

NIH GUIDE

for GRANTS and CONTRACTS

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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

REQUEST FOR RESEARCH GRANT APPLICATIONS - RFA

NIH-NHLBI-DHVD-81G-A

**ANIMAL MODELS FOR THE STUDY OF THE PATHOGENESIS OF SPECIFIC
HEART MUSCLE DISEASES**

Application receipt date: February 20, 1981

The Division of Heart and Vascular Diseases of the National Heart, Lung, and Blood Institute (NHLBI) is requesting grant applications for research involving the use of animal models of alcoholic, viral and adriamycin-induced heart muscle diseases, aimed at elucidating the pathogenetic mechanisms of these diseases.

The NHLBI will use the grant-in-aid as the support mechanism, but it will differ from other research grants both in its goal orientation and in the degree of participation by the National Heart, Lung, and Blood Institute. While it is expected that each successful applicant will plan, direct, and execute his/her own research project, any substantial modifications must be mutually agreed upon by the participant and the National Heart, Lung, and Blood Institute. Cooperation and communication between the program participants is another essential feature of this program.

The present announcement is for a single competition with a specified deadline of February 20, 1981 for receipt of applications. It is open to all interested investigators, including those who are already the recipients of investigator-initiated research grants from the NHLBI in this area. Applications should be prepared and submitted in accordance with the aims and requirements described in the following sections.

It is important to call attention to the fact that the RFA application differs from that for the regular research grant in that it is requested that a letter of intent to submit an application be sent by January 15, 1981, and that the applications be received by the February 20, 1981 deadline. More detailed instructions are provided under Section V, Method of Applying.

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.

I. BACKGROUND INFORMATION

The Cardiomyopathies and Infections of the Heart Program

The Cardiomyopathies and Infections of the Heart Program of the Division of Heart and Vascular Diseases of the National Heart, Lung, and Blood Institute is responsible for the design and administration of a national research program leading to the reduction of death and disability from cardiomyopathies and infectious diseases of the heart. The program is stimulating the development of new knowledge in this area of investigation as well as the translation of results into clinically useful methods and techniques.

At the present time, the program includes investigations of the physiologic, ultrastructural and metabolic derangements accompanying cardiomyopathies and infections of the heart; investigations of the agents which produce viral myocarditis and how the disease may alter the function of the heart acutely and chronically; and investigations of the factors which determine the induction of endocarditis and the development of effective antimicrobial therapies for these infections.

The term "cardiomyopathy" was introduced into clinical medicine in 1954 by Brigden. He defined cardiomyopathies as a form of generally fatal primary cardiac diseases in which there was enlargement of the heart accompanied by severe congestive heart failure. The diagnosis of these diseases required that the patient be free of known causes of cardiac enlargement and failure such as ischemic heart disease, valvular abnormalities, and hypertension. The clinicopathologic work which has taken place in the past 25 years has made it clear that this diagnosis includes a variety of serious, often fatal myocardial diseases.

These forms of myocardial diseases are described in diverse journals; moreover, definitions are often sketchy or controversial; the diagnosis is often made by exclusion of the usual causes of cardiac failure; and finally, the incidence of these forms of cardiac disease in the general population is not well known, in part due to confusion in the terminology and classification of these disorders.

It has been recently proposed by the Task Force on Cardiomyopathies, World Health Organization, and the Scientific Council on Cardiomyopathies, International Society and Federation of Cardiology, that the nomenclature for these disease entities be made more specific and less ambiguous. According to the new classification, the term cardiomyopathy should be used to describe the group previously known as "primary cardiomyopathy" or "heart muscle disease of unknown cause," and that "secondary cardiomyopathy" should be replaced by the term specific heart muscle disease. For example, a disease entity in which a viral agent is the proposed etiologic factor should be referred to as "viral heart muscle disease" and not "viral cardiomyopathy." The new terminology will be used

throughout this solicitation, and it should be used for research grant applications submitted in response to it in order to avoid confusion and ambiguity.

Since relatively little is known about both cardiomyopathies and specific heart muscle diseases, and since the information which is available is widely distributed in the literature in the form of case reports and experimental studies, a workshop on cardiomyopathies was conducted by the National Heart, Lung, and Blood Institute on July 11-12, 1978. The experts gathered for this workshop were selected to describe what is known about three specific heart muscle diseases: alcoholic heart muscle disease, viral heart muscle diseases, and adriamycin-induced heart muscle disease. Both clinical and experimental work was presented.

