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NOTICE

COMMUNICATIONS WITH NIH CONSULTANTS BY APPLICANT INVESTIGATORS

Rosters of Initial Review Group (IRG) members are attached to summary statements so that applicant principal investigators know who reviewed their applications. This practice is not intended to encourage investigators to contact the IRG members. Except during site visits, it is inappropriate for applicant investigators to enter into communications with NIH consultants about their applications. Such communications can be disruptive to an orderly and fair peer review process and are an imposition on NIH consultants who perform a public service.

NIH has instructed consultants to refer all communications from investigators about the review of applications to the Executive Secretary of the IRG. By the same token, consultants are asked to forward all informational requests to the investigator through the Executive Secretary. The cooperation of members of the scientific community is appreciated.

NOTICE

"NIH WEEK"

Some members of the grantee/contractor community have inquired as to whether or not a publication entitled "NIH Week" is an official issuance of the National Institutes of Health. "NIH Week" is a privately produced publication.

NOTICE

Protection of Human Subjects

Assurances of Compliance with 45 CFR 46

Samples of Assurances of Compliance which meet the requirement of the revised human subject regulations (45 CFR 46, effective July 27, 1981) have been prepared and are now available for distribution. Copies may be obtained from:

Office for Protection from Research Risks
National Institutes of Health
Westwood Building, Room 3A18
Bethesda, Maryland 20205
NOTICE
PROTECTION OF HUMAN SUBJECTS
UPDATE ON TEMPORARY REQUIREMENT FOR FORM HHS-596

Forms Rev. 4-75 and 5-80 only)

On July 27, 1981, final regulations amending basic HHS policy for the protection of human research subjects became effective. These regulations were published in the Federal Register (46 FR 8366) and provide exemption for certain broad categories of research which involve little or no risk to research subjects (see listing below). NIH is currently revising the application forms and instructions for grants and fellowships to conform to new procedures to be followed when the research involves human subjects. An announcement will be made in the Guide for Grants and Contracts when the new forms are available. The new application forms will provide applicants the opportunity to claim, on the face page of the application, exemption from the human subject regulations, when an exemption is applicable. When this procedure is followed on the new forms applicants will no longer be required to file Form HHS-596 for exempt research. However, until the new forms are available the applicants should continue to follow the temporary procedure outlined below, for filing Form HHS-596 for all research involving human subjects (as defined in 45 CFR 46), whether exempt or not. No response need be made to item number 4 on the Form HHS-596 when an exemption is claimed.

When an exemption to the human subjects regulations is claimed, the application or proposal must be accompanied by Form HHS-596 which should include the following statement: "Exemption is claimed based on number(s) 1 through 5. (Insert the identification number(s) of exemption(s) claimed using the numbers in 45 CFR 46.101(b) 1 through 5.) This statement should appear on the front page of the Form HHS-596 in the block entitled "5. and 6. See Reverse Side."

If there is any question concerning the interpretation of exempted categories please contact the Office for Protection from Research Risks, Room 3A-18, WW Bldg., National Institutes of Health, Bethesda, MD 20205, telephone (301) 496-7041. An inappropriate claim for an exemption may lead to delays in processing an application for funding.

This requirement is effective for applications submitted on or after June 1, 1981.

Exemption Categories (45 CFR 46.101(b))

Research activities in which the only involvement of human subjects will be in one or more of the following categories:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests, (cognitive, diagnostic, aptitude, achievement), if information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
(3) Research involving survey or interview procedures, except where all of the following conditions exist: (i) responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the subject's responses, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. All research involving survey or interview procedure is exempt, without exception, when the respondents are elected or appointed public officials or candidates for public office.

(4) Research involving the observation (including observation by participants) of public behavior, except where all of the following conditions exist: (i) observations are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the observations recorded about the individual, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

(5) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
REQUEST FOR RESEARCH GRANT APPLICATION: RFA

NIH-NIAID-81-6

PROGRAM PROJECTS IN TRANSPLANTATION IMMUNOLOGY

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Application receipt date: November 16, 1981

The National Institute of Allergy and Infectious Diseases (NIAID) invites applications for program project grants, to be initiated during FY 1982, to conduct investigations of the immune system in human recipients of allografts.

BACKGROUND INFORMATION

The Genetics and Transplantation Biology Branch of the Immunology, Allergic and Immunologic Diseases Program of the NIAID sponsors basic and applied research in immunogenetics and transplantation immunology through grants and contracts, and by providing cells and reagents for histocompatibility testing. This request for applications (RFA) is intended to stimulate the formulation of collaborative, coordinated approaches, involving transplant clinicians and basic immunologists, to the clarification and manipulation of the immune processes that determine acceptance or rejection of allografts.

The practice of transplantation has evolved to the point that the technical aspects of the surgery are not limiting. The major remaining hazards are associated with rejection and with the immunosuppressive therapy employed to prevent or control it. In immunology, momentous advances in technical procedures and in the understanding of molecular and cellular processes have been made very recently. The major new tools available to immunologists include cell culture and propagation techniques, monoclonal antibodies of exquisite specificity produced by cell hybridization, and techniques of genetic analysis and manipulation at the molecular level. The major conceptual advances are centered on the clarification of the complex regulatory mechanisms involving soluble factors and interactions among specialized cell populations. Transplant recipients subjected to manipulation of their immune system both by means of the immunosuppressive therapy and by the graft itself constitute a unique resource in which a large range of procedures is already accepted practice. They, therefore, offer a superb opportunity to basic immunologists for the investigation of the human immune system subjected to deliberate disturbances. In turn, the guidance to the clinician that will result from the understanding of the immunological events that transpire in connection with transplantation and its treatment and from the elucidation of the mechanisms that connect and control these events should prove invaluable.

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

1. The program project grant will be awarded to an institution on behalf of a program project director for the support of a broadly based but highly integrated long-term research program. It is anticipated that several awards will be made for work focused on organ and tissue transplantation. The beginning date of the awards is expected to be July 1, 1982 and their term can be for five years.

2. Support under the program project grant will be available for the acquisition of resources necessary for the conduct of the scientific studies (salaries, equipment, supplies, etc.) and for such development of research procedures as will render them useful in a clinical setting. Support will not be provided for other non-research activities such as routine patient care or continuing medical education.

3. Proposals should heavily emphasize collaboration in research between transplant clinicians and immunologists, and the application of the most up-to-date concepts and techniques of immunology to the evaluation of the immune system of the recipients in all circumstances attendant to the transplantation.

It is not the intent of this request to elicit proposals of large scale encompassing a variety of essentially independent research projects. Preference will be given to proposals for a core of tightly knit interdisciplinary research bringing together clinicians and basic scientists, without regard to its size. It is, however, expected that evidence of ongoing activity in the more specialized areas of interest to the participants, in the form of independent individual research grants, will be provided.

