA, and the PSA. The PSA is the most recently initiated and is designed to meet special research training needs of individuals with M.D. degrees. Similar awards are also available from non-Federal sources. These awards are intended to provide recipients with a broad systematic exposure to basic biomedical research, together with in-depth hands-on experience during their overall postdoctoral development. It is expected that the physician will acquire experience and skill in the fundamental and clinical scientific disciplines essential for a multidisciplinary approach to the problems of diabetes. The ever-increasing complexity of basic biomedical research may discourage individuals with an M.D. degree from entering research careers. PSA's are designed to overcome this difficulty, and they may prove to be essential in maintaining an adequate flow of well-trained physician scientists necessary to ensure the quality and clinical relevance of biomedical research. In general, DRTC's have two individuals holding PSA's in the area of diabetes research. Because the first PSA's were made during this fiscal year, it will be some time before their role and impact can be evaluated.

These programs are not unique to the centers. However, since the centers provide an environment supportive of high-quality diabetes-related research, they have a significant salutary effect in attracting talented young investigators for the NRSA programs as well as applicants for career development awards. Centers can provide high-quality training that includes an increased awareness of current diabetes research and of the opportunities for participation in such research. An additional advantage is the availability of specialized training from the center cores and the possibility of receiving funding for pilot and feasibility studies. These center training opportunities will be discussed later in this report.

Pilot and Feasibility Studies

Centers provide unique opportunities for conducting pilot and feasibility studies in biomedical and behavioral research. These studies are usually limited to 3 years, although many of the centers limit them to 2 years. Funding is modest and is intended to allow investigators to obtain preliminary data or test the feasibility of a research proposal. Support is limited to new investigators without prior NIH funding or to established investigators in a field other than diabetes willing to test their expertise on a problem related to diabetes. The proposals are presented in the format of NIH research grant applications and are peer reviewed.

While pilot and feasibility studies are a cost-effective means of providing new investigators with experience in preparing research grant applications and the process of peer review, they also allow investigators to amass preliminary data to substantiate their proposals for NIH grant applications. This concept is verified by data indicating that more than 40 percent of all investigators who have completed feasibility studies compete successfully for NIH grants in the field of diabetes. This mechanism has con-

tributed significantly to the infusion of new investigators into the area of diabetes research.

Investigators performing pilot and feasibility studies contribute to and benefit from other aspects of the centers. A primary benefit is the use of the cores. Not only can investigators take advantage of these shared facilities that provide specialized services, but they can learn specialized techniques and methodologies from the core personnel or from using the core themselves. They also have the benefit of working in a multidisciplinary environment and are included in the advantages resulting from the center funding for enrichment.

A study is in progress that analyzes the career progression of the recipients of pilot and feasibility studies. While early results indicate that a significant proportion continue in diabetes research, the real value of this program must await more long-term results. Whatever the ultimate outcome, the pilot and feasibility studies have contributed to the training and career development of new investigators.

Cores or Shared Resources

Cores are set up primarily as shared resources for specialized determinations, techniques, and methodologies. As such, their primary focus is the provision of services. However, cores vary depending on the nature of the service they provide. In some, the service is training in and supervision of complex techniques and methodologies. How cores provide training can be presented best by some examples.

Radioimmunoassay core facilities lend themselves well to the concept of shared facilities. These cores are set up to run radioimmunoassays for a wide variety of substances, mainly hormones. Determinations for insulin and glucagon predominate in the DRTC cores. The major incentives for an investigator to utilize the core for these determinations are lower costs, increased standardization of results, enhanced quality control, and savings in time. This concept might defeat its own purpose, however, if trainees and other investigators were not provided the opportunity to learn the methodologies. Almost all centers routinely require trainees and postdoctoral and graduate students to learn new techniques through participation in the core.

Animal cores may vary widely depending on the primary focus of research involving animals. Basically, the cores provide animals with specified characteristics (e.g., streptozotocin-diabetic rats) on a cost-efficient basis. Another important facet is that more intensive care for these animals is provided by specialists trained in the particular techniques being applied. (More detailed descriptions of specific animal cores have been presented in previous reports.) While investigators must perform their own experiments and be responsible for the animals, they also must learn all of the techniques and approaches for performing animal research from specially trained personnel. This ensures that the best methodologies will become an integral part of their research training.

Specialized instrumentation cores are also an important aspect of several centers. Typical examples are an electron microscope core, a mass spectrometry core, or a core providing high-pressure liquid chromatography. Training is the major service in these cores. The individual investigator must perform his own experiments but under the tutelage and supervision of a qualified expert in the field. In many cases, these center-shared resources are shared further with similar cores from other centers or resources, resulting in cost savings and greater efficiency for all investigators involved. An example is the mass spectrometry core at Washington University (St. Louis), which is an add-on to a mass spectrometry resource funded by the Division of Research Resources. For very expensive instruments, this approach is not only more cost effective, but it also provides wider availability of the instruments and a readily available source of training in the techniques and methodologies associated with the particular area. A wider application of the concept of shared resources for expensive and complicated instruments is one possible approach to the problem of growing obsolescence of expensive and complex instruments and is integral to an adequate provision of instrumentation to biomedical researchers.

