NIH GUIDE for GRANTS and CONTRACTS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Vol. 9, No. 8, June 6, 1980

IN THIS ISSUE:

(over)

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 B3BN10, 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.

IN THIS ISSUE: (continued)

NEW PHS 398 APPLICATION FORM AVAILABLE

The new grant application Form PHS 398 (revised October 1979) is now available for use by the research community. Copies of this form may be obtained by writing to:

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

Starting with the October-November 1980 receipt dates, NIH will accept only the newly revised Form PHS 398 with grant applications.

NOTE: Applicants for the Research Career Development Award (RCDA) should continue using the existing form (PHS 2557-1) until special instructions are issued for using Form PHS 398. After the instructions become available, Form PHS 398 will also be used for RCDA applications.

POLICY

ROLE OF THE PRINCIPAL INVESTIGATOR ON RESEARCH PROJECTS SUPPORTED BY NIH GRANTS

A. Purpose This is a statement of a long-standing policy defining the role of principal investigators on research projects supported by NIH grants and setting forth the principal investigators' responsibilities in regard to the research project. It supersedes *NIH Guide for Grants and Contracts*, No. 5, February 5, 1971.

B. Background Code of Federal Regulations, Title 42, Part 52, defines a principal investigator as "a single individual designated by the grantee in the grant application and approved by the Secretary, who is responsible for the scientific and technical direction of the project." The regulation also stipulates that applications for grants set forth the name and qualifications of the principal investigator and requires that he or she continue to be responsible for the conduct of the project for the duration of the project period.

C. Applicability This policy applies to all applications and grants for NIH research project grant support.

D. Policy The single individual identified by the applicant institution as the principal investigator in an application for research project grant support must be the person who has the major responsibility for the scientific and technical direction of the project. Any proposed change of the designated principal investigator must be approved in advance in writing by the NIH awarding Bureau, Institute, or Division.

E. Responsibilities

1. In instances where there are questions concerning the extent of participation or the relationship of the named principal investigator to the project, the application is subject to deferral by the initial review group and return to the institution by NIH staff for clarification of such relationship to the project under review.

2. If it is clear that the named principal investigator is not in fact primarily responsible for the scientific and technical direction of the project, the initial review group will make a recommendation for disapproval or the Bureau, Institute, or Division staff will administratively withdraw the application on that basis.

F. Effective Date This policy is effective on date of release.

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

ANNOUNCEMENT

NIH-NCI-DCBD-BCPCB-80-5

NATIONAL CANCER INSTITUTE

TITLE: *CORRELATION BETWEEN MICROSCOPIC CHARACTERISTICS OF PRIMARY BREAST TUMORS AND SUBSEQUENT PATIENT SURVIVAL*

Application receipt date, October 15, 1980

The Breast Cancer Program of the National Cancer Institute is inviting grant applications from interested investigators for the purpose of searching for parameters based on histological, histochemical, immunohistochemical, or other methods, that would allow more precise prediction of the survival of breast cancer patients.

This type of grant solicitation (the RFA) is utilized when it is desired to encourage investigator-initiated basic and clinical research projects in areas of special importance to the National Cancer Program. The research stimulated by this RFA is supported through the customary NIH grant-in-aid and follows the policies for regular research grants. However, the RFA solicitation represents a single competition, with a specified deadline for receipt of applications. All applications in response to the RFA will be reviewed by the same initial review group of NIH.

The present RFA announcement is for a single competition with a specified deadline of October 15, 1980 for receipt of applications. Applications should be prepared and submitted in accordance with the aims and requirements described in the following sections:

I. BACKGROUND INFORMATION

A. Division of Cancer Biology and Diagnosis (DCBD)

DCBD has major responsibility in the Breast Cancer Program for the totality of problems related to the etiology, epidemiology, diagnosis, treatment, and prevention of breast cancer. In this request for

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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 78-410, as amended; 42 USC 241; 42 USC 282. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

applications, the Program is expressing a special interest in soliciting research grant applications for investigations on correlation between microscopic characteristics of primary breast tumors and subsequent patient survival.

B. Statement of the Problem

Screening for breast cancer seems to have brought to light cases at a frequency exceeding the expectation based on incidence figures. It has therefore been suggested that perhaps some lesions rarely or ever make the transition to metastatic disease, or may appear or regress. Such lesions would then not be biologically important, in the sense of resulting in the death of the patient in the absence of treatment, and represent cases that would not otherwise be diagnosed.

Analysis of the survival data on breast cancer patients has similarly stimulated the hypothesis that the cases include at least two prominent populations, distinguished by a striking difference in relative mortality (1-3). On the basis of this analysis, about 40% of newly diagnosed cases would die at an exponential rate of about 25% per year, while the remaining 60% would die at a rate of only about 2.5% per year. Even if the survival experience is, instead, a continuum, and a significant number of cases dies at rates falling between these two extremes, there is nevertheless a major difference between the extremes of survival for less than two years, and survival for more than ten years, from the time of diagnosis. Patients with local breast cancer (no evident lymph node involvement) generally exhibit a lower mortality rate; however, of the patients diagnosed as having regional disease (i.e., with lymph node involvement), one third also have a low mortality. This survival pattern would be expected if two thirds of the patients with regional disease harbor a "virulent", biologically agressive form of breast cancer, while the remaining one third resemble most of the women diagnosed as having local disease. Women diagnosed as having regional breast cancer therefore provide the most promising opportunity for the identification of any possible, characteristic, histological features that might distinguish those with a mortality prospect as extreme as 25% per year from those with a mortality prospect of only 2.5% per year.

