

# NIH GUIDE

# for GRANTS and CONTRACTS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Vol. 10, No. 7, May 22, 1981

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### HAVE YOU MOVED?

If your present address differs from that shown on the address label, please send your new address to: Grants and Contract Guide Distribution Center, National Institutes of Health, Room B3B10, Building 31, Bethesda, Maryland 20205, and attach your address label to your letter. Prompt notice of your change of address will prevent your name from being removed from our mailing list.

The GUIDE is published at irregular intervals to announce scientific initiatives and to provide policy and administrative information to individuals and organizations who need to be kept informed of opportunities, requirements, and changes in grants and contracts activities administered by the National Institutes of Health.

Two types of supplements are published by the respective awarding units. Those printed on yellow paper concern contracts: solicitations of sources and announcement of availability of requests for proposals. Those printed on blue paper concern invitations for grant applications in well-defined scientific areas to accomplish specific program purposes.

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ANNOUNCEMENT

ADDENDUM - CONTROLLED CLINICAL TRIALS FOR PROPHYLAXIS OR  
IMPROVED ANTIMICROBIAL THERAPY OF SELECTED BACTERIAL AND  
MYCOTIC INFECTIONS

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

The National Institute of Allergy and Infectious Diseases announces the following addendum to the subject program announcement (NIH Guide for Grants and Contracts, Vol. 9, No. 11, September 19, 1980).

Under "Application Procedures" add:

The "yes" box of Item 2 (Response to Specific Program Announcement) of the face page of the application should be checked and the announcement title should be indicated.

NOTICE

NEW RCDA APPLICATION INSTRUCTIONS AND BROCHURE

A Research Career Development Award (RCDA--K04) instruction booklet is now available, which is to be used by RCDA applicants along with the PHS 398 grant application form and its instructions. This booklet also includes the latest printing of the RCDA policy brochure: "Policies Governing the National Institutes of Health Research Career Development Award, December 15, 1980." RCDA applicants should use this booklet and the PHS 398 form starting with the October 1, 1981 receipt date. Individual copies are available from:

Office of Grants Inquiries  
Division of Research Grants  
National Institutes of Health  
Bethesda, Maryland 20205.

Bulk supplies should be requested from:

Chief, Administrative Branch  
Division of Research Grants  
National Institutes of Health  
Bethesda, Maryland 20205

Any questions on the instruction booklet should be directed to:

Mr. Nicholas Moriarty  
Office of Research Manpower  
Division of Research Grants  
National Institutes of Health  
Bethesda, Maryland 20205  
Telephone: (301) 496-7221

## ANNOUNCEMENT

SOCIAL AND BEHAVIORAL RESEARCH

## NATIONAL INSTITUTE ON AGING

The National Institute on Aging announces the availability of a revised program announcement for Social and Behavioral Research. The announcement contains minor revisions primarily in the form of rephrasing and reorganization of information, but the substantive content has not changed. The original announcement was published in the NIH Guide for Grants and Contracts, Volume 8, No. 15, December 4, 1979.

Inquiries should be addressed to:

Social and Behavioral Research  
Building 31, Room 5C-05  
National Institute on Aging  
9000 Rockville Pike  
Bethesda, Maryland 20205  
Telephone: (301) 496-3136

ANNOUNCEMENT

CRANIOFACIAL DYSMORPHOLOGY RESEARCH GRANT

APPLICATIONS SOUGHT BY THE

NATIONAL INSTITUTE OF DENTAL RESEARCH

The NIDR's Craniofacial Anomalies Program Branch is seeking applications in Craniofacial Dysmorphology. Development and exploitation of animal models of human conditions is of particular interest. Research applications involving humans are also sought.

Applicants for studies involving humans are encouraged to focus clearly on particular entities with specific research protocols rather than attempting broad based descriptive studies of craniofacial malformations in general. The Institute is interested in supporting proposals aimed at elucidating etiology or improving diagnosis and treatment. Specifically, studies which identify and characterize heterogeneity and define clinical and/or etiologic subgroups are of special interest. Growth of affected children as an aid in diagnosis or a guide to optimizing treatment approaches are also of concern.

Applicants responding to this announcement should use form PHS 398 and follow the procedures described in the application kit. Kits are available at most institutional business offices or from the Division of Research Grants, NIH. Applications will be received and reviewed for scientific merit by the Division of Research Grants. Secondary review will be by the National Advisory Dental Research Council. There are three receipt dates each year for new applications: July 1, November 1, and March 1.

Additional information regarding this program may be obtained by contacting:

Dr. Jerry D. Niswander  
Craniofacial Anomalies Program Branch  
National Institute of Dental Research  
National Institutes of Health  
Westwood Building, Room 520  
Bethesda, Maryland 20205  
Telephone: (301) 496-7807

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This program is described in the Catalog of Federal Domestic Assistance number 13.842, Craniofacial Anomalies. Awards will be made under the authority of the Public Health Service Act, Title III, 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 A-95 Clearinghouse or Health Systems Agency Review.

**REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA****NIH-NCI-DCCP-CPCB-81-1****MECHANISMS OF BIOLOGICAL AND CHEMICAL PREVENTION****NATIONAL CANCER INSTITUTE**

Application receipt date, August 15, 1981

The Division of Cancer Cause and Prevention (DCCP) of the National Cancer Institute (NCI) invites grant applications from interested investigators for studies on the mechanisms of inhibition of carcinogenesis. The proposed studies would seek, as their major objective, to enhance present understandings concerning the mechanisms of action of representative members of the following categories of agents: (1) Antioxidants, Flavonoids, Disulfiram and related compounds, nucleophiles, including cellular nucleophiles, and other physiological trapping agents, Coumarins and other lactones; (2) Vitamins, Provitamins and other Cofactors; (3) Retinoids; (4) Protease Inhibitors; and (5) Biological agents such as Chalcones, Lymphokines/Lymphotoxins and Tumor Necrosis Factor.

Grants are awarded only to nonprofit organizations and institutions, governments and their agencies, and occasionally to individuals. This type of grant solicitation (the RFA) is utilized when it is desired to encourage investigator-initiated research projects in areas of special importance to the National Cancer Program. Applicants funded under the RFA are supported through the customary NIH grant-in-aid, in accordance with PHS policies applicable to Research Project Grants, including cost sharing. However, the RFA solicitation represents a single competition, with a specified deadline for receipt of applications. All applications received in response to the RFA will be reviewed by the same National Institutes of Health (NIH) Initial Review Group.

The present RFA announcement is for a single competition with a specified deadline of August 15, 1981, for receipt of applications. Applications should be prepared and submitted in accordance with the aims and requirements described in the following sections:

- I. BACKGROUND
- II. OBJECTIVES AND SCOPE
- III. MECHANISM OF SUPPORT
- IV. REVIEW PROCEDURES AND CRITERIA
- V. INQUIRIES

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This program is described in the Catalog of Federal Domestic Assistance number 13.393, Cancer Cause and Prevention Research. Awards are under authorization of the Public Health Service Act, Section 301(c) and Section 402 (Public Law-410, as amended; 42 USC 241; 42 USC 282) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency Review.

## I. BACKGROUND

Strategies for cancer prevention involving reduction or elimination of human exposure to environmental carcinogens may not always be possible. Further, significant portions of the human cancer burden may be due to endogenous carcinogens, cocarcinogens and promoters. Inhibition of the development of cancer by administration of chemical, biochemical and biological compounds, which directly and/or indirectly inhibit the cancer-producing effects of neoplastic and promoting substances, offers an alternate approach to cancer prevention.

Many studies on chemoprevention in experimental animal systems have already demonstrated the feasibility and relevance of this approach. A large number of compounds and substances have been shown to be effective chemopreventive agents against almost every major class of carcinogen in the prevention of carcinogenesis in organs comprising the majority of cancers in man. Among these are a variety of antioxidants, retinoids, protease inhibitors, flavonoids, coumarin and other lactones and disulfiram (and related compounds). However, very little is now known concerning the basic mechanisms of action of these chemopreventive agents. Similarly, recent evidence suggests that biological agents such as lymphokines may have significant anticarcinogenic potential.

The initiative for this RFA derives from the desire of the National Cancer Institute (NCI) to encourage both basic and applied studies on the mechanisms of biological and chemical prevention of carcinogenesis. In this regard, there is an intended emphasis on mechanisms of anticarcinogenesis, or biological chemoprophylaxis, as opposed to anticancer, or chemotherapy. Specifically, this intended emphasis is upon mechanisms of antipromotion (and/or antiprogession) of carcinogenesis, as well as upon mechanisms of inhibition of initiation and fixation.