The results of this workshop showed that much less was known about specific heart muscle diseases than was believed to be the case at the time the recommendation to hold a workshop was made. It was concluded that there is an important need to stimulate additional basic research on these conditions. Previous laboratory investigations of the pathophysiology of cardiomyopathies has resulted in an improved understanding of contractile mechanisms, cardiac hypertrophy, organelle turnover, atrophy, repair, toxic cell injury, etc. While these investigations have lead to an improved understanding of cardiomyopathies and specific heart muscle diseases, these topics need to be considered in terms of the diseases themselves, which means that good animal models of some representative specific heart muscle diseases are needed in order to study the pathogenesis of these disorders and to apply this knowledge to man. Applications are requested for research involving the use of animal models of alcoholic, viral and adriamycin-induced heart muscle diseases with the goal of learning more concerning the pathogenesis of these conditions.

II. RESEARCH GOALS AND SCOPE

For the purposes of this solicitation, an animal model will be defined as a living organism possessing an induced pathological process which resembles the same phenomenon occurring in man. Applications which propose to use new or existing animal models of alcoholic, viral, and adriamycin-induced heart muscle disease to elucidate the biochemical, metabolic, physiological, and/or morphological mechanisms involved in these disorders, will be considered responsive to this request. However, the development and characterization of animal models of these disorders, in itself, is not the sole goal of this request. Applications must include, as an important element of the research plan, proposed efforts to elucidate fundamental mechanisms concerning one of these three heart muscle diseases in an animal model in order to be considered responsive to this solicitation.

Applications must clearly specify the type and species of animal to be used; the complete procedure for the induction of the pathological process including a detailed description of the method(s) and time frame involved in the introduction of the etiologic factor; the methods for quantitative assessment of the derangements in cardiac structure and function produced

in response to the etiologic factor; and the probable rationale for a causal relation between the introduction of the etiologic factor and these observed derangements. It is most important to include a justification for the clinical relevance of the proposed animal model; that is, the extent to which the phenomena observed in the animal model correspond to the manifestations of the disease in humans. Applicants should then clearly outline their proposed series of investigations which will attempt to produce new information concerning the underlying mechanisms involved in these disease entities. It is strongly urged that applicants restrict their proposed investigations to only one of the three disease entities. Applications may include investigations of the efficacy and/or mechanism of action of one or more proposed therapeutic interventions in animal models, but research involving human subjects is specifically excluded.

The following listing of research topics is intended only to provide examples of possible research hypotheses and approaches. Other research topics conforming to the program guidelines are also solicited.

In the alcoholic form, it would be most desirable to develop an animal model of cardiac dilatation and congestive failure induced by alcohol ingestion. Large animal studies have been tried without too much success and are very expensive; accordingly, it would be preferable to develop a small animal model of this disease.

In the viral form, the mechanism through which viral infection causes cardiac dilatation and failure needs to be further elucidated. The hypothesis that a single, acute, viral infection can cause progressive cardiac disease should be tested. Immunologic mechanisms are believed to be an unimportant aspect of the underlying etiology of this disorder. Moreover, these mechanisms may be important in other cardiac diseases such as rheumatic fever or Chagas' disease.

In the adriamycin form, additional information concerning the mechanism through which adriamycin exerts its cardiotoxicity is needed. Models of this disease exist in several animal species, but the mechanism of toxicity is not fully understood. In the process of understanding the mechanisms of cell injury produced by adriamycin, more may be learned about the general reaction of myocytes to injury.

Because this program is one in which the various elements have relevance to one another and may depend upon each other, free communication is expected between the participants. The NHLBI will attempt to foster such communication in part through the conduct or support of symposia and conferences. In the preparation of the budget for the grant application, applicants should request travel funds for a two-day research conference each year, most likely to be held in Bethesda, Maryland.

While the program has considerable breadth of scope, potential applicants should review their research applications in the context of the stated program goals and review criteria in order to reassure themselves that their application is truly responsive; if the relevance and responsiveness of

an application to these goals and criteria are doubtful, the application should be considered for submission as a regular research grant application. Prior consultation with the NHLBI Program Office is encouraged (see item VI below). It should be clearly understood that the existence of a targeted program in this area and the distribution of a Request for Applications does not preempt this topic from the investigator-initiated research grant program.

