

# NIH GUIDE

---

---

## For Grants and Contracts

---

### NOTICE OF MAILING CHANGE

Check here if you wish to  
discontinue receiving this  
publication

Check here if your address has  
changed and you wish to con-  
tinue receiving this publication.  
Make corrections below and  
mail this page to:

NIH Guide  
Distribution Center  
National Institutes of Health  
Room B3BE07, Building 31  
Bethesda, Maryland 20892

---

U.S. DEPARTMENT OF HEALTH  
AND HUMAN SERVICES

OFFICIAL BUSINESS  
Penalty for Private Use, \$300

The NIH Guide announces scientific  
initiatives and provides policy and  
administrative information to indi-  
viduals and organizations who need to  
be kept informed of opportunities,  
requirements, and changes in extra-  
mural programs administered by the  
National Institutes of Health.

Vol. 17, No. 40  
December 2, 1988

First Class Mail Postages & Fees Paid PHS/NIH/OD Permit No. G-291
--

NOTICES

NIH REGIONAL WORKSHOPS ON IMPLEMENTATION OF THE PHS POLICY  
ON HUMANE CARE AND USE OF LABORATORY ANIMALS ..... 1  
National Institutes of Health  
Index: NATIONAL INSTITUTES OF HEALTH

CHANGE IN ELIGIBILITY REQUIREMENTS ..... 2  
National Institute on Aging  
Index: AGING

NOTICE OF AVAILABILITY ..... 2  
National Institute on Diabetes and Digestive and Kidney Diseases  
Index: DIABETES, DIGESTIVE AND KIDNEY DISEASES

MAILABILITY OF ETIOLOGIC AGENTS ..... 2  
National Institutes of Health  
Alcohol, Drug Abuse, and Mental Health Administration  
Index: NATIONAL INSTITUTES OF HEALTH

DATED ANNOUNCEMENTS (RFPs AND RFAs)

WORKSITE HEALTH PROMOTION INTERVENTIONS (RFA) ..... 3  
National Cancer Institute  
Index: CANCER

PROGRAM PROJECTS ON MECHANISMS OF IMMUNOLOGIC DISEASES (RFA) ..... 4  
National Institute of Allergy and Infectious Diseases  
Index: ALLERGY AND INFECTIOUS DISEASES

PROGRAM PROJECTS ON THE BIOLOGY OF THE IMMUNE SYSTEM (RFA) ..... 6  
National Institute of Allergy and Infectious Diseases  
Index: ALLERGY AND INFECTIOUS DISEASES

ONGOING PROGRAM ANNOUNCEMENTS

MECHANISMS AND MANAGEMENT OF PEDIATRIC LIVER DISEASES ..... 8  
National Institute of Diabetes and Digestive and Kidney Diseases  
National Institute of Child Health and Human Development  
Index: DIABETES, DIGESTIVE AND KIDNEY DISEASES  
CHILD HEALTH AND HUMAN DEVELOPMENT

MATERNAL AND PATERNAL DRUG ABUSE AND ITS EFFECTS ON OFFSPRING .....10  
National Institute on Drug Abuse  
Index: DRUG ABUSE

RESEARCH GRANTS RELATED TO BATTEN DISEASE AND OTHER NEURONAL  
CEROID LIPOFUSCINOSES .....11  
National Institute of Neurological and Communicative  
Disorders and Stroke  
Index: NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

NOTICES

NIH REGIONAL WORKSHOPS ON IMPLEMENTATION OF THE PHS POLICY  
ON HUMANE CARE AND USE OF LABORATORY ANIMALS

P.T. 42; K.W. 1014002, 0201011, 1014003

National Institutes of Health

The National Institutes of Health, Office for Protection from Research Risks, is continuing to sponsor a series of workshops in implementing the Public Health Service Policy on the Humane Care and Use of Laboratory Animals. The workshops are open to institutional administrators, members of animal care and use committees, laboratory animal veterinarians, investigators and other institutional staff who have responsibility for high-quality management of sound institutional animal care and use programs.

Date: January 24-25, 1989

Location: San Antonio, Texas

Contact: Ms. Molly Greene  
Institutional Animal Care Program  
University of Texas Health Science Center  
at San Antonio  
7703 Floyd Curl Drive  
San Antonio, Texas 78284-7822  
Telephone: (512) 567-3717

Date: February 9-10, 1989

Location: Salt Lake City, Utah

Contact: Joan Provost  
Conferences and Institutes  
University of Utah  
Salt Lake City, Utah 84112  
Telephone: (801) 581-5809

Date: March 30-31, 1989

Location: Newark, New Jersey

Contact: Ms. Pat Sarles  
Office of Education  
University of Medicine & Dentistry  
of New Jersey  
185 South Orange Avenue  
Newark, New Jersey 07103  
Telephone: (201) 456-4267