Molecular biology, along with protein and peptide sequencing and analysis, has brought biomedical research into an era of complex technologies and methodologies. Cores in this area are important in making these new technologies and approaches available to more investigators. In these cores also, training is the most important and prevalent service. Research in this area can be very expensive. Without appropriate training and supervision, costs for the learning process can be great. Additionally, cores in this area lend themselves to bulk purchasing, often at significant savings. Thus, these cores are able to provide highly specialized and technical training for a wide range of investigators economically. Not only is this important to the center involved, but excellent training of investigators in these complex technologies early in their careers will be reflected in their research approaches later.

A biostatistical core is listed usually under the training and information transfer component. However, biostatistical cores are used by all members of the center. The major function of such a core is to assist researchers in the design of experiments. Without a special core facility in biostatistics, the availability of this kind of consultation may be inadequate or it may even be unavailable. Centers with biostatistics cores have found increased usage over time, and many have developed courses for specialized areas to reach more investigators. The primary value of training in this core is an increased awareness of the importance of biostatistical expertise in wisely planning research experiments that will later lend themselves to statistical analysis.

Enrichment

While the enrichment program of centers is not training per se, the enrichment of the environment through addi-

tional seminars, visiting consultants, additional courses in specialized techniques, and the multidisciplinary approach will complement the training opportunities offered at the DRTC's.

Training and Information Transfer Component of DRTC's

Training in DRTC's refers most directly to the training of health professionals in the education, care, and treatment of the diabetic patient. The inclusion of this aspect of training was a new and innovative approach in the diabetes field when DRTC's were initiated. The approach (outlined in P.L. 93-354 and expanded in the recommendations of the National Commission on Diabetes) was a result of the opinions of the diabetes community and health care providers that this was a neglected area. Heretofore, opportunities for training of health professionals in diabetes were few, with no evaluation or followup on outcomes. Now, 6 to 7 years after establishing the first DRTC's, a host of programs and materials have been developed that reflect the most advanced and substantiated approaches to diabetes education, care, and treatment. Significant numbers of these innovative and sophisticated approaches have been tested and evaluated and are available to the general diabetes community. As other problems and needs are identified, the development of programs and materials continues at the DRTC's.

Dissemination of Material From the DRTC's

From the inception of the DRTC program, centers were urged to deposit with the NDIC completed programs or materials that were available and applicable to settings outside the immediate environment of the DRTC's. In 1983, the NDIC (whose advisory committee includes a representative from the DRTC's) compiled a compendium of programs and materials for health professionals, patients, and lay audiences. These programs and materials were developed by member organizations represented on the advisory committee. The DRTC's submitted descriptions of the programs, manuals, and materials that they had developed. Only those materials that were ready for national (or international) distribution were included. Development and testing of these materials have identified other needs that are currently being met at the centers.

The programs and materials available from the DRTC's are impressive. The contribution by the centers of programs and materials for training of health professionals is keeping pace with the need and is complementing the efforts from other sectors to improve the education, care, and treatment of diabetic patients.

DRTC Liaison With Groups Interested in Diabetes

One of the mandates of the legislation for the DRTC's was to develop liaison and cooperative efforts with other Federal agencies and organizations in the private sector with interests in diabetes. At approximately the same time that the DRTC's were established in 1977, other diabetes activities also were being initiated: the CDC Diabetes Demonstration Projects Program, the IHS Model Care Diabetes Program, the NDAB, and the NDIC. Already established was the Federal Diabetes Mellitus Interagency Coordinating Committee. Over subsequent years, the efforts of these various groups have complemented one another.

Previous reports have dealt with the development of collaborative arrangements and consultations with the CDC diabetes demonstration projects and the IHS Model Care Diabetes Program. Materials and programs developed by the centers have been used or adapted for use in these and other settings. DRTC personnel have acted in many instances in a consultative capacity, primarily for the CDC state projects, the IHS, and the Institute's Diabetes Control and Complications Trial. Some of the most recent interactions have stemmed from the publication prepared under the aegis of the NDAB, *Five Complications of Diabetes: A Guide for Primary Care Practitioners.* The need for such a document was one of the recommendations emerging from an NDAB-sponsored conference held in June 1981 to address priority issues in diabetes treatment, i.e., the need for a guide for primary health care providers relating to the treatment and prevention of five major complications of diabetes. The guide is designed to help the primary care practitioner in the day-to-day management of patients with diabetes. The draft of the document was prepared by a member of one of the DRTC's based on a program that had been developed at that DRTC. The guide was field-tested at selected CDC diabetes demonstration project sites. All DRTC's utilize the guide in their programs.

Physicians at the multipurpose arthritis centers conduct research, but they also explore problems such as the health economics of rheumatic disease and the effect of chronic illness on day-to-day life.