III. MECHANISM OF SUPPORT

Although the support mechanism of this program will be the grant-in-aid, it will differ from the investigator-initiated research grant both in its goal orientation and in the degree of participation by the National Heart, Lung, and Blood Institute. While it is expected that each successful applicant will plan, direct, and execute his/her own research program, any substantial modifications to it must be mutually agreed upon by the participant and the National Heart, Lung, and Blood Institute. Ongoing evaluation will include periodic visits and the review of formal progress reports.

Applicants are requested to furnish their own estimates of the time required to achieve specific objectives of the proposed work and an outline of the phases or segments into which the proposed project can be logically divided. The total project period will be three years in duration; it is desirable that a September 1, 1981 starting date for the project be requested.

Although this announcement is included and provided for in the financial plans for Fiscal Year 1981, support of grants pursuant to this Request for Applications is contingent upon ultimate receipt of funds for this purpose. The projected total annual funding level for this solicitation is \$500,000 (total costs). A variety of approaches would be responsive to this announcement; accordingly, it is anticipated that there will be a range of costs among the individual grants awarded. It is anticipated that approximately 6 awards will be made if a sufficient number of high quality applications are received; this should be considered in the preparation of the scope of work and budget. A recommended, but not mandatory, size for the proposed budget is \$45,000-\$60,000 per year (direct costs).

Unless specifically stated to the contrary, herein all policies and requirements which govern the grant program of the PHS apply, including the requirement for cost sharing.

IV. REVIEW PROCEDURES AND CRITERIA

Applications will be reviewed by the NHLBI Program Office to determine their responsiveness to this solicitation. Applications which are found to be not responsive will be considered ineligible and will be returned without being reviewed. Those which are considered responsive will be reviewed in a national competition with each other. Primary review will be conducted by an Initial Review Group composed primarily of non-Federal scientific consultants. Secondary review will be by the National Heart, Lung, and

Blood Advisory Council. Applicants will be informed of the results of the competition as soon as possible after the May, 1981 meeting of the Council.

The major factors considered in evaluating each application, in order of decreasing importance, are given below:

1. The scientific merit of the application; that is, the questions proposed for study, the research design and approaches, the methodology, and the analysis and interpretation of data.
2. The likelihood of arriving at meaningful and useful data to accomplish the goal of this solicitation.
3. The research experience and competence of the staff to carry out the proposed investigations and the time they will devote to the program.
4. The adequacy of existing and proposed facilities and resources.
5. In applications containing more than one project, the integration of various projects into an effective total program.
6. Willingness to work cooperatively with other participants in the program and with the National Heart, Lung, and Blood Institute.
7. The cost of proposed research.
8. The organizational and administrative structure of the proposed program.

V. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are asked to submit a brief, one-page letter of intent which includes a very brief synopsis of the proposed areas of research and identification of any other participating institutions. This letter should be sent no later than January 15, 1981, to:

Dr. Charles L. Turbyfill
Review Branch
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
National Institutes of Health
Westwood Building, Room 553
Bethesda, Maryland 20205

The Institute requests such letters for the sole purpose of providing an indication of the number and scope of applications to be received. A letter of intent is not binding, and it will not enter into the review of any application subsequently submitted, nor is it a necessary requirement for application.

B. Format for Applications

Applications should be submitted on form PHS-398, the application form for a regular research grant. This form is available at the applicant's institutional control office or from the Division of Research Grants, NIH. The conventional manner of research grant

applications should be utilized, ensuring that the points identified under "Review Procedures and Criteria" (see Section IV, above) are fulfilled. Specific attention is directed towards the inclusion of a statement indicating the willingness of the applicant to work cooperatively with other participants in the program and with the National Heart, Lung, and Blood Institute.

C. Application Procedure

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

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

In addition, please send eighteen (18) copies to:

Dr. Charles L. Turbyfill, Review Branch
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
Westwood Building, Room 553
5333 Westbard Avenue
Bethesda, Maryland 20205

To ensure their review, applications must be received by 5:00 p.m. EST on February 20, 1981. Applications not received by this deadline will be considered ineligible and will be returned without being reviewed.