4. The objectives of the research should be (A) the clarification of the status of the immune system, specifically of the immunoregulatory balance (1) prior to transplantation in its relatively normal state or, if the transplant is occasioned by a disturbance of the immune state, in the causative disordered state, (2) in the course of preparation for the transplant whose objective is the reduction of responsiveness (immunosuppression) or the induction of tolerance, (3) postoperatively during maintenance immunosuppression as the graft becomes established, (4) during rejection episodes, and (5) during treatment of rejection, and (B) the modulation of immunological activity on the basis of the information so obtained.

5. Appropriate approaches may include but are not restricted to investigations of:

   (1) cellular regulatory interactions among the lymphocyte subpopulations
   (2) modulation of immune activity by soluble factors, including antibodies specific for lymphocyte subsets and antiidiotype antibodies
   (3) effects of chemical and physical agents used for immuno-suppression on the metabolic processes and, overall, on the physiological functions of the lymphocytes of patients
   (4) molecular genetic manipulations of lymphocytes whose objective is
the production of cells with properties of use in therapeutic procedures

6. The investigations should center on human subjects and may deal with cells of the immune system maintained and/or propagated in vitro. Such studies on animal models may be undertaken as will provide direct guidance for the planning and conduct of the clinical investigations.

7. Designation of the Program Project Director should be based upon accomplishment, experience as a senior scientist, and ability to assume leadership of the investigative group and responsibility for scientific, professional and administrative functions. A substantial commitment of time is expected. Leaders of individually identified phases of the work should have demonstrated a substantial record of accomplishment in transplantation and/or immunology.

MECHANISM OF SUPPORT

In FY82 NIAID plans to award at least one Program Project in Transplantation Immunology, contingent upon the availability of funds. Support of the Program Projects will be limited to a maximum of five years. Funding beyond the first year will be contingent on satisfactory progress. Consideration of renewal will be subject to reissuance of this RFA.

The receipt date for applications will be November 15, 1981. They will undergo initial review in March 1982 by the Transplantation Biology and Immunology Subcommittee of the Allergy, Immunology and Transplantation Committee and subsequent review by the NIAID Advisory Council in May, 1982. July 1, 1982 will be the earliest starting date for successful applications.

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 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

Applications assigned to the NIAID will be reviewed initially by the Transplantation Biology and Immunology Subcommittee of the Allergy, Immunology and Transplantation Research Committee, managed by the Program and Project Review Branch, Extramural Activities Program, NIAID.

The steps in the review process may include a project site visit to evaluate the overall merit of the application.

Review Criteria

Review criteria include evaluation of the following, not necessarily in order of importance:
The scientific merit and significance of the overall program goals and the
development of a well-defined central research focus.

- The cohesiveness and multidisciplinary or multifaceted scope of the
program.

- The leadership, scientific ability, and administrative competence of the
Program Project Director and his or her commitment and ability to devote
substantial time and effort to the program.

- The qualifications, experience, and commitment of the collaborating
investigators responsible for the various aspects of the program including
their ability to devote adequate time and effort to the program.

- The academic and physical environment in which the research will be
conducted, including the availability of space, equipment, patients, and the
potential for interaction with active scientists from other departments
and/or institutions.

- A sound administrative and organizational structure that facilitates
attainment of the objective(s) of the program.

- Arrangements for internal quality control of ongoing research, allocation of
funds, day-to-day management, internal communications and cooperation
among the investigators involved in the program, contractual agreements,
and replacement of the Program Project Director, if required, on an interim
or permanent basis.

- The institutional strength, stability, and commitment to research and to the
program, including fiscal responsibility and management capability to assist
the Program Project Director and staff in following PHS policy.

- The appropriateness of the period of support and budget requested in relation
to the proposed program.

Advisory Council Review

The final review will be conducted by the National Allergy and Infectious Diseases
Advisory Council. Factors that will be considered in this review include:

- Results of the initial scientific and technical merit review.

- Significance to NIAID program goals.

- National needs and program balance.

- Policy and budgetary considerations.

LETTER OF INTENT

For preliminary screening by NIAID staff, a "letter of intent" must be submitted by the
prospective program director.

Letter 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 transplantation and immunology, identifying existing projects and sources of support.

4. Past research by members of the proposed investigative group in transplantation and immunology.

5. A description of all clinical facilities available for use by the proposed project.

6. Specific information on the institution's present relevant 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 project.

Letters of intent are due no later than October 1, 1981, and upon receipt will be screened by NIAID Staff to determine the eligibility and suitability of the projected proposals.

Inquiries and letters should be directed to:

Henry Krakauer, M.D., Ph.D.
Chief, Genetics and Transplantation
Biology Branch
Immunology, Allergic and Immunologic
Diseases Program
National Institute of Allergy and Infectious Diseases
Westwood Building, Room 752
5333 Westbard Avenue
Bethesda, MD 20205
(301) 496-7551

CONSEQUENCES OF LACK OF RESPONSIVENESS TO THE RFA OR LATE SUBMISSION

Based upon the letter of intent, potential applicants will be promptly advised whether or not their proposal is found to be within the research goals and scope of the program as defined in this RFA. Applicants will then have an opportunity to correct deficiencies or weaknesses and to restructure their submissions accordingly. Formal applications that are not responsive to the RFA or are not received by November 16, 1981 will not be accepted for review and will be returned to the applicant.

METHOD OF APPLYING

Before preparing an application, the prospective applicant should request from NIAID program staff a copy of the NIAID Information Brochure on Program Projects which contains details on the requirements for multidisciplinary grant applications.
Use the standard research grant application form PHS 398 (Rev. 5/80). Application kits are available at most institutional business offices or from the Division of Research Grants, NIH. 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 YES box in item 2 of the face page of the application should be marked and the words Program Project in Transplantation Immunology should be typed. A brief covering letter should be attached indicating submission is in response of this NIAID announcement.

Forward to:

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

Please forward a copy (not the original) of the cover letter and the application 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, Room 703, Westwood Building, National Institutes of Health, Bethesda, Maryland 20205.
NOTICE

INCREASE IN PRICE OF AGED MICE

NATIONAL INSTITUTE ON AGING

Investigators currently using mice from the National Institute on Aging (NIA) contract-supported colonies are hereby notified that an increase in the price of the mice became effective on July 1, 1981. Investigators on new and renewal applications should use the new cost figures in estimating cost needs on grant applications.

In order to regain part of the cost of the contract, users are being charged a price that is equal to the acquisition cost of the mouse plus the product of $0.90 and the age in months minus 1. Thus, a 30-month old male C57BL/6NNia mouse will cost the user $3.10 plus $26.10, or a total of $29.20.