There are a number of gross and histological parameters in breast cancer that have been used to predict prognosis and estimate survival. These include size and/or contour of the primary lesion, growth rate (mitoses or doubling time), histologic type, tumor differentation (histologic grade and nuclear grade), extent of lymphocytic infiltration, mucin secretion, lipid content, necrosis, lymphatic and/or blood vessel invasion, number of axillary nodes involved with tumor, and histology of the nodes. However, these parameters are not absolute predictors, are subject to individual subjective determination, and depend upon the sampling of the primary lesion for histology and the detail of the pathology review.

Because of the possibility that some breast cancers are not biologically important, and because an analysis of survival experience suggests a less "virulent" and a more "virulent" type of the disease (1-3), the Breast Cancer Program is interested in delineating other parameters (in addition to current gross and histological ones) that might better correlate with, or be used to predict, prognosis and survival. These parameters should be detectible in tissue specimens fixed by routine pathology laboratory procedures; they could, however, be delineated by histological, histochemical, immunohistochemical, or other methods. If types of regional breast cancer differ in biological agressiveness, tissues originally obtained at the time of surgery, from patients whose subsequent survival is known (i.e., from women who died from metastatic disease less than two years after diagnosis, and from women living more than ten years from the time of diagnosis) could be used to search for features that distinguish them.

Clinical trials on breast cancer have been complicated by the heterogeneity evident in the survival experience of assemblies of treated patients. If this heterogeneity is, even in part, a reflection of differences in biological behavior of breast cancer, predictable at the time of diagnosis, clinical trials could consider these types separately. It would also be important to ascertain whether these different types of breast cancer, if identified, differ in epidemiologic characteristics and in etiology.

References

1. Fox, M.S. On the Diagnosis and Treatment of Breast Cancer. J. Amer. Med. Assoc. 241: 489-494, 1979.

2. Bergson, J. and Gage, R.P. Survival Curve for Breast Cancer Patients Following Treatment. J. Amer. Statis. Assoc. 47: 501-515, 1952

3. Cutler, S.J. and Axtell, L.M. Partitioning of a Patient Population with Respect to Different Mortality Risks. J. Amer. Statis. Assoc. 58: 701-712, 1963.

II. RESEARCH GOALS AND SCOPE

It is the intent of this RFA to stimulate retrospective studies to search for parameters based on histological, histochemical, immunohistochemical, or other methods, that would permit more precise prediction of the survival of patients with regional or local breast cancer (regional breast cancer defined as breast cancer with axillary lymph node involvement, confirmed by pathology, and with no evidence of distant metastases; local breast cancer defined as invasive breast cancer with no histologic evidence of lymph node involvement or metastatic disease). Primary breast cancer tissue and possibly other

material from patients who subsequently survived more than ten years from time of diagnosis would be compared to equivalent material from patients who died from metastatic disease less than two years from the time of diagnosis. Material to be compared should be from cases identified in the same span of years and in the same hospitals. It would be desirable to begin the investigation with (but not necessarily confine it to) samples from patients who had lymph node involvement, since differences in survival would be more likely to depend upon differences in the tumor and the host response to it. For such regional breast cancer cases, only duration of subsequent survival (less than two years as opposed to more than ten years) would select the two groups rather than any differences originally noted at the time of diagnosis. Any variety or combination of tissue slide or specimen preparations could be employed in this search for differences in these two groups. Known epidemiologic risk factors for breast cancer, such as age, menstrual status, reproductive history, family history of breast cancer, etc., should not be considered in the selection of the patients in the two groups, although subsequent correlation with these variables could well be examined. Applications could be submitted from single or from several collaborating institutions.

III. MECHANISM OF SUPPORT

The support mechanism for this program will be the traditional National Institutes of Health grant-in-aid. Applicants are expected to plan and execute their own research protocol. It is anticipated that this project need not exceed two years. At least two projects will be funded totaling an approximate direct cost of $100,000 for the first year, and $125,000 for the second year. Project start dates in mid-1981 are anticipated. Although this program is provided for in the financial plans for fiscal year 1981, award of grants pursuant to this request for application is contingent upon availability of funds for this purpose.

IV. REVIEW PROCEDURES AND CRITERIA

A. Review Method

Upon receipt, applications will be reviewed by Division of Research Grants (DRG) and NCI staff for their responsiveness to the specific objectives of this RFA. If an application is judged unresponsive, the applicant will be contacted and given an opportunity to withdraw the application or to submit it for consideration with all other unsolicited grant applications received by NIH for that review cycle. For those applications judged responsive, DRG will arrange for the scientific merit review by an appropriate, single, initial peer review group. Secondary review will be carried out by the National Cancer Advisory Board.

B. Review Criteria

In addition to the usual elements of scientific merit, the factors considered in evaluating each application will be:

1. Innovativeness of proposed methodologic approach and research design.

2. Expertise and experience of the investigators in the methodologies proposed for inclusion in the search for parameters.