The outside of the mailing package and Item 2 of the face page of the application should be labeled "RFA NIH-NHLBI-DHVD-81G-A, Animal Models for the Study of the Pathogenesis of Specific Heart Muscle Diseases."

VI. IDENTIFICATION OF NHLBI CONTACT POINTS

Inquiries may be directed to:

Dr. Richard P. Schwarz, Jr.
Cardiac Diseases Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
Federal Building, Room 3C06
Bethesda, Maryland 20205
Telephone: (301) 496-1081

Prior consultation with the above is strongly encouraged.

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFANIH-NIAID-81-1

NATIONAL INSTITUTE OF ALLERGY & INFECTIOUS DISEASES

TITLE: INTESTINAL ABSORPTION OF PEPTIDE HORMONES

Application receipt date: March 1, 1981

BACKGROUND INFORMATION

The NIAID has responsibility for managing the NIH Program to Assess the Risks of Recombinant DNA Research. As part of that responsibility it convened a Workshop in April 1980 to consider if there are potential risks that might be associated with E. coli K-12 producing biologically active peptides, including hormones. For the purposes of this workshop, it was assumed that an extremely improbable series of events had occurred and the peptide-producing host-vector system had colonized the gastrointestinal tract or had established some other focus of infection or colonization. One purpose of the meeting was to decide if, under those conditions, the individual colonized by the bacterium would be adversely affected by a direct action of the peptide.

The meeting brought together 92 outstanding scientists from the fields of immunology, endocrinology, physiology, microbiology, infectious diseases, and other appropriate disciplines. After analyzing the potential risks to man from the production of hormones, such as proinsulin and growth hormone, and other polypeptides by recombinant DNA-containing bacteria, the group felt that risks to the individual are minimal. This judgement was heavily influenced by calculations that demonstrated that even if the complete E. coli flora of the gastrointestinal tract became active in producing the material under maximal in vitro levels, only insignificant amounts of hormone would be produced daily.

However, because no substantial data base exists on absorption of hormones from the distal small intestine and from the large bowel and because the production of hormones was calculated on the basis of current technology, the workshop recommended that the Institute sponsor the studies outlined in this RFA. The Recombinant DNA Advisory Committee subsequently endorsed the need for such studies. The project will fill a significant void in present knowledge of risks

This program is described in the Catalog of Federal Domestic Assistance number 13.856, Microbiology and Infectious Disease 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.

associated with recombinant DNA research and will assist in making future judgements concerning risk should improved technology result in significantly greater yields. It is also hoped that these studies will stimulate development of a larger body of knowledge related to intestinal absorption.

RESEARCH GOALS AND SCOPE

To determine the fate of peptide hormones when deposited in the distal small intestine and large intestine of humans. The primary focus is on obtaining data on insulin and growth hormone, but those wishing to investigate additionally other active peptides (e.g., digestive enzymes and gastrointestinal hormones) are encouraged to include them in the applications. Primary emphasis should be placed on determining if the active hormones are absorbed in an active form, degraded or otherwise inactivated, or excreted in the fecal mass. Four potential situations exist:

1. not absorbed at all;
2. absorbed but inactive
3. absorbed in an active form but has no effect on target organs;
4. absorbed in an active form and effects changes in target organs.

It is recognized that preliminary trials in laboratory animals will be required to establish measurement technology, dosage, and other parameters. The investigations must be relevant to the risk assessment scenario described in the background statement, namely, the production of peptide hormones within the gastrointestinal tract by E. coli host-vector systems. The distal small intestine and large intestine were selected because these regions are where E. coli are found in normal individuals.

MECHANISM OF SUPPORT

Any public, nonprofit institutional organization or association is eligible to apply for a research grant under this RFA. The same guidelines as for the submission of regular research grants will apply.

The length of support will be for three to five years, according to the recommendations of the Initial Review Group. Renewability will depend on a new announcement of this program.

Funding will be under the regular research grant program of the NIAID and a special "set aside" of funds has not been made. It is anticipated that up to three awards will be made, depending on the availability of funds and the number and quality of applications received. Final decision on funding of projects received under this RFA will be made in concert with the National Advisory Allergy and Infectious Diseases Council. These applications will be considered for fiscal year 1982 funding and therefore complete details on available funds are not yet known.