The acquisition costs are as follows:

<table>
<thead>
<tr>
<th>Inbred Mouse Strain</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/HeNNia</td>
<td>$3.49</td>
<td>$3.49</td>
</tr>
<tr>
<td>BALB/cNNia</td>
<td>$2.77</td>
<td>$2.97</td>
</tr>
<tr>
<td>CBA/CaHNNia</td>
<td>$2.96</td>
<td>$2.96</td>
</tr>
<tr>
<td>C57BL/6NNia</td>
<td>$3.10</td>
<td>$3.37</td>
</tr>
<tr>
<td>DBA/2NNia</td>
<td>$3.30</td>
<td>$3.50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hybrid Mouse Stocks</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B6C3F1 (C57BL/6NNia x C3H/NNia)</td>
<td>$2.77</td>
<td>---</td>
</tr>
<tr>
<td>B6D2F1 (C57BL/6NNia x DBA/2NNia)</td>
<td>$2.77</td>
<td>$2.97</td>
</tr>
<tr>
<td>CB6F1 (BALB/cNNia x C57BL/6NNia)</td>
<td>$2.76</td>
<td>---</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cogenic Mouse Strains</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BALB/cAnNNia-nu (nude)</td>
<td>$13.00</td>
<td>---</td>
</tr>
<tr>
<td>B10.129/JNnia</td>
<td>$3.49</td>
<td>$3.49</td>
</tr>
<tr>
<td>CBA/CaHNNia-T6</td>
<td>$2.96</td>
<td>$2.96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outbred Mouse Stock</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CrI:COBS CFW (SW) (The Charles River Breeding Laboratories, Inc., Wilmington, MA)</td>
<td>$0.90</td>
<td>$0.90</td>
</tr>
</tbody>
</table>

Animals required for pilot or pre-doctoral studies will continue to be provided without charge if it is determined that the data or thesis developed from the study are relevant to the NIA's program on aging research. A final summary paper, or copy of the dissertation, must be provided to the NIA on completion of the studies.
Prices are subject to market fluctuations, and are charged at the rates set by the contract. Notices of change are printed in the NIH Guide for Grants and Contracts and individually sent to current users.

Questions concerning these price changes or information on ordering animals should be directed to:

Mrs. Jane L. Soban  
National Institute on Aging  
Room 5C-19, Building 31  
Bethesda, Maryland 20205  
(301) 496-6402
ANNOUNCEMENT

HEALTH AND EFFECTIVE FUNCTIONING IN THE MIDDLE AND LATER YEARS

NATIONAL INSTITUTE ON AGING

I. INTRODUCTION

The National Institute on Aging (NIA) invites qualified researchers to submit grant applications for research projects designed to specify how psychosocial processes, interacting with biological processes, influence health and functioning in the middle and later years.

This announcement is part of the broad program of the Institute, which was established by law in 1974 for the "conduct and support of biomedical, social, and behavioral research and training related to the aging process and the diseases and other special problems and needs of the aged." Under this mandate, health and well-being are viewed, not narrowly within the framework of biological aging alone, but as the outcome of complex psychological, social, environmental, physiological, and medical processes. Four principles guiding NIA research are: (1) the dynamic character of aging as a process, and of social and historical changes which affect the age structure of society and the ways in which individuals age; (2) the interrelatedness of old age with earlier ages; (3) the social, cultural, and individual variability of age and aging; and (4) the continuing interplay between psychosocial and biomedical aging processes.

The special initiative on health and effective functioning in the middle and later years is coordinated with related programs in other organizations including the National Institute of Child Health and Human Development, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Mental Health.

II. BACKGROUND

The 20th century's triumph of extension of life means not only that the numbers of old people are increasing, but that more and more individuals can look forward to living out their lives to the full. As life expectancy has been extended, the proportion of adult life that might be spent in retirement has also been increased. However, it remains to be seen whether and how people will benefit from these added years. How can the relatively vigorous health, effective functioning, and productivity of the middle years be continued into the later years? How can disability and dependency be postponed until the last years of the extended life course?

Recent research findings are beginning to suggest how the productive middle years might be extended; how many disabilities of old age might be prevented or postponed; and how the costs of health care and dependency might be contained. For example, we now know that intellectual decline with aging (when it occurs) can often be slowed or reversed by

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relatively simple training interventions; that older people can often learn to compensate for declines in reaction time, memory, and other age-related deficits (e.g., through mnemonic strategies, carefulness, and persistence); that for the visual impairments suffered by many older people, particular styles and sizes of type can facilitate reading, and improved environmental design can offset inability to see large objects in low contrast; that for the serious malnutrition of many older people, food can be adapted to the age-related changes in taste and smell that influence eating behaviors; that health can be promoted through changes in smoking, diet, and exercise across the lifespan; that illness can often be alleviated through social supports and improved coping behaviors; that many serious disabilities (even when experienced in nursing homes) can be reduced by regimens that reward activity and independence.

We know that death is inevitable; but we also know in a most general sense, that biological, psychological, and social processes of growing old are to a considerable extent malleable. However, we need to specify the mechanisms and conditions that influence health and functioning during the middle and later years. NIA's goal in issuing this announcement is to encourage basic research studies of these mechanisms and conditions that can extend the productive middle years of life by preventing, postponing, or reversing current disabilities of old age.

III. SPECIFIC OBJECTIVES

The NIA seeks research grant applications for the study of specific mechanisms and conditions affecting particular aspects of health and functioning in the middle and later years of life. Such proposals will often require the formation of multidisciplinary research teams, given NIA's commitment to research on the linkages among behavioral, social, and biomedical processes.

Many researchable issues fall within the realm of health and effective functioning in the middle and later years. The following are offered as illustrations of appropriate topics. Applications need not, however, be limited to these issues.

Work and Retirement

- Aspects of work situations that stimulate intellectual competence, provide incentives and opportunities for sustained or enhanced performance.
- Factors influencing vigor, intellectual functioning, memory and other physical and psychological capacities and motivations for continuing productivity and creativity.
- Processes and conditions associated with retirement that influence physical and mental functioning.
- Age-related disabilities specific to particular occupations; organizational and technological innovations to remedy or compensate for these deficits.

The standard NIH referral guidelines will be followed in assigning applications to NIA or to other Institutes.
Health Institutions

- Psychological and social factors that reduce the need for long-term care of older people; alternatives to institutionalization.
- Influence of institutionalization on health and functioning of the institutionalized elderly and of their significant others (spouse, children, other relatives, friends).
- Psychosocial factors in the diagnosis and treatment of elderly by health-care practitioners.

Social Support

- Changes and stabilities in social networks as protections against disabilities in the middle and later years.
- Positive and negative consequences of social networks for health and functioning.

Health and behaviors and attitudes

- Specific changes in life style or behavior that maintain health or prevent particular diseases.
- Age and/or cohort differences in health behaviors, attitudes, and beliefs.
- Ways of converting awareness of healthful practices into sustained behaviors.
- Ways of eliciting adherence to unpleasant therapies.
- Ways of coping with stress, ranging from "daily hassles" to life-threatening events.