Date: April 13-14, 1989

Location: New Orleans, Louisiana

Contact: Mrs. Lois Herbez  
Administrative Secretary  
Louisiana State University Medical Center  
1542 Tulane Avenue  
New Orleans, Louisiana 70112-2822  
Telephone: (504) 568-4198

Date: May 8-9, 1989

Location: Davis, California

Contact: Mrs. Julie Lamoree  
Administrative Assistant  
Office of Campus Veterinarian  
University of California, Davis  
Davis, California 95616  
Telephone: (916) 752-2364

Other workshops are being planned and will be announced in future issues of the NIH Guide for Grants and Contracts.

For additional information contact:

Ms. Roberta H. Sonneborn  
Executive Assistant for Animal Welfare Education  
National Institutes of Health  
Office for Protection from Research Risks  
Building 31, Room 4B09  
Bethesda, Maryland 20892

#### CHANGE IN ELIGIBILITY REQUIREMENTS

P.T. 34; K.W. 0710010, 0710030, 1014002

National Institute on Aging

Notice of change in eligibility requirements for the Geriatric Leadership Academic Award (NIH Guide Vol. 13, No. 10, September 7, 1984, revised NIH Guide Vol. 14, No. 9, July 18, 1985).

The purpose of the Geriatric Leadership Academic Award is to support leadership activities in the development of research and research training programs in aging. In order to increase the limited number of well trained potential applicants, the NIA has removed the restriction barring previous recipients of NIA's Geriatric Medicine Academic Award from applying for the Geriatric Leadership Academic Award.

#### NOTICE OF AVAILABILITY

P.T. 34, 36; K.W. 0785165, 0765035, 0780025

National Institute on Diabetes and Digestive and Kidney Diseases

The Liver Tissue Procurement and Distribution System (LTPADS) is an NIH service contract to obtain human liver from regional centers for distribution to scientific investigators throughout the United States. These regional centers have active liver transplant programs with human subjects approval to provide portions of the resected pathologic liver for which the transplant is performed. Human pathologic liver prepared according to the investigator's specifications provides the opportunity to verify if animal liver investigations are relevant to human liver pathophysiology. The preparation of these livers has been excellent for the usual molecular biologic techniques. Therefore, we are primarily interested in soliciting proposals from investigators interested in studying pathologic liver specimens. Examples would include a particular metabolic disorder or disease process or the general process of cirrhosis. A very limited supply of "normal" liver specimens may also be requested. Because 21 investigators are presently listed for "normal" liver, preferences in the future will be given to new proposals also requesting pathologic tissue.

For further information and proposal forms, interested investigators should contact:

Harvey L. Sharp, M.D.  
Principal Investigator, LTPADS  
c/o Elizabeth Webster  
Box 279 Mayo Bldg.  
University of Minnesota Hospitals  
Minneapolis, Minnesota 55455  
Telephone: (612) 624-1133

#### MAILABILITY OF ETIOLOGIC AGENTS

P.T. 36; K.W. 1014002

National Institutes of Health  
Alcohol, Drug Abuse, and Mental Health Administration

The United States Postal Service has recently expressed concern about the shipment of etiologic agents. There are existing regulations regarding the shipment of etiologic agents. Specifically, these regulations require that transportation in interstate traffic of any material known to contain, or reasonably believed to contain, an etiologic agent is prohibited unless such material is packaged, labeled, and shipped in accordance with specified requirements.

Etiologic agents, as defined by the regulations, include any viable microorganism, or its toxin, which causes or may cause human disease. The Department of Health and Human Services has published a list of etiologic agents (42 CFR 72.3).

Organizations receiving grant or contract awards are responsible for assuring compliance with the existing regulations. Procedures for the Domestic Handling and Transport of Diagnostic Specimens and Etiologic Agents, published by the National Committee for Clinical Laboratory Standards (July 17, 1985, Vol. 5, No. 1), may be obtained from:

National Committee for Clinical Laboratory Standards  
771 East Lancaster Avenue  
Villanova, Pennsylvania 19085

#### DATED ANNOUNCEMENTS (RFPs AND RFAs)

##### WORKSITE HEALTH PROMOTION INTERVENTIONS

RFA AVAILABLE: 89-CA-05

P.T. 34; K.W. 0725020, 0745035, 0404000

National Cancer Institute

Letter of Intent Receipt Date: January 24, 1989  
Application Receipt Date: May 5, 1989

The Division of Cancer Prevention and Control (DCPC) of the National Cancer Institute (NCI), invites applications for cooperative agreements to expand and improve cancer prevention and control programs offered in worksites. A worksite is defined as a geographically contiguous employment setting. Applications for a Data Coordination Unit to assist in coordination of comparative data analyses across awardees are also invited.