REVIEW PROCEDURES AND CRITERIA

Applications will be reviewed for scientific merit by an appropriate initial review group in the Division of Research Grants. The National Advisory Allergy and

Infectious Diseases Council will conduct the final review of these applications. The first final review will be at the September Council meeting in 1981 and approved applications will be considered for fiscal year 1982 funding. The earliest that an award can be made is December 1, 1981.

Applications will be evaluated on the basis of the technical merit of the proposal, the appropriateness of the research to the needs of the Recombinant DNA Advisory Committee recommendations as stated in RESEARCH GOALS AND SCOPE above, the technical competence of the applicant and his collaborating staff and the potential of the project for responding to the goals of this RFA. Applications which are not responsive to the RFA will be considered as regular research grants in the general program.

METHOD OF APPLYING

Applications should be made on the regular research grant form PHS 398. An original and six copies should be mailed to:

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

The next regular receipt date is March 1, 1981, and the one following that is July 1, 1981. Applications which are late for the first deadline will have to be considered for the second. Applicants should identify on the application face page that this application is in response to this Request for Applications (RFA). Application forms may be obtained in your institutional business office, or requested from the Division of Research Grants at the above address.

INQUIRIES

Further information and assistance may be obtained by contacting:

Dr. John E. Nutter
Chief, Office of Specialized Research
and Facilities
National Institute of Allergy and
Infectious Diseases
Building 31, Room 7A04
National Institutes of Health
Bethesda, Maryland 20205
Telephone: (301) 496-5643

ANNOUNCEMENT

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

NIH-NIAID-81-2

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

TITLE: PROGRAM PROJECTS IN MECHANISMS OF IMMUNOLOGIC DISEASES

Application receipt date: June 1, 1981

BACKGROUND INFORMATION

The Allergy and Clinical Immunology Branch of the Immunology, Allergic, and Immunologic Diseases Program of NIAID is concerned with asthma, allergic, and immunologic diseases and with relevant mechanisms of hypersensitivity and inflammation. This request for applications (RFA) is intended to encourage the development of proposals 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. As such, this program is intended to complement the Branch's Asthma and Allergic Disease Center program as well as the Centers for Interdisciplinary Research in Immunologic Diseases program.

Immunologic diseases together with asthma, allergic diseases, and hypersensitivity and inflammatory disorders constitute major areas of endeavor of the Allergy and Clinical Immunology Branch. The programmatic activity on immunologic diseases is designed to further investigate underlying mechanisms of disease and to enhance basic knowledge relevant to the etiology, prevention, and management of immunologic disorders. Studies are effected from either one of two disciplinary approaches: clinical immunology or immunopathology. Clinical immunology studies are directed toward acquired and inherited diseases associated with dysfunctions of the immune system. Immunopathology studies include specific areas of genetics, cytology, biochemistry, physiology, and pharmacology of the immune system and its disorders.

This program is described in the Catalog of Federal Domestic Assistance number 13.855, Pharmacological Sciences. 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.

The research to be supported by this announcement is concerned with and seeks to define the etiologic factors, pathogenic mechanisms, development of critical diagnostic measures and approaches to effective prevention, control, and treatment of immunologic abnormalities.

RESEARCH GOALS AND SCOPE

1. Program project grants are awarded to an institution in 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 basic resources shared by individuals in a program where the sharing facilitates the total research effort. Each project supported under a program project grant is expected to contribute to and be directly related to the common theme of the program; the projects under the direction of a principal investigator should demonstrate an essential element of unity and interdependence. This program does not provide support for nonresearch components, such as a clinical referral service, programs in continuing medical education, or programs for a demonstration and technology transfer.
2. Proposals should emphasize new ideas and new initiatives and should be concerned with the clinical relevance of new knowledge to the immune system and its disorders deriving from studies in related disciplines.
3. Protocols focused on the study of immune mechanisms in disease should be designed to favor integration and coordination of intra-institutional research projects concerned with immunologic disorders and those in basic biomedical sciences. Programs should include clinical investigative components drawing upon immunologically relevant endeavors in medicine, pediatrics, surgery, pathology, and their subspecialties.
4. While proposals should be based on clinical investigation as the major requirement, the value and place of experimental studies are recognized. Inclusion of basic research components utilizing samples of human source materials in in vitro procedures and those involving laboratory animals serving as feasible models for required indepth studies are acceptable. Such work, however, should clearly demonstrate relevance to human diseases.
5. Patient oriented studies and those involving in vitro laboratory procedures and the use of experimental animal models should have an immunologic base or draw upon immunologically relevant areas in the disciplines of biochemistry, pharmacology, microbiology, virology, genetics, or pathology.
6. The proposals should consist of a number of demonstrably integrated projects utilizing multifaceted experimental approaches and investigative probes bearing upon either a well defined immunologic disease or upon immune mechanisms common to multiple human disorders.