Personality

- Etiology and developmental course of disease-prone personality configurations over the life course (e.g., Type A vs. Type B behavior patterns).
- Individual differences in psychological and physiological response to chronic

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3/ The NIA will support research that extends the knowledge base underlying the provision of health services for the aging and the aged. The NIA does not support demonstration, control, and evaluation projects. Services per se are not supported except in cases in which a service, or package of services, may be one of the experimental variables in a proposed study.
or persistent stressful situations.

**Nutrition, Exercise, Sleep**

- Psychosocial factors influencing age-related changes in food preferences, eating habits, and nutrition.
- Cohort differences in nutrition and consequences for health in the middle and later years of life.
- Long-term and short-term effects on health and effective functioning of various types of exercise.
- Psychosocial factors in etiology and therapies for age-related sleep disorders.
- Behavioral consequences of age-related sleep disorders.

**Family and Household**

- Psychosocial, physiological, and medical consequences of bereavement and the processes linking bereavement with health and functioning.
- Changes in household composition and resources and their interaction with health and functioning.
- Family and household decision-making, and patterns of intergenerational exchanges of material and emotional support, as they affect health and later-life development.

**Methodological Studies**

In addition to substantive topics, applications are sought for methodological projects which promise new understanding of the complex processes which influence health and effective functioning in the middle and later years.

- Improved longitudinal designs for examining the linkages between psychosocial and biomedical aging processes.
- Development of cohort-comparative, cross-cultural, and historical-comparative designs for examining the interrelationship between societal changes and variations in the individual aging process.
- Development of statistical and mathematical models of age-related behavioral changes that are suitable for the analysis of longitudinal and cohort-comparative data.
- Improved measures of health, productivity, and functioning, suitable for use in the field or in the laboratory.
- Development and improvement of measures of human performance and functioning suitable for tracing changes over the full life course.
IV. METHODOLOGY

While research applications need not be limited to any particular methodology of data collection or analysis, the use of objective, reliable, and valid measures of psychosocial, or biological health and performance is essential. Consideration should be given to the relative advantage and disadvantages of cross-sectional vs. longitudinal or cohort design, or to the use of experimental and quasi-experimental designs in a variety of settings (including the laboratory, nursing home, health-care institution, residence, the community, and the workplace). Given the expense associated with collecting original data, the employment of pre-existing data sets and their secondary analysis is encouraged, though in many instances collection of new data may be required to meet particular objectives.

V. BACKGROUND READINGS

Among the topics for background readings that may be useful to investigators new to the study of aging, in general, and of health and functioning in particular, are such treatments as the following:

D.S. Krantz, D.C. Glass, and N.E. Miller, Behavior and Health. In the National Science Foundation's "Five-Year Outlook on Science and Technology," November 1981. (Available through NIA.)

Conference on Epidemiology of Aging, DHEW Publication No. (NIH) 77-711 and NIH Publication No. 80-969.

D.L. Featherman, The Life-Span Perspective. In the National Science Foundation's "Five-Year Outlook on Science and Technology," November 1981. (Available through NIA.)


VII. APPLICATION SUBMISSION AND REVIEW

Researchers considering submitting an application in response to this program announcement are strongly encouraged to discuss their project with NIA staff in advance of formal submission. This can either be done through a telephone conversation or through a written and brief (4-5 pages) research prospectus.

Applicants should use the regular research grant application form (PHS 398), which is available at the applicant's institutional Application Control Office or from the Office of Grants Inquiries, Division of Research Grants, NIH (Tel.: 301-496-7441). In order to expedite the application's routing within NIH, please (1) check the box on the application form's face sheet indicating that your proposal is in response to this announcement and print (next to the checked box) NIA HEALTH AND EFFECTIVE FUNCTIONING IN MIDDLE AND LATER YEARS, and (2) enclose a cover letter repeating that this application is in response to this announcement.
The cover letter and the completed application (along with six copies) should be mailed to:

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

The Division of Research Grants will assign applications to study sections for review according to the NIH process for regular research grant applications. Approved applications will compete for available funds with all other approved grant applications assigned to the National Institute on Aging.

Address requests for additional information, research prospectuses, and/or letters of intent to:

National Institute on Aging  
Behavioral Science Research  
Building 31C, Room 5C05  
Bethesda, MD 20205  
Tel.: 301-496-3136

This program is described in the Catalog of Federal Domestic Assistance Number 13.866, Aging Research. Awards will be made under the authority of Public Health Service Act, Title III, Section 301 (Public Law 78-610, 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.
ANNOUNCEMENT

RESEARCH ON URINARY INCONTINENCE IN THE ELDERLY

NATIONAL INSTITUTE ON AGING (NIA)

The National Institute on Aging announces a continuing interest in support of research on urinary incontinence in the elderly.

BACKGROUND

Urinary incontinence in the elderly is a major health problem, affecting at least one in ten persons over 65 years of age. It can range from the nuisance of occasional slight losses of urine to the disability of severe, frequent incontinence. Incontinence is an important factor contributing to institutionalization, and is responsible for a very large proportion of nursing and custodial costs. In addition to its large psychologic and social impact, incontinence places subjects at increased risk for other significant medical problems, including decubitus ulcers and complications of catheterization.

RESEARCH GOALS AND SCOPE

Epidemiology: There is a need for rigorous population studies of incontinence in the elderly. In particular, more knowledge is needed about the distribution of incontinence in terms of degree of severity, responsiveness to treatment, and transient vs. long-standing incontinence, as well as subjects' age, sex, functional status, and living arrangements. Medical economic data are needed on the direct and indirect costs associated with incontinence. Coordination of diagnostic and epidemiologic studies would improve knowledge of the distribution of the various etiologic categories of incontinence (detrusor instability, overflow incontinence, sphincter insufficiency, etc.) in the elderly. The association between incontinence and various disorders (e.g. Parkinsonism, dementia) and other risk factors requires further clarification.

Etiology and Pathophysiology: Success in treating incontinence is limited in many areas by a lack of fundamental knowledge. In particular, data are needed on pertinent neurologic and muscular changes occurring in both normal aging and the various types of incontinence, particularly in the widespread problem of detrusor instability. Fundamental work is needed on the etiologic role of other factors, including bladder outlet obstruction, elevated residual urine volume, infection, mucosal changes in the bladder and urethra, and altered behavioral patterns in the elderly.

Diagnosis: In the diagnostic evaluation of incontinence in the elderly, there is a great need to know which abnormal findings indicate contributory pathology, and which are "normal" in old age. These findings should be incorporated in assessments of the sensitivity and specificity of urodynamic studies and other diagnostic procedures in the elderly. The large number of elderly incontinent patients with impairment of mobility or cognition poses major problems in the use and interpretation of many conventional

This program is described in the Catalog of Federal Domestic Assistance Number 13.866, Aging Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulations 42 Part 52 and 45 CFR Part 74. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.
diagnostic tests. The development of procedures which demand less mobility and active subject compliance would increase the ease and reliability of evaluation of incontinence in the elderly.