##### RESEARCH GOALS AND SCOPE

The intent of this RFA is to stimulate the design, implementation and evaluation of nutrition, screening and tobacco control worksite interventions aimed at cancer prevention and control. It is anticipated that the designed worksite interventions will reflect some model of behavioral and environmental changes applicable to the worksite setting and capable of changing individual behavior and affecting worksite norms. Researchers are expected to address at least two of the three components (i.e., nutrition, screening, tobacco control) as part of the total intervention.

Any occupational exposures to carcinogens should be addressed in the design of programs under this RFA. It would be appropriate to target worksites in which there is an enhanced risk created by the interaction of environmental factors such as occupational exposure to carcinogens and lifestyle factors such as smoking.

Because little is known about how to effectively modify eating behaviors in the work environment, nutrition will be given a high priority. This means that all else being equal in terms of the quality of applications as assessed by peer review, applications with a nutrition component will be given priority over those without a component during the funding decision-making process.

The major research question to be answered is: Will employees in an intervention worksite demonstrate cancer-risk reducing behaviors to a greater extent than workers in a non-intervention worksite? Corollary questions might be: What approaches are effective in generating participation of worksites and workers in health promotion programs? What is the impact of worksite policies, such as nutrition and smoking policies, on worker behavior? How should cancer prevention interventions be integrated into existing chronic disease interventions or existing occupational health programs?

##### DATA COORDINATION UNIT

Separate applications for the Data Coordination Unit are invited. The purpose of this unit is to provide capacity in research design, research data management of multiple large data sets, statistical analysis, and program content necessary for the creation of compatible data bases. These data bases will be used for performing comparative analyses across the awards. Each awardee is responsible for the data collection and analysis within his or her cooperative agreement. The Data Coordination Unit will be responsible for the

data management functions required for analysis across the awardees. The design and interpretation of such an analysis will be a joint endeavor of the awardees, the Data Coordination Unit and NCI.

#### ELIGIBILITY

Applicants may be universities, corporations, public health agencies, wellness councils, business coalitions, unions, voluntary organizations, consultant firms, etc., or combinations thereof. Teams of applicants are encouraged. Among a team of applicants, one institution must be proposed as the lead institution to serve as the applicant and assume responsibility for the conduct of the award.

#### MECHANISM OF SUPPORT

Support of this program will be through the Cooperative Agreement mechanism. Three or more total awards are anticipated including the Data Coordination Unit. The number of awards depends on the quality of the applications and the availability of funding. Funding is limited to a maximum of five years at approximately \$330,000 per year.

#### INQUIRIES

Copies of the complete RFA and additional information may be obtained from:

Jerianne Heimendinger, D.Sc., Program Director  
National Cancer Institute, Health Promotion Sciences Branch  
Executive Plaza North, Room 239E  
9000 Rockville Pike  
Bethesda, Maryland 20892  
Telephone: (301) 496-0273

#### PROGRAM PROJECTS ON MECHANISMS OF IMMUNOLOGIC DISEASES

RFA AVAILABLE: 89-AI-03

P.T. 34; K.W. 0710070, 0715120, 1002004, 1002008, 0765033, 0755030

National Institute of Allergy and Infectious Diseases

Letter of Intent Receipt Date: April 17, 1989

Application Receipt Date: June 14, 1989

#### BACKGROUND INFORMATION

The Clinical Immunology and Immunopathology Branch of the Allergy, Immunology and Transplantation\* Program of the National Institute of Allergy and Infectious Diseases (NIAID) supports research on the cellular and molecular mechanisms of immunologic diseases and the application of this knowledge to clinical problems. This Request for Applications (RFA) is intended to encourage the development of applications from collaborative basic science and clinical investigative groups, and to coordinate the submission of new and renewal program project applications providing equitable opportunity for both to compete for funds currently available for existing programmatic activities concerned with the study of mechanisms of immunologic diseases. Fourteen such program projects are currently funded and support for four is scheduled to conclude in FY 1990. In FY 1990 NIAID plans to award at least four new and competing renewal Program Projects on Mechanisms of Immunologic Diseases.

\*Formerly Immunology, Allergic and Immunologic Diseases Program

#### RESEARCH GOALS AND SCOPE

Realizing that immunologic and inflammatory disorders constitute major areas of endeavor of the Clinical Immunology and Immunopathology Branch, the goals of these program projects are aimed at understanding the underlying mechanisms of disease and the development of diagnostic measures and approaches to effective prevention, control and treatment of a wide variety of immunologic diseases.

The scope of these program projects is intended to include studies on all aspects of immunologic responses aimed at defining etiologic factors and pathogenetic mechanisms. Research approaches may include clinical immunology studies of acquired and inherited diseases associated with dysfunctions of the immune system, as well as basic immunopharmacology studies of the immune system and its disorders.