## II. OBJECTIVES AND SCOPE

The research encompassed by the present RFA relates to both basic and applied studies intended to provide insights and approaches to an understanding of mechanisms of inhibition of carcinogenesis. The proposed studies would seek to enhance such knowledge with respect to the following categories of biological and chemical agents:

Category 1. Antioxidants, Flavonoids, Disulfiram and related compounds, nucleophiles, including cellular nucleophiles such as glutathione, and other physiological trapping agents, and Coumarins and other lactones - These chemically diverse inhibitors appear to act by preventing carcinogens from reaching or reacting with critical target sites, when given prior to and/or simultaneously with exposure to neoplastic substances. Inhibition of tumorigenesis at many organ sites has been demonstrated, such as liver and lung, large and small intestine, breast, skin, bladder and forestomach. Proposed research might include (but by no means be restricted to) studies on effects of these inhibitors on cellular activation and detoxification systems, the role of free radical scavengers and the superoxide dismutases in chemoprevention,

inhibitor-induced changes in cellular permeability or transport of carcinogens, competitive inhibition for carcinogen receptors, inhibitor structure/activity relationship, and inhibitor metabolism.

Category 2. Vitamins, Provitamins and other Cofactors - The role of the vitamins, provitamins (such as the carotenoids) and other cofactors in chemoprevention is largely unknown. Vitamins A, C, E and B2 (riboflavin) have been reported as inhibitors of carcinogenesis, while the first three named (A, C and E) have been reported to inhibit tumor initiation. Many vitamin A analogs are known to act as anti-promoters of phorbol-ester promoted, DMBA-initiated skin tumorigenesis; and beta-carotene (a precursor to vitamin A having vitamin A activity) inhibits skin tumorigenesis initiated by DMBA and promoted by croton oil, as well as skin tumors induced by repeated UV exposure. On the other hand, carotenoids lacking vitamin A activity are effective only against UV-induced skin tumorigenesis. In cell culture, vitamin A suppresses malignant and phenotypic transformation caused by chemical and physical carcinogens or by transforming polypeptides; and recent results indicate that vitamin C can not only inhibit progression of methylcholanthrene-induced transformation in vitro, but also cause morphologic reversion of transformed cells to the normal phenotype. Proposed research might include (but by no means be restricted to) the biochemical interactions of these compounds among themselves and with other substances, as for example with selenium and the selenoenzymes such as glutathione peroxidase, effects on other systems of glutathione metabolism, studies on mechanisms of inhibition of chemical and physical transformation and carcinogenesis, effects on composition and structure of cellular and subcellular distribution of these agents and changes in carcinogenesis; binding proteins; molecular sites of action; regulation of gene expression; clarification of enhancing and inhibiting effects on mutagenesis; role in oxidative metabolism; modification of cytotoxicity; and interactions with endocrine and immunological systems leading to inhibition or suppression of the carcinogenic process.

Category 3. Retinoids - These compounds have been shown to effectively inhibit cancer development in bladder, breast, skin and respiratory tract in experimental animals, and to suppress malignant and phenotypic transformation in vitro whether caused by chemical carcinogens, ionizing radiation or polypeptide transforming factors derived from virally transformed cells. Additional studies are particularly need in such areas as: retinoid metabolism, pharmacokinetics and structure/activity relationships; retinoid binding proteins; molecular mechanisms of retinoid action; effects of retinoids on cellular differentiation; effects of retinoids on membrane topology, cell surface biochemistry, cellular interactions, and biochemical processes linked to carcinogenesis.

Category 4. Protease Inhibitors - These compounds have been shown to inhibit tumorigenesis in skin, colon, esophagus and mammary gland; suppress both radiation-induced and chemical carcinogen-induced transformation in culture; and inhibit both UV- and carcinogen-induced



bacterial mutagenesis. Proposed research might include (but by no means be restricted to) effects of protease inhibitors on the cell surface, DNA synthesis, growth control mechanisms, and gene activation and repression.

Category 5. Biological Agents such as Chalones, Lymphokines/Lymphotoxins and Tumor Necrosis Factors - Recent data indicates that lymphokine/lymphotoxin preparations possess anticarcinogenic in addition to anticancer activity. The potential for prevention of development of cancer and the exploration of the biological and biochemical mechanisms involved, requires increased and deeper investigation for this and other biological agents such as chalones and tumor necrosis factors, including preparations of animal and human origin. Research on isolation, purification and biochemical identification are needed, as well as determination of the species, organ sites and cell types against which anticarcinogenic activity exists, in addition to fundamental investigations of mechanisms of action.

Further, combination chemoprevention or combined biological and chemical prevention of carcinogenesis presents a new, virtually unexplored area for studies on the inhibition of the carcinogenic process(es). Several recent investigations have demonstrated the feasibility of this important approach.

In this regard, it should be emphasized that the interest of the NCI (DCCP) in mechanisms of inhibition of carcinogenesis (that is, in this RFA) ranges from the most early events associated with initiation and fixation through early and later stages of promotion, progression and expression of malignancy.

An understanding of the mechanisms which underlie successful intervention at one or more stages of the carcinogenic process by one or more agents is obviously of great importance. In this regard, applications proposing use of one of the chemicals/agents indicated above in combination with a chemical (e.g., anti-inflammatory agent), factor (e.g., anti-tumor growth factor) or biological agent (e.g., normal human globulins, interferon) not so indicated will be considered acceptable applications, in addition to those proposing use of more than one of the substances which are listed above.

### III. MECHANISM OF SUPPORT

This RFA will use the traditional National Institutes of Health grant-in-aid. Responsibility for the planning, direction and execution of the proposed research will be solely that of the applicant. The total project period for applications submitted in response to the present RFA should not exceed three years. The intent is to fund multiple projects, with total costs amounting to approximately \$2.0 million for the first year. This funding level is dependent on the receipt of a sufficient number of applications of high scientific merit. Although this program is provided for in the financial plans of the National Cancer Institute, the award of grant pursuant to this RFA is also contingent upon the availability of funds for this purpose.

#### IV. REVIEW PROCEDURES AND CRITERIA

##### A. Review Method

Each application submitted in response to the RFA will be reviewed by: (1) an appropriate review panel of the Division of Research Grants, National Institutes of Health, and (2) the National Cancer Advisory Board at its February, 1982 meeting. All applications will be evaluated on a competitive basis.

##### B. Review Criteria

Applications must be responsive to this RFA, in the sense of being directed towards the attainment of the stated programmatic goals and fall within one or more of the specified research categories (see II. OBJECTIVES AND SCOPE). If the application is judged by the National Cancer Institute not to be responsive, the applicant will have the opportunity of having the application considered along with other unsolicited applications received by the National Institutes of Health in the review cycle which is current at that time.

The factors considered in evaluating each response to this RFA will be:

1. Scientific merit of research approach, design, and methodology.
2. Scientific, technical, or medical significance and originality of the proposed research.
3. Research experience and/or competence of the Principal Investigator and staff to conduct the proposed studies.
4. Adequacy of time (effort) which the Principal Investigator and staff would devote to the proposed studies.
5. Adequacy of existing/proposed facilities and resources. Applications which specify a proposed use of human cells/tissues/fluids/excreta, need to provide assurance and details concerning the nature, source, and availability of those specimens.
6. Adequacy of practices, procedures, and facilities relative to the safe handling and use of chemical carcinogens.
7. Reasonableness of the proposed budget and duration.

#### V. METHOD OF APPLYING

##### A. Format of Application

Applications must be submitted on form PHS-398, the application form for research project grants. Application kits are available at most institutional business offices, or may be obtained from the Division of Research Grants, NIH. The conventional presentation in format and detail applicable to regular research grant applications should be followed, and the requirements specified under Review Criteria (IV. B.) must be fulfilled. The words "PROPOSAL IN RESPONSE TO RFA NIH-NCI-DCCP-CPCB-81-1, MECHANISMS OF BIOLOGICAL AND CHEMICAL PREVENTION OF CARCINOGENESIS" must be typed in bold letters across the face page of the application.

B. Application Procedures

The completed original application and six (6) copies should be sent or delivered to:

Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
5333 Westbard Avenue  
Bethesda, Maryland 20205

To ensure their review, applications should be received by August 15, 1981. If applications received after that date the applicant will have the opportunity of having them considered in the next regular review cycle. Also, the Division of Research Grants (DRG) will not accept any application in response to this announcement, that is the same as one currently being considered by any other NIH awarding unit. A copy of the application should also be sent to Dr. Smith at the address shown below.