Therapy: There are numerous pharmacologic, surgical, prosthetic, behavioral, and exercise therapies for the various types of urinary incontinence, but in many cases there is a lack of consensus on their effectiveness and applicability. The impact of improved nursing home practices, organization, and staffing on the degree of incontinence in institutions is another therapeutic issue which is presently unclear. Alternative palliative strategies employing special garments, pads, and other products may alleviate many problems of the refractory incontinent patient. Hence these strategies should receive the same critical evaluation as more definitive therapies.

To date, knowledge on the effectiveness of such interventions in the elderly has been limited by a scarcity of studies combining the following critical features, where applicable: double blind-crossover-placebo design, definitive diagnosis of the type of incontinence being treated, and objective, age-specific data on response to treatment, including side effects. As yet there is little consensus on which techniques should be "first-line" strategies and which should be reserved for refractory cases. Hence, in addition to the evaluation of individual techniques, there is a need for testing various combinations of treatment modalities, and for the development of rational sequential approaches to incontinence.

The research areas discussed above are mentioned only to illustrate the breadth of fertile topics for investigation and are not intended to limit applications in any research area related to urinary incontinence in the elderly. The NIA is interested in all innovative research on the epidemiology, etiology, pathophysiology, diagnosis and treatment of this problem. A more detailed outline of research issues, based on an NIA workshop on urinary incontinence in the elderly, is available from the NIA staff contact listed at the end of this announcement.

MECHANISMS OF SUPPORT

Applications may be submitted for any of the conventional NIH grant support mechanisms, including the individual research project grant, program project, clinical investigator, new investigator, Research Career Development Awards (RCDAs), and special initiative awards, and individual and institutional post-doctoral National Research Service Awards (NRSAs). The above list is not exhaustive; potential applicants are encouraged to communicate with the NIA staff contact listed at the end of this announcement regarding funding mechanisms and program design. Potential applicants for program project awards should contact NIA staff very early in the planning stages.

APPLICATION AND REVIEW PROCEDURES:

Applications should be submitted on PHS Form 398 (research grants), PHS Form 6025 (Institutional NRSA) or PHS Forms 416-1, 416-2, and 416-3 (individual NRSA).

1/ NRSAs will be supported under the authority of the Public Health Service Act, Section 472, 42 USC 289-1, and administered under PHS grants policy and Federal Regulations 42 CFR Part 66.
Applicants may obtain information and the appropriate application kits from their institution's grants office or by writing or calling:

Office of Grants Inquiries  
Division of Research Grants  
NIH  
Bethesda, MD 20205  
Phone: (301) 496-7441

When sending the completed application to the Division of Research grants, applicants should include the phrase "Prepared in response to the NIA Program Announcement: Urinary Incontinence in the Elderly" across the upper margin of the first (face) page of the application. A covering letter stating that the application is in response to this announcement should be enclosed. The original and six copies should be mailed to:

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

A copy of the application and covering letter should be mailed to the NIA staff contact listed below. Applications will be reviewed for scientific merit either by an appropriate study section of the Division of Research Grants or by a NIA review committee, depending on the funding mechanism being sought. Review will be conducted in accordance with NIH policy and procedure involving peer review. Awards will be made on a competitive basis with all applications competing for NIA funding.

Application Receipt Dates:

For institutional and individual NRSAs, RCDAs, program projects, and competing continuations: October 1, February 1, June 1.

For new research grant applications not identified above: November 1, March 1, July 1.

Inquiries and Correspondence:

Correspondence, including requests for information, letters of intent, and advice should be directed to:

Evan Hadley, M.D.  
Biomedical Research and Clinical Medicine Program  
National Institute on Aging  
National Institutes of Health  
Building 31, Room 5C11  
Betheasda, MD 20205  
(301) 496-4996
ANNOUNCEMENT

TINNITUS

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

The Communicative Disorders Program (CDP), National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) invites applications for support of research to increase our knowledge and understanding of tinnitus.

Approaches considered to be appropriate for support by NINCDS include studies directed toward:

1. Definition of the auditory properties of tinnitus including temporal and spectral characteristics, loudness, adaptation and suppression.

2. Exploration of the masking of tinnitus.

3. Identification of the etiologies and physiological correlates.

4. Development of an animal model.


Applicants are encouraged to address any specific aspects of the areas presented above. However, NINCDS would be receptive to any regular research grant applications which offer an innovative approach to understanding tinnitus.

APPLICATION PROCEDURE

Applications should be prepared on research grant application form PHS 398, available in the business or grants and contracts offices of most academic and research institutions, or from the Division of Research Grants, NIH. Applications must be received on or before the regular receipt dates of March 1, July 1, or November 1. The original and six (6) copies of the application should be sent to:

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

Applications submitted should have the statement "IN RESPONSE TO TINNITUS PROGRAM ANNOUNCEMENT" on the top of the first page. One copy of the completed

This program is described in the Catalog of Federal Domestic Assistance, number 13.851, Communicative Disorders Research. Grants will be awarded 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.
application should also be sent to Dr. Elkins at the address shown below.

REVIEW PROCEDURES

The initial review of applications for scientific and technical merit will be by an appropriate study section of the Division of Research Grants; secondary review will be by the National Advisory Neurological and Communicative Disorders and Stroke Council.

STAFF CONTACT

Inquiries may be directed to:

Earleen Elkins, Ph.D.
Communicative Disorders Program
National Institute of Neurological
and Communicative Disorders and Stroke
Federal Building, Room 1C08
7550 Wisconsin Avenue
Bethesda, Maryland 20205
Telephone: (301) 496-5061
ANNOUNCEMENT

INSTITUTIONAL NATIONAL RESEARCH SERVICE AWARDS
FOR CLINICAL RESEARCH TRAINING
SPEECH AND LANGUAGE DISORDERS

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

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

BACKGROUND INFORMATION

The Communicative Disorders Program (CDP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is inviting institutions to propose programs for training research fellows in methods of investigating speech and language disorders in children and/or adults. Of particular interest are applications proposing research training for the study of some of the following disorders: impaired language development of unknown etiology; language impairment in infantile autism; stuttering; impaired speech development; voice disorders in children and adults; adult aphasia; and dysarthrias associated with neurological disorders.

GOALS AND SCOPE

Clinical research training is being encouraged to meet the needs of the speech and language field for increased numbers of well-trained investigators. The goal is to support programs which will provide individuals interested in pursuing a research career in speech and language disorders with laboratory and clinical research experiences in the speech and language sciences as well as some other related disciplines providing techniques for studying speech and language functions such as neurolinguistics, neuropsychology, clinical neuropsychology, neuroanatomy, laryngology, psycholinguistics, speech science and speech perception. Domestic nonprofit private or public institutions may apply for grants to support research training programs. Emphasis should be placed on postdoctoral training for applicants demonstrating an active interest in pursuing a research career in speech and language disorders and wishing to broaden their scientific background. Postdoctoral training programs can include a limited number of predoctoral trainees.