Of special interest to NIAID are program projects with an emphasis on one of several areas of investigation which appear to be particularly promising in terms of elucidation of basic immune mechanisms and their application to clinical disorders. Thus in addition to program projects which may approach a wide variety of immunologic disorders, we wish to encourage the development of program projects which have a central research theme.

Including the following:

**Immunodeficiency Diseases:**

- o Major advances have occurred in our understanding of childhood immunodeficiency disorders. Investigators are encouraged to devise studies which further our understanding of basic mechanisms, as well as develop new approaches to diagnosis, treatment and prevention of these disorders.
- o Basic studies of immune mechanisms regulating host defense and host inflammation are encouraged in a wide variety of acquired immunodeficiency diseases. Such studies may include not only the investigation of responses of differing cell populations (lymphocytes, monocytes/macrophages and neutrophils) but also how immune modulators may influence cellular responses. They may range in emphasis from basic studies to clinical application of appropriate agents.

**Dermatologic Diseases Modulated by Immune Mechanisms**

- o There have now been a wide variety of dermatologic disorders described in which immune mechanisms play an important role in their pathogenesis. Basic studies of the immunopathogenesis, diagnosis, therapy of these disorders are encouraged.

**MECHANISM OF SUPPORT**

Program project grants are awarded to an institution on behalf of a program director for the support of a broadly-based, multidisciplinary, long-term research program which has a specific major objective or basic theme. A program project generally involves the organized efforts of groups of investigators, members of which conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain core resources shared by individuals in a program where the sharing facilitates the total research effort. Each component project supported under a program project grant is expected to contribute to and be directly related to the common theme of the program; they should demonstrate an essential element of unity and interdependence. At least four awards are planned for FY 1990.

**ELIGIBILITY**

ONLY DOMESTIC INSTITUTIONS ARE ELIGIBLE TO APPLY.

**METHOD OF APPLYING**

Applications may be submitted by any domestic public or private nonprofit or profit-making organizations. Before preparing an application, the prospective applicant should request a copy of the NIAID Information Brochure on Program Project and Center Grants from:

Dr. Nirmal K. Das  
Executive Secretary  
Allergy, Immunology and Transplantation  
Research Committee  
National Institute of Allergy and  
Infectious Diseases  
National Institutes of Health  
Westwood Building, Room 3A-07  
Bethesda, Maryland 20892  
Telephone: (301) 496-7966

## STAFF CONTACT

A more detailed RFA may be obtained from:

Robert A. Goldstein, M.D., Ph.D.  
Chief, Clinical Immunology and  
Immunopathology Branch, AITP  
National Institute of Allergy  
and Infectious Diseases  
Westwood Building, Room 757  
Bethesda, Maryland 20892  
Telephone: (301) 496-7104  
Telefax Number: (301) 480-3780

Prospective applicants are encouraged to submit a one-page letter of intent to Dr. Goldstein that includes a descriptive title and identification of any other participating institutions. The Institute requests such letters by April 17, 1989, for the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding. It will not enter into the review of any application subsequently submitted and is not a necessary requirement for application.

THE RFA LABEL AVAILABLE IN THE 9/86 REVISION OF APPLICATION FORM 398 MUST BE AFFIXED TO THE BOTTOM OF THE FACE PAGE. FAILURE TO USE THIS LABEL COULD RESULT IN DELAYED PROCESSING OF YOUR APPLICATION SUCH THAT IT MAY NOT REACH THE REVIEW COMMITTEE IN TIME FOR REVIEW.

## PROGRAM PROJECTS ON THE BIOLOGY OF THE IMMUNE SYSTEM

RFA AVAILABLE: 89-AI-04

P.T. 34; K.W. 0705040, 0710070, 1002004, 1002008, 0710065, 0790000

National Institute of Allergy and Infectious Diseases

Letter of Intent Receipt Date: April 17, 1989

Application Receipt Date: June 14, 1989

## BACKGROUND INFORMATION

The Immunobiology and Immunochemistry Branch of the Allergy, Immunology and Transplantation Program\* of the National Institute of Allergy and Infectious Diseases (NIAID), supports fundamental studies on the structure and function of the immune system to gain an understanding of immune response mechanisms at their basic cellular and molecular levels as they function in health and disease. Program Projects on the Biology of the Immune System represent an award mechanism which the Branch employs to meet this objective. They are intended to support integrated, multidisciplinary, basic studies of immunologically-functional lymphocytes and other relevant cell populations. Twelve such program projects are currently funded although support for one is scheduled to conclude in 1990. In fiscal year 1990 NIAID plans to award at least one Program Project on the Biology of the Immune System. This request for applications is intended to encourage the development of proposals from collaborating investigators and to coordinate the submission and review of new and renewal program project applications.