VI. INQUIRIES

Inquiries may be directed to:

Dr. Carl E. Smith  
Chemical and Physical Carcinogenesis Branch  
Division of Cancer Cause and Prevention  
National Cancer Institute  
Landow Building, Room 8C-37  
Bethesda, Maryland 20205  
Telephone: (301) 496-4141

**REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA****NIH-NIAID-81-4****MECHANISMS IN FOOD ALLERGY****NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**

Application receipt date: October 15, 1981

**I. BACKGROUND**

The Allergy and Clinical Immunology Branch (ACIB) of the Immunology, Allergic and Immunologic Diseases Program (IAIDP) of the NIAID is concerned with asthma, allergic, and immunologic diseases and with relevant mechanisms involved in hypersensitivity and inflammation. In an effort to promote research in the area of food allergy, the ACIB is soliciting applications to study specific problems associated with allergic reactions to foods.

Present efforts to diagnose clinical conditions as being caused by allergic and/or adverse reactions to food ingestion are both difficult and frustrating, partly because of a lack of correlation between results of currently available techniques and specific clinical symptoms in all instances.

Asthma, rhinitis, eczema, urticaria, and angioedema have all been reported as possible clinical manifestations of food allergy, either alone or in conjunction with other defined allergies. Similarly, other symptom complexes such as tension fatigue, headaches, muscular cramps, gastrointestinal symptoms, and behavior or learning disorders have been attributed to adverse reactions to ingestion of foods or their components.

The most dramatic examples of allergic reactions to food appear as shock, anaphylaxis, asthma or urticaria syndrome. When these clinical presentations are well defined and occur promptly after the ingestion of a specific food substance, it generally is not difficult to ascribe cause and effect between ingestion and clinical manifestation. On the other hand, less obvious clinical manifestations may be diagnosed only by oral challenge tests combined with elimination diets, which though useful, are cumbersome and may not

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This program is described in the Catalog of Federal Domestic Assistance number 13.855, Immunology, Allergic and Immunologic Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, 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 A-95 Clearinghouse or Health Systems Agency Review.

necessarily prove definitive. Currently available procedures to aid in diagnosis, such as skin tests with food extracts and RAST assays, have limited value owing to lack of standardization and lack of uniform clinical correlation between laboratory results and symptoms.

NIAID is concerned about the lack of availability of uniform test materials and assays and is undertaking efforts to make available materials as well as to establish a reference laboratory. However, it is stressed that such efforts may be conducted independently of any investigation proposed in response to this RFA.

## II. RESEARCH GOALS AND SCOPE

The ACIB intends to support research directed at elucidation of basic mechanisms essential for an understanding of the role of food in causing a variety of allergic and/or adverse reactions in people. Only by addressing basic mechanisms of causation do we anticipate that progress in this important clinical area will be accomplished.

For this purpose, proposals are sought which incorporate a detailed examination of the role of a single allergen in causing various allergic manifestations. For example, one widely studied model could be peanut. It is conceived that chemical purification of peanut to define the component responsible for causing clinical reactions, combined with an indepth assessment of diagnostic methods and definition of specific clinical reactions would be highly desirable. Other single allergen models might also prove useful.

Alternatively, proposals designed to describe and assess precisely which allergic disorders can be ascribed to allergic and/or adverse reactions to one or more food substances would be welcomed. It is envisioned that such a proposal might attempt to define precisely the role of food as a causative factor in the production of asthma, rhinitis, eczema, or other symptoms. Clarification of the role of specific diagnostic tests or approaches would be mandatory.

It must be emphasized that while new initiatives and approaches to the study of this problem are encouraged, studies of basic immunologic or other pathophysiological mechanisms must be integral to these attempts. Studies of behavioral disorders, for example, which do not address such mechanisms but are descriptive in nature, would not be acceptable.

## III. MECHANISM OF SUPPORT

The support of work proposed in response to this RFA will be through the traditional research grant mechanism. Applicants are expected to devise and execute their own protocols. Support for a minimum of three grants is anticipated, contingent upon the availability of funds. However, applications submitted in response to this RFA will be funded primarily on the basis of scientific merit.

#### IV. REVIEW PROCEDURES AND CRITERIA

##### A. Application Review

The receipt date for applications will be October 15, 1981. They will undergo initial review in February - March, 1982 and subsequent review by the National Advisory and Infectious Disease Council in May 1982. July 1, 1982 will be the earliest starting date for successful applicants.

##### B. Review Criteria

Applications responsive to this RFA must:

1. demonstrate high merit of research design, approaches, and methodology;
2. hold substantial promise of significantly advancing the state of the art and of developing information to deepen our understanding of food allergy;
3. have adequate facilities and resources;
4. have staff with sufficient qualifications and experience.

#### V. METHOD OF APPLYING

The standard research grant application form PHS 398 (Rev. 10/79) should be used. If copies are not available at the applicant institution's business office, they may be obtained from:

Office of Grants Inquiries  
Division of Research Grants  
National Institutes of Health  
Bethesda, Maryland 20205

For the purposes of identification, the RFA number, **NIH-NIAID-81-4** and the words **"Mechanisms in Food Allergy"** should be typed in item 2 on the face page of the application and a brief letter specifying that the application is in response to this RFA should be included. The application is to be forwarded to:

Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
5333 Westbard Avenue  
Bethesda, Maryland 20205

The deadline for receipt of applications is October 15, 1981. Applications received after this date will be held for the next review cycle and will compete with other research project grant applications for funding.

VI. INQUIRIES AND CORRESPONDENCE

Please forward a copy (not the original) of the cover letter and the application face page to:

Robert A. Goldstein, M.D., Ph.D.  
Chief, Allergy and Clinical Immunology Branch  
Immunology, Allergic and Immunologic  
Diseases Program  
National Institute of Allergy and  
Infectious Diseases  
Westwood Building, Room 755  
National Institutes of Health  
Bethesda, Maryland 20205

Inquiries regarding this RFA should also be addressed to Dr. Goldstein. He can be reached by telephone at (301) 496-7104.

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

NIH-NIAID-81-5

ASTHMA AND ALLERGIC DISEASE CENTERS

THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Application receipt date: October 15, 1981

BACKGROUND INFORMATION

The National Institute of Allergy and Infectious Diseases (NIAID) invites applications for grants to be initiated during FY 1982 for participation in the ongoing Asthma and Allergic, and Immunologic Disease Centers (AADC) program.

The Allergy and Clinical Immunology Branch of the Immunology, Allergic, and Immunologic Diseases program of NIAID sponsors fundamental and clinical research grants and contracts and the procurement and application of research resource and reference reagents concerned with asthma, allergic and immunologic diseases and with relevant mechanisms of hypersensitivity and inflammation. This request for applications is intended to encourage the development of proposals from clinical investigative groups meeting the criteria and requirements for an AADC and to coordinate the submission of new and renewal applications providing equitable opportunity for both to compete for funds currently available for this program.

Since its inception in 1971, the AADC program has progressively expanded with the gradual addition of new Centers on an open application basis. In accordance with established policy announced in the NIH Guide for Grants and Contracts, Vol. 7, No. 8, p. 1, June 9, 1978, proposals for AADCs are received only periodically and at designated times. Applications for both renewal of existing AADCs and creation of new Center programs will be expected to compete for funds available through the periodically announced awards.

The AADC program currently consists of 17 centers. During FY 1982, six Centers are scheduled to terminate and may compete for renewal.

NIAID's fundamental objective in continuing the AADC program remains unchanged: acceleration of the application of emerging knowledge on the immune system and from relevant biomedical sciences to clinical investigations concerned

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This program is described in the Catalog of Federal Domestic Assistance number 13.855, Immunology, Allergic and Immunologic Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulation 42 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency Review.



with asthma, allergic diseases, and hypersensitivity disorders. Especially sought as the requisite factors within a participating institution are quality research in basic science(s) and clinical investigation supported by adequate clinical facilities, staff expertise in diagnosis and management of asthmatic and allergic patients, and access to appropriate patient population(s) within a suitable academic/investigative setting designed to favor multidisciplinary interaction.