7. The proposal should clearly explain how the projected multidisciplinary integrated program can be expected to accomplish the stated goal more efficiently and effectively than a series of independent individual grant supported studies.
8. Designation of a program director should be based upon accomplishment, experience as a senior scientist, and ability to assume both leadership of the investigative group and responsibility for scientific, professional, and administrative functions, and commitment devoting a significant amount of his/her time to the project. Each project or subproject in the program should have a designated principal investigator also with a demonstrable record of accomplishment in clinical immunology, immunopathology, or one of the basic science disciplines or clinical specialties relevant to the particular subject of investigation.

MECHANISM OF SUPPORT

Support of a program project in Mechanisms of Immunologic Diseases will be limited to a maximum of five years. If a competing renewal application is planned, it should be submitted only in response to an RFA. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years.

The receipt date for applications will be **June 1, 1981**. They will undergo initial review in **October** by the Allergy and Clinical Immunology Research Committee and subsequent review by the National Advisory Allergy and Infectious Diseases Council in **January 1982**. It is planned that awards will be made during the fiscal year 1982 to support at least one program project grant depending on the availability of funds. **April 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 project. However, moderate alterations or renovations to enhance clinical or laboratory facilities may be allowed if they are necessary to meet objectives of the proposed program.

REVIEW PROCEDURES AND CRITERIA

For preliminary screening by NIAID staff, a "letter of intent" must be submitted by the prospective program director. Letters of intent should cover the following points:

1. A brief description of the intended project.
2. A description of available laboratory facilities.
3. Ongoing basic and clinical research relating to immunologic diseases, identifying existing projects and sources of support.

4. Past research by members of the proposed investigative group in basic and clinical immunology.
5. A description of all clinic facilities available for use by the proposed project.
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 program director and his professional staff who will be involved in the work of the program projects.
8. Collaborative arrangements 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 are due no later than **March 15, 1981**, and upon receipt will be screened by NIAID staff to determine the eligibility and suitability of the project proposals for this announcement.

Inquiries should be directed to:

Robert A. Goldstein, M.D., Ph.D.
 Chief, Allergy and Clinical Immunology Branch, IAIDP
 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 OF LATE SUBMISSION

Based on 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 **June 1, 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. In addition to following accompanying format instructions for the development of the application, include expanded material listed above under the eight points for the letter of intent. For purposes of identification and processing, the words **PROGRAM PROJECT ON MECHANISMS OF IMMUNOLOGIC DISEASES** should be

typed 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 Grants
National Institutes of Health
Westwood Building, Room 448
Bethesda, Maryland 20205

Forward the original application and six (6) copies 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.

ANNOUNCEMENT

CANCER CLINICAL TREATMENT RESEARCH

NATIONAL CANCER INSTITUTE

The National Cancer Institute's Division of Cancer Treatment desires to expand its support of clinical treatment research. The program is seeking applications for research grants concerned with the clinical treatment of cancer. Appropriate studies include the elucidation of the effects of various treatments and related tissue responses, toxicology and the importance of host factors in disease occurrence, rate of progression and curability. Improved experimental design, data management, statistical analysis, as well as specific experimental developments in supportive care methods and modalities are integral aspects of this program. Applications dealing with innovative approaches in surgical oncology are of particular interest. In making this program announcement, it is not the intent of the National Cancer Institute to make or imply any delimitation related to cancer clinical treatment research, but rather to stimulate investigator-initiated research in clinical treatment.

REVIEW PROCEDURES AND CRITERIA

Applications in response to this announcement will be reviewed on a nationwide basis in competition with each other, and in accord with the usual National Institutes of Health peer review procedures. They will first be reviewed for scientific and technical merit by a review group composed mostly of non-Federal scientific consultants. Following this initial review, the application will be evaluated for program relevance by the National Cancer Advisory Board. The review criteria customarily employed by the National Institutes of Health for regular research grant applications will prevail.