3. Availability of retrospectively obtained tissue samples from adequate numbers of cases in each of the two survival categories.

4. Adequacy of appropriate personnel, facilities, and/or collaborative arrangements.

5. Evaluation plan and timetable for completion.

V. METHOD OF APPLYING

A. Format of Applications

Applications must be submitted on form PHS 398, the application form for the traditional research grant. Application kits are available in most institutional business offices, or from the Division of Research Grants, NIH. The conventional presentation in format and detail for regular research grant applications should be followed and the points identified under the "Review Criteria" must be addressed. The words "PROPOSAL IN RESPONSE TO RFA: CORRELATION BETWEEN MICROSCOPIC CHARACTERISTICS OF PRIMARY BREAST TUMORS AND SUBSEQUENT PATTENT SURVIVAL" should be typed across the top of the face page of the application.

B. Application Procedure

The present RFA announcement is open to all interested and scientifically qualified investigators. 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
Room 240, Westwood Building
5333 Westbard Avenue
Bethesda, Maryland 20205

To ensure their review, applications must be received by close of business, October 15, 1980. Applications received after this date will be returned. The DRG will also not accept any application in response to this announcement that is the same as one concurrently being considered by any other NIH awarding unit. A copy of the face page should be sent to:

Dr. Elizabeth P. Anderson
Chief, Epidemiology Projects Section
Breast Cancer Program Coordinating Branch
Division of Cancer Biology and Diagnosis
National Cancer Institute
Room 4A-06, Landow Building
7910 Woodmont Avenue
Bethesda, Maryland 20205

Inquiries concerning this announcement should also be directed to Dr. Elizabeth Anderson at this address (telephone, 301/496-6718).

REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

NIH-NIAMDD-ABSD-80-1

NATIONAL INSTITUTE OF ARTHRITIS,

METABOLISM AND DIGESTIVE DISEASES

ANNOUNCEMENT

TITLE: *CLINICAL TRIAL OF FLUORIDE IN OSTEOPOROSIS*

Application receipt date, September 15, 1980

I. BACKGROUND INFORMATION

The National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD) invites grant applications for support of a clinical trial to assess the efficacy of fluoride as a therapeutic agent in treating patients with osteoporosis. Descriptions of the scientific goals, application methods, and review procedures are contained in the following sections. This RFA will be issued only once.

Osteoporosis is a bone disease characterized by decreased total bone mass; i.e., a decrease in the amount of essentially normal bone tissue within an undiminished outer bone volume. Although osteoporosis occurs in both females and males, the ratio of females to males is about four to one. Skeletal bone loss is distinctly accelerated during menopause and in the early post-menopause. The prevalence of osteoporosis in post-menopausal females may be 25-30 percent. With our steadily increasing aged population, the prevalence of this disease is rising dramatically. The major consequence of osteoporosis is fracture, often caused by minimal trauma. It is estimated that in the United States today, two to five million individuals manifest sufficient symptoms of osteoporosis to seek medical advice.

Proximal femur (hip) fracture illustrates the importance and prevalence of this disease. After age fifty, approximately 150,000 individuals suffer hip fractures each year. The morbidity and mortality from these fractures result in an annual cost estimated at approximately one billion dollars. Less serious (in terms of complications), but more prevalent, are crush fracture of the vertebrae and fracture of the wrist and other bones.

Fluoride, in the form of sodium fluoride salt in low-dosage tablets (2.2mg), is a readily available ingestible agent proven effective against dental caries and without toxic effect when used as prescribed. Sodium fluoride is also often prescribed, in considerably larger dosages, for the treatment of osteoporosis; however, clinical data to ascertain its effectiveness or toxicity at the higher dosage levels used are limited. Because it is apparently already in wide use as a treatment for bone loss, there is an urgent need to assess the value of this mode of flouride therapy.

Fluoride is one of the few agents generally thought to be capable of stimulating osteoblastic activity and increasing trabecular bone mass. Therefore, fluoride should be evaluated for efficacy in the therapy of osteoporosis.

II. RESEARCH GOALS

The primary goal is to provide a double-blind, randomized clinical trial of fluoride treatment in osteoporotic patients. Fracture incidence will be the primary evaluative criterion. Correlative goals involve studies of basic biological mechanisms in a population receiving therapeutic doses of fluoride.

A. Clinical Trial

The following is a suggested outline of the clinical trial organization. The applicant must provide adequate details and explanation of specific protocols to permit competitive evaluation. Grant support may be awarded to a single institution or several institutions coordinating through a multi-center agreement. If any consortium arrangement is proposed, written agreement to collaborate by all investigators and their institutions is requested. Furthermore, the applicant should justify the use of a collaborative arrangement in terms of balance among patient numbers, trial duration, and the need for and nature of coordination mechanisms.

1. Subject Selection

The subjects should be selected from an osteoporotic group representing the typical postmenopausal patient. The trial may utilize either or both of the following diagnostic categories: (1) prior fracture with a degree of bone loss consistent with the clinical presence of osteoporosis; (2) substantial evidence of decreased bone mass. The absence of a prior fracture requires a detailed description of the available techniques and baseline normal data utilized to determine "substantial" bone loss.