\*Formerly Immunology, Allergic and Immunologic Diseases Program

## RESEARCH GOALS AND SCOPE

The goal of these Program Projects is the attainment of a complete understanding of the structure and function of the immune system and its products, its interaction with other body systems, and full knowledge of the genetic and other factors which regulate its development and function. An ultimate practical application of this information is the use of selected cloned cells of the system, or their products, for the clinical care or reconstitution of immunodeficient individuals, to alleviate allergic states, to provide resistance to life-threatening infections and to correct aberrant or defective immunoregulatory mechanisms.

The scope of these program projects includes studies of every facet of the immune response, ranging from the initial step of antigen recognition to the final elaboration of immunologically distinctive products of specific immunocytes. Research currently supported by this mechanism was designed to expand knowledge of the morphologic and functional heterogeneity of lymphocyte populations and develop the capability for identification and selection of



lymphocyte subpopulations, with specific immune reactivity or molecular composition, for use in somatic hybridization and selective production of specific, biologically active, lymphocyte products. Similar studies of macrophages, other accessory and effector cells, and networks of cells and molecules that affect the activation, differentiation and regulation of cells of the immune system are appropriate. Projects that involve improving the efficiency or scale of preparing and selecting hybridomas and other relevant cell lines for defined purposes, and projects designed to modify genes encoding immunologically relevant macromolecules to improve their biological efficiency, or diagnostic and therapeutic utility, are encouraged.

#### MECHANISM OF SUPPORT

Program project grants are awarded to an institution on behalf of a program director for the support of a broadly-based, multidisciplinary, long-term research program which has a specific major objective or basic theme. A program project generally involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain core resources shared by individuals where the sharing facilitates the total research effort. Each component project, supported under a program project grant, is expected to contribute and be directly related to a common theme. The projects should demonstrate an essential element of unity and interdependence.

#### METHOD OF APPLYING

Before preparing an application, the prospective applicant should request a copy of the Information Brochure: Program Projects and Center Grants, NIAID, from:

Dr. Nirmal K. Das  
Executive Secretary  
Allergy, Immunology and Transplantation  
Research Committee  
National Institute of Allergy  
and Infectious Diseases  
National Institutes of Health  
Westwood Building, Room 3A-07  
Bethesda, Maryland 20892  
Telephone: (301) 497-7966

#### STAFF CONTACT

For further programmatic information and a copy of the detailed RFA, contact:

Joseph F. Albright, Ph.D.  
Chief, Immunobiology and Immunochemistry Branch, AITP  
National Institute of Allergy and Infectious Diseases  
Westwood Building, Room 757  
National Institutes of Health  
Bethesda, Maryland 20892  
Telephone: (301) 496-7551  
Telefax Number: (301) 480-3780

Prospective applicants are encouraged to submit a one-page letter of intent that includes a descriptive title and identification of any other participating institutions. The Institute requests such letters by April 17, 1989, for the purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding. It will not enter into the review of any application subsequently submitted and is not a necessary requirement for application. Letters of intent should be directed to Dr. Albright at the address shown above.

THE RFA LABEL AVAILABLE IN THE 9/86 REVISION OF THE APPLICATION FORM 398 MUST BE AFFIXED TO THE BOTTOM OF THE FACE PAGE. FAILURE TO USE THIS LABEL COULD RESULT IN DELAYED PROCESSING OF YOUR APPLICATION SUCH THAT IT MAY NOT REACH THE REVIEW COMMITTEE IN TIME FOR REVIEW.

## ONGOING PROGRAM ANNOUNCEMENTS

### MECHANISMS AND MANAGEMENT OF PEDIATRIC LIVER DISEASES

P.T. 34; K.W. 0715135, 1002004, 1002008, 1002019, 0785050, 0785170, 0715085

National Institute of Diabetes and Digestive and Kidney Diseases  
National Institute of Child Health and Human Development

Application Receipt Dates: February 1, June 1, October 1

#### I. INTRODUCTION

Extrahepatic biliary atresia accounts for a majority of the liver transplants being done currently in the pediatric population to treat end-stage liver disease. This and other forms of infantile bile duct abnormalities such as idiopathic neonatal hepatitis have no known cause. Few data exist regarding their pathophysiologic basis. In addition, their management is empiric and imprecise, most often borrowing techniques utilized in adult patients with end-stage liver disease. Thus, both clinicians and investigators share a high degree of uncertainty in managing these patients and in investigating the pathogenesis of their disease. In depth studies of mechanisms and modes of management are clearly needed.