Within the Federal sector, distribution of the guide began through a conference sponsored in February 1983 by the DMICC in conjunction with the Uniformed Services University of the Health Sciences at which the Veterans Administration, Department of Defense, and Health Resources and Services Administration (particularly the IHS) developed plans for use of the guide. These plans resulted in a relatively wide distribution within the Federal sector. The distribution in the non-Federal sector was phased—the guide was sent first to key individuals who teach other health providers about diabetes (including the DRTC personnel) and later to primary care providers through established programs of continuing education, update courses, and community outreach activities. The DRTC's, the CDC diabetes demonstration projects, the IHS Model Care Diabetes Program, the ADA, the American Association of Diabetes Educators, and others constituted a major network to implement this distribution.

The guide also resulted in creation of many related instructional materials. A slide set and narrative to introduce the guide was prepared by the Michigan DRTC. DRTC's have been involved throughout this process and are using the guide in conjunction with some of their programs and aiding in distribution through presentations to primary health care professionals.

The NDAB Committee on Diabetes Patient Education has developed standards for diabetes patient education during the past 2 years. They are continuing to develop an official recognition process for hospitals or groups presenting patient education programs in diabetes. Participants from the DRTC's have served as consultants to many of the workshops held in preparation of the standards. Two DRTC's are participants in testing the feasibility of the recognition process.

Training in Teaching Skills for Health Care Professionals

Health care professionals are increasingly required to teach patients how to manage their chronic illnesses or to change their lifestyles to prevent disease. This is particularly true in diabetes. Most health care professionals have had no training in teaching skills, although many have expressed a high degree of interest in such training. In response to these expressed needs, programs have been or are being developed by the DRTC's. An example from each center will illustrate the scope of this response.

The Vanderbilt DRTC has developed a model course in effective teaching skills. The content includes skills required for effective presentations in the cognitive domain as well as behavioral principles applicable to the health field. This center also has developed a self-instruction module that was commissioned and paid for by the American Association of Diabetes Educators, which is distributing a copy to each of its over 2,700 members.

The University of Michigan DRTC annually offers a teaching and learning strategies workshop for DRTC staff and a teaching and learning strategies symposium for health care professionals outside the center. The workshop is more intense and focuses on developing individualized skills. The symposium session includes an assessment of each participant's teaching style and methods to identify patient motivations, adherence, and satisfaction factors.

The University of Virginia DRTC and the CDC's Diabetes Demonstration Projects Program are collaborating on the development of a program for educational skills in diabetes designed primarily for use in states with diabetes demonstration projects. This program will provide training in educational principles and techniques for diabetes educators. This is a timely development relative to the NDAB initiative for national recognition of diabetes education programs.

The University of Chicago DRTC presents annually a 2-day workshop on Improving Patient Education Programs for nurses, dietitians, and other health professionals who are responsible for hospital-based diabetes patient education programs. The workshop is designed to help health professionals manage their programs more efficiently and effectively, increase their teaching skills, and apply appropriate criteria in the selection and use of teaching aids. This workshop fills a need that is not met by diabetes professional education programs that are limited to a review or an update of information about diabetes. The skills that are taught and practiced in this workshop help health professionals to improve many aspects of their diabetes patient education programs. The participants in these programs teach several hundred diabetes patients a year. This activity also coordinates well with the NDAB recognition program. The Albert Einstein DRTC uses the team concept for most activities, including training of diabetes educators. (This concept was presented in detail in a previous DRTC annual evaluation report.) The center's team development program includes teaching teamwork skills and concepts, management decisionmaking, problem solving, and communications geared toward each professional in terms of his or her knowledge, skills, and overall competence. The center usually trains groups in their home settings, and these teams are able to train other teams. This is an effective approach for larger hospitals in urban settings.

The Washington University (St. Louis) DRTC recently developed a course on counseling skills in diabetes management that includes psychological counseling techniques and the use of extensive role playing in professional education. Participants return after 6 months for a followup to identify progress they have made and their continuing needs. The followups are used to evaluate and modify the course. In other courses designed for specific aspects of diabetes care, counseling skills rarely receive much attention.

Diabetes educators rarely know how to evaluate their efforts. The University of Indiana DRTC presents the course education program evaluation as a teaching skill to

fill this need. This 4-day program includes formulating goals and objectives for diabetes patient education, learner assessment for diagnosing educational needs of diabetes patients, selection of teaching methods and materials, support mechanisms and followup techniques to enhance patient compliance, and evaluation of diabetes patient education.

Conclusions

The Department of Health and Human Services finds that the DRTC's are continuing to progress significantly toward achieving their congressionally mandated objectives. As the DRTC's continue to mature, additional benefits from this type of program are identified. This report focuses on the enhanced opportunities for training and career development available in the center setting. These opportunities go beyond the traditional concepts. The contributions from the cores, the pilot and feasibility studies, and the training and information transfer component are presented. Interactive collaborations and liaisons with other groups with interest in diabetes continue to expand. Significant progress has been made since the initiation of the DRTC program; the DRTC's are, indeed, fulfilling their role as a national resource.

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Although the term research suggests an image of the laboratory, many new insights come from working with patients in the clinical setting. The ultimate focus of NIADDK research is improving the quality of medical care—and the quality of life for patients.

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