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 from the Division of Research Grants, NIH. The phrase, "**Prepared in response to program announcement on Cancer Clinical Treatment Research**" should be typed across the top of the first page of the application. Additionally a brief

This program is described in the Catalog of Federal Domestic Assistance number 13.395, Cancer Treatment 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.

covering letter should accompany the application indicating it is being submitted in response to this program announcement.

APPLICATION RECEIPT DATES

Applications will be accepted in accordance with the usual NIH receipt dates for new applications: March 1, July 1, November 1.

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

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

For further information, investigators are encouraged to contact:

Dr. William DeWys
Program Director for
Clinical Treatment Grants
Landow Building, Room 8C17
Bethesda, Maryland 20205
Telephone: (301) 496-4844

In order to alert the Division of Cancer Treatment to the submission of the proposals with primary thrust directed to clinical treatment research, a copy of the covering letter should be sent under separate cover to Dr. DeWys.

ANNOUNCEMENT

SODIUM FLUORIDE IN THE TREATMENT OF SENSORINEURAL HEARING LOSS
IN OTOSCLEROSISNATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE
DISORDERS AND STROKE

The Communicative Disorders Program (CDP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is inviting grant applications from interested investigators for the purpose of conducting a controlled objective study of the efficacy of sodium fluoride in the treatment of sensorineural hearing loss due to otosclerosis.

I. BACKGROUND INFORMATION

Otosclerosis is a well-documented cause of adolescent to adult onset conductive hearing loss secondary to a focus of pathology in the stapedial footplate. There is evidence that indicates that involvement of the otic capsule by otosclerotic foci can lead to damage of the cochlea and sensorineural hearing loss. Histological studies have documented: (1) The cyclic nature of the destructive/resorptive phase of the deposition of mucopolysaccharide and new bone phase, and (2) formation of highly mineralized bone in otosclerotic foci. Hydrolytic enzymes thought to be released from the otosclerotic foci have been suggested as possible causes for the sensorineural component of the hearing loss in some otosclerotic patients. Medical therapy with sodium fluoride has been suggested by some investigators to be beneficial in promoting maturation of existing otosclerotic foci and preventing progression of sensorineural loss due to cochlea involvement. The study of otosclerosis presents several problems including the lack of an animal model, the dearth of information concerning the molecular biology of otosclerosis, and the minute quantities of bony tissue available for study.

This program is described in the Catalog of Federal Domestic Assistance number 13.851, Communicative Disorders 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.

II. GOALS AND SCOPE

It is the intent of the Institute that potential investigators retain the freedom to design a scientifically meritorious study utilizing the attribute of the investigator's institution(s) and patient population(s). A collaborative arrangement between two or more institutions may constitute an acceptable response to this announcement. In the design of an objective clinical trial many requirements should be met including, but not limited to: (1) an operational definition of the disease; (2) objective documentation of the disease (validity and reliability of observations); (3) appropriate randomization techniques; (4) documentation of control for other disorders or factors which may affect the natural course of the disease, the metabolism of pharmacologic agents, etc.; (5) an operational definition of successful treatment.

III. REVIEW PROCEDURES AND CRITERIA

A. Review Procedures

Applications will be reviewed initially for scientific merit in the Division of Research Grants by an NIH peer review group and secondly by the National Advisory Neurological and Communicative Disorders and Stroke Council (NANCDSC).

B. Review Criteria

Factors considered in evaluating each application will be:

1. Relevance of proposal to the scope and objectives provided in this announcement.
2. Merit of proposed approaches to this problem.
3. Expertise and qualifications of the proposed staff.
4. Commitment of time by proposed staff.
5. Evaluation plan and timetable.
6. Evaluation of resources and environment.

IV. METHOD OF APPLYING

A. Application Format

Applications should be submitted on form PHS 398. The conventional presentation for grant applications should be utilized. If the institution's business office or central application control office does not have this form, an individual copy may be requested by writing to:

Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Bethesda, Maryland 20205
Telephone: (301) 496-7441

B. Application Procedure

Prospective principal investigators are urged to contact the Communicative Disorders Program (Ralph F. Naunton, M.D.) prior to the submission of a formal application.