A conference addressing the issues of Mechanisms and Management of Pediatric Hepatobiliary Disease was organized and sponsored by the National Digestive Diseases Advisory Board, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Child Health and Human Development and the American Liver Foundation. It was held February 28 - March 1, 1988, in Arlington, Virginia. From this meeting, whose sessions covered (a) morphology and functional differentiation of the liver, (b) development of hepatic excretory function, (c) neonatal cholestasis and viral disease, (d) neonatal cholestasis and metabolic diseases, and (e) therapeutic strategies for chronic liver diseases, areas of research needs were identified by the members of the planning committee.

#### II. RESEARCH GOALS AND SCOPE

This Program Announcement is an attempt to bring to the attention of the research community some of the perceived research needs so identified by the above referenced conference, and to encourage research in the area of pediatric hepatobiliary disease in general. Areas identified as a result of the above cited conference were as follows. However, research applications are not limited to the following examples.

- a. Learning the nature of the cell population which functions in a "reserve" (stem cell) compartment in the normal liver. Learning the mechanism(s) by which these cells can be stimulated to proliferate and differentiate under certain pathologic conditions in which hepatocyte replication is inhibited or after liver cell necrosis may provide insight into the control of regeneration and repair.
- b. Understanding the expression and regulation of cell surface receptors should provide important insights into liver cell biology and development and offer the potential of new therapeutic strategies.
- c. Characterization of the unique features of various viral infections in the developing organ is needed to understand certain aspects of viral pathogenesis. For example, in the hepatitis B carrier state, at a certain stage viral replication continues but viral assembly and/or secretion ceases, leading to the accumulation of replicative forms of HBV DNA in the liver. Possibly this leads to an increased propensity in young carriers for viral integration into the host genome.
- d. Defining the mechanisms responsible for regulating bile flow might be important in understanding certain forms of neonatal cholestasis, such as idiopathic neonatal hepatitis and intrahepatic bile duct paucity. Following the recognition of bile salt carriers, defects in bile salt transport may become evident.
- e. Advances in the understanding of bilirubin chemistry may lead to new methods for treatment of defects in bilirubin metabolism, such as the use of compounds like tin-protoporphyrin.
- f. Since a common complication of the sole administration of parenteral nutrition to infants is cholestasis with cirrhosis, better insight into the

mechanism of this injury is needed in order to develop better management modalities.

g. The paucity of small donor livers for transplantation into infants with end-stage liver disease has stimulated innovative surgical reduction techniques. However, studies directed toward hepatocyte transplantation, the development of cultures which would support the in vitro growth of liver tissue, and measures such as hepatocyte dialysis could lead to ways of providing interim support for acute liver failure.

h. The inadequacy of current "liver function studies" suggests that quantitative liver function tests, based on clearance techniques, may provide more precise diagnostic and prognostic information before and after liver transplantation.

i. Collaborative studies in certain clinical areas in which any one individual center cannot provide enough patients for study are encouraged, for example, in biliary atresia. Prediction of outcome and validation of quantitative liver function tests, the role of choloretic agents in enhancing the success rate of the hepatoportoenterostomy procedure, treatments to slow progression of fibrosis, evaluation of abnormalities in bile acid synthesis as a cause of cholestasis, and ways to support the growth of the child until liver transplantation is practicable are some examples of research in which collaborative efforts may provide sufficient data to answer specific questions.

### III. MECHANISM OF SUPPORT

The mechanisms of support for this activity will be the individual research grant (R01) and FIRST Award (R29). There are no set-aside funds for funding these applications. Applications compete on the basis of scientific merit with all other applications. The review criteria are the traditional considerations underlying scientific merit.

### IV. APPLICATION AND REVIEW PROCEDURES

#### A. Deadline

Applications will be accepted in accordance with the usual receipt dates for new research grant applications; i.e., February 1, June 1, and October 1. The earliest possible award dates are approximately nine months after the respective receipt dates.

#### B. Method of Applying and Review

Applications will be received and referred to an appropriate study section for scientific merit review by the Division of Research Grants of the NIH. Following the initial scientific review, the applications will be evaluated by the National Diabetes and Digestive and Kidney Diseases Advisory Council and/or the National Advisory Child Health and Human Development Council.

Applications should be submitted on form PHS-398 (revised 9/86) which is available in the business or grants and contract offices at most academic and research institutions or from the NIH. To identify the application as a response to this announcement, check "YES" in Item 2 on the face page of the application and enter the title "Mechanisms and Management of Pediatric Liver Diseases".