The investigator must define the entry or exclusion criteria, consent procedures, and randomization methods. Also, the investigator must describe and document patient availability as well as specify and justify the trial size and duration.

2. Treatments

All women entered into the trial should receive supplemental calcium and Vitamin D at appropriate levels. Patients should be randomly assigned to a fluoride treatment group or to a control group receiving a placebo.

The applicant should provide the rationale, in detail, for selecting the proposed fluoride dosage to be used in the trial.

3. Outcomes

Both effectiveness as a treatment for osteoporosis and potential toxicity must be assessed. Because maintaining the structural integrity of the skeletal system is the major objective in treating osteoporosis, fracture incidence will be the key factor in determining effectiveness. Other indicators of bone mass and bone quality may also be pertinent. Appropriate biochemical assays may be necessary to elucidate the status of bone metabolism or toxicity. Any additional diagnostic or evaluative tests or procedures should be fully described and justified. Tests should be included to assess compliance with the prescribed treatment.

4. Follow-up

The applicant should specify the setting and frequency of follow-up visits including the observations to be made at each point. Methods for contacting non-returners and/or for following them for fractures through surveillance of medical providers, should be addressed.

5. Data Processing and Analysis

All data gathering, processing, and analysis methods should be discussed including the rationale for selecting the described procedure.

B. Correlative Studies

The availability of a population on prolonged fluoride therapy may provide a unique opportunity to conduct additional research observations as adjuncts to the clinical trial. Some areas that might be considered are bone metabolism, calcium absorption, influence on hormonal system, and effects on other connective tissues.

Applicants for the clinical trial are invited to submit a grant proposal for correlative studies under a separate cover. This additional application is optional. Further details are contained in Section IV.B., "REVIEW PROCEDURES AND CRITERIA."

III. MECHANISM OF SUPPORT

Eligibility: Domestic universities, colleges, hospitals, laboratories, and other public or private non-profit institutions, including State and local governmental units, are eligible.

Length of Support: The project can be supported for a maximum of five years. If the basic clinical trial requires an additional period of time, a renewal application may be submitted, subject to competitive review procedures. Applicants are requested to furnish their own estimates of the time required (up to five years) to achieve the proposed objectives.

The support mechanism for this program will be the grant-in-aid. Contingent upon the receipt of appropriate funds, the Institute will allocate a portion of the FY 1981 funds specifically for project(s) generated in response to this RFA. Current policies and regulations which govern research grants of the NIH will prevail. The Catalog of Federal Domestic Assistance number is 13.846. This program is supported under authorization 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.

IV. REVIEW PROCEDURES AND CRITERIA

Upon receipt, applications will be reviewed for their responsiveness to the specific objectives described in the announcement. If an application is judged unresponsive, the applicant will be contacted and given an opportunity to withdraw the application or to submit it for consideration in the traditional research grant program of the NIH.

All responsive proposals will receive initial review by an appropriate group of peers as arranged by the Division of Research Grants. Because a broad range of skills are required to successfully design and complete a clinical trial, the review panel will have multi-disciplinary expertise. Final review will be made by the National Arthritis, Metabolism and Digestive Diseases Advisory Council in May 1981. The earliest possible funding date will be July 1, 1981.

The following is a list of some (but not necessarily all) of the review criteria that may be considered. There is no significance to the order in which the items are listed.

A. Clinical Trial

1. The technical and scientific merits of the medical approach and medical aspects of the study such as subject selection, treatment rationale, diagnostic and evaluative procedures.

2. The technical and scientific merits of the statistical features of the study including such characteristics as: sample size projections, statistical power, methods of analyses, and sequential analyses of data where indicated.

3. The technical and scientific merit of the logistical features including such items as the accumulation, flow, and quality control of data, proper blinding procedures, coordinated laboratory procedures, and plans for defining access and restrictions to the data.

4. The experience and qualifications of the investigators with regard to studies on osteoporosis and clinical trials in general.

5. The experience and qualifications of those responsible for the coordinating, data management, and statistical analysis functions.

6. The effectiveness of the organization and administration of the clinical trial including, where appropriate, committees responsible for steering and executive responsibility, overall policy, publications, and data monitoring. In the case of collaborative efforts special emphasis must be placed on demonstrating the ability to produce a uniform and cohesive effort by all contributing institutions.

7. The availability of patients suitable for the trial and the likelihood of their participation.

8. An adequately documented working plan for the trial.

9. Ethical and human safety issues.

10. The appropriateness of the budget.

B. Correlative Studies

Only application(s) that successfully compete for the osteoporosis clinical trial will be considered for funding of the correlative studies. Creative and meritorious projects are sought; however, these additional studies should represent only a moderate percentage of the total effort. Such applications should also use form PHS 398 and be sufficiently complete to enable an independent peer review for scientific merit without recourse to the clinical trial application.

A Division of Research Grants Study Section will review this application utilizing normal review criteria. A covering letter should explain the relation of this application to the clinical trial proposal. In addition, the face page should be labeled, "IN RESPONSE TO RFA NIH-NIAMDD-ABSD-80-1: CORRELATIVE STUDY."