#### RESEARCH GOALS AND SCOPE

1. There should be indication by the sponsoring university or medical institution of willingness and preparedness to commit resources to insure development, operation, support, and function of the proposed Center in devoting its efforts to an identified study on asthma and/or allergic disease as a fundamental prerequisite.
2. The applicant's achievements in basic science research should have reached that stage of development where experimental leads are sufficiently encouraging to warrant transition from promising laboratory findings to corresponding investigations at the clinical level with the ultimate goal of developing new and improved methods for diagnosis, prevention, and treatment of asthma and/or the other allergic diseases.
3. A prospective Center should be in a position to present evidence of experience, orientation, laboratory and clinical facilities, scientific and professional staff, support personnel and the expertise to design proposals, execute protocols representing a multifaceted long-term approach, and bring diverse institutional strengths to bear upon the study of major problems in asthma, other allergic diseases and/or pathophysiologic mechanisms underlying these disorders.
4. Suitable subjects for study within the provision of this program may include those relevant to:
  - a. asthma and its multifactoral aspects;
  - b. atopic diseases (e.g., allergic rhinitis, urticaria, atopic dermatitis);
  - c. identification, isolation, and characterization of etiologic agents of allergy (e.g., drugs, chemicals, foods, airborne allergens);
  - d. pathologic expressions, pathophysiologic mechanisms, and genetic factors of allergic disease and allergic inflammation;
  - e. immune mechanisms and agents of immediate hypersensitivity and of related hypersensitivity manifestations of antigen-antibody reactions of cell mediated immunity (e.g., hypersensitivity pneumonitis, allergic dermatitis, vasculitis, allergic gastroenteritis, drug reactions) and the development of corresponding improved diagnostic materials and methods;

- f. immunopharmacology, immunotherapy, and the development of specific pharmacologic agents designed for prevention and treatment of asthma and the other allergic diseases.
5. Study of animal models will be considered acceptable as a partial segment or adjunct to a Center's program only if this line of research is applicable to the character of the primary investigation of asthma or the human allergic disease central to the proposal.
6. Designation of a Center Director should be based upon accomplishment and experience as a senior scientist and ability to assume both leadership of the investigative group and responsibility for scientific, professional, and administrative functions.
7. More than one delineated avenue of research may be pursued within a Center with provision for unified operation and coordination of component projects and collaborative investigators.
8. A Center should not rely upon its ability to conduct research activity solely within the confines of a single discipline, but rather should have established the associations to involve participation by workers in the pertinent biomedical fields and medical specialties allied to asthma, allergy, and clinical immunology (e.g. immunobiology, biochemistry, microbiology, biostatistics, bioinstrumentation and computer science, and the clinical subspecialties, e.g. dermatology, rheumatology, infectious diseases, pulmonary medicine, hematology, otorhinolaryngology).
9. The Center Director will be expected to communicate freely with the NIAID and other designated Centers for effective exchange of new information, to interact with scientists working in other Centers on related investigative problems, and to present progress reports and share experimental data with other Centers through exchanges and attendance at NIAID sponsored meetings of study groups and AADC workshops.

#### MECHANISM OF SUPPORT

In fiscal year 1982, the NIAID plans to fund at least six new or competing renewal Asthma and Allergic Disease Center applications. Each grant will have a duration of not more than five years. Funding beyond the first year of the grant will be contingent upon satisfactory progress during the preceding year.

The receipt date for applications will be October 15, 1981. They will undergo initial review in February-March 1982, and subsequent review by the National Advisory Allergy and Infectious Disease Council in May 1982. September 1, 1982 will be the earliest starting date for successful applicants.

Grant funds may be utilized to support the research activities of scientific and professional personnel, administration, consultation services, central support services, equipment, supplies, travel, and publication costs. Support for research-related costs of patient involvement and medical care may be authorized. Since the program cannot provide funds for new construction, adequate physical

facilities must be available for the primary needs of the Center. However, moderate alterations or renovations to enhance clinical facilities may be allowed if they are necessary to meet objectives of the Center's program.

Only those institutions that can demonstrate expertise in both basic and clinical areas and can direct their resources toward a multifaceted attack on asthma or the other allergic diseases can be supported under the provisions of the AADC program.

#### REVIEW PROCEDURES AND CRITERIA

Prospective Center Directors are strongly urged to prepare a "letter of intent" for preliminary screening by NIAID staff.

Letters of intent should cover the following points:

1. a brief description of the intended project;
2. a description of available laboratory facilities;
3. a brief description of ongoing basic immunologic and clinical research relating to asthma, allergy, or hypersensitivity with especial reference to any studies of the immediate type;
4. a brief description of, or reference to, published research work by the investigators on asthma, allergy, or hypersensitivities especially pointing out those that may relate to the immediate type and identification of existing projects and sources of support;
5. a description of all clinic facilities available for use by the proposed Center;
6. specific information on the institution's present patient load and projections for patient involvement in clinical investigation;
7. the academic positions and major research interests of the Center Director and his professional staff who will be involved in the work of the Asthma and Allergic Disease Center;
8. collaborative possibilities with other area laboratories and investigators and delineation of the roles and manner of anticipated participation and interaction of the principal investigators, consultants, and collaborators.

Letters of intent should be submitted by July 15, 1981, and upon receipt will be screened by NIAID staff to determine the eligibility and suitability of the projected proposals for the Asthma and Allergic Diseases Centers program.

Inquiries and letters should be directed and addressed to:

Robert A. Goldstein, M.D., Ph.D.  
Chief, Allergy and Clinical Immunology Branch  
Immunology, Allergic and Immunologic Diseases Program  
National Institute of Allergy and Infectious Diseases  
Westwood Building, Room 755  
National Institutes of Health  
Bethesda, Maryland 20205  
Telephone: (301) 496-7104

#### CONSEQUENCES OF LACK OF RESPONSIVENESS TO THE RFA OR LATE SUBMISSION

Based upon the letter of intent, potential applicants will be promptly advised whether or not their proposal is found to be within the research goals and scope of the program as defined in this RFA. Applicants will then have an opportunity to correct deficiencies or weaknesses and to restructure their submissions accordingly. Formal applications that are not responsive to the RFA or are not received by October 15, 1981, will not be accepted for review and will be returned to the applicant.

#### METHOD OF APPLYING

Before preparing an application, the prospective applicant should request from NIAID program staff a copy of the NIAID Information Brochure on Program Projects which contains details on the requirements for multidisciplinary grant applications.

Use the standard research grant application form PHS 398 (Rev. 10/79). In addition to following accompanying format instructions for the development of a Center application, include expanded material listed above under the eight points for the "letter of intent." For purpose of identification and processing, the RFA number NIH-NIAID-81-5 and the words "**ASTHMA AND ALLERGIC DISEASE CENTER**" should be typed in item 2 on the face page of the application and a brief covering letter should be attached indicating submission is in response to this NIAID announcement.

Application kits may be obtained from the institution's application control office. If not available there, they may be obtained from:

Office of Grants Inquiries  
Division of Research  
National Institutes of Health  
Westwood Building, Room 448  
Bethesda, Maryland 20205

Forward the complete application to:

Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, Maryland 20205

Please forward a copy (not the original) of the cover letter and the application face page to: (1) the NIAID Program Director in order to alert NIAID to the submission of the proposal, and (2) the Chief, Program and Project Review Branch, NIAID, Westwood Building, Room 703, National Institutes of Health, Bethesda, Maryland 20205.

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

NIH-NIEHS-EP-81-3

IMMUNOTOXICOLOGY OF ENVIRONMENTAL AGENTS

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Application receipt date: August 1, 1981

I. BACKGROUND INFORMATION

Although it is known that a variety of drugs and chemicals as well as ionizing radiation and altered nutritional states can influence the immune system, little definitive information is available concerning the effects of a wide variety of environmental agents on immunologic homeostasis. Undesirable effects resulting from the interaction of environmental agents and the immune system can be manifested as immunodeficient disease or immunopathology resulting from an adverse response of the immune defense mechanism.

There is increasing evidence that chronic low-dose exposure to agents in the environment, including heavy metals and chlorinated hydrocarbons, can depress immune responsiveness and may, in some cases, increase susceptibility of animals to infection. The relevance of these findings for human disease is unknown and additional information on the basic mechanisms of immunopathologic reactions and their detection is needed.

II. GOALS AND SCOPE

The objective of this announcement is to indicate that the NIEHS has an interest in supporting high quality research in areas of immunotoxicology which will elucidate the role of environmental agents in producing adverse effects on the immune system.

Although all areas of research which will contribute to an understanding of the mechanisms of action of these agents will be considered, emphasis is placed on the development and validation of immunologic methods and host resistance models to study the effects of chemicals of environmental concern on the immune response.

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This program is described in the Catalog of Federal Domestic Assistance number 13.892, Prediction, Detection and Assessment of Environmentally Caused Diseases and Disorders; and 13.893, Mechanisms of Environmental Diseases and Disorders. Awards will be made under the authority of the Public Health Service Act, Title III, 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 A-95 Clearinghouse or Health Systems Agency Review.

In order to accomplish the goals of the program, the following areas of research have been identified for priority consideration:

1. The development and validation of viral, bacterial or tumor susceptibility models to better define alterations in host resistance following subchronic chemical exposure.
2. The application of tests of immune function to study changes in the immune response following exposure to chemicals of environmental concern.
3. The development of immunological and biochemical methods to define the effects of chemicals of environmental concern on macrophage function.
4. The potential of microsomal enzyme activation systems coupled with in vitro immune function assays as a novel approach to screen chemicals for immune alteration.
5. The examination of bone marrow progenitor cells as targets for chemical induced immunotoxicity.
6. The development of animal models to study the potentials of chemicals to induce hypersensitization and allergy.
7. Studies to examine the effect of inhalation exposure of chemicals on the functional integrity of the immune elements of the lung.