The training program director at the institution will be responsible for the selection and appointment of trainees to the program. However, the program should be structured to permit the appointment of applicants who may not have been involved previously in research on speech and language disorders but who propose to bring to the study of these disorders, methods and knowledge they have gained in other fields. Provision should also be made for the appointment of those who have already begun to pursue a research

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, Section 472, 42 USC 2891-1, and administered under PHS and Federal Regulations 42 CFR Part 66. This program is not subject to Agency Review.
career in speech and language disorders but who require research training in a related field of the neurosciences or behavioral science relevant to their research goals in speech and language disorders. Training in scientific methodology should be available for those who have previously attained a health professional degree.

The participating faculty should be scientists well qualified and willing to offer and direct appropriate research fellowship training. Different disciplines should be represented among the faculty with some members actively involved in clinical investigations on speech and/or language disorders. Clinical research settings providing access to patients with speech and language disorders would be essential and may be achieved through collaborative agreements between institutions.

It is expected that only a limited number of awards will be made during one fiscal year.

REVIEW PROCEDURE AND CRITERIA

A. Review Procedures

Applications will be reviewed for scientific merit by the NINCDS Communicative Disorders Review Committee with secondary review by the National Institute of Neurological and Communicative Disorders and Stroke Council.

B. Review Criteria

Factors considered in evaluating each application are as follows:

1. Relevance of application to scope and objectives provided in this announcement.

2. Merit of proposed research training objectives and program design.

3. Evaluation of research facilities and environment and institutional commitment to the proposed facilities.

4. Ability of the institution to attract high caliber students and the previous training record of the program.

5. Expertise and qualification of proposed participating faculty and the appropriateness of the training program proposed.

METHOD OF APPLYING

Application receipt dates are October 1, February 1, and June 1. The National Research Service Award Institutional Grant Application Form PHS 6025 should be used for applying in response to this Program Announcement. 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 the staff contact listed below or to:

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

For additional information on the above program and application procedures contact:

Dr. Christy L. Ludlow
Communicative Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke
7550 Wisconsin Avenue, Room IC-13
Bethesda, MD 20205
(301) 496-5061

The original and six copies should be mailed to:

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

INDIVIDUAL OR INSTITUTIONAL NATIONAL RESEARCH SERVICE AWARDS FOR POSTDOCTORAL TRAINING

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

"Clinical Studies of Chemosensory Disorders"

I. BACKGROUND INFORMATION

The Communicative Disorders Program (CDP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is inviting applications for postdoctoral research training of clinical investigators under Individual or Institutional National Research Service Awards (NRSA) that are specifically directed toward the clinical measurement of taste or smell function: gaining the skills of psychophysical measurement and experimental design and using them in clinical investigations of taste and smell disorders.

II. GOALS AND SCOPE

The training is aimed at increasing the participation of clinical investigators in multidisciplinary clinical chemosensory programs. There is a need for otolaryngologists, neurologists, and other clinical investigators to obtain reproducible and valid psychophysical measurements of the chemosensory ability of patients and normal subjects, especially because measurement of taste and olfactory abilities at either threshold or suprathreshold levels are rarely included in clinical examinations. Although measurement may be attempted as part of a neurological examination, the measurements are often rough thresholds for only a few chemicals. The control and determination of stimuli are common in laboratory measurements of chemosensory abilities: these are the measurements needed in clinical examinations. Applicants must have an active interest in clinical research and prepare for training under scientists qualified in psychophysical measurement and experimental design.

III. REVIEW PROCEDURES AND CRITERIA

A. Review Procedures

All applications will be reviewed for scientific merit by an NIH peer review group. Review applications for individual National Research Service Awards (NRSAs) will be managed by the Division of Research Grants. Applications

This program is described in the Catalog of Federal Domestic Assistance Number 13.851, Communicative Disorders. Awards will be made under the authority of the Public Health Service Act, Section 472, 42 USC 2891-1, and administered under PHS grants policy and Federal Regulations 42 CFR Part 66. This program is not subject to A-95 Clearinghouse or Health Systems Agency review.
for institutional awards will be reviewed for scientific merit by an National
Institute of Neurological and Communicative Disorders and Stroke review
committee, with secondary review by the National Advisory Neurological
and Communicative Disorders and Stroke Council.

B. Review Criteria

The review criteria are several:

1. Relevance of application to scope and objectives provided in this
   announcement.

2. Merit of proposed approaches to the training.

3. Expertise and qualifications of training personnel.

4. Appropriateness of resources and environment.

IV. METHOD OF APPLYING

Application receipt deadline dates are October 1, February 1, and June 1. The
application kits are self-explanatory. The kits for NRSA for Institutional grants
include PHS Form 6025 and those for NRSA for Individual Postdoctoral Fellows
include PHS Form 416-1, 416-2, and 416-3.

If the institution's business office or central application control office does not
have the forms, single copies may be requested by writing to:

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

Type either the words INDIVIDUAL NRSA ON CHEMOSENSORY DISORDERS or
INSTITUTIONAL NRSA ON CHEMOSENSORY DISORDERS in block letters in the
upper right hand corner of the face page of the application. Include with the
application a brief letter indicating that it is in response to this program
announcement. Send the original and six copies to:

Application Receipt Office, DRG
National Institutes of Health
Westwood Building, Room 240
Bethesda, Maryland 20205

Send a copy of the letter to:

Dr. Jack Pearl
Communicative Disorders Program
National Institute of Neurological and Communicative
Disorders and Stroke
Federal Building Room 1C14
7550 Wisconsin Avenue
Bethesda, Maryland 20205
If the applicants have not obtained a copy of the Report of the Panel on Communicative Disorders, they are encouraged to do so by writing to Dr. Jack Pearl.
DIET AND NUTRITION RESEARCH
NATIONAL INSTITUTE OF DENTAL RESEARCH

Application Receipt Dates: July 1, November 1, March 1

I. BACKGROUND

The Soft Tissue Stomatology and Nutrition Program Branch of the National Institute of Dental Research is encouraging submission of individual research grant applications for studies to define the influence of diet and nutrition on the growth and development of oral facial structures or repair of lesions and prevention of diseases in these structures.

While many direct and indirect effects of human nutrition are known, a greater understanding is needed of their relationship to the prevention of disease and the pathogenesis initiated by other factors as well as their effects on normal growth and development.

II. RESEARCH GOALS

This NIDR program announcement is meant to encourage any basic or clinical nutrition research related to oral facial functions or structures. The goals are not meant to be limiting nor are they necessarily more important than others not covered in this announcement. The following research goals are therefore not necessarily listed in order of priority.

1) To understand the influence of diet and nutrition on the oral and para-oral structures during all tates of life.