V. METHOD OF APPLYING

A. Letter of Intent

Prospective applicants are asked to submit a one-page letter of intent which includes a brief synopsis of the proposed area(s) of research. This letter should be sent by August 1, 1980 to:

Stephen L. Gordon, Ph.D.
Director, Musculoskeletal Diseases Program
National Institute of Arthritis, Metabolism
and Digestive Diseases
National Institutes of Health
Room 407, Westwood Building
Bethesda, Maryland 20205

The Institute requests such letters only to provide an indication of the number and scope of applications to be received. A letter of intent is not binding, it will not enter into the review of any proposal subsequently submitted, and it is not a requirement for application. Applicants intending to submit a separate proposal related to correlative studies should indicate this fact in the Letter of Intent.

B. Application Format

Applications should be submitted on form PHS 398, the application form for the traditional research grant. Application forms are available from most institutional business offices or from the Division of Research Grants, NIH. The conventional presentation in format and detail for regular research grant applications should be used, ensuring that the points identified under the Review Procedures and Criteria are fulfilled. A statement from collaborators (if any) indicating their willingness to work and interact in the project should be included.

C. Application Procedure

The receipt date for applications is before 5:00 p.m., EST of September 15, 1980. The original and six copies of the application should be sent or delivered to:

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

Both the outside of the mailing package and the top of the application's face page should be labeled, "IN RESPONSE TO RFA NIH-NIAMDD-ABSD-80-1."

An additional copy of the application should be sent directly to Dr. Stephen L. Gordon whose address appears above.

RESEARCH GRANTS RELATED TO MOVEMENT DISORDERS

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

ANNOUNCEMENT

The Neurological Disorders Program of the National Institute of Neurological and Communicative Disorders and Stroke, a component of the National Institutes of Health, invites grant applications to support research leading to a better understanding of the etiology and pathogenesis of a variety of movement disorders, with the intent of improving the early diagnosis and the treatment of these diseases and ultimately their prevention.

BACKGROUND

Disorders of movement include Parkinson's and Huntington's diseases and other basal ganglia degenerations, as well as Tourette's Syndrome, and other diseases characterized by tics; dystonias, dyskinesias, . mors and ballism. Most of these disorders are progressive, and may be associated with dementia, ataxia and other neurological abnormalities, in addition to abnormal motor activity. In some cases, the symptoms reflect abnormal function of specific classes of neurons, e.g., aminergic neurons; in others the abnormality is unknown. In no case is the pathophysiological process adequately understood.

RESEARCH GOALS AND SCOPE

Multidisciplinary or collaborative studies are encouraged. Experimental studies may focus on anatomical, pathological, biochemical, physiological or pharmacological aspects of any of these diseases.

There is particular need for work in the following: 1) more precise definition of the anatomical and/or physiological lesion, 2) identification of characteristic abnormalities in non-neural tissues such as blood, skin, or muscle which are more amenable to biopsy or tissue culture, and 3) development of animal models, experimental or genetic, which mimic significant aspects of a movement disorder.

Existing therapies for the movement disorders are in general unsatisfactory: many drugs currently used are either ineffective over long periods of time or associated with undesirable side effects. For this reason, experimental therapeutic studies on animal models of movement disorders and studies of

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This program is described in the Catalog of Federal Domestic Assistance number 13.852. 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.

appropriate in vitro systems are encouraged.

MECHANISM OF SUPPORT

Applications may be submitted for: a) program project grants (P01), or b) individual research project grants (R01).

a) Program projects may include clinical as well as fundamental approaches, depending upon the local facilities and/or those of cooperating institutions. The application should indicate the availability of technical and professional expertise, resources, possibly patients and the ability to carry out the desired objectives. Applicants should develop a comprehensive research program, each phase of which is directed to a movement disorder. Potential applicants are encouraged to consult with the staff of the Neurological Disorders Program as early as possible in the preliminary stages of preparation. Deadlines for receipt of P01 applications are October 1, February 1, and June 1.

b) Individual applications may propose any investigational aspect of movement disorders. Deadlines for receipt of R01 applications are July 1, November 1, and March 1.

REVIEW PROCEDURES AND CRITERIA

Applications should be prepared on form PHS 398 following instructions contained in the application kit. Application kits are available in most institutional business offices or from the Division of Research Grants, NIH. Program projects should conform to the style and format recommended by this Institute; this information is available from the staff contact listed below. Program project applications will be reviewed initially and judged for scientific merit by one of the NINCDS 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 NIH policy and procedures involving peer review. Applicants may request amounts commensurate with the objectives to be accomplished for a period not to exceed five years. The support mechanism for this program will be the grant-in-aid. Awards will be made on a competitive basis with the entire group of applicants competing for funds from the Neurological Disorders Program.

The phrase "PREPARED IN RESPONSE TO NINCDS INVITATIONS FOR RESEARCH GRANTS IN THE AREA OF MOVEMENT DISORDERS" 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
National Institutes of Health
Room 240, Westwood Building
Bethesda, Maryland 20205

INQUIRIES AND CORRESPONDENCE

One copy of the application is to be sent to the address below. Applicants needing further information including format for program project applications may contact:

Dr. Eugene Oliver
Health Scientist Administrator
Neurological Disorders Program
National Institute of Neurological
and Communicative Disorders and Stroke
Room 716, Federal Building
Bethesda, Maryland 20205

WORKSHOP ANNOUNCEMENT FOR DIGESTIVE DISEASES AND NUTRITION, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM AND DIGESTIVE DISEASES

The Digestive Diseases and Nutrition Programs would like to receive Letters of Intent from individuals planning to submit applications for workshops or conferences to be held between October 1981 and the end of September 1982. This is to facilitate planning and coordination of workshops and conferences by the National Institute of Arthritis, Metabolism and Digestive Diseases within the limits of available conference support. Letters of Intent should be received by October 1, 1980.