### III. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional NIH research project grant. This type of announcement (the RFA) is used when an Institute--with the concurrence of its National Advisory Council or another appropriate advisory group--wishes to stimulate investigator interest in a particular research problem that is important to its program. The RFA solicitation represents a single competition with usually one specified deadline for receipt of applications. All applications in response to an RFA are reviewed by the same initial review group in competition with each other, usually for a designated amount of funds or number of awards.

The RFA identifies the scope of the Institute's interest but does not require that the proposal conform to a specific research protocol. Thus it is expected that each successful applicant will plan, direct, and carry out the research program. As with any research grant, the recipient must obtain prior approval for any major change in the scope or objectives of the approved project. Applicants should be aware that this general requirement is particularly pertinent when, as in the case of RFA solicitations, the awarding Institute has committed funds in response to a specific program need.

It is anticipated that \$600,000 will be allocated for this program during the first year; however, award of grants is contingent upon the availability of funds. The project period should adequately reflect the time required to accomplish the stated goals and be consistent with the NIH policy for grant support.

#### IV. REVIEW PROCEDURES AND CRITERIA

##### A. Review Procedure

Proposals in response to this solicitation will be reviewed in competition with each other on a nationwide basis. The initial review will be for scientific merit and will be carried out by an appropriate peer review group. Assignment to an institute for possible funding will be made in accordance with referral guidelines of the Division of Research Grants. The secondary review for relevance and responsiveness to the announcement will be made by the National Advisory Environmental Health Sciences Council or other institute advisory council, as appropriate.

##### B. Review Criteria

Applications should be responsive to the RFA and, therefore, relevant to the program goals of the sponsoring institute. Those factors considered to be important for review include a demonstrated knowledge of the applicable science, adequacy of facilities and commitment, availability of subject population when applicable and in-depth knowledge of the state-of-the-art to which the RFA is directed. The application will be judged upon the overall scientific merit, adequacy of methodology, facilities and resources, commitment of time and cost effectiveness of proposal. The sponsoring institution should indicate a commitment of facilities and resources to the program.

#### V. METHOD OF APPLYING

Applications should be submitted on form PHS 398, the application form for the traditional research grant. Application kits containing this form and the necessary instructions are available in most institutional business offices or from the Division of Research Grants, NIH. The original and six copies of the application must be received by August 1, 1981. Applications should be sent to:

Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
5333 Westbard Avenue  
Bethesda, Maryland 20205

The face page of the application should be labeled "IN RESPONSE TO RFA NIH-NIEHS-EP-81-3." One copy of the application should be sent to:

Dr. Edward Gardner, Jr.  
Program Director  
Regular Research Programs Section  
Scientific Programs Branch  
Extramural Programs  
National Institutes of Environmental  
Health Sciences  
P.O. Box 12233  
Research Triangle Park, North Carolina 27709



VI. STAFF CONTACT

Questions relating to this announcement may be directed to Dr. Edward Gardner, Jr. (address above) or (919) 755-4021.

SPECIALIZED CLINICAL RESEARCH CENTERS  
FOR PERIODONTAL DISEASES

THE NATIONAL INSTITUTE OF DENTAL RESEARCH

INTRODUCTION

The National Institute of Dental Research (NIDR) is currently supporting three Specialized Clinical Research Centers for Periodontal Diseases. One of the Centers will complete a 5 year project period in 1983. The original announcement (NIH Guide for Grants and Contracts, Vol. 5, No. 22, December 20, 1976) stated that the grants would be awarded to the centers for an initial period of five years, and that support for subsequent project periods would be determined by competitive reviews of new and renewal applications. Accordingly, the NIDR now invites applications from all institutions wishing to compete for center grant support. The present announcement provides revised guidelines for preparing an application. Applicants are advised to contact Dr. Paul Parakkal, Extramural Programs, National Institute of Dental Research, Room 519, Westwood Building, National Institutes of Health, Bethesda, Maryland 20205, (301) 496-7784 for additional information.

The Periodontal Diseases Centers were established to accelerate the acquisition of new information for preventing, diagnosing and treating periodontal diseases and to bring their resources, facilities and manpower to bear on these problems in a concerted way. In the span of three years, the centers have already made significant progress in microbiological and immunological research. They have identified numerous new species of bacteria from the diseased periodontal pockets, and are continuing the task of classifying the total flora of the periodontal pockets. The basic finding that polymorphonuclear leucocytes show impaired chemotactic function in patients with juvenile periodontitis has now been confirmed and amplified. The role of complement in host response to periodontal disease has also been further clarified. The centers will continue these efforts and also focus their attention on the many other cellular and chemical reactions which may protect the host, or cause soft tissue and bone destruction. The development of therapeutic techniques and preventive measures has been slow and the centers are expected to accelerate their efforts in this area.

BACKGROUND

Periodontal diseases include inflammatory conditions which affect the tissues around the roots of the teeth and lead to tooth loss. It is estimated that 94 million Americans have active periodontal disease, and approximately 32 million of these individuals have an advanced stage of the disease. Thus, these diseases constitute a major health problem of increasing concern in our society. Not only are the current treatment methods difficult, but the results are uncertain. The American public pays approximately \$1.5 billion every year for periodontal therapy even though only a fraction of those who need treatment actually receive it.

## OBJECTIVES

The main objective of the clinical research centers is to facilitate the application of basic research findings in the areas of pharmacology, microbiology, and immunology in clinical investigations of patients having periodontal disease. Even though these centers should emphasize studies of human patients, it is recognized that laboratory and animal studies may also be needed to aid in understanding the disease processes. Specifically, these centers should develop programs to accomplish some or all of the following objectives:

1. Develop preventive measures;
2. Improve therapeutic techniques and regimens;
3. Establish the causative organisms in periodontal diseases;
4. Determine the host response to these causative organisms.

The substance of each research program may vary according to local expertise, interest, resources, and recruitment possibilities, but the projects developed by each center must relate to the above objectives. Applicants should attempt to develop a unique program which is complementary to rather than duplicative of ongoing research. The institution must be willing to make a commitment of resources and staff to ensure the development, operation, and function of the proposed center.

Characteristics of a Clinical Research Center Within the institution, the clinical research center must become an identifiable organizational unit which can develop relevant clinical investigations. The Institution must have an adequate base of ongoing research in at least one of the following areas: pharmacology, microbiology, or immunology. The director of each clinical research center should be an established scientist who can provide both scientific and administrative leadership and is willing to make a significant time and effort commitment to the center. The director will be responsible for organizing and operating the center and for communicating with the NIDR on scientific and operational matters. An internal review board consisting of staff members of the center and other expert consultants who are not members of the clinical center program should be established. This board will assess the center's progress on current projects, will inform the director of its findings, and will conduct an initial review of new initiatives.

Administrative Items & Costs The center grant may include funding for pilot projects as well as for a cluster of interrelated regular projects. Funds may be used for central support services, equipment, supplies, renovations, consultation services, travel, publication costs, and also for professional, technical, and administrative personnel. Only those patient costs directly related to research may be charged to the center grant. The program does not provide funds for new construction. Each participating scientist is expected to obtain independent research support from sources other than the center grant during the award period, thereby releasing the center funds to attract other scientists to enter the center's research program. New applicants may request up to \$250,000 for the first year with appropriate increases in subsequent years.

Mechanism and Length of Support These centers will be supported by the research grant mechanism for a period of five years; support for subsequent project periods will be contingent upon program needs, successful competitive reviews (new and renewals) and the availability of funds. Once a clinical research center grant has been awarded, a cooperative relationship will be established between the NIDR to work closely with the center to discuss progress and to provide assistance. Each center is also expected to collaborate with other centers. As part of an overall evaluation, annual site visits will be made to each center. The budget will be negotiated yearly, and will be based upon the assessment of progress of each center, and the availability of funds.

Review Procedures The applications will be reviewed by the NIDR Special Grants Review Committee and the National Advisory Dental Research Council.

Review Criteria Applications will be judged on the basis of the following criteria:

1. Scientific merit of the proposed research and its relevance to periodontal diseases;
2. Adequacy of ongoing research in basic pharmacology, microbiology, or immunology;
3. Availability of competent clinical investigators;
4. Access to appropriate patient populations;
5. Adequacy of facilities for clinical research;
6. A favorable environment for research training.