This goal includes studies which identify and characterize the metabolic roles of nutrients and dietary conditions necessary for optimum growth, development and aging as well as function, maintenance and repair of oral facial structure.

2) To understand the effect of diet and nutritional deficiencies, excesses, imbalances and other related factors on the pathogenesis and systemic sequelae of oral diseases and anomalies.

The role of specific nutrients, food components and dietary patterns on the pathogenesis of periodontal and oral soft tissue diseases and other oral diseases...
and conditions is of interest to the program. Also, the interaction between nutrition and systemic factors in relation to the above diseases, is of importance.

3) To understand and use dietary and nutritional approaches in prevention and management of oral facial diseases, and conditions.

In order to improve disease prevention and disease management procedures related to nutrition, improved procedures to assess the nutritional status of individuals must be developed. Also of interest is the identification and testing of methods which might lead to modification of the dietary pattern which would promote both oral and general health.

The NIDR National Caries Program, has similar nutrition related research goals focused on dental caries.

III. APPLICATION AND REVIEW PROCEDURES

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

The phrase "Prepared in Response to NIDR Nutrition Announcement" should be typed across the top of the first page of the application. The original and six copies of the application should be sent or delivered to:

Application Receipt Office, DRG
National Institutes of Health
Westwood Building, Room 240
Bethesda, Maryland 20205

Additional information regarding this program may be obtained by contacting:

Dr. Paul D. Frazier, Chief, or
Dr. David A. Wolff, Health Scientist Administrator
Soft Tissue Stomatology and
Nutrition Program Branch
National Institutes of Dental Research
National Institutes of Health
Westwood Building, Room 510
Bethesda, Maryland 20205
Telephone: (301) 496-7808

Individuals interested in obtaining information on nutrition related caries research may contact:

Dr. John D. Townsley, Chief
Caries Research Grants and Contracts Branch
National Institute of Dental Research
National Institutes of Health
Westwood Building, Room 522
Bethesda, Maryland 20205
Telephone: (301) 496-7884
EXPERIMENTAL RESEARCH RELATED TO BIOLOGICAL EFFECTS OF LOW DOSES OF IONIZING RADIATION

NATIONAL CANCER INSTITUTE

The Low Level Radiation Effects Branch of the National Cancer Institute is inviting grant applications for the purpose of encouraging cellular and animal studies that will provide new and relevant information on the molecular and cellular processes leading to mutagenesis, cell transformation, and carcinogenesis by low doses of ionizing radiation.

Uncertainties in the risk estimates for human cancers and mutation are due to our lack of understanding of the basic principles of radiation mutagenesis, carcinogenesis, and cocarcinogenesis. The area of mutagenic and carcinogenic mechanisms was identified by the U.S. Congress in Public Law 95-622 as requiring special emphasis for additional research. One of the objectives of the Low Level Radiation Effects Branch is the discovery of principles that allow the extrapolation of radiation effects from the relatively high doses used in the laboratory to the low range of doses encountered in the environment. The primary goal of this program is the elucidation of the steps that lead from the initial ionizing event to the expression of mutations or neoplasia by cells in mammalian tissues.

I. BACKGROUND INFORMATION

A. Radiation Mutagenesis

Mutations have long been known to arise from exposure to ionizing radiation and have been clearly demonstrated in microbial, plant, animal, and in vitro cell studies. It is expected that mutations would occur in humans as a result of radiation exposure; however, to date there has been no definitive demonstration of mutagenesis resulting from the exposure of human populations to ionizing radiation. Radiation may be viewed not only as a potential mutagen but as a tool to aid in the elucidation of the mutation process. Furthermore, mutational events are likely to be involved in the process of carcinogenesis.

In studies of the production of mutations in plants and insects by ionizing radiation, a linear dependence of specific-locus mutation frequency on dose at low doses has been found. However, in experimental systems in which the molecular details of the mutation process are more accessible to study (somatic cells and microorganisms), a linear dose-response relationship is not usually observed. The specific molecular mechanism of mutagenesis (transition, transversion, frame-shift, deletion, etc.) differs depending on the locus under study and the nature of the mutagenic agent.

A number of controllable variables can be exploited in the study of the processes that lead to radiation-induced mutations. In mammalian cells, for example, different loci have been found to be sensitive to mutagenesis at different phases of the cell cycle. Mammalian cell lines with useful genetic properties, such as DNA repair defects, are available and are suitable for
studies on mutation mechanisms. Continued research is needed in the development of suitable cell lines. Variables such as dose rate, radiation quality (usually expressed as linear energy transfer, LET), chemical sensitization and protection, DNA repair perturbation, etc. may be used as variables in experiments designed to characterize the mutation process.

It is expected that the research will emphasize cellular and molecular studies. An understanding of the basic mechanisms of mutagenesis may permit the construction of models which could predict the incidence of mutations in human beings following a given exposure to ionizing radiation. The extrapolation of laboratory results to human populations is an important goal of the research on radiation mutagenesis and is considered necessary for the successful assessment of genetic risks in human beings.

B. Radiation-Induced Cell Transformation

Of all of the biological effects of ionizing radiation, carcinogenesis is presently of the greatest concern. Heightened awareness of environmental carcinogenic agents in general has made neoplasia the most widely-feared result of radiation exposure. Epidemiological studies of irradiated human populations and a wide variety of studies on experimental animals clearly indicate that radiation causes cancer. It has long been recognized that animal data alone cannot be used to make quantitative predictions for the number of human cancers expected to be induced by radiation. However, animal and cellular data can provide information on general principles and mechanisms of radiation effects. Predicting dose-response relationships at low doses and dose rates must depend upon understanding the phenomena that give rise to these functions.

Transformation toward malignant behavior can be induced in animal cells in culture by a number of different agents, including radiation, viruses, and certain families of chemicals. While it is important that research continue to determine the relationship between cancer in vivo and cell transformation in vitro a number of specific research needs in radiation carcinogenesis using cell transformation in vitro can be identified. In vitro transformation represents one of the most sensitive mammalian systems for the study of radiation responses and requires only a few weeks for an experiment, compared to months or years required for tumor expression.

Factors considered as important determinants in radiation-induced transformation are dose rate, radiation quality, the action of chemical modifiers of radiation action, DNA repair processes, cytogenetic damage, and the action of substances that modify cell transformation in general (such as retinoids, antioxidants, tumor promoters, protease inhibitors, etc.).

C. Radiation Carcinogenesis in Animals

The carcinogenic risk to human populations exposed to low doses of ionizing radiation may depend largely upon other environmental factors. For example, a possible correlation exists between cigarette smoking and the induction of lung cancer by alpha radiation, and certain chemical agents can strongly enhance cellular transformation in vitro and tumor induction in animals. "Initiation" and "promotion" are considered steps on the way to the neoplastic state; other steps may exist. Ionizing radiation can apparently
act as both initiator and promoter. Host factors are known to be paramount in animal tumor production: oncogenic virus genes, the immune system, hormonal status, and inherited DNA repair capacity. In order to evaluate radiation as an initiator and/or promoter of cancer the role of other chemical and biological factors need to be explored as well. It will therefore be necessary to integrate effectively radiation biological data with the greater body of knowledge concerning carcinogenesis.