Individuals submitting Letters of Intent should be willing to chair or co-chair the meeting. Approaches, size and topics of meetings may vary considerably, but an ultimate objective of the meeting should be to stimulate new approaches to a problem and encourage new investigators to become involved with a problem. Beginning investigators should be considered as attendees or participants.

Letters of Intent will be reviewed by the Digestive Diseases and Nutrition subcommittee of the National Advisory Arthritis, Metabolism and Digestive Diseases Council or an ad hoc committee. Those applicants and topics considered to be meritorious will be asked to submit full applications to be reviewed by an ad hoc committee and funded on the basis of merit and program relevance, depending on the availability of funds for this purpose. 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.

The Letter of Intent should contain a synopsis (not to exceed 3 pages) of:

- Title
- Aims of meeting
- Timeliness
- Disciplines of speakers
- Approximate size and cost
- Tentative topics and speakers
- Form of publication

Additional information on the review process is available from Program Directors listed below. It is advisable to contact the appropriate Program Director before submitting a Letter of Intent.

George Kitzes, Ph.D.
Digestive Diseases Program
National Institute of Arthritis,
Metabolism and Digestive Diseases
Room 604, Westwood Building
Bethesda, Maryland 20205

Telephone: (301) 496-7821

Sarah C. Kalser, Ph.D.
Liver Diseases Program
National Institute of Arthritis,
Metabolism and Digestive Diseases
Room 602, Westwood Building
Bethesda, Maryland 20205

Telephone: (301) 496-7858

Gerald N. Combs, Ph.D.
Nutrition Program
National Institute of Arthritis,
Metabolism and Digestive Diseases
Room 606, Westwood Building
Bethesda, Maryland 20205

Telephone: (301) 496-7823

G. G. Roussos, Ph.D.
Biliary Tract and Pancreatic
Diseases Program
National Institute of Arthritis,
Metabolism and Digestive Diseases
Room 602, Westwood Building
Bethesda, Maryland 20205

Telephone: (301) 496-7121

REPRODUCTIVE EFFECTS FROM OCCUPATIONAL HAZARDS

ANNOUNCEMENT

GRANTS ADMINISTRATION AND REVIEW BRANCH, OFFICE OF EXTRAMURAL COORDINATION AND SPECIAL PROJECTS

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH, CENTER FOR DISEASE CONTROL

Altered fertility, low birth weight, spontaneous abortion, transplacental carcinogenesis, congenital malformation, mutagenesis, and developmental abnormalities are among the effects on reproduction that have been recognized to result from toxic occupational exposure. Exposure to both men and women can produce these effects. The knowledge base in the area of toxic reproductive hazards is relatively small. The National Institute for Occupational Safety and Health (NIOSH) would like to expand its involvement in the identification and prevention of reproductive effects from occupational hazards. The scope of this announcement is flexible to encourage various interactive combinations of research approaches that might yield insight into the issues and problems surrounding reproductive effects as a consequence of physical and chemical occupational hazards. The Institute is seeking applications for research and demonstration grants concerned with basic and applied projects in areas such as epidemiology, toxicology, control technology, and health education.

I. BACKGROUND INFORMATION

The current responsibilities of NIOSH were established by the Public Health Service Act, the Occupational Safety and Health Act of 1970 and the Federal Mine Safety and Health Amendments Act of 1977. A major NIOSH responsibility under those Acts is to conduct research necessary to ensure, insofar as possible, that no worker will suffer diminished health, reduced functional capacity, or decreased life expectancy as a result of his or her work experience. As a part of this responsibility NIOSH is concerned with discovering the identity and, if possible, the prevalence of physical and chemical hazards to which male and female workers are exposed that might affect the development of their unborn children. While a relatively few chemical and physical agents are generally accepted as proven mutagens, teratogens, or carcinogens in humans, over a thousand agents are reported to have these effects in animals. Furthermore, many of these agents are reported to be mutagenic in biologic test systems and thus might be suspected as capable of causing reproductive effects in humans.

Over the past several decades there has been a threefold increase in the number of women employed in the U.S. workforce. During this period women have been employed in more hazardous occupations including those traditionally restricted to men. In recent years an increasing number of pregnant women have remained on the job until near the end of pregnancy. Thus, many more women and their unborn children are being exposed to chemical, physical, and psychological hazards of the workplace. Despite this fact, very little is known about the impact of such exposures on fetal wastage and growth and development.

Because of the unique role of women in the reproductive process, exposure to chemical and physical hazards has targeted attention on the risks to the offspring of maternal exposure. In so doing, we tend to forget that the working male exposed to mutagenic agents also places the health of his offspring at risk.