Application Process Applications should be prepared on form PHS 398, "Application for Research Grants," and should include:

1. A table of contents;
2. A complete, consolidated first-year budget for the entire center and detailed sub-budgets for the component projects with appropriate justification.
3. Detailed information for each item listed below:
  - a. Rationale and justification for the center;
  - b. Description of intended projects;
  - c. Description of ongoing basic and clinical research related to periodontal disease;
  - d. Description of available laboratory facilities;

- e. Description of available clinical facilities;
- f. Specific information on patient availability;
- g. Evidence of capability of performing statistical and data analysis;
- h. Curriculum vitae of the program director and his immediate staff;
- i. Planned collaboration with other research groups and a delineation of the roles and modus operandi of expected interaction.

Timetable for Review

- A. Deadline for receipt of application - October 1, 1981.
- B. The earliest beginning date for award of grants - July 1, 1983

The original and six copies of the completed application should be mailed to:

Division of Research Grants  
National Institutes of Health  
Bethesda, Maryland 20205

In addition, two copies should be sent under separate cover to:

Dr. Paul Parakkal  
Periodontal Diseases Program Branch  
Extramural Programs  
National Institute of Dental Research  
Westwood Building, Room 519  
National Institutes of Health  
Bethesda, Maryland 20205

## ANNOUNCEMENT

DIETARY SODIUM AND ITS ROLE IN THE PREVENTION  
AND MANAGEMENT OF HYPERTENSION

## THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The National Heart, Lung, and Blood Institute (NHLBI) supports a variety of research programs related to the prevention, treatment, and control of hypertension. Since this broad area of research is important to several programs in the Division of Heart and Vascular Diseases (DHVD) of the Institute, the present program announcement is being issued from the Division. A program announcement is designed to focus attention upon a topic or problem. Applications will be considered as applications for the regular research grant program, without special set-aside funds.

The objective of this program announcement is to encourage the submission of scientifically meritorious applications concerning a broad range of investigations, including physiological, clinical, preventive, and therapeutic research, regarding the role of dietary sodium in hypertension and the prevention of hypertension.

It is estimated that 35 million persons in the United States have high blood pressure. This fact, coupled with recent evidence from the Hypertension Detection and Followup Program that significant reductions in mortality can result from sustained drug treatment of high blood pressure, makes research into the role of dietary sodium in the prevention and management of high blood pressure of special interest. This research area has been identified by the Salt and Water Subgroup of NHLBI's Hypertension Task Force, the NHLBI Clinical Applications and Prevention Advisory Committee and the Arteriosclerosis, Hypertension, and Lipid Metabolism Advisory Committee as needing emphasis.

Examples of needed research include studies of:

- The relationship between sodium and weight.
- The interrelationship of sodium and potassium.
- Sodium sensitivity.

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This program is described in the Catalog of Federal Domestic Assistance number 13.837, Heart and Vascular Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, 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 A-95 Clearinghouse or Health Systems Agency Review.

- Salt appetite.
- Methodology for determining sodium intake in humans.

Investigations that take account of other dietary factors, caloric intake, and energy expenditure are encouraged.

The above list is intended to provide examples only and does not preclude the submission of applications involving other research approaches to the issues under consideration. In addition, this program announcement is not intended to discourage investigators from their pursuit of promising ideas in related or unrelated topics.

#### Application Submission and Review

Application receipt dates for new applications are the regular application receipt dates of July 1, November 1, and March 1. Applications received after any one receipt date are considered and reviewed together with those received by the next receipt date. The earliest possible award date is approximately nine months after the receipt date. Applicants should use the regular research grant application form PHS-398, which is available at the applicant's institutional application control office or from the Division of Research Grants, NIH.

In order to identify the response to this announcement, check **"yes"** and put **"Dietary Sodium/Hypertension"** under item 2 on page 1 of those grant applications relating to the topics identified herein. The completed application should be mailed to:

Division of Research Grants  
Westwood Building, Room 240  
National Institutes of Health  
Bethesda, Maryland 20205

The Division of Research Grants will assign applications to study sections for review according to the NIH process for regular research grant applications. Approved applications will compete for available funds with all other approved grant applications assigned to the NHLBI. Additional information may be obtained by contacting:

Marilyn Farrand, R.D.  
Preventive Cardiology Branch  
Division of Heart and Vascular Diseases  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
Federal Building, Room 6A18  
7550 Wisconsin Avenue  
Bethesda, Maryland 20205  
Telephone: (301) 496-3503

or

Armando Sandoval  
Hypertension Branch  
Division of Heart and Vascular Diseases  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
Federal Building, Room 4C08  
Bethesda, Maryland 20205  
Telephone: (301) 496-1857



ANNOUNCEMENT

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD)  
AS A MAINTENANCE THERAPY FOR THE CHRONIC RENAL  
FAILURE PATIENT

THE CHRONIC RENAL DISEASE PROGRAM

THE NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM,  
AND DIGESTIVE DISEASES

The Chronic Renal Disease Program of the National Institute of Arthritis, Metabolism, and Digestive Diseases is inviting research grant applications for studies of a variety of factors related to Continuous Ambulatory Peritoneal Dialysis (CAPD) as a Maintenance Therapy for the chronic renal failure patient.

Program interests include maintenance therapies for end stage kidney disease, renal transplantation, and pathophysiology of chronic renal failure. This announcement is intended to encourage submission of individual research grant applications designed to:

1. Increase our understanding of the relative merit of Continuous Ambulatory Peritoneal Dialysis (CAPD) as a maintenance therapy for chronic renal failure patients.
2. Increase our knowledge of the pathophysiology of uremia by use of the CAPD patient as a model.
3. Develop an understanding of the complications experienced by CAPD patients with the goal of minimizing these problems.

RESEARCH SCOPE

The ultimate goal of research projects arising from this request is to expand the available knowledge base on the relative merits of CAPD. Some examples of needed research are noted below. They are examples only and are not listed in any order of priority. Other areas of research which are related to CAPD may appropriately be suggested by the applicant.

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This program is described in the Catalog of Federal Domestic Assistance number 13.849, Kidney Diseases, Urology and Hematology Research. Awards will be made under the authority of the Public Health Service Act, Title III, 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 A-95 Clearinghouse or Health Systems Agency Review.

1. Infection, especially peritonitis.

Currently available information, primarily derived from small patient series, indicates that the incidence of peritonitis in CAPD patients is high. Basic questions as to the relative immune status of CAPD patients are unanswered. For example, does the persistent loss of immunoglobulins (characteristic of CAPD) adversely affect a patient's immune function? Evaluation of alternative techniques of CAPD in statistically sound studies would be beneficial to our understanding of the ultimate role for CAPD therapy.

2. Blood Pressure Control

Patients maintained with CAPD generally exhibit excellent control of hypertension with less medication than is the experience with patients maintained on hemodialysis. Additionally, it should be noted that patients maintained by CAPD do not experience hypotensive episodes common to patients on hemodialysis. Not only does the validity of these clinical impressions require confirmation, but studies to provide an understanding of the mechanisms responsible for these apparent differences are needed.

3. Nutritional and Metabolic Issues

Patients undergoing CAPD therapy are subjected to a constant glucose load through the peritoneal cavity. Certain individuals on CAPD therapy have been observed to develop hyperlipidemia with elevated levels of LDL and decreased levels of HDL. There is concern that continuous exposure to glucose may lead to hyperglycemic states in some individuals. There is need for additional basic information on both carbohydrate and lipid metabolism in patients undergoing CAPD therapy. A potentially serious long term problem is the possible influence on vasculopathies including acceleration of atherosclerosis, ultimately increasing cardiovascular complications.

4. Anemia

A number of reports on patient series have noted that many patients placed on CAPD therapy may experience an apparent rise in hematocrit (to the low thirties) especially during the first few months of therapy. Apparently after a longer interval of six months to one year, hematocrits are in the range of the high twenties. There are a number of questions concerning anemia which deserve study. For example, does the red cell mass of a CAPD patient actually increase, and after some months decline? If so, what are the mechanisms responsible?

5. Mineral Metabolism, Bone Disease and Other Hormonal Influences

Available data from reports of short patient series indicate that CAPD patients exhibit lower serum levels of PTH, calcium and phosphate than their counterparts on hemodialysis. The observation in some series is that phosphate binders are

unnecessary in about half the patients. Short term data (one-two years) have shown no development of overt bone disease. If outcomes differ compared to hemodialysis, what are the mechanisms responsible?

#### 6. The CAPD Patient as a Unique Model for Study of Uremia

The fact that the chronic renal disease patient maintained on CAPD exhibits essentially constant blood chemistries represents an opportunity to study other aspects of uremia in a unique way. Investigators are invited to consider this option as possibly contributing to a better understanding of anomalies, and/or mechanisms leading to complications of uremia.

Investigator-initiated grant applications are encouraged in these and other areas related to CAPD therapy or the CAPD patient as a model.