The original and six (6) copies of the application should be mailed to:

Application Receipt Office  
Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, Maryland 20892\*\*

Inquiries related to this Program Announcement should be directed to:

Dr. Sarah C. Kalser  
Program Director/Medical Officer  
Liver and Biliary Diseases  
Program  
National Institute of Diabetes and  
Digestive and Kidney Diseases  
5333 Westwood Bldg., Room 3A-17  
Bethesda, Maryland 20892  
Telephone: (301) 496-7858

Dr. Ephraim Y. Levin  
Endocrinology, Nutrition and  
Growth Branch  
National Institute of Child  
Health and Human Development  
Executive Plaza North, Room 637  
Bethesda, Maryland 20892  
Telephone: (301) 496-5593

This program is described in the Catalog of Federal Domestic Assistance No. 13.865, Research for Mothers and Children. Awards will be made under the authority of the Public Health Service Act, Section 301 (42 USC241), and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to review by a Health Systems Agency.

This program is described in the Catalog of Federal Domestic Assistance No. 13.847, Diabetes, Endocrinology and Metabolic Diseases. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410 as amended, 42 USC241), and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to review requirements of Executive Order 12372 or by a Health Systems Agency Review.

#### MATERNAL AND PATERNAL DRUG ABUSE AND ITS EFFECTS ON OFFSPRING

P.T. 34; K.W. 0404009, 0404000, 0755000, 0785105, 0710070, 0710030

National Institute on Drug Abuse

The use of any drug during pregnancy is not without risk. Drugs such as heroin, cocaine, PCP, a variety of inhalants and marijuana all cross the placental barrier and have the capacity to produce profound and potentially irreversible damage in the newborn. Indeed, developmental problems caused by these drugs are becoming an increasing burden to society. This burden is made worse because the kinds of toxic effects that are being encountered, their incidence and prevalence, the mechanisms underlying toxicity, and prevention and treatment strategies to deal with these outcomes are not now known.

The National Institute on Drug Abuse has designated research on the developmental effects of abused drugs as one of its priorities for the coming years. We therefore encourage the submission of research proposals to study the effects of abused drugs on reproductive and developmental processes with four major goals in mind: to identify the consequences of maternal and paternal drug abuse in the newborn; to identify the mechanisms underlying the organic and behavioral effects resulting from exposure in utero and/or lactation to drugs of abuse; to develop strategies and procedures to prevent, ameliorate, and/or reverse these toxic effects and their developmental consequences; to identify multigenerational consequences of maternal or paternal drug abuse.

Many of the methodological issues related to the study of drugs on development are particularly complex and the subject of debate. As a result, applicants are encouraged to address important methodological issues in their research proposals.

Examples of the types of research projects being encouraged follow. This list is not exclusive and applicants are invited to submit any proposal they believe important in understanding, treating, or preventing the effects of parental drug abuse on the offspring.

- o Basic biological studies related to pharmacokinetics, genetics, neuroendocrine and immune systems, and the cardiovascular and other organ systems;
- o Neuroscientific and behavioral studies of period of vulnerability of the developing nervous system, neurotransmitters and modulators, functional evaluation of drug induced CNS behavioral measures, and persistence of drug induced brain changes.
- o Human studies on CNS development, epidemiology of parental drug abuse and its effects on offspring, pre- and peri-natal care and newborn treatment.

The National Institute of Child Health and Human Development supports research on prenatal and perinatal care, especially studies of preterm labor secondary to maternal drug abuse and managed maternal withdrawal. They may also be a source of funding for such studies.

#### CONTACTS FOR DETAILED PROGRAM INFORMATION

Dr. David P. Friedman  
Division of Preclinical Research  
Telephone: (301) 443-1887

Dr. Ernestine Vanderveen  
Division of Clinical Research  
Telephone: (301) 443-6697

Dr. Jagjitsing H. Khalsa  
Division of Epidemiology and Statistical Analysis  
Telephone: (301) 443-6647

Dr. Charlotte Catz  
Pregnancy and Perinatology Branch, NICHD  
Telephone: (301) 496-5575

#### CONTACT FOR A COPY OF THE COMPLETE PROGRAM ANNOUNCEMENT

Mr. Desmond McLearn  
Grants Management Branch  
Telephone: (301) 443-6710

Cat. of Fed. Domestic Assistance No. 13.279

#### RESEARCH GRANTS RELATED TO BATTEN DISEASE AND OTHER NEURONAL CEROID LIPOFUSCINOSES

P.T. 34; K.W. 0715138, 1002019, 0765035, 1003002, 1002004, 1002008

National Institute of Neurological and Communicative Disorders and Stroke

This solicitation is a reissuance of the announcement that appeared in this Guide on October 10, 1986.

The Developmental Neurology Branch, Division of Convulsive, Developmental and Neuromuscular Disorders, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), encourages the submission of traditional research project grant applications (R01) related to the etiology, developmental embryology, pathogenesis, genetics and prevention of the ceroid lipofuscinoses, particularly the juvenile type known as Batten disease or Spielmeier-Sjogren disease.