The sensitivity to radiogenic cancer among different organs and tissues varies with the strain or species of animal studied. This fact should be useful in the study of the host factors controlling sensitivity (or resistance) to radiation-induced cancer and eventually help lead to an understanding of what may be large differences in radiation sensitivity among individuals in a heterogeneous human population.

The rate and manner in which a radiation dose is delivered has profound influence upon the carcinogenic response in animals. As dose rate is decreased, the slope of the dose-response curve for low-LET radiation is reduced and approaches a limiting low value. High-LET radiation is more effective than are X and gamma rays in the malignant transformation of cells in culture and in the induction of tumors in animals. Research is needed on the influence of these variables on the carcinogenic response and the mechanisms involved.

D. Approach

The applicant is encouraged to consider promising areas of research that may lead to the prediction of mammalian and human dose-response relationships at low doses and dose rates. The application should deal with any of the various steps involved in mutagenesis or the induction of neoplasia. The roles of molecular damage and its repair, the differentiated state of affected cells, organ-specific reactions to transformed cells, tumor promoting events, the immune response, endocrine status, and environmental and intrinsic factors other than radiation are to be considered. Proposed experiments should be designed to produce information that can be used in the development of a conceptual framework that predicts a priori what form dose-response functions will have at low dose and at low dose rate.

Specific research needs are considered to exist in the following areas:

The correlation of the biological endpoints (mutation, transformation, carcinogenesis) with chemically defined lesions in DNA or other structures.

The understanding of "single-hit" or linear dose effects, their possible dependence on dose rate, and how they are influenced by molecular and cellular repair processes.

Investigations that determine the functional significance of radiation-induced chromosome anomalies with respect to mutagenesis and carcinogenesis.

Determination of the relationships between cell transformation in vitro and tumor induction in vivo.
The development of cell and animal systems with properties that permit the study of the role of specific molecular processes mutagenesis in and carcinogenesis, such as radiation sensitive, repair deficient, and other specialized strains of cells and animals.

Studies on promoting and modifying conditions that may form the underlying bases for variations in susceptibility to cancer induction.

II. MECHANISM OF SUPPORT

The mechanism of support will be the traditional research grant. Policies that govern the research grant programs of the National Institutes of Health will prevail. The award of grants pursuant to this Program Announcement is contingent upon receipt of proposals of high scientific merit and the availability of appropriated funds.

This program is described in the Catalog of Federal Domestic Assistance No. 13.393, Cancer Cause and Prevention Research. Grants will be awarded under the authority of the Public Health Service Act, Sections 301(c) and 402; (Public Law 78-910, as amended; 42 U.S.C. 241 & 282). This program is not subject to A-95 Clearinghouse or Health Systems Agency review.

III. METHODS AND CRITERIA OF REVIEW

A. Assignment of Applications. Applications will be received by the Division of Research Grants (DRG), National Institutes of Health. DRG will refer the proposals to the appropriate Study Section for scientific review, and will assign them to the National Cancer Institute for possible funding and management. These decisions will be governed by normal programmatic considerations as specified in the DRG Referral Guidelines.

B. Review Procedures. Applications in response to this announcement will be reviewed in accordance with the usual NIH peer review procedures (Study Section). Factors considered in the scientific merit evaluation of each application will include an assessment of the importance of the proposed research problem, the novelty and originality of approach, the training experience and research competence of the investigator(s), the adequacy of experimental design, the suitability of the facilities, and the appropriateness of the requested budget relative to the work proposed. Following Study Section review, applications referred to NCI will be evaluated for program relevance by members of the Low-Level Radiation Effects Branch, NCI, and reviewed by the National Cancer Advisory Board. Funding decisions will be based upon relative scientific merit, program relevance and the Institute's ability to fund.

C. Deadlines. Applications will be accepted on or before the usual dates for new applications on an indefinite basis: March 1, July 1, and November 1.

IV. METHOD OF APPLYING

Applications should be submitted on Form PHS-398, which is available in the business or grant offices of most academic and research institutions or from the Division of Research Grants, NIH.
The phrase "PREPARED IN RESPONSE TO NCI ANNOUNCEMENT ON BIOLOGICAL EFFECTS OF LOW DOSES OF IONIZING RADIATION" should be typed across the top of the application. The original and six copies should be sent or delivered to:

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

In order to alert the Low Level Radiation Effects Branch to the submission or proposals as requested above, copies of the face page and summary page of such applications should be forwarded under separate cover to:

Dr. Oddvar F. Nygaard  
Low Level Radiation Effects Branch  
National Cancer Institute  
Room 4B29, Building 31  
National Institutes of Health  
Bethesda, Maryland 20205
REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

GRANTS IN NUTRITION

NATIONAL CANCER INSTITUTE - TRAINING

The National Cancer Institute invites applications for institutional grants for National Research Service Awards (NRSAs) in nutrition as it relates to cancer cause, prevention, detection, diagnosis, treatment, and restorative care. Proposed projects may encompass both predoctoral and postdoctoral research training, or may support postdoctoral training only. The first deadline for receipt of applications is February 1, 1982. Those applications will be reviewed by the Cancer Research Manpower Review Committee at its scheduled meeting in May, 1982, and by the National Cancer Advisory Board at its scheduled meeting in October, 1982. Qualifying applications will be considered for funding thereafter, in accordance with the usual NRSA receipt dates of February 1, June 1, and October 1.

The current NIH definition of nutrition as it applies to this effort is:

"The term nutrition research includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including man, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular and subcellular level. This definition also includes:

Research designed to elucidate the metabolic role or function of nutrients in both animal models and man.

All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.

Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in man. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies."

Applications should be submitted on Standard Form PHS 6025. At the top of the first page of said application form the applicant should type in capital letters "Submitted in Response to Nutrition Program Announcement." Before writing and submitting applications, applicants should discuss their plans with NCI staff and should request a copy of the National Cancer Institute's Guidelines on Cancer Orientation in Research Training Grants. The NCI staff representative is:

This program is described in the Catalog of Federal Domestic Assistance Number 13.398, Cancer Research Manpower. Awards will be made under the authority of the Public Health Service Act, Section 472, 42 USC 2891-1, and administered under PHS grants policy and Federal Regulations 42 CFR Part 66.
Barney C. Lepovetsky, Ph.D., J.D.
Chief, Research Manpower Branch
Division of Resources, Centers
and Community Activities, NCI
Blair Building, Room 717
8300 Colesville Road
Silver Spring, MD 20910
Tel.: (301) 427-8898