#### MECHANISM OF SUPPORT

The mechanism of support for this program will be the research project grant. The award of grants pursuant to this program announcement is contingent upon ultimate receipt of appropriated funds for this purpose.

#### METHOD AND CRITERIA FOR REVIEW

##### 1. Assignment of Applications

Applications will be received by the NIH Division of Research Grants, referred to an appropriate study section for scientific review, and assigned to individual Institutes for possible funding. These decisions will be governed by normal programmatic considerations as specified by the Division of Research Grants Referral Guidelines.

##### 2. Review Procedures

Applications in response to this announcement will be reviewed on a nationwide basis in competition with other research grant applications, and in accord with the usual National Institutes of Health peer review procedures. Applications will first be reviewed for scientific and technical merit by a review group composed mostly of non-Federal scientific consultants (study section), and then the National Advisory Council of the appropriate Institute(s). The review criteria customarily employed by the National Institutes of Health for regular research grant applications will prevail.

##### 3. Deadline

Applications will be accepted in accordance with the usual NIH receipt dates for new applications as follows:

<u>Application receipt</u>	<u>Initial review</u>	<u>Council review</u>	<u>Earliest start date</u>
March 1	June	Sept./Oct.	Dec. 1
July 1	Oct./Nov.	Jan./Feb.*	April 1*
Nov. 1	Feb./March*	May*	July 1*

\*of the year following application receipt.

#### METHOD OF APPLYING

Applications should be submitted on form PHS-398, which is available in the business or grants and contracts office at most academic and research institutions or may be obtained from:

Office of Grants Inquiries  
Division of Research Grants,  
National Institutes of Health  
Bethesda, Maryland 20205

The phrase **"PREPARED IN RESPONSE TO NIAMDD PROGRAM ANNOUNCEMENT FOR CAPD"** should be typed on line 2 of the first page of the application.

The original and six copies of the application should be sent or delivered to:

Application Receipt  
Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, Maryland 20205

For further information, investigators are encouraged to contact:

Robert J. Wineman, Ph.D.  
Chronic Renal Disease Program Director  
Kidney, Urologic and Blood Diseases Program  
National Institute of Arthritis, Metabolism,  
and Digestive Diseases  
National Institutes of Health  
Bethesda, Maryland 20205  
Telephone: (301) 496-7571

ANNOUNCEMENT

ALZHEIMER'S DISEASE AND OTHER RELATED DEMENTIAS OF AGING

NEUROLOGICAL DISORDERS PROGRAM

NEUROSCIENCE OF AGING PROGRAM

NATIONAL INSTITUTE OF  
NEUROLOGICAL AND COMMUNICATIVE  
DISORDERS AND STROKE

NATIONAL INSTITUTE ON AGING

The NIA and the NINCDS jointly announce a continuing interest in support of research on Alzheimer's disease and other related dementias of aging. The NINCDS and the NIA invite research grant applications concerned with both fundamental and/or clinical investigations on the etiology, pathogenesis, diagnosis, treatment and prevention of Alzheimer's disease and other related dementias of aging.

BACKGROUND

Dementia affects 5 percent of the population over 65, or one million people. An additional 10 percent of the population shows varying degrees of cognitive dysfunction. Pathological studies indicate that at least 55 percent of persons dying with the diagnosis of dementia have Alzheimer's disease. Chronic dementias account for a significant number of nursing home patients. The current expenditure for nursing home care is approximately \$12 billion per year. Even a 10 percent reduction in the number of patients with dementia would result in considerable savings annually. The enormous societal costs of this disease indicate the need for an increase in research efforts.

RESEARCH GOALS AND SCOPE

The NIA and the NINCDS are interested in innovative research projects designed to elucidate the etiology or pathogenesis of Alzheimer's disease, improve diagnosis, and eventually provide a sound basis for effective therapy. In view of the gaps in our knowledge, the following types of research topics are of particular interest.

- Differential Diagnosis: There is a need to refine existing diagnostic procedures and/or develop more sensitive and reliable techniques to detect treatable patient populations. The diagnosis of Alzheimer's

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This program is described in the Catalog of Federal Domestic Assistance number 13.852, Neurological Disorders, and 13.866, Aging Research. Awards will be made under the authority of the Public Health Service Act, Title III, 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 A-95 Clearinghouse or Health Systems Agency Review.

disease usually is based on the clinical history and examination, concurrence of psychometric, EEG, CSF, CT findings and exclusion of other known causes of dementia. Some degree of diagnostic accuracy can be achieved by these means. Further understanding of the etiology, pathogenesis and treatment of Alzheimer's disease is needed to improve the overall diagnostic precision and identification of very early cases.

- Clinical and/or Pathological Studies: Recent progress in understanding Alzheimer's disease has relied upon systematic correlations of clinical observations and pathological findings. Further studies are needed to correlate the quantitative morphometric measurements of the anatomic distribution of specific Alzheimer's lesions (neuritic plaques and neurofibrillary tangles) with physiological, cognitive and other gross behavioral changes. There is a need to determine the exact relationship between the variance in psychological impairment and such neuropathological variables as loss in cell numbers, cell types affected, changes in tissue volume and the presence of infarcts in various parts of the brain.
- Cerebral Circulation and Metabolism: Impaired local perfusion has been suggested as a causal factor in Alzheimer's disease. Efforts to study the relationship between brain circulation and metabolic changes in subjects with Alzheimer's disease or at risk for this disease need to be expanded. Studies using new in vivo methods (e.g., positron emission tomography) to examine local brain metabolism in man, as well as to evaluate specific pharmacotherapeutic regimens are of particular interest.
- Neurochemistry: Current work in neurotransmitter deficits in Alzheimer's disease needs to be expanded into clinical trials aimed at replacement therapy. An understanding of the basic biochemical and neuropharmacological mechanisms and morphological changes underlying the chronic dementias are the key to elucidating the pathogenesis of Alzheimer's disease.
- Neuroendocrinology: Studies directed at explaining the role of brain peptides and hormones in regulating a complex variety of biochemical functions (enzymatic, metabolic, histological and neurotransmitter activities) are crucial to understanding some of the clinical manifestations of the dementias of old age.
- Genetics - Population Studies: Both environmental and genetic factors have been implicated in the etiology of Alzheimer's disease. Further epidemiologic and genetic studies are needed to clarify the relationship between genetic and possible environmental factors (e.g., aluminum, certain viruses).
- Immunology - Virology: There is evidence that at least two human spongiform encephalopathies, Kuru and Creutzfeldt-Jacob disease, are caused by transferrable or atypical slow or latent viral agents. There is a need to explore the possible role of a latent or slow virus in Alzheimer's disease. Also there is a need to further characterize the

decline in immune function with age. Such a decline might prevent the brain from protecting itself against external invasion of noxious agents, activation of a latent agent, and autoimmune brain damage.

- Animal and Other Model Systems: The development of a valid animal model is critical to the study of Alzheimer's disease. The research necessary to develop model systems is encouraged.

**NOTE:** The research topics indicated above are not intended to be an exhaustive or exclusive listing of interests. The list is compiled merely to indicate examples of topics. Applications on other related topics or problem areas are welcome.

### MECHANISMS OF SUPPORT

Applications may be submitted for either one of two support mechanisms:

- a) Program project grants (P01): Program project grants are awarded for the support of a broadly based, often multi-disciplinary research program with a particular major objective or theme. Clinical as well as fundamental research can be supported via program project grants. Applications should indicate the availability of patients, and the ability to carry out the desired objectives. Applicants should develop a comprehensive research program, with each phase directed to a specific aspect of Alzheimer's disease. Potential applicants are encouraged to consult with the staff of the Neurological Disorders Program, NINCDS, or the Neuroscience of Aging Program, NIA, early in the planning stage. Deadlines for receipt of P01 applications are June 1, October 1, and February 1.
- b) Individual research project grants (R01): Applications may propose any topic or problem area related to Alzheimer's disease. Deadline for receipt of new R01 applications are July 1, November 1, and March 1.

### REVIEW PROCEDURES AND CRITERIA

The support mechanism for this program will be the grant-in-aid. Applications should be prepared on form PHS 398 following the instructions contained in the application kit. This kit can be obtained from the Division of Research Grants, NIH. Applications for program projects should conform to the style and format recommended by the NIA and NINCDS. Program project applications will be reviewed initially and judged for scientific merit by one of the NINCDS or the NIA program project review committees. Individual research projects receive a similar review by the appropriate study section of the Division of Research Grants. Both reviews will be conducted in accordance with the NIH policy and procedures involving peer review. Awards will be made to the applicants who have successfully competed against all those requesting funds from the Neurological Disorders Program and/or the Neuroscience of Aging Program.