#### BACKGROUND

The ceroid lipofuscinoses are a group of hereditary degenerative diseases in which an autofluorescent lipopigment, ceroid, accumulates in the central nervous system and other tissues. Clinically they are characterized by a progressive encephalopathy, loss of vision, seizures, and a downhill course. There are three childhood types of ceroid lipofuscinosis and one, possibly two, adult types. Although in general these types are clinically distinct, combined and transitional forms occur. The ceroid lipofuscinoses are inherited in autosomal recessive fashion with the exception of one rare adult type which shows autosomal dominant transmission.

The juvenile type, or Batten disease, exemplifies the devastating effects that these disorders have on affected individuals and their families. Onset is between 5 and 10 years usually with visual failure and seizures, and the course is that of a slowly progressive encephalopathy leading to death in 8-10 years. Pathologically the brain shows moderate atrophy. There is massive accumulation of ceroid in neurons and macrophages, in the ganglionic layer of the retina, and in other tissues. The etiology of Batten disease is unknown; its incidence is about 3 per 100,000 births. There is no effective therapy.

#### RESEARCH GOALS AND SCOPE

The goal of this program announcement is to encourage research to delineate clinical and genetic types of the ceroid lipofuscinoses, to identify and localize the gene(s) responsible for them, to determine the biochemical defects that result from the action of these genes, and to develop measures for the prevention, early diagnosis and treatment of these disorders.

The research scope of this program encompasses the developmental, genetic and biochemical aspects of the ceroid lipofuscinoses, particularly the juvenile type, or Batten disease, by a variety of experimental approaches and methods. Some examples are given below, but applications are not limited to them, and proposals with new ideas and initiatives would be welcome.

#### 1 Subjects

These may include experimental animals and human subjects. Large informative families are particularly useful in identifying and mapping the gene or genes

responsible for the ceroid lipofuscinoses. Animal models exactly comparable to the human disease should provide direct crucial information about the pathogenesis and genetics of these disorders, and make possible the determination of the basic metabolic defect, detection of early biochemical changes, characterization of the chemical pathology and recognition of the heterozygous carriers.

## 2 Pathology

Comparative studies in humans and experimental animals should be instrumental in characterizing precisely the pathological changes and the nature of the accumulating lipopigment. Examination by computerized scanning procedures and neuroimaging techniques may be useful in identifying early intracranial changes.

## 3 Biochemistry

Very little is known about the biochemistry of the ceroid lipofuscinoses in general and Batten disease in particular. It is not known if the accumulated lipofuscin is the same as that which is normally found in the brain of the older individuals, and if it is a causal or associated defect. A disturbance of dolichol metabolism has been reported in patients with Batten disease but its relation to the presence of lipofuscin or to the disease itself is not clear. Biochemical studies should be pursued at the cellular and molecular level with state-of-the-art precise and sensitive techniques of immunochemistry and membrane microchemistry, tissue culture, and the high resolution methodologies of rapid flow microfluorimetry and two-dimensional electrophoresis.

## 4 Genetics

Classical genetic studies have not resolved whether or not the conventional clinical classification, based mainly on age of onset, represents different forms of the same genetic disorder. Further genetic studies, using advanced molecular and biochemical genetic techniques are needed to resolve this question, and to identify and map the genes involved.

## 5 Detection of the genetic carrier

Identification of a biochemical marker should make possible heterozygote detection, prenatal diagnosis and early clinical recognition of cases, and thus lead to prudent management and treatment.

## MECHANISM OF SUPPORT

Support for this program will be through the traditional research grant-in-aid. Successful applicants will direct and carry out the individual research projects.

## APPLICATION AND REVIEW PROCEDURES

Applications should be prepared on Form PHS 398 (revised 9/86) according to instructions contained in the application kit. Application kits are available from most institutional business offices, or may be obtained from the Division of Research Grants (DRG), at the address given below. Check "Yes" in item 2 on the face sheet of the application and type "Grants Related to Batten Disease" in the space provided.

The original and five copies of the application should be mailed to the following address:

Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, Maryland 20892\*\*

Deadline dates for the receipt of individual research grant (R01) applications are October 1, February 1, and June 1.

An information copy of the application may be sent to the address below. Also, for further information applicants may contact:

Dr. Ntinios C. Myriantopoulos  
National Institute of Neurological and Communicative  
Disorders and Stroke  
National Institutes of Health  
Federal Building, Room 8C-04  
Bethesda, Maryland 20892  
Telephone: (301) 496-5821

This program is described in the Catalog of Federal Domestic Assistance No.13.853, Clinical Basis Research, NINCDS. Awards will be made under the authority of the Public Health Service Act, Title IV, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to Health Systems Agency Review.