Other areas of concern are:

1. Recognition of the potential that exists for harm to the germ cells of parents of both sexes, signaling a need to investigate the possibility that occupational hazards might affect the fertility of both men and women;

2. The realization that significant quantities of industrial materials may be brought home in clothing resulting in the potential exposure of non-working pregnant women, making studies of teratogenicity of agents to which male workers are exposed as important as studies of infertility and mutagenicity; and

3. The possibility that childhood cancers may be related to pre-natal environmental exposures.

NIOSH is offering both a challenge and an opportunity to talented researchers interested in the study of reproductive effects from occupational exposures.

II. AREAS OF RESEARCH INTEREST

The goal of this announcement is to stimulate and encourage high quality research and demonstration grants in the areas of research listed below. These areas are not mutually exclusive. It is anticipated that a given research study may cut across several areas. Included under each listed area are examples of the types of studies which would be of interest to NIOSH. They are not meant to be restrictive and are cited for illustrative purposes only.

A. EPIDEMIOLOGY AND BIOMETRY: Projects which consider the epidemiology of reproductive effects, including altered fertility, spontaneous abortion, fetal deaths, genetic diseases and disorders and childhood cancer, resulting from chemical and physical occupational hazards. Of particular interest are studies where dose-effect relationships are identified or determined. NIOSH is interested in epidemiological research using a variety of methods or approaches. Such methods include those which generate hypotheses and typically use registries, medical records or statistics as the primary data source and those methods which tend to confirm hypotheses by demonstrating dose-effect relationship or the prevention of an effect by interruption of exposure. Specific examples of epidemiology studies include:

- Studies which identify groups of workers with abnormal reproductive experience and determine probable cause.

- Studies to determine whether an incidence of infertility, spontaneous abortion, or fetal mortality in the reproductive experience of a specific group of workers and/or spouses is abnormal.

- Studies to assess the parental employment relatedness of cancer in childhood.

- Studies on known reproductive hazards to evaluate and compare methodologies and to determine association between endpoints of the methodologies.

B. TOXICOLOGY: Projects to identify reproductive (mutagenic, teratogenic, etc.) hazards of chemicals to workers and to provide an early warning of the possible deleterious effects. Specific examples include:

- Research which develops test systems to detect mutagenic activity of air particulates, chemical mixtures or complexes found in the workplace.

- Projects which study the possible synergistic effect of mutagenic and teratogenic chemicals produced in workplaces.

- Research to validate human cell mutagenic assay systems.

- Studies which evaluate the usefulness of body fluid analysis and cytogenic assay systems for the assessment of the mutagenic hazard of chemicals to workers.

C. EXPERIMENTAL LABORATORY INVESTIGATIONS: Projects to elucidate the biochemical and physiological mechanisms of activity and nature of reproductive hazards in the workplace. Examples include:

- Studies to develop and validate screening systems based upon biochemical, enzymatic, or hormonal components of body fluids (e.g., blood, urine, semen) that can be used as reliable indices of the functional state of the reproductive system.

- Investigations to develop, improve, or validate short-term or in vitro methods for teratogenesis testing.

- Studies of mechanisms of teratogenesis, with the goal to improve the ability to predict relative teratogenic potential of chemically related compounds or to make inter-species extrapolations of teratogenesis data.

- Research on the mechanisms by which abnormalities are induced in sperm head morphology and the implications of morphological changes as indicators of induced mutations or of impaired reproductive capacity.

D. CONTROL TECHNOLOGY: Projects to develop new and improved methods or equipment to prevent reproductive effects from occupational hazards, including:

- Studies which identify workers potentially or actually exposed to reproductive hazards and design new or improved controls for the hazards.

- Research which adapts existing methods, as well as developing new methods of monitoring and controlling reproductive hazards in the workplace.

- Research which seeks to use innovative approaches, such as alternative materials, engineering controls, process modification and protective equipment to prevent known or suspected reproductive problems.

E. HEALTH EDUCATION RESEARCH AND DEMONSTRATION PROJECTS: Projects to increase awareness of the importance of reproductive hazards in the workplace. Examples include:

- Development of educational programs for health professionals, and worker educators to increase their awareness of the issues and problems surrounding reproductive effects from occupational hazards.

III. MECHANISM OF SUPPORT

The traditional grant-in-aid mechanism will be used to support grants pursuant to this Program Announcement.

Nonprofit organizations and institutions, State and local governments and their agencies, are eligible to apply.

Grants may be supported for up to three years, and may be renewed for an additional period, subject to the competitive review procedure and availability of funds.

Awards will be made based on priority score ranking, as well as availability of funds for this Program.

Grantees will be required to cost share a minimum of five percent.

Grants will be made under the legislative authorization in Section 20(a)(1) of the Occupational Safety and Health Act of 1970, Public Law 91-596. The Catalogue of Federal Domestic Assistance Citation is Section 13.262. Applications responsive to this program announcement are not subject to OMB Circular A-95 Clearinghouse or Health Systems Agency review.

IV. REVIEW PROCEDURES AND CRITERIA

The initial review of applications responsive to this program announcement will be arranged by the Division of Research Grants, NIH. Major factors considered in evaluating each application include:

- training, experience, and research competence, or promise, of the applicant(s) to carry out the proposed investigations, and the adequacy of effort (time) to be devoted to the project.
- the scientific merit of the proposal: the questions proposed for study, the research design, the proposed methodology, the proposed methods for analysis and interpretation of data.
- adequacy and suitability of the existing and proposed facilities and resources.
- appropriateness of the requested budget relative to the work proposed.
- adequacy of collaborative arrangement(s), if applicable.