The phrase "**PREPARED IN RESPONSE TO NIA AND NINCDS ANNOUNCEMENT-ALZHEIMER'S DISEASE**" should be typed across the top of the first (face) page of the application.

Completed applications should be submitted according to the deadlines for the review schedule mentioned above (also supplied in the application kit) and mailed to the following address:

Division of Research Grants  
Westwood Building, Room 240  
National Institutes of Health  
Bethesda, Maryland 20205

#### INQUIRIES AND CORRESPONDENCE

Prior to submitting a formal proposal, the applicant is requested to send a brief letter of intent to the project officers at both the NINCDS and the NIA. At the time of formal submission, one copy of the application is to be sent to each of the addresses below. Applicants needing further information, including guidelines on format for program project applications may contact:

Dr. Eugene J. Oliver  
Health Scientist Administrator  
Neurological Disorders Program  
National Institute of Neurological  
and Communicative Disorders  
and Stroke  
Federal Building, Room 710  
Bethesda, Maryland 20205  
Telephone: (301) 496-6541

Dr. Zaven S. Khachaturian  
Head, Neuroscience of Aging Program  
Biomedical Research and  
Clinical Medicine  
National Institute on Aging  
National Institutes of Health  
Bethesda, Maryland 20205  
Telephone: (301) 496-1033



ANNOUNCEMENT - REVISED

BASIC AND CLINICAL STUDIES OF NORMAL

DEVELOPMENT AND DEVELOPMENTAL DEFECTS

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

I. PROGRAM SPECIFICATIONS

A. Program Objectives

Seven percent of all babies are born in the United States each year with mental or physical defects. One fifth of all infants who die by the age of four do so because of congenital defects. In addition, a major proportion of spontaneously miscarried pregnancies are associated with developmental defects.

Congenital defects are defined as structural, functional, and biochemical anomalies that are initiated in the human organism prior to birth or shortly thereafter and cause immediate or delayed abnormality. Causes of developmental defects may either be genetic, i.e., gene mutations or chromosomal aberrations, or may include diverse agents in the internal or external environment of the developing embryo, fetus, or child. Most often developmental defects appear to result from abnormal interactions of genetic and environmental factors. The etiology of 65 to 75 percent of all congenital defects is, however, still unknown.

The Institute therefore encourages research into the causes of birth defects. Studies of etiologic factors, normal and abnormal basic developmental mechanisms, and clinical entities are emphasized. A combined clinical and developmental biologic approach should lead to a better understanding of the processes of development of birth defects.

B. Research Scope

This announcement emphasizes research on normal and abnormal human development during the periods prior to conception through early maturity. Investigations may be at the basic and/or clinical level, utilizing knowledge and techniques employed in disciplines such as

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This program is described in the Catalog of Federal Domestic Assistance number 13.865, Research for Mothers and Children. Awards will be made under the authority of the Public Health Service Act, Title III, 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 A-95 Clearinghouse or Health Systems Agency Review.

developmental genetics, developmental biology, teratology, and developmental immunology. They may include human and other mammalian models but may also use those nonmammalian models relevant to the understanding of normal human development and the production of birth defects.

Some areas of research interest are listed below. They are not presented in order of priority, but serve as examples only. Other research areas related to normal and abnormal human development, derived by the applicant, would be equally welcome.

#### Developmental Genetics

Essential to a better understanding of human development is an increased knowledge of the role of genetic factors in normal human maturation and susceptibility to disease. NICHD thus encourages studies in human and clinical genetics, including family investigations of mutant genes affecting metabolic and morphologic development, twin studies to distinguish genetic from environmental determinants of development, and population genetic studies to establish distributions and frequencies of abnormal genes. Of interest also are screening, diagnostic, and treatment studies of human genetic diseases which would investigate autosomal and sex chromosomal abnormalities underlying developmental problems as well as DNA sequence polymorphisms as markers of hereditary disease. Studies of basic genetic regulatory mechanisms are encouraged insofar as they provide understanding of human developmental processes. They may include identification of genes specifying normal and abnormal developmental processes; determination of gene structure, function, and mechanisms of gene action; determination of genetic regulatory elements; study of developmental expression of "structural" genes in specific tissues at certain developmental stages; and assignment of genetic loci on chromosomes to specific normal and abnormal gene products.

#### Developmental Biology

Our understanding of human development would be further advanced by studies on the integration of epigenetic factors into the maturation of a complete organism or human being. Such investigations would include the contribution of maternal cytoplasmic substances to the early development of the fertilized egg, as well as the role of physiological and chemical gradients in oocyte asymmetry and subsequent organization of the developing embryo. Studies relevant to human development are also encouraged of intra- and extracellular as well as cell surface components in morphogenetic tissue interactions, and of the biogenesis of subcellular particles (e.g. mitochondria) and the biosynthesis of biologically important macromolecules (e.g. proteoglycans, collagen, fibronectin) and organ-specific products (e.g. myelin, actin, myosin) during biochemical and morphological maturation, as well as investigations of trophic and endocrine influences on organogenesis. Of special interest are studies of the development of the limb.

### Teratology

An increased understanding of deviant human development leading to congenital defects requires investigations of the causes and mechanisms producing disruptions in the normal human developmental program prior to conception through early childhood. NICHD therefore encourages studies of inborn structural, functional, and biochemical defects that are initiated in the human being prior to birth or shortly thereafter and cause immediate or delayed abnormality. Of interest are anomalies which have a hereditary basis and those which are caused by a nonhereditary insult such as infections, maternal metabolic imbalances, immunologic reactions, drugs, environmental chemicals, nutrition, ionizing radiation, ultrasound, or thermal variations, as well as abnormalities which are of multifactorial origin. Investigations are encouraged at the basic gene and chromosome level, as well as at the cell, tissue, and organ levels, to determine specific divergent developmental processes which would result in the production of specific developmental disorders. Of further interest are clinical studies for the identification of new defects and the derivation of new treatment modalities, epidemiological studies to separate genetic from environmental causes of birth defects, family and population genetic studies to define the mode of inheritance of congenital disorders and establish frequencies of abnormal genes, and studies which would derive animal models for abnormal developmental mechanisms in man. Emphasis is given to studies of limb malformations involving both hereditary and environmental causes.

### Developmental Immunology

This category includes investigations on the ontogeny of the immune system during human embryonic, fetal, and infant development, and on the phylogeny of immunity to gain insight into the normal evolution of the reticuloendothelial system. Encouraged are studies of immune system development during periods of malnutrition, immunological properties of breast milk, the mechanisms that may pertain to the mother's experiences with infection, the transfer of protection to the infant through breastfeeding, the events following ingestion of milk in the infant's digestive tract, and possible hazardous effects of breast feeding. Also of interest are studies of the immunologic vulnerability of prematures and newborns resulting in increased morbidity and mortality due to infections and diseases with emphasis on factors influencing or altering the immune response due to age dependent events. Reproductive immunological investigations of the fetus as an allograft during pregnancy are encouraged, as are studies of the placenta as an immunological barrier and in regulation of the maternal immune response.

## II. METHOD AND CRITERIA OF REVIEW

### A. Assignment of Applications

Applications will be received by the Division of Research Grants, NIH; referred to an appropriate study section for review; and assigned to an

institute for possible funding. Assignments to institutes will be made by the DRG according to the NIH Handbook of Referral.

B. Review Procedures

Applications received in response to this program announcement will be reviewed on a nationwide competitive basis in accord with the usual NIH peer review procedures. Proposals will first be evaluated for scientific and technical merit by an initial review group of mostly non-Federal scientific consultants. Following study section review, applications will further be reviewed for program relevance by the Institute's National Advisory Council. The customary NIH review criteria for regular research grant applications will prevail.

III. METHOD OF APPLYING

A. Format for Applications

Applications are to be submitted on form PHS 398 which is available in the business or grants and contracts office at most academic and research institutions or from the Division of Research Grants, NIH. The phrase "**PREPARED IN RESPONSE TO THE BASIC AND CLINICAL STUDIES OF NORMAL DEVELOPMENT AND DEVELOPMENTAL DEFECTS ANNOUNCEMENT**" should be typed across the margin at the top of the first page of applications. Original applications and six copies should be sent or delivered to:

Application Receipt Office  
Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, Maryland 20205

B. Deadline

Applications will be accepted by the usual receipt dates for new proposals: July 1, November 1, and March 1.

IV. INQUIRIES

Inquiries may be directed to:

Head, Genetics and Teratology Section  
Clinical Nutrition and Early Development Branch  
Center for Research for Mothers and Children  
National Institute of Child Health  
and Human Development  
National Institutes of Health  
Landow Building, Room 7C09  
Bethesda, Maryland 20205  
Telephone: (301) 496-5575