The standard procedures for submitting grant applications to DRG should be followed. A brief letter should accompany the application indicating that it is in response to the program announcement, NINCDS-CDP on Fluorides and Sensorineural Hearing Loss in Otosclerosis. The words "FLUORIDES SENSORINEURAL LOSS AND OTOSCLEROSIS" should be typed in block letters in the upper right hand corner of the first page of the application. A copy of the letter should be sent to:

Ralph F. Naunton, M.D.
Director
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke
National Institutes of Health
Federal Building, Room 1C-11
7550 Wisconsin Avenue
Bethesda, Maryland 20205

C. Application Receipt Dates

Application receipt dates are: March 1, July 1, and November 1.

ANNOUNCEMENT

GENETIC AND BIOCHEMICAL BASES OF OTOSCLEROSIS

**NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE
DISORDERS AND STROKE**

The Communicative Disorders Program (CDP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is inviting grant applications from interested investigators for the purpose of augmenting knowledge of the genetic and biochemical bases of otosclerosis and sensorineural hearing loss due to otosclerosis.

I. BACKGROUND INFORMATION

Otosclerosis is a well documented cause of adolescent to adult onset conductive hearing loss secondary to a focus of pathology in the stapedial footplate. There is evidence that indicates that involvement of the otic capsule by otosclerotic foci can lead to damage of the cochlea and sensorineural hearing loss.

While the disease has genetic tendencies, the mode of transmission and degree of penetrance are uncertain. Histological studies have documented (1) the cyclical nature of the destructive/resorptive phase and the deposition of mucopolysaccharide and new bone phase and (2) formation of highly mineralized bone in otosclerotic foci. Hydrolytic enzymes thought to be released from the otosclerotic foci have been suggested as possible causes for the sensorineural component of the hearing loss in some otosclerotic patients.

The study of otosclerosis presents several problems including the lack of animal model, the dearth of information concerning the molecular biology of otosclerosis, and the minute quantities of bony tissue available for study.

This program is described in the Catalog of Federal Domestic Assistance number 13.851, Communicative Disorders 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.

II. GOALS AND SCOPE

Under the broader goal of "augmenting knowledge of genetic and biochemical defects in otosclerosis" are specific goals to be addressed by investigators.

1. Innovative approaches must be developed for handling minute quantities of bony tissue for studies to determine the possible biochemical defects in otosclerosis.
2. Clarification is needed of the mode of transmission of otosclerosis along with elucidation of any role such factors as environment, diet, concomitant diseases, etc., may play in the disease process.
3. The mechanism of sensorineural hearing loss in otosclerosis is not known although some suggest that it is a biochemically mediated event. The mechanism of sensorineural hearing loss in these disorders is an important objective for study. Biochemical study of the inner ear fluids might clarify the causes of sensorineural hearing loss.

III. REVIEW PROCEDURES AND CRITERIA

A. Review Procedures

Applications will be reviewed initially for scientific merit by an NIH peer review group and secondly by the National Advisory Neurological and Communicative Disorders and Stroke Council (NANCDSC).

B. Review Criteria

Factors considered in evaluating each application will be:

1. Relevance of proposal to the scope and objectives provided in this announcement.
2. Merit of proposed approaches to the problem.
3. Expertise and qualifications of the proposed staff.
4. Commitment of time by proposed staff.
5. Evaluation plan and timetable
6. Evaluation of resources and environment.

IV. METHOD OF APPLYING

A. Application Format

Applications should be submitted on form PHS 398. The conventional presentation for grant applications should be utilized. If the institutions's business office or central application control office does not have this form, an individual copy may be requested by writing to: Office of Grants Inquiries, NIH.

B. Application Procedure

The standard procedures for submitting grant applications to DRG should be followed. The original and six copies of the application should be sent or delivered to:

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

Deadlines for the receipt of applications are: March 1, July 1, and November 1.

A brief letter should accompany the application indicating that it is in response to the program announcement NINCDS-CDP on the Genetic and Biochemical Bases of Otosclerosis. The words **"GENETICS AND BIOCHEMISTRY OF OTOSCLEROSIS"** should be typed in block letters in the upper right hand corner of the first page of the application. A copy of the letter should be sent to:

Ralph F. Naunton, M.D.
Director
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke
National Institutes of Health
Federal Building, Room 1C-11
Bethesda, Maryland 20205

Prospective principal investigators are urged to contact the Communicative Disorders Program (Dr. Ralph F. Naunton) prior to the submission of a formal application.