A secondary review process will be conducted by NIOSH. Factors considered in this review include:

- the results of the initial review;
- the significance of the proposed research to the research program of NIOSH.
- national needs and program balance, and
- policy and budgetary considerations.

Proposals considered to be non-responsive to the terms outlined in this program announcement will be appropriately reassigned for review or returned to the investigator, as indicated. Returned proposals may be revised and resubmitted.

V. METHOD OF APPLYING

Applications should be submitted on a form PHS 398 (State and local governments use form PHS 5161-1). Application kits may be obtained from most institutional business offices or from the Division of Research, NIH.

Care should be taken in following the instructions included with the application form making certain to fulfill the points identified under the heading "REVIEW CRITERIA."

An original and six copies (original and two copies for State and local governments) must be received no later than: July 1, November 1, and March 1, as applicable. Applications received after the designated deadline will be considered with the applications received for the following deadline. Completed applications must be sent or delivered to:

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

A brief covering letter must accompany the application indicating that it is submitted in response to this program announcement. A copy of this covering letter along with an additional copy of the application should be sent to the Research Grants Program Officer (see below).

IDENTIFICATION OF CONTACT POINT

Questions related to this announcement should be addressed to:

Faye Calhoun
Chief, Grants and Administration
and Review Branch
National Institute for Occupational
Safety and Health
Room 8-63, Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: (301) 443-4493

or

Mr. Joseph West
Grants Management Officer
National Institute for Occupational
Safety and Health
Room 8-29, Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: (301) 443-3122

PROGRAM PROJECT RESEARCH GRANT APPLICATION (PO1) SPECIAL DIRECTIVES NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

The National Institute of Child Health and Human Development (NICHD) announces special directives for investigators submitting applications for Program Project Research Grants (PO1's) which are likely to be assigned to NICHD for support. These directives will apply to all new and renewal applications submitted for the NIH-DRG application receipt date, October 1, 1980 and thereafter.

I. Scope and Scale of NICHD Program Project Applications

A. To be eligible for award as a program project an approved application must contain a minimum of three subprojects.

B. The total direct costs requested for the first year may not exceed $350,000. Budget increments for subsequent years generally will be limited to necessary cost-of-living increases, in line with current policies of the applicant institution. Budgets of applications for new and renewal support will be stringently reviewed within these guidelines.

II. Preapplication Process

A. Applicants are encouraged to communicate with NICHD prior to preparation and submission of a formal application through a "letter of intent" submitted by the prospective principal investigator. This letter of intent will assist NICHD staff to determine if the proposal falls within the mission and research interests of the Institute and meets the criteria for a program project. It will also permit the applicant to benefit from consultation with NICHD staff.

B. The letter of intent should provide, in no more than two single spaced, typewritten pages, the following information:

1. A statement highlighting the central theme and objectives of the proposed program project.

2. A brief description of each subproject including the name of the Project Director and a statement of how each specific subproject will contribute to the overall goal of the program project.

3. An estimate of the annual budget and the number of years of support requested for the total program project and for each subproject.

4. Depending on the subject matter of the proposal, letters of intent should be directed to:

Director, Center for Population Research
National Institute of Child Health and
Human Development
Room 7A-21, Landow Building
Bethesda, Maryland 20205

Telephone: (301) 496-5097

or

Acting Director, Center for Research
for Mothers and Children
National Institute of Child Health and
Human Development
Room 7C-03, Landow Building
Bethesda, Maryland 20205

Telephone: (301) 496-5097

Population research may include the reproductive sciences and the related social and behavioral sciences. Research related to mothers and children may include mental retardation, human learning and behavior, pregnancy and perinatology, clinical nutrition and endoctrinology, genetics and teratology, and developmental biology.

C. In response to the letter of intent, potential applicants will be contacted promptly by an Institute Health Scientist Administrator who will be available for further consultation.

III. The Application

The program project application should be prepared on PHS form 398 and identified by typing "PROGRAM PROJECT" at the top of the top of the first page. NIH-DRG receipt and review dates for a program project application are:

Application Receipt Dates	Initial Review	Council Review	Earliest Beginning Dates
February 1	June	September-October	December 1
June 1	October-November	January-February	April 1
October 1	February-March	May	July 1

Applications should be mailed to:

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

Applications received too late for one cylce of review will be held for the next review cycle. At the time that the formal application is mailed to DRG, the applicant is requested to inform the Associate Director for Scientific Review, NICHD, in writing, that his/her program project application has been submitted to DRG. The address is:

Associate Director for Scientific Review
National Institute of Child Health
and Human Development
Room 7C09, Landow Building
Bethesda, Maryland 20205

The scientific review of the formal application will be conducted by an NICHD initial review group. All communications regarding the review of the application should be addressed to the Executive Secretary of the assigned review committee. A project site visit is not a prerequisite for review by the review committee.

Final review is provided by the National Advisory Child Health and Human Development Council.

*U.S. GOVERNMENT PRINTING OFFICE: 1980 311-215/4 1-3